Transferosome: A Vesicular Transdermal Delivery System For Enhanced Drug Permeation Of Antihypertensive Drug Bisoprolol Fumarate

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Abstract
The barrier function of the skin limits transdermal medication delivery. Vesicular systems are one of the most contentious mechanisms for delivering active compounds transdermally. The discovery of elastic vesicles such transferosomes, ethosomes, cubosomes, phytosomes, and others reignited interest in creating transdermal delivery systems. Transferosomes are ultradeformable vesicles for transdermal applications consisting of a lipid bilayer with phospholipids and an edge activator and an ethanol/aqueous core. In another definition transferosmes are the carriers for the targeted drug delivery system. Transferosomes are the specialised types of liposomes consist of phosphatidylcholine and an age activator. Bisoprolol is a β-blocker selective cardiovascular drug. It is given in salt form of fumarate for the management of hypertension and angina pectoris. On oral administration, bioavailability of drug is very poor because of extensive first pass metabolism. Delivery of bisoprolol fumarate via transdermal route would minimize some of the deficiencies associated with the oral delivery and increase the bioavailability of the drug. This review will focus on an innovative drug delivery system for permeation of an antihypertensive drug with low permeability.

Keywords: Transferosomes, Transdermal Drug Delivery System, Bisorpolol Fumarate, Drug Permeation, Permeation Enhancer

I. INTRODUCTION

In most situations, an effective and successful therapeutic therapy is not achievable due to many reasons like, hepatic first-pass metabolism, undesirable side effects, refusal of invasive treatments, and poor patient acceptance. To address these issues, many medication delivery systems have been formed and studied over the last few decades. Transdermal delivery systems are a promising strategy because they are simply painless and bypass first pass metabolism. However, the skin semi-permeability nature blocks or dampens therapeutic agent transdermal transport, must be addressed.[1] Topical drug therapy systems are characterized as independent, distinct dosage forms that are when applied to unbroken skin, transport the drug to the systemic circulation at an orderly rate and keep the drug concentration within the therapeutic window for a long period of time. [2] Niosomes and transferosomes are vesicular carrier systems that have gained a lot of attention in recent decades as a way to deliver drugs transdermally. The features of vesicles structures have been studied in order to improve medication administration within their cavities, as well as to tag the vesicles for cell selectivity. Vesicles are used in transdermal drug administration because they serve as drug carriers, delivering entrapped drug molecules over the skin, and because of their composition, they also act as penetration enhancers. Furthermore, in the case of topical formulations, these vesicles serve as a depot for the sustained release of active substances, as well as a rate-limiting membrane barrier for the control of systemic absorption in the case of topical preparations.[3]

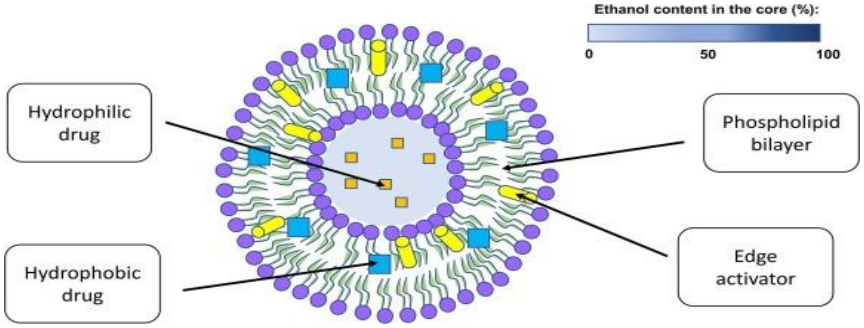

Fig. 1Diagrammatically representation of Transfersomes

A. Advantages:

Vesicular drug delivery systems have a numerousadvantages over conventional dosage forms and prolonged-release dosage forms, including the following: [4]

i. Ability to encapsulate both hydrophilic and hydrophobic medicines.
ii. Drug bioavailability can also be increased.
iii. It is possible to extend the elimination of a fast metabolizable medication.
iv. Drugs circulation life in the body can be extended.
v. Drugs can often be delivered in a targeted manner.
vi. Liability drug stability difficulties can be overcome.
vii. Toxicity problems with specific medications are frequently overcome.

B. Disadvantages:

i. Ineffective drug loading.
ii. Drug leakage during final product processing and storage.
iii. Drug leakage during in vivo transfer.
iv. Oxidative lipid degradation.
v. Natural phospholipids are not pure.
vi. Expensive ingredients.

C. purpose of Vesicular Drug Delivery System (VDDS)

Conventional chemotherapy treatment for intracellular infections is not fully effective because of limited diffusion of drug molecules into cell. So for the better bioavailability at the point of disease and reduce the undesirable side effects of conventional and controlled release drug delivery methods the vesicular drug delivery system is used.[5]

D. significant characteristics of Transfersomes:

1. Transfersomes have wide range solubility because of their structure which contains two types of hydrophobic and hydrophilic moieties.
2. The high deformability of transfersomes gives better penetration of vesicles[6].
3. Transferosomes are the ideal choice for both types of drugs that high and low molecular weight likes analgesic, corticosteroids, anticancer, insulin and albumin.
4. Transfersomes can release their contents in slow and gradual manner hence act as a depot. Because of transfersomes now it is possible to pass drugs systemic and topically.
5. Preparation of transfersomes is easy and not involves long procedure or pharmaceutically unacceptable and unnecessary additives; hence it is easy to scale up[7, 8, 9].

II. DRUG PROFILE [10]

A. Bisoprolol fumarate

1) *Physicochemical properties:*

Molecular formula: C18H31NO4
Molecular weight: 325.443
Structure

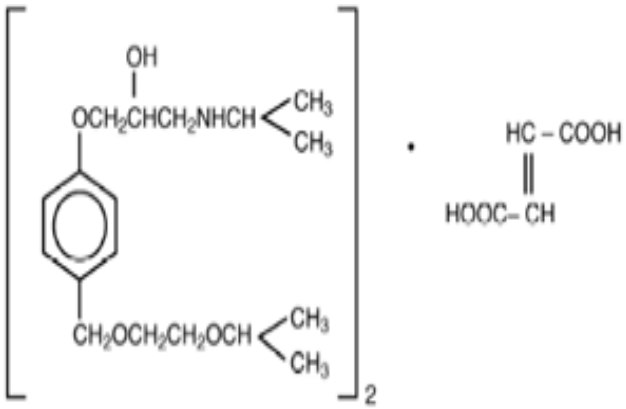

Fig.2 Structure of Bisoprolol fumarate

IUPAC Name: 1-(propan-2-ylamino)-3-[4-(2-propan-2- yloxyethoxymethyl) phenoxy] propan-2-ol.
Category: Adrenergic beta-Antagonists: Antihypertensive Agents

Description:
It is a white crystalline powder which is approximately equally hydrophilic and lipophilic, and is readily soluble in water, methanol, ethanol, and chloroform.
Melting point: 100 ºC.
Storage: Should be preserved in airtight container.

2) Pharmacokinetic data:
Oral bioavailability: 80 %
Urinary excretion: 50 %
Bound in plasma: Binding to serum proteins is approximately 30 %
Volume of distribution: 226 L/Kg
Half-life: 9-12 h
Peak concentration: 16 ng /mL at 5 mg to 70 ng /mL at 20 mg
Total plasma clearance: 40mL/min.

3) Absorption, fate and excretion
The best property of bisoprolol fumarate is that its absorption not affected by presence of food and its bioavailability is also noticeable around 80% when taken orally. Around 20% of drug undergone for loss in hepatic metabolism. Bisoprolol fumarate is eliminated by renal and non renal route.

4) Mechanism of action
Bisoprolol selectively act on the beta-adrenergic receptors that are present in cardiac and vascular smooth muscles and cause a reduction of heart rate, cardiac output, systolic and diastolic blood pressure, and possibly reflexorthostatic hypotension. Bisoprolol also competitively block beta (2)-adrenergic responses in the bronchial and vascular smooth muscles, causing bronchospasm.s

5) Side effect
Abdominal cramps, Diarrhoea, Dizziness, Insomnia.

6) Uses
Used for the treatment of hypertension, angina pectoris and heart failure.

7) Dose
Commence with 2.5 mg or 5 mg per day up to 10 to 20 mg. Dose reduction in renal impairment.

8) Contraindications
Bisoprolol fumarate is contraindicated in patients with carcinogenic shock, overt cardiac failure, second or third degree AV block, and marked sinus bradycardia

9) Marketed dosage forms
: Zebeta®
: Lodoz
: Concor®

III. PERMEATION ENHANCER[11,1]
Organic solvents such as DMSO, ethanol, or propylene glycol, are highly absorb by the skin because they may have an increased partition coefficient for the therapeutic agent of interest. The substances temporarily diminishing the barrier of skin also known as accelerants or sorption promotors. These substances are used to increased permeability by disorders or fluidizing the lipid structure of the stratum corneum.

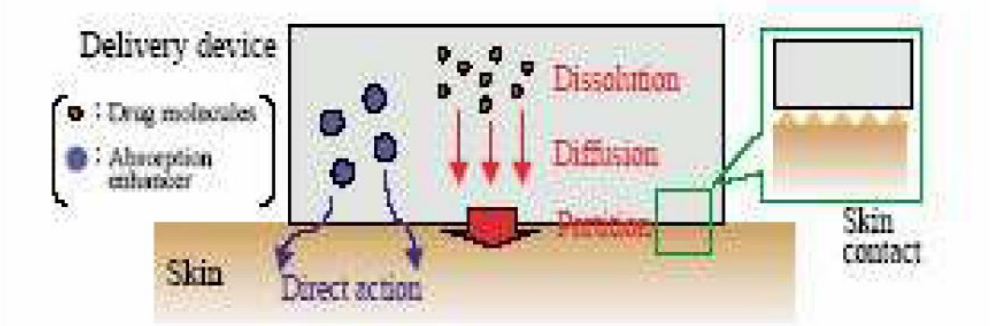

Fig.3 Action of permeation enhancers

A. Chemical enhancers

By definition, a chemical skin permeation enhancer increases skin permeability by reversibly damaging or altering the physicochemical nature of the stratum corneum to reduce its diffusional resistance. Among the alterations are increase in hydration of stratum corneum, a change in the structure of the lipids and lipoproteins in the intracellular channels through the solvent action or denaturation, or both.

More than 275 chemical compounds have been cited in the literature as skin penetration enhancers; they include acetone, dimethyl acetamide, dimethyl formamide, dimethyl sulfoxide (DMSO), ethanol, oleic acid, propylene glycol, and polyethylene glycol and sodium lauryl sulphate.[13]

The selection of a permeation enhancer should be based not only on its efficacy in enhancing skin permeation but also on its physicochemical and biologic compatibility with the system's other components.

The synthesis of alkyl di-siloxane containing sugar moiety with various alkyl chain lengths was developed with unique property of penetration enhancer and low skin irritation. [14]

IV. PREPARATION OF TRANSFERSOMES

There are various patented and published procedures available for the preparation of transfersome. General procedure involves mixing of phosphatidylcholine in ethanol with sodium cholate or some suitable surfactant [14,15] .

A. Suspension Homogenization Process:

In this method, an ethanolic soybean phosphatidylcholine is mixed with edge activators of an appropriate amount, e.g. sodium cholate. To this prepared suspension Triethanolamine-HCl buffer solution is mixed to yield a total lipid concentration and then it is sonicated, frozen, and thawed for 2 to 3 times after which they are brought to desired size which is then measured by using photon correlation spectroscopy. Sterilization is done by filtering through a 0.2mm micro porous filter. Dynamic light scattering technique is used to confirm the final vesicle size.[16]

B. Rotary Film Evaporation Method:

Bangham initially invented hand shaking process, which is also known as rotary film evaporator method[17]. In this method, to organize a thin film, the need of phospholipids and surfactants is essential[18,19]. A combination of crude solvent such as chloroform and methanol in which a solution of phospholipids and ethanol are organized. For research purpose of multilamellar vesicles, this method is largely been used. After transferring the prepared solution to a round bottomed flask, it is rotated at a constant temperature (greater than the glass transition temperature of lipids) and pressure. On the walls of the flask, a film of lipids and edge activators is formed. Using aqueous media containing drug the twisted film is hydrated on account of which lipids tend to swell and form bilayer vesicles. By using sonication of the superior vesicles or by extrusion, vesicles of desired size can be obtained[20].

C. Thin Film Hydration Technique:

There are three steps involved in this technique:

1) To get thin film of vesicle phospholipids along with surfactants in an organic solvent (such as chloroform and methanol) is dissolved. Heating is carried out above the transition temperature of the lipid. To free the mixture of organic solvent the process is carried out in a rotary evaporator. By placing it overnight in vacuum, any traces of solvent are removed.

2) For one hour with suitable buffer at 60RPM the formed film undergoes hydration. At roomtemperature, the formed vesicles are left to swell for 2 hours.

3) Using bath sonicator for 30 mins at 50°C or at room temperature the prepared vesicles are subjected to sonication in order to prepare small vesicles. In case of probe sonicator, at 40°C sonication is carried out for 30 mins. By homogenizing the sonicated vesicles through manual extrusion 10 times through a polycarbonate membrane yields of 200nm - 100nm sandwich layer[15,21,22].

D. Ethanol Injection Method:

With unremitting stirring at constant temperature the aqueous solution containing drug is heated. Edge activators along with ethanolic solution of phospholipids is injected dropwise into the aqueous solution. The lipid molecules are precipitated as the aqueous media comes into contact with the solution and form bilayered structures. The process is easy to scaleup, simple and highly reproduceable, hence serves various benefits when compared to other methods[23,24].

E. Modified Handshaking Process:

This method is also known as lipid film hydration technique. In the ratio of 1:1 ethanol and chloroform are mixed. In this mixture drug, lipid and edge activators are dissolved. By evaporation the solvent is removed. At temperature above liquid transition temperature (i.e.) 43°C, hand shaking is achieved. with a constant rotation, inside the flask wall a thin lipid film is formed. For complete evaporation of the solvent, the preparation is left overnight. For 15 minutes with gentle shaking the film is hydrated with phosphate buffer and gentle shaking is done at corresponding temperature[25].

F. Freeze–Thaw Method:
This method includes exposure to both low and high temperature. The multilamellar vesicles are subjected to alternative cycles for freezing at very low temperature followed by very high temperatures. The prepared suspension is dipped in a nitrogen bath after transferring to a tube at −30°C for 30 seconds. They are exposed to high temperature in a water bath after freezing. This procedure is repeated 8-9 times[26].

G. Vortexing Sonication Method:
In phosphate buffer, the mixed lipids (edge activators, phosphatidyl choline, therapeutic agents) are all blended. Further to obtain a milky suspension it is vortexed. The suspension undergoes extrusion undergoes extrusion through polycarbonate membranes after sonication[27].

V. OPTIMIZATION OF FORMULATION CONTAINING TRANSFERSOMES

The preparation and properties of transfersomes are affected by various process variables. Therefore optimization and validation are carried out to the preparation procedure. Depending upon the manufacturing procedure involved in the formulation, the process variables are selected. The process variables involved in the manufacturing of formulation are:

A. Hydration medium.
B. Lecithin: surfactant ratio.
C. Effect of various surfactants.
D. Effect of various solvents.

By selecting entrapment efficiency of the drug, optimization was done. The other variables were kept constant during the preparation of particular system [25,28,29].

VI.CHARACTERIZATION OF TRANSFERSOMES

Liposomes, niosomes and micelles possess the same characterization as that of transfersomes**[30].**

A. Vesicle Size, Size Distribution And Vesicle Diameter:
The vesicular shape is studied using transmission electron microscopic studies. The dynamic light scattering (DLS) method or photon correlation spectroscopy gives details on the diameter of the vesicle. Generally, light scattering technique is used to study the size of the vesicle and also the size distribution. Distilled water is used in the preparation of sample .after passing through a membrane filter of 0.2 mm, the samples are diluted with filtered saline[31].

B. Entrapment Efficiency:
Amount of drug entrapped in percent of what that is added is called as entrapment efficiency. By using mini-column centrifugation the unentrapped drug is separated. 0.1% Triton X-100 or 50% n-propanol is used for the disruption of vesicles.

C. Entrapment Efficiency:

Amount Entrapped
---------- X 100
Total Amount Added

Hence entrapment efficiency can be determined using these steps[32].

D. Penetration Ability:
Using fluorescence microscopy, the penetration ability of transfersomes can be determined [21,33].

E. Turbidity Measurement:
Nephelometer can be used to measure the turbidity of drug in aqueous solution[15].

F. Degree of Deformability or Permeability Measurement:
Using dynamic light scattering (DLS) measurements, after each pass the particle size and the size distributions are noted. As a standard, the deformability study is done against pure water[15,33]**.**

G. Physical Stability:
Sealed glass ampoules are used to store the drug after determining the initial percentage of entrapped drug in the formulation. The ampoules are placed at three different temperature at least for three months (i.e.) in refrigeration at 4°c ± 2°c, then in room temperature at 25°c ± 2°c, later in body temperature at 37°c ± 2°c. After 30 days to determine the drug leakage, each ampoules containing the samples were analysed. By keeping the initial entrapment of drug at 100%, the percentage drug loss was calculated[28,29].

H. Skin Deposition Studies of Optimized Formulation:
The surface of animal skin (Goat) washed up to five times with a solution of PBS having pH 7.4 after complete 24 hrs study. By this process excess drug wash out and cut the skin into small pieces. Now kept aside for around six hours and add to it phosphate buffer solution of pH 7.4 after shaking and centrifuge for five minutes at 500 RPM. Statistical T-Test is used to compare result with control. [15]

I. Drug Content:
The drug content is determined using various instrumental analytical methods like modified HPLC using a UV detector. Depending on the pharmacopoeial analytical method, the choice of other parameters reside [28].

J. Number of vesicles per cubic mm:
Dilution is carried out 5 times with 0.9% Nacl solution for non-sonicated transfersome formulations. For further study optical microscope and Haemocytometer can be used. For optimizing the other process variables and the composition, this is an important parameter[21].

K. In vitro Drug release:
Before expensive *in vivo* studies are carried out, the formulation is carried out by the information from *invitro* studies and the time needed to reach steady state permeation along with its flux. The drug that entrapped at 0 times is the initial amount, indirectly the amount of drug released now it is calculated [15, 21].

L. In vitro Skin Permeation Studies:
Modified trans diffusion apparatus is used for this study, whose effective diffusion area is 2.50cm^2 and the volume of receiver compartment is 50ml. Goat skin in phosphate buffer solution of pH 7.4 is utilized for performing *in vitro* drug study. In the calculation of release profile for each aliquot, their correction factors were also considered. By using instrumental analytical technique the samples were analysed[25,34].

M. Occlusion Effect:
In case of traditional tropical preparations, occlusion of skin is found to assist the permeation of drug. Whereas, in case of elastic vesicles, occlusion of skin is proved to be have deleterious effect. Movement of vesicles from a dry surface to deep water rich region is due to a mechanism called hydrotaxis (movement in the direction of water) which serves as the major driving force for penetration of skin by the vesicles. Occlusion prevents evaporation of water from the skin and hence affects the hydration forces[15].

N. Confocal Scanning Laser Microscopy Study:
Staining of the skin, fixing the tissues in a position and sectioning of cells is found to be a major problem in both electron microscopy and conventional light microscopy. There occur many miscalculation as most of the processing techniques are found to be incompatible with the structures to be examined. All these errors and misinterpretations can be reduced by the use of Confocal Scanning Laser Microscopy (CSLM). In transfersomes, lipophilic fluorescence markers are incorporated. Some markers being used are:
*1)*Nile red
2) Rhodamine- DHPE (1, 2- dihexadecanoyl- sn- glycero- 3ogisogietgabikanube-Lissamine Tmrhodamine-B- sulfonyl), triethanol- amine salt)[35].

O. Surface Charge and Charge Density:
Using zetasizer, the charge density and surface charge of transfersomes can be determined[15,21]

VII. APPLICATIONS OF TRANSFERSOMES

A. Delivery of Anaesthetics:

1) Within less than 10 minutes under appropriate conditions anaesthetics when applied in the form of transfersomes induce a topical anaesthesia. As strong as 80% of pain insensitivity occurs as that of a comparable bolus injection but the effects of transfersomal anaesthetics have longer duration[36] .

2) Mahmoud M Omar et.al. Developed a topical gel formulation that contains lidocaine which acts as another option for the pain causing anaesthetic injectables. The thickening agent used in the formulation was HPMC k15. Various parameters like Drug content, pH, viscosity and ex-vivo permeation were evaluated for the lidocaine formulated gel. For the evaluation Tail flick test was used to detect the analgesic effect of the gel. The positive results was recorded that show that thickening agent increase analgesic action as well as skin permeation effect of topical gel containing the transfersomal lidocaine.[37]

3) Planas ME et.al. Found in their study that when local anaesthetics and common analgesics were applied dermatogically on rats and humans in form of transfersomes study shows that transfersomes offers a promising means for non-invasive treatment of local pain as they are direct, topical drug application. The related subcutaneous

injection of comparable drug quantities are found to have the identical effectiveness of dermally applied anaesthetic transfersomes[38].

B. Delivery of NSAIDS:

1) In case of NSAIDS, there are some problems like GI irritation, which can be overcome by transdermal delivery of transfersomes. Ketoprofen and diclofenac using transfersomes are already studied for efficacy and it is notable that swiss regulatory agency has already approved ketoprofen formulation[39].

2) Sureewan Duangjit et.al. Studied in vitro Skin Permeation of Meloxicam-Loaded Liposomes versus Transfersomes. This research involved transdermal release of meloxicam (MX) using liposome and transfersosme vesicles and to carried out evaluation their prospective application. Skin permeation capacity of MX loaded transfersomes were found to be high when compared to meloxicam loaded liposomes as the meloxicam loaded transfersomes were evaluated for various parameters like particle size, loading efficiency, zeta-potential, *in vitro* skin permeation and stability after preparation. For the confirmation of Stratum corneum lipid transfersomes Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared Spectroscopy (FT-IR) were used.[40].

3) Makhmalzadeh et.al. Studied the trolamine salicylate-loaded transfersomes their Formulation, characterization and *in vitro*/*ex vivo* evaluation as a transdermal drug delivery carriers. The aim of this reasearch was to evaluate the permeability parameters of trolamine salicylate through rat skin using different transfersome formulation. Franz diffusion cell was used to compare it with controls. Preparation technique used is solvent evaporation, whereas for data analysis and for the design of experiment, full factorial design was applied. Hence their study concluded that for trolamine salicylate to permeate through rat skin, the rate limiting step is found to be the portioning from the vehicle into the skin. Transfersomes has improved this rate limiting barrier of trolamine salicylate[41].

4) Pravin K. Shende et.al. Studied transdermal patch of serratiopeptidase that was a lipid-based transfersomes. For their study serratiopeptidase, which is an analgesic and anti-inflammatory drug extracted from a gram negative bacteria serratia marcescens stain E-15.There are many limitations found in delivering serratiopeptidase for which transdermal drug delivery system is chosen to avoid such limitations. Many characterization parameters like thickness, Particle size, tensile strength, adhesion test, *invitro* and *invivo* release, encapsulation efficiency, differential scanning calorimeter DSC, FTIR were taken into consideration[42].

C. Delivery of Herbal Drugs:

R.Patel et.al., studied on the Curcumin Loaded Transfersome that was Developed and Characterized for Transdermal Delivery. In their study, for transdermal delivery of curcumin, transfersomal formulation was potentially investigated. Curcumin has potent anti-inflammatory properties, has an activity which is like to non steroidal anti inflammatory drugs during management of pain. On the other hand when administered orally, curcumin due to decreased GI absorption becomes poorly bioavailable. Various process variables such as surfactant ratio, effect of lecithin, effect of surfactants and the effect of various solvents were selected for optimization of the formulation. Hence from their studies it was concluded that permeability of curcumin can be improved in a duration of time using transfersomes formed from PC: span 80 (in the ratio 8:15 mmol)[25].

D. Transdermal Immunization:

Soluble proteins like human serum albumin, gap junction proteins and integral membrane proteins can be loaded into transfersomes. Two major significance of this approach are found to be:

1) It gives rise to high IgA levels.

2) There occurs high titer.

3) It can be administered without the need of injections [36].

A. Prem N. Gupta et.al. Studied on transfersomes that are toxoid-loaded for topical immunization of tetanus. The focus of their study was to develop a special non-invasive vesicular delivery system for tetanus toxoid (TT). A comparison was made for immune response with equal quantity of alum adsorbed tetanus toxoid (AATT) solution of tetanus toxoid administered topically and a physical mixture containing transfersomes and tetanus toxoid given topically. This was studied through invitro study. Further the antigen is delivered to the immunocompetent Langerhans cells through the skin. This penetration of transfersomes through skin is revealed by fluorescence microscopy[43].

E. Delivery of Anticancer Drugs:

Since last few years transfersomes were found most promising for cancer treatment especially skin cancer for drugs like methotrexate and favourable results in delivering the drug[36,44].

1) Z.Zhang et.al. Studied the *invivo* permeation of transfersomal gel loaded with anti-scarring agent (5-FU) into hypertrophic scars. Rhodamine 6GO, a fluorescent agent is labelled to it and *in vitro* scar permeation studies were carried out. By this study, they concluded that floura uracil in transfersomal gel form had high permeation depth and rate with greater content retention of agent in scar tissues when compared to PBS gel of 5FU. In rabbits the hyperplasia of ear scars were inhibited for some period by local administration of the agent. Hence from their study transfersomes were shown to be an efficient transdermal drug delivery system[45].

2) Lu Y et.al. Studied vincristine transdermal and lymph targeting transfersomes. For the conduction of this study, Vincristine was choosen for treating leukemia and hogkin /non-hogkin lymphoma. On the contrary, its clinical

use has been limited due to its local stimulation and neuro toxicity. The focus of this research was to minimise side effects and increase their curative effects. For the preparation of Vincristine transfersome Ultra-sonic dispersion methods and dry film were used. HPLC method is used for the determination of targeting ability, pharmaceutical properties and pharmacokinetic characters. This research concluded that transfersomes have excellent lymph targeting ability[46].

F. Corticosteroids Delivery:

Another important application of transfersomes is the delivery of corticosteroids. The administered drug dose is epicutaneously optimized, hence the overall safety as well as site specificity of corticosteroids is enhanced by transfersomes. The transfersome loaded corticosteroids show many advantages as they are biologically active at a very low dose when compared to currently used formulation in treating skin diseases[14].

Gregor Cevc et.al. Studied in vivo regio-specificity and biological activity of corticosteroids on Transfersomes-mediated transepidermal delivery. In their study, it was shown that overall drug safety and specificity of topical drug delivery were increased by transfersomes. It is found to show high systematic drug availability as there is an increased dose per area as well as total applied drug dose. Due to superior potential of drug targeting in organ, the transfersomal corticosteroid formulation has an anti-oedema activity exceeding several commercial products[47.]

G. Delivery Of Proteins And Peptides:

1) When given through oral route, proteins get degraded easily and is difficult for administration as they are large in size. Subcutaneous injections are chosen widely for administration of proteins into the body. Transfersomes have the same bioavailability as that of subcutaneous (S.C) injectables that deliver proteins in suspension form. When applied in repetitive epicutaneous manner, transfersomes are found to generate strong immune responses. Using transfersomes as carrier, albumin remains immunologically active even after several dermal challenges [48,49].

2) De Marco Almeida et.al. Studied Skin Permeation of Cationic Transfersomes Containing the Synthetic Peptide PnPP-19 and thier Physicochemical Characterization in the treatment of erectile dysfunction. In their study PnPP-19 (19 amino acid synthetic peptide) skin permeating ability of PnPP-19 as well as PnPP loaded transfersomes were compared. Three different types of liposomal preparation methods were evaluated.From their study it was concluded that topical administration is favoured by transfersomes as they protected the peptide from degradation[50].

H. Delivery Of Insulin:

Subcutaneous injections are generally used to deliver insulin. However insulin can also be administered through topical means on skin in an intact manner by enclosing it in a transfersome carrier.[51]

I. Interferons Delivery:

A. Hofer C et.al. Studied the formulation and evaluation of interferon-alpha containing transfersomes and interleukin 2. About 75-80% of IFN and IL-2 has been incorporated in transfersomes and were found to be biologically active. From their study it was concluded that the incorporated IFN and IL-2 were in sufficient bioactive form of concentration for the purpose of immune therapy. In cell line model of murine RENCA, these IL-2 and IFN entrapped transfersomes were used in upcoming experiments as a transdermal approach[52]

J. Other Applications:

1) Mona Qushawy et.al. Studied Miconazole Nitrate for the Treatment of Candida Skin Infections and gave Design, Optimization and Characterization of a Transfersomal Gel. For their study, they chose antifungal drug Miconazole nitrate which is used for the cure of superficial fungal infection. The objective of their study was to develop a formulation containing transfersomes loaded with Miconazole nitrate as they have low skin permeability which can be easily avoided when formulated with transfersomes as they can overcome skin barrier mechanism. The optimized formulation is evaluated for *invivo* and *invitro* antifungal activity, pH, viscosity, drug content, spreadability and *invitro* permeation with a marketed product (Daktarin®cream 2%). From their study it was concluded that the skin barrier can be efficiently avoided using transfersomes[53].

2) Sakshi Sharma Dogra et.al., studied on transfersomes as a novel approach for intranasal delivery. Nasal route which has rapid absorption of drug can locally exert the effects of drug. In spite of these advantages nasal route of drug delivery has short residence time of drug in nose and the bioavailability of hydrophilic drugs is very low. These drawbacks can be rectified by using transfersomes, as they have the ability to increase the penetration power of both high and low molecular weight drugs. Hence their study concluded that transfersomes can be used as an efficient penetration of drug in nasal and conventional delivery systems[54].

3) Marwa h. abdallah studied how to overcome the poor solubility of nystatin, an antifungal drug and to improve its bioavailability by formulating with transfersome on transfersomes as a transdermal drug delivery system for enhancement the antifungal activity of nystatin. The aim of their study. Rotary evaporation sonication method was used to hydrate lipid film in preparation of transfersomes loaded with Nystatin. Transmission Electron Microscopy is

used to confirm the spherical structure of vesicle with prolonged delivery and high stability characteristics. Their study proved transfersomes as a good carrier of nystatin to enhance penetration[19].

IV. CONCLUSION

Vesicular systems are one of the most contentious mechanisms for delivering active compounds transdermally. The discovery of elastic vesicles such transferosomes. Transferosomes, also known as transfersomes, are ultradeformable vesicles for transdermal applications consisting of a lipid bilayer with phospholipids and an edge activator and an ethanol/aqueous core. Transfersomes can undergo even tiny pores (100 mm) nearly as efficiently as water, which is 1500 times smaller. Ultra-deformable vesicles can provide the solution for the transport related problems. It enhanced delivery of bioactive materials through the skin by means of a vesicular carrier opens new challenges and opportunities for the event of novel improved therapies. Bisoprolol is a cardio selective β-blocker It is given as the fumarate in the management of hypertension and angina pectoris. On oral administration, the drug under goes extensive first pass metabolism. Delivery of bisoprolol fumarate via transdermal route would minimize some of the deficiencies associated with the oral delivery and increase the bioavailability of the drug. It concluded that the drug delivery through ultraflexible transfersomes can overcome all the issues related to the transdermal drug delivery system.

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