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TRANSFEROSOMES: A TRANSDERMAL APPROACH FOR BCS III AND BCS IV DRUGS

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ABSTRACT

In today's drug development world, combinatorial chemistry, high-throughput screening, and genomics have provided a technologic platform that produces a large number of new chemical entities with therapeutic potential each year. Its outcome the new chemical entities shifted towards higher molecular weight, low lipophilicity and poor aqueous solubility which primarily affects the bioavailability of drugs. Hence, the poor aqueous solubility not only limits the drug's biological application but also challenges its pharmaceutical development. Novel drug delivery systems are now a days is creating a new interest in development of drug deliveries. TDDS is the permeability of the skin, it is permeable to small molecules, lipophilic drug and highly impermeable to the macromolecules and hydrophilic drugs. .This review highlights the significant solubility problem and BCS formulation choices, and importance of Transferosomes. Also, this review summarizes the role of lipids in the enhancement of bioavailability, Mechanism of Transferosomes and BCS class III and IV drugs as an ideal candidate for the transferosomes formulation with their significant finding in research. Based on the available data, the Transferosomes makes this drug delivery systems as one of the promising delivery systems and will be a solution to the formulation scientist.

KEYWORDS: BCS, Transferosomes, Solubility, Lipophilicity.

INTRODUCTION

The largest of the body organs is the skin, It is one of the most easily accessible organs of the human body and consists of three functional layers: epidermis, dermis, and subcutaneous. It has a wide variety of functions.[1] 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.[2] 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 corneum 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.[3] Recently, various strategies have been used to augment the Transdermal delivery of bioactive. Mainly, they include electrophoresis, iontophoresis, chemical permeation enhancers, Microneedles, sonophoresis, and vesicular system like liposomes, niosomes, elastic liposomes such as ethosomes and transferosomes. Among these strategies transferosomes appear promising. A novel vesicular drug carrier system called transfersomes, which is composed of phospholipids, surfactant, and water for enhanced Transdermal delivery. Transferosomes are a form of elastic or deformable vesicle, which were first introduced in the early 1990s78-79.[4,24] Transferosomes 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.[5] 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.[6]

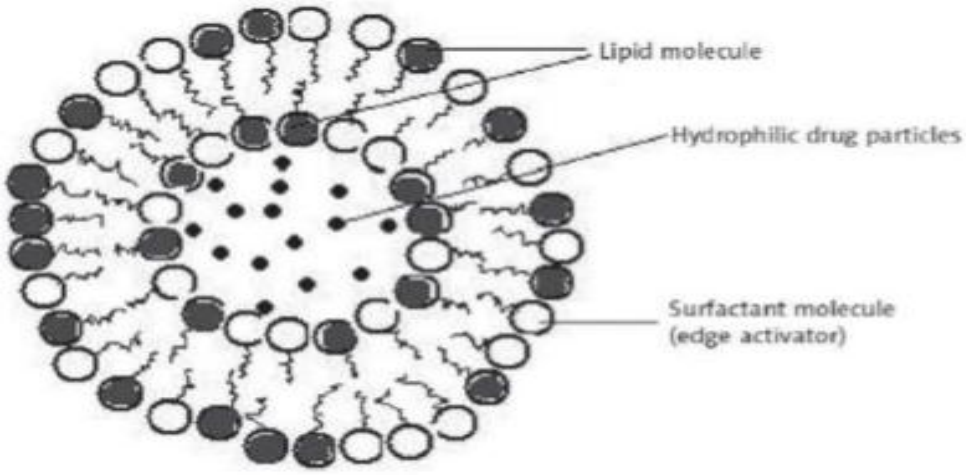

Fig no. 1: Structure of transferosomes.

Biopharmaceutical classification system

A better understanding of the biopharmaceutical and physicochemical properties of drugs would be of great help for developing pharmaceutical products. Biopharmaceutics classification system (BCS)[7,8] is a useful tool for decision-making in formulation development from a bio-pharmaceutical point of view. Based on the two key physicochemical parameters, such as intestinal permeability and solubility Amidon et al. developed Biopharmaceutical Classification System (BCS)[9] for the drugs. Because the absorption of orally administered most of the drugs are either limited by their solubility in GIT or permeation across the intestinal membrane. It is evidenced by the following Equation.[10,11]

M ¼ A: tres: Peff : Capp (2)

M is the amount of drug absorbed; A is the surface area available for absorption, tres is the residence time during which the drug remains within the site(s) of absorption, Peff is the effective membrane permeability, and Capp is the apparent luminal drug concentration (Capp). According to this system, drug substances can be classified into four groups as shown in Table 2.[12,13 ,14]

Class I: High Solubility high permeability	**Class II:** Low Solubility high permeability
Absorption pattern: Well absorbed	**Absorption pattern:** Variable
Rate-Limiting step in Absorption: Gastric Emptying	**Rate-Limiting step in Absorption:** Dissolution
Examples: Diltiazem, Propranolol, Metoprolol Challenges in Drug Delivery: No major challenges for immediate release forms but major challenges need for CR forms to control the dissolution or drug release.	**Examples:** Nifedipine, Carbamazepine, Naproxen Challenges in Drug Delivery: Formulations are designed to overcome solubility or dissolution problem by various means. Particle size reduction, Solid dispersion, Lipid-based formulations[22,23,24]

Class III: High Solubility low permeability	**Class IV:** Low Solubility low permeability
Absorption pattern: Variable	**Absorption pattern:** Poorly absorbed
Rate-Limiting step in absorption: Permeability	**Rate-Limiting step in absorption:** Case by case
Examples: Insulin, Metformin, Cimetidine	**Examples:** Taxol, Chlorthiazide, Furosemide
Challenges in drug delivery: Approaches are employed to enhance permeability Prodrugs, Permeation enhancer	**Challenges in drug delivery:** Combination of strategies used for Class II and Class III drugs are employed to improve both dissolution and permeability.[18,19]

BCS class III and IV drugs: an ideal candidate for the transferosome formulation

Based on the BCS classification formulation selection guidelines, the Transferosomes are more efficient carrier system for BCS-III and BCS- IV drugs. Although the Transferomes are more efficient carrier system for BCS IV drugs in order to increase the solubility and permeability, the extensively metabolized Class IV drugs are ideal candidate for Transferosomes formulation to decrease the side effect, first pass metabolism, efflux transporters effect[50] Nowadays most of the drugs coming out of the drug discovery and development process are belongs to either BCS Class II or Class IV drugs with high molecular weight. The poor solubility with an increase in molecular weight drug faces many problems starting from the drug development (during formulation, pharmacological, toxicological and pharmacokinetic studies) to its biological application

(solubility of the drug and its permeability across cell membranes). Hence there is a need to increase the solubility of the drug (BCS Class II Drugs). When compare to BCS Class IV drugs, the Class II drugs are the most suitable choice to formulate into a novel drug delivery system. in the case of Class III drugs the only barrier and way to alter the problem is Permeability only whereas in Class IV drugs, both solubility and permeability act as barriers. Hence it is the best choice to select the Transferosomes to formulate into a novel drug delivery system.[53,58]

Mechanism of action of transferosomes

Transferosomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipids of stratum corneum.[26,27]

(i) Mechanism of Penetration

Transfersomes when applied to the intact skin are able to transfer about 0.1mg to 0.5mg of lipid per hour across the intact skin. This value is high when compare to the values driven by the transdermal concentration gradients. There is an attraction of hydrophilic lipids towards water due to active interaction between hydrophilic lipid residues and their adjacent water.[26,28] Thus, induced dehydration is resisted by most of the lipid bilayers. Therefore, all hydrophilic lipid vesicles move from dry location sites to the sites which have considerably high-water content. When Transfersomes are applied on the skin, they will get dehydrated to some extent due to water loss by evaporation and when lipid vesicles sense this osmotic gradient, they try to avoid completely drying by migrating along the gradient. They can escape complete drying only if they are considerably deformable to pass through the narrow pores in the skin.[29,31,33,] As Transfersomes are sufficiently flexible and have suitable rheologic and hydration properties and they can easily pass through the narrow pores in the skin. Conventional liposomes which are less flexible compare to Transfersomes get confined to skin surface, where they get completely dehydrated and fused together and because of these conventional liposomes have less penetration power than Transfersomes.[23,27,34]

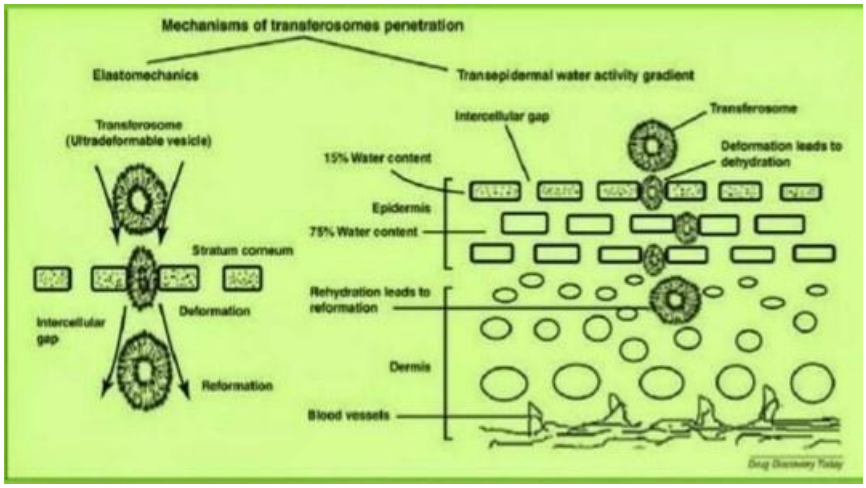

Fig. no. 2: Mechanism of action of transferosomes.

(ii) Propensity of penetration

Epicutaneous lipid application leads to transepidermal concentration gradient and this result in movement of lipids from application site in to body. The movement of lipid depends on the mobility of molecule administered and the permeability of skin. The magnitude of the transport driving force also plays an important role:[35,37]

Flow = Area x (Barrier) Permeability x (Trans-barrier) force.

(iii) Advantages of transfersomes

- First-pass metabolism of drugs is restraint.
- Enhances the permeation through small pores of skin.
- Fewer side effects can be observed.
- Lipophilic drugs have 90% entrapment efficiency.
- Transfersomes are carriers which are suitable for both low and high molecular weight drugs such as analgesic, protein, anesthetic, corticosteroids, hormone, anticancer etc.
- Transfersomes are convenient for drug molecules with wide range of solubility.
- They also act as depot preparation as they release the contents slowly and gradually.
- They are biocompatible and bio- degradable. [30,31]
- They are suitable for both systemic and topical drug delivery.
- Metabolic degradation of encapsulated drugs can be prevented.
- Preparation of Transfersomes is easy and they are easy to scale up.
- In case of toxicity, termination of drugs can be achieved easily.
- Decrease in dosing frequency and improvement in patient compliance can be achieved. (22,26,39)

(iv) Limitations of transfersomes

- Transfersomes are prone to oxidative degradation.

- Lack of purity of the natural phospholipids cause problems in choosing of Transfersomes as drug delivery vehicles. [30]

Material for transferosomes

Transferosomes is a self adaptable and optimized mixed lipid aggregate and 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 bi layer flexibility and permeability. This second component is called as edge activator.

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 30. Flexibility of tranferosomes membrane can be altered by mixing suitable surface active agents in the proper ratios. The resulting, flexibility and permeability optimized, transferosome vesicle can therefore adapt its shape to surrounding stress easily and rapidly, by adjusting local concentration of each bi layer component to the local stress experienced by the bi layer.

This flexibility also minimizes the risk of complete vesicle rupture in the skin and allows transferosomes to follow the natural water gradient across the epidermis, when applied under non occlusive condition. Vesicles composed of phospholipids as the main ingredient (soya phosphatidylcholine, egg phosphatidylcholine, dipalmitylphosphatidylcholine, etc), 10-25% surfactant for providing flexibility (ethanol, methanol) and hydrating medium consisting of saline phosphate buffer (pH 6.5-7). Dye like Rhodamine 123, Nile red for Confocal Scanning Laser Microscopy.[36,38]

Materials commonly used for the preparation of transfersomes are summarized.

Chemicals	Examples	Functions
Phospholipid	Soya Phosphatidylcholine Egg Phosphatidylcholine Disteryl Phosphatidylcholine	Vesicle forming Component
Surfactant	Sodium Cholate Sodium deoxy Cholate Tween 80 Span 80	For Providing Flexibilit
Alcohol	Ethanol Methanol	solvent
Buffering Agent	Saline phosphate buffer (PH 6.5) 7% v/v ethanol Tris buffer (PH 6.5)	hydrating medium

Methods for preparation of transfersomes

1. **Modified vortexing sonication method:** A blend of lipids, edge activator and drug were dispersed in appropriate phosphate buffer and vortexed for required time to attain a milky suspension. the suspension formed was sonicated by LUC 410 power sonicator for 30 minutes followed by freezing at -20°C for 18hrs and thawing at room temperature for 6hrs for 3 times. The suspension is extruded through 0.2 mm sartorius membrane filter for 5 times at 50°C. The final product is stored in refrigerator.[59]

2. **Reverse phase evaporation method:** A blend of soy lecithin and cholesterol were taken in a beaker containing tween 80 as a surfactant. Organic solvents were added. This mixture was kept at room temperature for 24 hrs until thin film formed. Later drug was added and sonicated by probe sonicator at a frequency of 20kHz for 2 minutes. Sodium deoxycholate is added as edge activator and hydrated with pH 7.4 phosphate buffer and sonicated for 2 minutes.[60]

3. **Lipid film hydration technique:** Weighed amounts of drug, lecithin and edge activator were dissolved in round bottomed flask containing solvent mixture. Organic solvents were evaporated above lipid transition temperature (40°C) and fine traces of solvent were removed by vacuum. A thin lipid film was formed inside the flask. Prepared thin film was hydrated with appropriate buffer solution and stirred at speed of 60rpm for 1hr. The resultant vesicles are allowed to swell for 2hrs at room temperature.[61]

4. **Ethanol injection method:** Aqueous phase is prepared by dissolving drug into phosphate buffer and stirred at 400rpm. The organic phase containing lipids, edge activator, solvent is injected into aqueous phase under continuous stirring for 30minutes. Larger multilamellar vesicles formed are further sonicated for required time to form small uni-lamellar vesicles.[62]

5. **Modified handshaking process:** The modified handshaking method has the same basic principle as the rotary evaporation-sonication method. In the modified handshaking process, the organic solvent, the lipophilic drug, the phospholipids and edge activator are added in a round-bottom flask. All the excipients should completely dissolve in the solvent and obtain a clear transparent solution. Then, the

organic solvent is removed by evaporation while handshaking instead of using the rotary vacuum evaporator. In the meantime, the round-bottom flask is partially immersed in the water bath maintained at a high temperature (example: 40–60 ◦C). A thin lipid film is then formed inside the flask wall. The flask is kept overnight for complete evaporation of the solvent. The formed film is then hydrated with the appropriate buffer solution with gentle shaking at a temperature above its phase transition temperature. The hydrophilic drug incorporation can be done in this stage.[43]

6. **Suspension homogenization method:** Transfersomes are prepared by mixing an ethanolic phospholipid solution with an appropriate amount of edge activator. The prepared suspension is subsequently mixed with buffer to yield a total lipid concentration. The resulting formulation is then sonicated, frozen and thawed respectively two to three times.[44]

7. **Centrifugation process:** The phospholipids, edge activator and the lipophilic drug are dissolved in the organic solvent. The solvent is then removed using a rotary evaporator under reduced pressure at the respective temperature. The remaining traces of solvent are removed under vacuum. The deposited lipid film is hydrated with the appropriate buffer solution by centrifuging at room temperature. The hydrophilic drug incorporation can be done in this stage. The resulting vesicles are swollen at room temperature. The obtained multilamellar lipid vesicles are further sonicated at room temperature.[45]

8. **High-Pressure homogenization technique:** The phospholipids, edge activator and the drug are uniformly dispersed in PBS or distilled water containing alcohol and followed by ultrasonic shaking and stirred simultaneously. The mixture is then subjected to intermittent ultrasonic shaking. The resulting mixture is then homogenized using a high-pressure homogenizer. Finally, the transfersomes are stored in appropriate conditions.[44,47]

Characterization of transferosomes

1. **Vesicle Morphology and Size characterization:** Vesicle morphology studies were conducted by scanning electron microscopy (SEM) and transmission electron microscopy (TEM). The mean diameter and the polydispersity index (PDI) of the transferosomes were determined by Laser particle size analyser. PDI value of less than 0.1 was considered as a homogeneous distribution of vesicles, whereas a value of greater than 0.3 was of higher heterogeneity.[35, 39]

2. **Entrapment efficiency:** Transferosomes were centrifuged at high rpm (10,000 - 20,000 rpm) for 3h. The supernatant was collected, diluted with suitable buffer and analysed for the entrapment efficiency.[41]

3. **Zeta potential:** The magnitude of the zeta potential provides in sequence about particle stability. Zeta potential is an assessment of the efficient electric charge on the transferosomes surface, quantifying the charges. The higher the magnitude of zeta potential exhibit amplified electrostatic repulsion and therefore amplified stability. The zeta potential of the transferosomes was measured using a zetasizer. The zetasizer consists of capillary cell which was cleaned with 90% ethanol and distilled water before analyses.[36,40]

4. **Fourier Transform Infrared Spectroscopy (FTIR):** Studies Fourier transform infrared spectroscopy studies are conducted to study the interaction between drug and excipients. The drug, lipids, edge activators and physicalmixture of drug and lipid samples are prepared with potassium bromide (KBr). All the prepared samples were subjected to FTIR spectroscopic studies to determine drug-carrier interaction.[49,60]

5. **Elasticity measurement:** This study was carried out by extrusion method at 7.5 psi pressure through 0.2 µm polycarbonate filter membrane fixed to stainless steel pressure holder of 50 millilitre(mL) capacity barrel. 0.5mL of the suspension was diluted up to 10 mL with phosphate buffer saline(PBS) pH 7.4 and then extruded for 10 min through the filter medium.[43]

6. **In-vitro diffusion studies:** In vitro drug release studies are performed in open end tube in which one end of the tube is tied with cellophane membrane, acts as donor compartment the tube end which is tied with membrane is dipped into the receptor compartment which consists of pH 7.4 phosphate buffer. 2 mL of transferosomes are taken and placed into the donor compartment. The setup is placed on magnetic stirrer and agitated at speed of 1000rpm under optimized temperature. The samples were withdrawn at predetermined intervals and replaced with fresh buffer in receptor chamber. Finally, the release was quantified by spectroscopy methods.[45,61]

7. **Ex-vivo skin permeation studies:** The tested formulations contained equivalent amount of drug to those of the control. The skin was placed onto vertical Franz diffusion cells with the stratum corneum side up and dermal side down facing the dissolution medium (22 mL of phosphate buffer pH 7.4). The medium was maintained under stirring at 50 rpm and thermostated at 32 ± 0.5 C. 1mL Sample

were withdrawn from the receptor compartment at predetermined time intervals and replaced with fresh dissolution medium to maintain sink conditions.[47,53]

8. **Stability studies** Samples of the selected formula were kept in glass amber vials and stored in a dark place at three different temperatures (0°C, 4°C and 25°C) for three months. Samples were withdrawn every two weeks and observed for their appearance and growth of microorganisms and drug content.[44,52]

Applications

Transferosomes in herbal drug delivery: Green tea leaves contain epigallocatechin gallate (EGCG) which is responsible for antioxidant activity. Due its high molecular weight and high hydrophilicity it is difficult to penetrate through the skin. Hence, they were prepared as transferosomes by thin film hydration technique and formulated as cream. The invitro permeation studies were conducted and the amount of epigallocatechin gallate penetrated from Transferosomal and non-Transferosomal cream were 1003.6 and 400.09 µg/cm2 /hr respectively Permeation studies on caffeine nanovesicles like transferosomes, phytosomes, niosomes were prepared by different penetration enhancers like oleic acid, eucalyptol and decyl polyglucoside as a nonionic surfactant. Among that caffeine encapsulated as transferosomes showed higher permeation. Capsaicin (obtained from capsicum) loaded transferosomes formulated for the treatment of rheumatoid arthritis. Arthritic activity study shows that transferosomal formulation possesses superior inhibitory activity than the marketed Thermagel formulation at the same dosage level.

Transferosomes as nutricosmetics: Commonly used cosmetics have little percutaneous absorption and also side effects. By incorporating biologically active phytoconstituents into transferosomes can improve both the aesthetics and performance of a cosmetic product, increased absorption, enhanced delivery to the tissues. The alteration of retinoids levels in the skin cause different disorders in the maturation of epithelial skin cells. Retinyl palmitate is formulated into transferosomes evaluated for penetration of the active ingredients and biodistribution by in vitro and in ex-vivo studies. Transferosomes showed a significant increase in the administration of retinyl palmitate to the epidermis by quantification of the active ingredients in the different layers of the skin, as well as by fluorescence microscopy of biopsies of pig-ear skin. These results suggest that transferosomes may be an efficient vehicle for the delivery of retinoids to inner layers of the skin, such as the epidermis. Curcuma longa extract loaded transferosomal cream showed better absorption and stability compared to base cream. Saponification value of base cream was found to be higher than transferosomal cream and also possible microbial growth. Due to their poor lipid solubility and molecular size, studies on quercetin, naringin, simonenine, piperine, glycyrrhizin etc., demonstrated that by formulating into transferosomes has a capability to enhance their bioavailability.[39,42]

Transferosomes in wound healing: Conventional topical burn formulations are required to be applied 3 to 4 times a day. By applying transferosomal cream of acriflavine patient compliance can be increased by reducing its dosage frequency. They are also used in the treatment of vitiligo and in diabetic caused wounds and other skin diseases. Miconazole nitrate was formulated as transferosomes. Miconazole transferosomes were incorporated into a carbopol 934 gel base, the prepared transferosomal gel showed higher antifungal activity than miconazole cream.[44,46]

Transferosomes in targeted drug delivery: Transferosomes have the ability to localize activity of drug at the site or organ of action there by lowering its concentration at the other sites in body. They protect the encapsulated drug from metabolic degradation. They act as a carrier for low and high molecular weight drugs. Size rages from 1 to 300nanometers (nm), hence move more freely in systemic circulation compared to bigger particles. To overcome the difficulties of subcutaneous delivery of insulin, transferosomal gel was prepared by rotary evaporation sonication technique. Lactoferrin has antiviral activity against Human papillomavirus (HPV). Transferosomes prepared by two methods including reverse phase evaporation and thin film hydration with different ratios of cholesterol: lecithin: DOTAP in the presence of Tween 80. The optimized transferosomes have 100nm size with good polydispersity index and encapsulation efficiency of 91% for lactoferrin. The viral inhibitory concentration (IC50) of transferosomal lactoferrin has been significantly improved to nearly one tenth in comparison to free lactoferrin.[49,52]

Resveratrol is used to treat Alzheimer disease for brain targeting drug delivery due to its low bioavailability and solubility and extensive hepatic metabolism, resveratrol is formulated as transferosomes by reverse phase evaporation method. Transferosomes displayed higher permeation of up to 81.29 ± 2.64%. Transferosomes significantly enhanced behavioural acquisition and spatial memory function in the amnesic rats compared with both the nano emulsion formulation and the pure drug. The developed transferosomes may be considered as a well-designed brain targeting system that might further be applied for targeting many drugs to be used in the treatment of central nervous system diseases. Transferosomes bearing loratadine were prepared by conventional thin film hydration method and optimized using sequential Quality-by-Design approach. The transferosomal gel proved superior to control, transferosome-free gel. Bioavailability of the transferosomal gel was comparable to Claritin® oral tablets.

Raloxifene used for breast cancer protection in HIV patients. Due to its poor bioavailability (2%) formulated as transferosomes using D alpha tocopheryl polyethylene glycol 1000 succinate which augments (Trans-Activator of transcription) TAT- HIV protein., inhibitory concentration IC50 results showed 1.42-fold improvement in cytotoxicity compared to raw raloxifene against MCF-7 cells.[50]

Transferosome as bioenhancer: Topical clindamycin phosphate has less bioavailability, to overcome these limitations an attempt has been made to prepare transferosomes and optimize it for enhanced delivery through the skin. To increase the solubility of sertraline, the drug was formulated into transfersomal gel by using span 80, soya lecithin, and Carbopol. Enhance skin delivery of sertraline because of excellent drug release and permeation of the drug. Also, no skin irritation was observed when the gel formulation of transethosomes were applied for enhancing the transdermal delivery of olmesartan and medoxomil. In vivo evaluation studies showed higher permeation ratescompared to oral tablets. Autoimmune disorders are distinct with over production and accumulation of free radicals due to its undisclosed genesis. The imbalance could only be combat by supplementing natural defensive antioxidant enzymes such as superoxide dismutase and catalase. The efficiency of these enzymes is enhanced by use of colloidal carriers which include cellular carriers, vesicular and particulate systems like transferosomes. Felodipine, Risperidone and Piroxicam loaded transferosomal gels shows excellent drug release and better therapeutic effect. Permeation rate is improved by incorporation of different permeation enhancers.[59,62]

CONCLUSION

In addition, BCS is the foundation upon which medicines are categorised into respective groups based on their solubility in water and permeability through the GIT; as a result, the issues associated with pharmaceuticals may be recognised and possibly addressed using BCS. For the determination of solubility and permeability, BCS uses a number of different techniques. For BCS class III medicines, a number of different drug delivery methods are available, with Transferomes being the most cost-effective and safest carriers available compared to liposomes and other carriers. It is hoped that this study will serve as an informative reference for the different administration and preparation techniques, as well as the assessment criteria and uses of Transferomes in many areas of medicine

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