Transferosomes: A Liposomal Carrier System for Controlled Drug Release

ADITYA KESARKAR *, SARDAR SHELAKE , DR.N.B.CHOUGALE ,

AVADHUT TALWAR , AVINASH MANGAVE , RADHIKA SUBHEDAR

Ashokrao Mane Institute of Pharmacy, Ambap.

Tal – Hatkanangale Dist – Kolhapur 416112

Abstract

Transdermal drug delivery systems (TDDS) offer numerous advantages over conventional delivery methods, such as oral and injection routes, including improved patient compliance and reduced side effects. However, the inherent impermeability of the skin, particularly the stratum corneum, poses a significant challenge for the effective delivery of hydrophilic and macromolecular drugs. Recent advancements in vesicular carriers, specifically transferosomes, have been developed to overcome these limitations. Transferosomes are ultra-deformable lipid-based vesicles that can encapsulate both hydrophilic and lipophilic drugs, enhancing their stability, bioavailability, and transdermal penetration. The incorporation of edge activators into their bilayer composition grants them exceptional flexibility, allowing them to traverse biological membranes and deliver drugs efficiently. This review explores the unique structure, salient features, methods of preparation, characterization techniques, and broad applications of transferosomes in pharmaceuticals. The findings suggest that transferosomes present a novel approach for non-invasive drug administration, with significant implications for targeted drug delivery, vaccine development, and the treatment of various medical conditions. Future research aims to optimize transferosome formulations further and expand their therapeutic applications, solidifying their role in innovative drug delivery systems.

Introduction

Transdermal drug delivery systems (TDDS) provide several potential benefits over traditional techniques including oral and injection delivery. [1] However, the skin's permeability is the main drawback of TDDS; it is highly impermeable to hydrophilic and macromolecules and permeable to small molecules and lipophilic medicines. Stratum corneum, the outermost layer of the skin, is the primary barrier and rate-limiting step for drug diffusion across the skin.[2] In order to create systems that can transport medications and macromolecules to deeper tissues, recent methods for modifying vesicle composition have been studied. These methods have produced two new vesicular carriers: transferosomes, which are extremely flexible lipid-based elastic vesicles, and ethosomes.[3] Transferosomes are highly deformable vesicles with a complex lipid bilayer enclosing an aqueous core. The vesicle is self-regulating and self-optimizing due to the interdependence of the bilayer's structure and local composition.[4] Transferosomes, which can administer both high and low molecular weight medications transdermally, have just been developed.[5] Transferosomes are highly flexible, lipid supra molecular aggregates that have been carefully engineered to pass through intact mammalian skin and function as drug carriers for targeted, non-invasive drug delivery and long-term release of medicinal substances.[6] Every transferosome has at least one inner aqueous compartment that is encircled by a lipid bilayer with unique characteristics because "edge activators" have been incorporated into the vesicular membrane. Span 80, Tween 80, sodium cholate, and sodium deoxycholate are examples of surfactants that have been employed as edge activators.[7] Transferosomes make excellent candidates for the non-invasive administration of tiny, medium, and large medicines because of their deformability.

Delivery through the transdermal route is an intriguing choice in this regard due to its convenience and safety. This has a number of potential benefits over traditional routes, including avoiding first pass metabolism, extending and predicting the duration of activity, minimizing unwanted side effects, enhancing physiological and pharmacological response, avoiding drug level fluctuations, avoiding intra- and inter-patient variations, and—above all—providing patients with convenience. Numerous physical and chemical techniques, including the use of colloidal carriers like lipid vesicles and nonionic surfactant vesicles, penetration enhancers, enhancers, iontophoresis, and

sonophoresis, have been used up to this point to improve the effectiveness of material transfer across intact skin.

Defination

A “transferosome” is an advanced drug delivery system, classified as an ultra-deformable vesicle. It is composed of phospholipids, surfactants, and an edge activator that enhances its flexibility. This unique composition allows transferosomes to penetrate deep through the skin and other biological barriers, making them highly effective for transdermal drug delivery. They can encapsulate both hydrophilic and lipophilic drugs, improving drug stability and bioavailability while enabling targeted and controlled release. Transferosomes are especially valuable in delivering large molecules like proteins and peptides, offering an innovative approach for non-invasive drug administration.

Structure of Transferosome

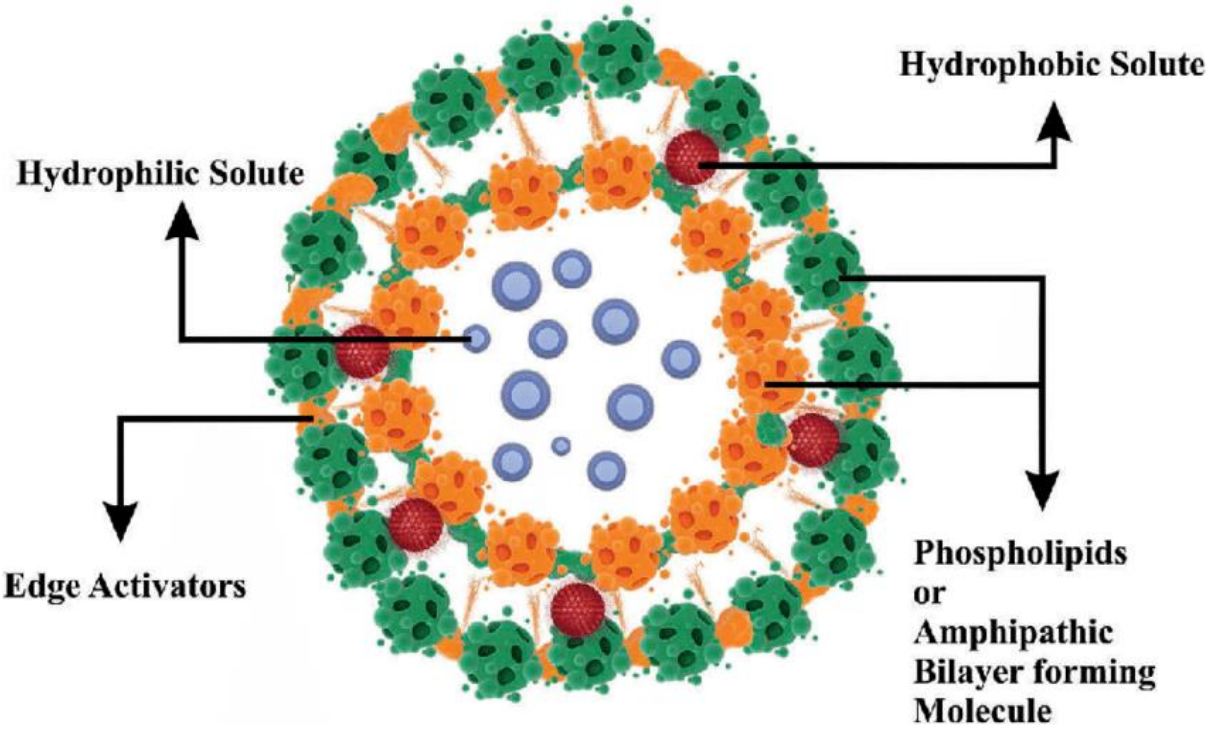

Figure 1 : Structure of transferosome

The structure of a transferosome is composed of several key components that give it the ability to be ultra-deformable and penetrate biological barriers. (figure-1) Here's a breakdown of its structure

1. Phospholipid Bilayer:

- The main structural component is a phospholipid bilayer, similar to other liposomal vesicles. Phospholipids consist of two hydrophobic tails and a hydrophilic head. This arrangement forms a bilayer that encapsulates the drug within the core.

2. Edge Activators (Surfactants):

- What sets transferosomes apart from regular liposomes is the presence of edge activators. These are typically surfactants such as sodium cholate, Span 80 (sorbitan monooleate), or Tween 80. They increase the vesicle's flexibility by reducing the interfacial tension within the lipid bilayer.

- The edge activators allow the vesicle to be highly deformable, enabling it to squeeze through tiny pores and gaps in biological membranes without breaking.

3. Aqueous Core:

- Inside the vesicle, there is an aqueous core that can hold hydrophilic drugs. This allows transferosomes to encapsulate and protect water-soluble drugs from degradation.

4. Hydrophobic Region:

- The lipid bilayer also contains a hydrophobic region that can house lipophilic (fat-soluble) drugs. This gives transferosomes the versatility to carry a wide range of therapeutic agents.

5. Additional Components (optional):

- Cholesterol may be added to stabilize the bilayer, depending on the formulation.

- Other stabilizers or targeting ligands can also be added to the surface to improve drug delivery efficiency or enhance specific targeting to diseased tissues.

In summary, transferosomes are deformable lipid vesicles with a structure that allows them to pass through tight spaces, making them an excellent vehicle for delivering drugs across skin, membranes, or other barriers in the body. the (table 2) shows the different additives used in formulation of transferosome.

Class	Example	Uses

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

Table 2: Different additives used in formulation of transferosomes

Salient Features

1) High Deformability: Transferosomes possess the ability to deform and squeeze through pores or constrictions significantly smaller than their own diameter, making them highly effective for transdermal and deep tissue drug delivery.

2) Versatile Solubility: Their structure, composed of both hydrophilic and hydrophobic regions, allows them to encapsulate a wide range of drug molecules with varying solubilities.

3) Enhanced Penetration: Their deformable nature enables superior penetration of intact vesicles through biological membranes, allowing for efficient drug delivery to targeted sites.

4) Biocompatibility and Biodegradability: Made from natural phospholipids, transferosomes are safe and biodegradable, reducing the risk of toxicity or adverse reactions.

5) High Entrapment Efficiency: They have a high capacity to encapsulate drugs, particularly lipophilic drugs, with entrapment efficiencies close to 90%.

6) Protection of Encapsulated Drugs: Transferosomes protect the enclosed drug molecules from enzymatic or metabolic degradation, ensuring more stable and effective delivery.

7) Slow and Sustained Release: They act as a drug depot, gradually releasing their contents over time, allowing for sustained therapeutic effects.

8) Applicability for Various Drug Types: Transferosomes can carry a broad spectrum of drugs, including low and high molecular weight molecules like analgesics, corticosteroids, hormones, anticancer agents, and proteins (e.g., insulin).

9) Systemic and Topical Delivery: They are suitable for both systemic circulation and topical application, making them a flexible platform for diverse therapeutic needs.

10) Simple Manufacturing Process: Transferosome production is straightforward and scalable, involving simple procedures without the need for complex or pharmaceutically unacceptable additives.

Advantages of Transferosomes

1) Their entrapment efficiency is great; for a lipophilic medication, it is close to 90%.

2) This great deformability improves intact vesicle penetration.

3) They can serve as a vehicle for both high and low molecular weight medications, for example. insulin, gap junction protein, sex hormone, analgesic, corticosteroids, anesthetic, and anticancer.

4) The infrastructure of transferosomes can hold medicinal molecules with a broad range of solubility since it is composed of both hydrophobic and hydrophilic moieties.

5) They serve as a depot, gradually releasing their contents.

6) They can be applied topically or systemically to deliver drugs.

7) It is easy to scale up because the process is straightforward, doesn't require a long process or needless use of Unacceptable pharmaceutical additives. [8,9,10]

Disadvantages of Transferosomes

1) Transfersomes are prone to oxidative destruction, which makes them chemically unstable.

2) Natural phospholipid purity is another factor that works against the use of transfersomes as drug delivery systems.

3) Transfersomes formulations are expensive. [11,12]

Characterization of Transferosomes

The characterization of transferosomes is crucial to ensure their efficiency and suitability for drug delivery. Below are the key parameters used to characterize transferosomes:

1. Vesicle Size and Size Distribution

- Technique: Dynamic Light Scattering (DLS), Photon Correlation Spectroscopy (PCS), and Transmission Electron Microscopy (TEM).
- Purpose: Determines the average size and uniformity of the transferosome vesicles, typically in the nanometer to micrometer range.

2. Shape and Morphology

- Techniques: Scanning electron microscopy (SEM) and transmission electron microscopy (TEM).
- Purpose: To observe the structural integrity, shape, and surface characteristics of transferosomes.

3.Vesicle Deformability (Elasticity)

- Technique: Extrusion through membranes of varying pore sizes and deformability studies.
- Purpose: Measures the ability of transferosomes to pass through constrictions much smaller than their own diameter without loss of integrity, a key feature that differentiates them from conventional liposomes.

4. Entrapment Efficiency (EE%)

- Technique: Ultracentrifugation or dialysis followed by drug quantification (UV spectrophotometry, High-Performance Liquid Chromatography - HPLC).
- Purpose: Determines the amount of drug encapsulated within the transferosomes as compared to the total drug used in formulation, usually expressed as a percentage.

5. Zeta Potential (Surface Charge)

- Technique: Zeta potential analyzer.
- Purpose: Measures the surface charge of the vesicles, which influences their stability and interaction with biological membranes. A high absolute zeta potential suggests better stability of the formulation.

6. Drug Release Profile

- Technique: In vitro drug release studies (dialysis membrane or Franz diffusion cell) with UV or HPLC analysis.
- Purpose: Evaluates the rate and extent of drug release from transferosomes over time, which helps in determining the sustained or controlled release properties.

7. Vesicle Lamellarity

- Technique: Transmission Electron Microscopy (TEM) or Small Angle X-ray Scattering (SAXS).
- Purpose: determines how many bilayers are present in the transferosome vesicles, which may have an impact on the kinetics of drug loading and release.

8. Encapsulation Stability

- Technique: Stability studies over time under various storage conditions (temperature, humidity) with evaluation of size, drug content, and leakage.
- Purpose: Assesses the shelf-life and stability of the transferosome formulation by monitoring changes in physical and chemical properties over time.

9. In vitro Permeability Studies

- Technique: Animal or synthetic membranes can be used in Franz diffusion cells.
- Purpose: Tests the ability of transferosomes to penetrate through biological membranes, mimicking transdermal or topical drug delivery.

10. In vitro and In vivo Cytotoxicity/Compatibility

- Technique: Cell viability assays (MTT, LDH release) and animal models.
- Purpose: Assesses the biocompatibility, toxicity, and safety profile of the transferosomes in cells or organisms.

11. Thermodynamic Stability Studies

-Technique: Centrifugation, freeze-thaw cycles, and stress tests (heating and cooling).

- Purpose: To evaluate the physical stability of transferosomes under varying environmental conditions.

These characterization techniques provide a comprehensive understanding of transferosome behavior, stability, and efficacy, ensuring they are suitable for targeted and controlled drug delivery.

Method of preparation of transferosome

Transferosomes are prepared using several methods, each tailored to produce stable, deformable vesicles capable of carrying both hydrophilic and lipophilic drugs. The following are the common methods of preparation:

1. Thin Film Hydration Method

This is the most widely used method for preparing transferosomes.

Steps:

1.Dissolution of Lipid Components: Phospholipids and edge activators (such as sodium cholate or Tween-80) are dissolved in a volatile organic solvent like chloroform or methanol.

2. Formation of Thin Film: The solvent is evaporated under reduced pressure using a rotary evaporator, forming a thin lipid film on the walls of a round-bottom flask.

3. Hydration: After drying, the lipid film is rehydrated at a temperature higher than the lipid transition temperature using an aqueous solution (such as a buffer or drug-containing solution).

4.Vesicle Formation: The hydrated lipid film spontaneously forms multilamellar vesicles. These vesicles are then subjected to mechanical agitation (e.g., vortexing or stirring).

5.Size Reduction: The vesicles are reduced to the desired size using techniques such as sonication or extrusion through polycarbonate membranes.

Advantages:

- Simple and scalable.
- Good control over vesicle size.

Disadvantages:

- Involves the use of organic solvents, which may require complete removal to avoid toxicity.

2. Reverse Phase Evaporation Method

This method is useful for high drug entrapment efficiency, particularly for hydrophilic drugs.

Steps:

1.Lipid Dissolution: Lipids are dissolved in a mixture of organic solvents such as ether and chloroform.
2. Formation of Water-in-Oil Emulsion: The drug is dissolved in an aqueous solution, and this solution is emulsified with the lipid solution, forming a water-in-oil emulsion.
3.Solvent Removal: The organic solvent is slowly removed under reduced pressure, which results in the formation of large unilamellar vesicles.
4.Vesicle Size Reduction: The vesicles are subjected to size reduction by sonication or extrusion to achieve uniform vesicle size.

Advantages:

- High drug loading capacity.
- Suitable for both hydrophilic and hydrophobic drugs.

Disadvantages:

- Involves organic solvents, which require careful removal.

3.Ethanol Injection Method

A simple, solvent-based method that avoids the use of harsh conditions.

Steps:

1.Preparation of Organic Solution: The phospholipids and edge activators are dissolved in ethanol.
2.Injection: The ethanol solution is injected rapidly into an aqueous phase (drug solution or buffer) under continuous stirring.
3.Vesicle Formation: Spontaneous vesicle formation occurs as the ethanol disperses into the aqueous phase.
4.Size Reduction: The resulting transferosomes are subjected to size reduction using sonication or extrusion.

Advantages:

- Simple and rapid method.
- Avoids the need for high temperatures.

Disadvantages:

- Residual ethanol may need to be removed, and the method may have low entrapment efficiency for some drugs.

4.Sonication Method

This method uses ultrasonic energy to prepare transferosomes.

Steps:

1. Lipid Dispersion: An organic solvent is used to dissolve phospholipids and edge activators, and then an aqueous drug solution is added to hydrate them.
2.Sonication: The hydrated solution is sonicated using a probe sonicator or bath sonicator, leading to the formation of transferosomes.
3. Size Control: The vesicle size can be controlled by adjusting the sonication time and intensity.

Advantages:

- Easy to implement.
- Produces smaller vesicles with uniform size distribution.

Disadvantages:

- May lead to degradation of sensitive molecules due to the use of ultrasonic energy.

5.Microfluidization

This is a more advanced technique used for the preparation of transferosomes.

Steps:

1. Lipid and Drug Mixture: Lipids and drugs are mixed and passed through a microfluidizer at high pressure.

2. Shearing Forces : The solution is subjected to high shear forces as it passes through microchannels, resulting in the formation of small vesicles.

3. Size Control: Multiple passes through the microfluidizer help achieve uniform and small vesicle sizes.

Advantages:

- Produces highly uniform and small-sized vesicles.
- Scalable for industrial production.

Disadvantages:

- Expensive equipment and complex setup.

6. Extrusion Method

This is often used in combination with other techniques for size reduction and uniformity.

Steps:
1. Lipid Film Hydration: Similar to the thin-film hydration method, vesicles are first formed.
2.Extrusion: The vesicles are then passed through polycarbonate membranes with defined pore sizes under pressure. This step is repeated multiple times to ensure uniformity.

Advantages:
- Produces vesicles with a controlled size.
- Simple process for size reduction.

Disadvantages:
- May not be suitable for large-scale production without modifications.

7. Freeze-Thaw Method
This method improves drug encapsulation efficiency and stability.

Steps:
1. Lipid Dispersion: Lipids and drugs are dissolved in suitable solvents.
2. Freezing: The solution is rapidly frozen using liquid nitrogen or a deep freezer.
3. Thawing: The frozen mixture is then thawed at room temperature or in a water bath.
4. Repeat: The freeze-thaw cycle is repeated several times to achieve high encapsulation efficiency and homogeneity.

Advantages:
- Improved drug loading and vesicle stability.
- Simple process without requiring complex equipment.

Disadvantages:
- Time-consuming due to multiple freeze-thaw cycles.

Applications

Transferosomes are versatile drug delivery systems with various applications in pharmaceuticals and therapeutics. Their unique structure, which allows them to deform and penetrate biological barriers, makes them suitable for several applications:

1. Transdermal Drug Delivery

- Enhanced Skin Penetration: Transferosomes can effectively penetrate the stratum corneum, allowing for the delivery of both hydrophilic and hydrophobic drugs through the skin. This is particularly useful for systemic drug delivery without the need for injections.
- Pain Management: They are commonly used for analgesics and anti-inflammatory medications, providing localized treatment while minimizing systemic side effects.

2. Targeted Drug Delivery

- Cancer Therapy: Transferosomes can be engineered to target specific cancer cells, reducing the toxicity of chemotherapeutic agents on healthy tissues. This targeted delivery improves treatment efficacy and reduces side effects.
- Hormonal Therapies: They are used for delivering hormones, such as corticosteroids and sex hormones, to specific sites in the body, ensuring more efficient treatment with lower dosages.

3. Vaccination

- Vaccine Delivery: Transferosomes can encapsulate antigens and adjuvants, improving their stability and enhancing immune response when administered transdermally or intranasally. This technique can decrease the need for needles while increasing the effectiveness of vaccines.

4. Insulin Delivery

- Diabetes Management: Transferosomes have been investigated for delivering insulin through the skin, providing a non-invasive alternative to traditional injections. This can improve patient compliance and comfort in diabetes management.

5. Gene Delivery

- Nucleic Acid Transport: They can encapsulate nucleic acids (like DNA or RNA), facilitating gene therapy applications by protecting these molecules from degradation and enhancing their delivery into target cells.

6.Ocular Drug Delivery

- Eye Treatments: Transferosomes can be used to deliver drugs directly to the eye, improving bioavailability and reducing side effects associated with traditional ocular delivery methods, such as drops or injections.

7.Delivery of Biologics

- Proteins and Peptides: Transferosomes can effectively encapsulate large biomolecules such as proteins and peptides, which are often poorly absorbed through conventional delivery methods, allowing for their effective systemic or localized delivery.

8.Local and Systemic Therapeutics

- Topical Treatments: Used for delivering anti-fungal, anti-bacterial, and anti-inflammatory agents directly to the site of action, improving therapeutic outcomes in local infections or conditions.
- Systemic Treatments: By facilitating the transport of drugs into systemic circulation, transferosomes can be utilized for a wide range of therapies, including cardiovascular drugs, antiretrovirals, and more.

9.Combination Therapy

- Multi-Drug Delivery: Transferosomes can simultaneously deliver multiple drugs, enabling combination therapies that can target different pathways in diseases, such as in cancer treatment.

10.Sustained Release Formulations

- Depot Effect: Transferosomes can be designed to release their drug content gradually over time, providing sustained therapeutic effects and reducing the frequency of administration.

11.Pharmaceutical Formulation Development

- Formulation of Poorly Soluble Drugs: Transferosomes can be used to enhance the solubility and bioavailability of poorly soluble drugs, improving their therapeutic efficacy.

Conclusion

In conclusion, transferosomes emerge as a promising liposomal carrier system for controlled drug release, demonstrating significant potential in enhancing the efficacy of therapeutic agents. Their unique structural

properties, characterized by the ability to deform and penetrate biological barriers, enable efficient delivery of both hydrophilic and lipophilic drugs. Transferosomes not only improve drug stability and bioavailability but also facilitate targeted and sustained release, minimizing systemic side effects. The versatility of transferosomes extends to various applications, including transdermal delivery, cancer therapy, and gene therapy, making them valuable tools in modern pharmacotherapy. Ongoing research and development in this field are expected to further optimize transferosome formulations and expand their applications, paving the way for innovative and effective treatment strategies in diverse medical conditions. As we advance in our understanding of transferosome technology, it holds the promise of transforming conventional drug delivery paradigms and improving patient outcomes in clinical practice.

Refrences –

1) Irfan M, Verma S, Ram A. Preparation and characterization of ibuprofen loaded transferosomes as a novel carrier for transdermal drug delivery system. Asian j Pharm. clin resear. 2012. (162-165).

2) Trommer H, Neubert RHH: Overcoming the stratum corneum. The modulation of skin penetration. A review, Skin Pharmacology and Physiology. 2006. (106-121).
3) El Zaafarany GM, Awad GAS, Holayel SM, Mortada ND. Role of edge activators and surface charge in developing ultra deformable vesicles with enhanced skin delivery. Int J Pharm. 2010. (164-172).
4) Cevc G, Grbauer D, Schatzlein A, Blume G. Ultraflexible vesicles, transferosomes, have an extremely low pore penetration resistance ant transport therapeutic amounts of insulin across the intact mammalian skin. Biochem Biophys Act. 1998. (201-215).
5) El-Maghraby GM, Williams AC. Vesicular systems for delivering conventional small organic molecules and larger macromolecules to and through human skin. Expert Opin Drug Deliv. 2009. (149 163)
6) Walve JR, Bakliwal SR, Rane BR, Pawar SP. Transferosomes: A surrogated carrier for transdermal drug delivery system. Int J App Bio Pharm Tech. 2011.(201-214)
7) Cevc G, Blume G. Lipid vesicles penetrate into intact skin owing to transdermal osmotic gradient and hydration force. Biochem Biophys Act 1992.(226-332).
8) Prajapati ST, Patel CG, Patel CN. “Transferosomes: A Vesicular Carrier System for Transdermal Drug Delivery”. Asian Journal of Biochemical and Pharmaceutical Research, 2011.(507 524).

9) Kombath RV, Minimal SK, Sockalingam A, Subadhra S, Parre S, Reddy TR, David B. “Critical issues related to transferosomes – novel Vesicular system”. Act Sci.(67-82)
10) Walve JR, Bakliwal SR, Rane BR, Pawar SP. “Transferosomes: A surrogated carrier for transdermal drug delivery system”. International Journal of Applied Biology and Pharmaceutical Technology, 2011.Pol. Technol. Aliment, 2012.(204-213).
11) Kumar R., Singh M., Bala R., Seth N., RanaA.c., “ Transferosomes : A Novel Approach For Trans Dermal Drug Delivery” International Research Journal Of Pharmacy, 2012; 3(1)
12) Patel SN, Patel N, Patel K.R., Patel N.M. “A Vesicular Transdermal Delivery System For enhance Drug Permeation-Ethosomes and Transfeosomed” International Pharmaceutical Sciencia, 2012; 2(2).