



Novel vesicular carriers for topical drug delivery and their application's

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Accepted on: 07-04-2013; Finalized on: 30-06-2013.

ABSTRACT

Delivery of drug through topical route represents a most convenient and novel approach. The major difficulty arises while delivering a drug through skin is its action as a natural barrier nature which makes it difficult for most drugs to penetrate into and permeate through it. Conventional topical formulations have not proved to be effective in dermal delivery of drug. Novel drug delivery systems bear great potential for dermal delivery. Among them lipidic and non-lipidic vesicular systems like liposome, niosome, transfersome and ethosome have been suggested to overcome the problems associated with conventional topical formulations. These vesicular systems were found to be more effective as they render controlled release of drug due to depot formation in skin and some were more effective in transdermal delivery. This article summarizes the potential of novel vesicular drug delivery carrier based dermal applications of the drug.

Keywords: ethosomes, liposomes, niosomes, topical delivery, transfersomes, Vesicular carriers.

INTRODUCTION

The field of pharmaceutical science has been developing steadily over the years, and has today become invaluable in helping to keep us healthy and prevent disease. In the past few decades, considerable attention has been focused on the development of topical delivery of drugs because of number of advantages offered by this route. Skin in an average adult body covers a surface of approximately 2 m² and receives about one-third of the blood circulating through the body. Topical drug delivery means the application of drug to skin for localized effect and in transdermal drug delivery system (TDDS) skin is used as a potential route for the delivery of systemic action of drugs. TDDS system offers a number of advantages like longer duration of action, flexibility in dosing, reduced side effects, uniform plasma levels, high patient compliance etc. But at the same time it also bears some drawbacks like possibility of local irritation effect, erythema, itching, and most important is the low permeability of drugs in the stratum corneum. Stratum corneum is the top layer of the epidermis consists of keratinized, flattened remnants of once actively dividing epidermal cells, impermeable to water and behaves as a tough flexible membrane. Many technologies and systems have been investigated to evade this barrier, and one of the most promising technique is to formulate novel vesicular carriers for delivery through the skin.^{1, 2} These novel drug delivery systems bear great potential for dermal delivery. Among them lipidic and non-lipid vesicular systems like liposome, niosome, transfersome and ethosome have been suggested to overcome the problems associated with conventional topical formulations. These vesicular systems are highly ordered assemblies of one or several concentric lipid bilayers formed, when certain amphiphilic building blocks are confronted with water. Vesicles can be formed from a

diverse range of amphiphilic building blocks.³ Most commonly used materials for the formation of vesicles are phospholipids cholesterol and non-ionic surfactants. Vesicle shape, size, structure, lamellarity and entrapment efficiency of these vesicular carriers depend upon the composition of vesicles and all these parameters provide major impact on the efficacy of the systems. Vesicular system offers number of advantages in drug delivery through the skin such as biocompatibility, non-toxicity, incorporated both hydrophilic and lipophilic drugs, controlled drug delivery rate and extent, act as a depot formation for sustained release of drug, increased permeation of drugs through the skin and penetration enhancer because of their unique composition etc.^{4, 5} Principal components used in different vesicular systems for topical drug delivery are mentioned in table 1.

Table 1: Composition of various vesicular systems

Vesicular systems	Component
Liposomes	Phospholipids (natural or synthetic)
Niosomes	Nonionic surfactants + lipids
Ethosomes	Phospholipids + ethanol
Transfersomes	Phospholipids + single chain surfactants

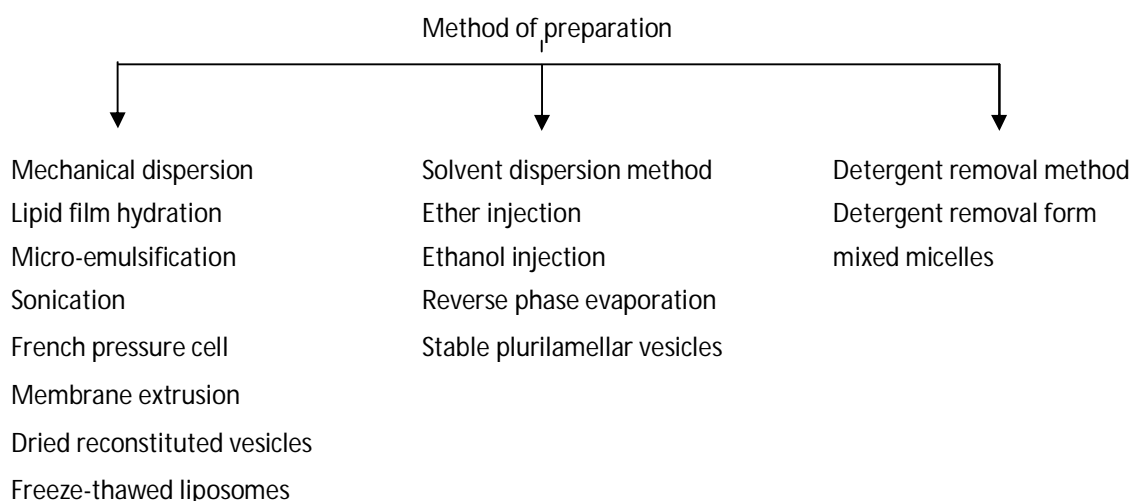
LIPOSOME

Liposome is a term originated from two Greek words: 'Lipos' that means fat and 'Soma' implies body. The vesicular system was first described by British haematologist Dr Alec D Bangham in 1961 (published 1964), at the Babraham Institute, in Cambridge. Liposome can be defined as "a colloidal, vesicular structures composed of one or more lipid bilayers surrounding a number of aqueous compartments".⁶ These are spherical vesicles with particle size ranging from 20nm to several micrometers which composed of a phospholipid bilayer membrane and used to deliver drugs

or genetic material into a cell. Phospholipids are the backbone of these structures. Liposomes can be composed of naturally-derived phospholipids with mixed lipid chain like egg phosphatidylethanolamine or of pure components like DOPE (dioleoylphosphatidyl ethanolamine) and cholesterol.⁷ A number of evidences demonstrated the ability of liposomes to enhance the efficiency of drug delivery via several routes of administration.⁸ Liposome as a vesicular system offers a number of advantages, such as biocompatibility, non-toxicity and flexibility, protection from the inactivating effect of external conditions, unique ability to deliver the

pharmaceutical agents into cells or even inside individual cellular compartments. Apart from the given advantages, liposomes are associated with the some limitations such as high production cost, prone to leakage and short half life.^{9, 10} They can be formulated by variety of techniques as given in scheme 1 and they are classified on the basis of structural parameters, method of preparation, composition and applications. Liposome can be characterized for its surface morphology, surface charge, size distribution, lamellarity, entrapped volume, and stability etc.⁹

Scheme 1: Method of preparation of liposomes:⁹



Applications of Liposomes

Liposomes are used as a carrier in immunology, vaccine adjuvant, eye disorders, brain targeting, infective disease and in tumour therapy. They are also used in topical drug delivery system as they can improve the drug deposition within the skin at the site of action where the goal is to reduce systemic absorption and thus minimise side effects and increases the patient compliance.

A large number of attempts have been made to design new vehicles to ensure adequate penetration and more importantly, localization of the drug within the skin. Research on liposomes as a topical drug delivery system was carried out by Mezei in 1980¹¹. However, contrary to earlier findings, it is reported that the improved delivery was due to the penetration enhancement effect caused by changes in the structure of vesicular lipids. After occlusion, no penetration of liposomes occurs which supports the fact that liposomes can form trans-epidermal osmotic gradient and can penetrate into epidermis by hydration force.¹² 5-Fluorouracil was incorporated into liposome to formulate SPLV (Stable Plurilamellar Vesicles) liposomes for the dermal delivery of drug. Aiming at increasing stability of 5-fluorouracil liposomal dispersion, freshly prepared liposomal concentrates were directly incorporated in hydroxypropyl methylcellulose gel (HPMC). Stability release profiles of liposomal gels and concentrates indicated a significant increase in stability of liposomal formulations. Also,

lyophilization increases the shelf life of liposomes by preserving it in a dry form as a lyophilized cake to be reconstituted immediately prior to administration or direct incorporation into a final dosage form.¹³ Gabrijelcic found enhanced transport of liposome-entrapped substances into the skin from hydrogels prepared from xanthan gum. The enhanced drug transport into the skin is attributed to the lipid nature of the vesicles, which serve as carriers for the drug.¹⁴ Liposomal gel of antifungal drug fluconazole for topical candidiasis by incorporating in carbopol 934 gel base and it show a good release rate. Liposomal dispersion and gels were found to increase the skin permeation and deposition compared to control and marketed gel. Liposome dispersion and gel formulation were found to be stable for 60 days.¹⁵ Anti-inflammatory drug Diclofenac sodium liposomal gel was prepared by thin film hydration technique and characterized for its in vitro and ex vivo studies. The studies show better sustained and prolonged release of Diclofenac sodium from the liposomal gel.¹⁶ Lidocaine liposomal gel was formulated by incorporating in carbopol 934 base and the results shows the release of entrapped drug for extended period of time.¹⁷ Tretinoin (TRE) liposomal gel was formulated and by incorporating in carbopol 934 which show enhanced efficacy. Diffusion studies of plain TRE gel and liposomal TRE gel suggested prolongation (3.4 times reduction in flux value) of drug diffusion and almost two- fold increase in skin drug retention after liposomal encapsulation of drug.¹⁸

Triamcinolone acetonide is a glucocorticoid that it is used in treatment of skin inflammatory diseases. Liposomes of Triamcinolone acetonide was formulated by thin film method and then converted to gel form by incorporating into carbomer 940 polymer and the results showed a prolonged and controlled release of the drug.¹⁹ Ketoconazole liposomal gel was formulated by incorporating in carbopol 940 base and the results shows the increase release reaction capacity in skin. The percentage cumulative drug release from the optimized batch i.e. was found to be $34.96 \pm 0.86\%$ after 12 hours of diffusion studies. Stability studies showed maximum percent drug retention at refrigerated temperature (2-8°C).²⁰ Ketoprofen (NSAID) liposomal gel was formulated and evaluated by incorporating in carbopol 934 gel base. Ketoprofen liposomal gel was found to have reasonable drug loading, controlled release rate, particle size, and stability and phase transition behaviour, and showed an appreciably enhanced retention of drug molecules in the skin.²¹

NIOSOME

Niosomes were first introduced as a feature of cosmetic industry. The first report of non-ionic surfactant vesicles came from the cosmetic applications devised by L'Oreal.²² Vigorous conditions required for preparation and handling of liposomes under cryogenic atmosphere, leakage of active ingredient, high formulation cost and limited shelf life are key factors that prompted the use of non-ionic surfactant in novel vesicular drug delivery system, instead of phospholipids. These new vesicular systems are called as niosomes, which consist of microscopic lamellar structures formed with admixture of non-ionic surfactant and cholesterol having a bilayer structure formed by self-assembly of hydrated surfactant monomers.^{3, 23} There are mainly two types of components i.e. non-ionic surfactant and the additives (cholesterol and charged inducers etc). The non-ionic surfactants form the vesicular layer and cholesterol improves the rigidity of the bilayer. Cholesterol is an important component of the cell membrane and also their presence in membrane affects bilayer fluidity and permeability and charged inducers helps in electrostatic stabilization of the vesicles.²³ A diverse range of non-ionic surfactants such as alkyl ethers, alkyl glyceryl ethers, poly oxy ethylene 4 lauryl ether (Brij 30), poly oxy ethylene acetyl ethers (Brij 58), sorbitan fatty acid esters, etc., can be used in the formulation of various niosomes. A new type of non-ionic surfactant has been introduced recently, known as Gemini non-ionic surfactant. Gemini surfactants have two hydrophobic chains and two hydrophilic head groups linked with spacers.²² There are different types of positive charge inducers viz. sterylamine and cetyl pyridinium chloride and negative charge inducers like dicetyl phosphate, dihexadecyl phosphate and lipoamine acid.^{23, 24} There are a number of advantages offered by the niosomes as a drug delivery system like high bioavailability, biodegradable, biocompatible, controlled and sustained release of drugs

due to depot formation, more stable than liposomes and increased permeation of drugs through the skin.²⁵ Niosomes can be formulated by a variety of methods. Niosomes are characterized for different attributes such as size, shape and charge, phase behavior, vesicle diameter, entrapment efficiency, and in vitro release rate as given in the table 2. Other aspects studied are drug stability, lamellarity, pharmacokinetic aspect etc.^{25, 26} The HLB value of different surfactants has their own and specific impact on the formulation and entrapment efficiency of niosome as given in table 3.

Applications of Niosomes

Niosomal drug delivery is widely reported to be used for various pharmaceutical agents. They are used as a carrier for protein, peptides, vaccines, antigen, haemoglobin etc. Topical delivery of NSAIDs and other drugs is the best way to avoid gastric disturbances and niosomes are widely used in topical drug delivery as they provides site specific action, reduced side effects, low dose several times than the currently available formulations for the treatment of skin diseases and increased patient compliance.

Anti-Fungal Agents

Presence of 50% alcohol in marketed gel of naftifine hydrochloride an antifungal drug has been detrimental to skin after repeated exposure. Non alcoholic niosomal formulation of the drug was prepared and incorporated in the gel to overcome the problem.²⁷ Fluconazole loaded niosomes of Span 40, Span 60, and Brij 72 surfactant were prepared and evaluated. The prepared formulation accumulated and formed localized drug depots in the skin, thereby releasing the contents in a sustained manner and is able to greatly enhance cutaneous retention of the drug.²⁸

NSAID'S

Topical niosomes of aceclofenac have been prepared for topical use after incorporation into carbopol gel. The gel showed improved penetration and therapeutic efficacy of the drug.²⁹ Shahiwala and Misra (2002) prepared niosomal gel of nimesulide in terms of drug delivery by incorporating into carbopol 934 gel base and it was observed that niosomal gel showed prolonged release of nimesulide, thereby enhancing the anti-inflammatory activity.³⁰ Despite of having high oral bioavailability rofecoxib was withdrawn due to its gastrointestinal adverse effects and cardiac toxicities. So an attempt was made to reduce its side effects and toxicities by encapsulation in niosomes. The niosomal gel of rofecoxib showed prolonged and sustained drug release of rofecoxib, thereby reducing its severe adverse effects.³¹ Ketoprofen was encapsulated in niosomes for topical application which released the drug in slow and sustained manner.³² Celecoxib, a selective COX-2 inhibitor used in the treatment of arthritis, as it is associated with cardio toxic effects so an alternate dosage form is suggested. Celecoxib was entrapped in niosomal gel and the results showed better skin permeation and deposition of

celecoxib from niosomal gel as compared to conventional gel and also demonstrated that the formulation possess great potential for enhanced skin accumulation, prolonging drug release and improving the site specificity of celecoxib.³³ On oral administration of ibuprofen it shows poor water solubility and limits its entry in systemic circulation before gastric emptying, so to counter that, niosomal gel of ibuprofen has been prepared for topical use by incorporating into carbopol 934 gel base and it improves the drug retention and prolongs the drug release.³⁴ Lornoxicam niosomal gel was prepared by using carbopol 934 gel base, for the transdermal application of the hydrophobic anti-inflammatory drug and it shown reasonable drug entrapment, suitable size and good permeation of drug.³⁵

Anti-acne drug

Erythromycin niosomes was formulated by thin film hydration technique and converted to niosomal gel by incorporating into carbopol 934 gel base for topical use and provides prolonged drug release, enhanced drug retention into skin and improved permeation across the skin after encapsulation which results in considerably reduced adverse symptoms.³⁶ Niosomal formulation using span-60 of Tretinoin (TRT) was prepared and then incorporated in Carbopol 971 gel base to provide niosomal gel. The invitro diffusion study shows the sustained release pattern of TRT from niosomal gel.³⁷

Cosmetics

Niosomes of N-acetyl glucosamine is reported to be prepared in topical form and improved penetration into the skin. N-acetyl glucosamine (NAG) has been considered in the treatment of hyper pigmentation disorders due to its inhibitory effect on tyrosinase enzymes in melanocytes. Prepared niosomal formulations showed improved extent of drug localized in the skin, as needed in hyper pigmentation disorders. In addition, lower systemic absorption, and thus, reduced side effects can be achieved by topical NAG-niosomes.³⁸ Gallic acids containing elastic and non elastic niosomes were prepared for the topical application and it was observed that non elastic niosomes showed a slight increase in entrapment efficiency whereas elastic niosomes showed increased permeation through the skin which will be beneficial for topical anti aging application.³⁹ Minoxidil niosomes were prepared for the topical application to improve the low skin penetration and bioavailability as compared to conventional topical vehicle. The percutaneous absorption study was carried out in vitro using vertical diffusion Franz cells using human skin and the results compared with dissolved minoxidil in propylene glycol-water-ethanol solution as a control. The results suggest that niosomal formulations could constitute a promising approach for the topical delivery of minoxidil in hair loss treatment.⁴⁰ Ellagic acid (EA) is a potent antioxidant phytochemical substance which has limited use due to poor biopharmaceutical properties, low solubility and low permeability. Topical niosomes of

ellagic acid was prepared with added solubilizers which enhanced the permeation of ellagic acid into the skin with increased efficacy.⁴¹ Finasteride topical niosomes have been formulated for effective treatment of androgenetic alopecia. In vitro permeation and in vivo deposition studies demonstrated the potentials of niosomes for successful delivery of finasteride to the pilosebaceous unit.⁴²

Muscle Relaxants

Niosomes containing Baclofen a muscle relaxant have been prepared to improve the skin penetration and bioavailability characteristics as shown by conventional topical vehicle. The prepared niosomes provide some advantages in entrapment efficiency, stability studies and showed improved muscle relaxation activity.⁴³

Various applications of niosomal formulations to wide variety of drugs for topical delivery are summarized in table 4.

TRANSFERSOME

The term transfersome and the underlying concept was introduced in 1991 by Gregor Cevc. Transfersomes are ultradeformable vesicles, elastic in nature, which can squeeze itself through a pore which is many times smaller than its size owing to its elasticity. The name transfersome means "carrying body", and it was derived from the Latin word 'transferre', meaning 'to carry across', and the Greek word 'soma', for a 'body'. Transfersome is a term registered as a trademark by the German company IDEA AG. Most suitable form of transfersome is an ultradeformable vesicle possessing an aqueous core surrounded by the complex lipid bilayer.⁴⁴ In terms of delivering of drugs through transdermal route, there are some problems encountered with some other vesicular systems like poor skin permeability, breaking of vesicles, leakage of drug, aggregation and fusion of vesicles.⁴⁵ To overcome all the aforementioned problems, a new type of vesicular carrier has been developed called "transfersome" which is capable of transdermal delivery of low as well as high molecular weight drugs.⁴⁶ Transfersomes are artificial vesicles, and they are more deformable than standard Liposomes.⁴⁷ Transfersome have been reported to enhance the transdermal delivery of drugs, when applied onto the skin non-occlusively.⁴⁸ Transfersome usually composed of at least one inner aqueous compartment, which is surrounded by a lipid bilayer. It also possesses some specially tailored properties due to the incorporation of "edge activators" into the vesicular structure. Span 80, tween 80, sodium cholate, sodium deoxycholate, are some surfactants that have been used as an edge activators. Transfersome are usually applied in the form of semi-dilute suspension. Because of their property of deformability, this vesicular system is a good candidate for the non-invasive delivery of small, medium, and large sized drugs.³ A number of advantages were offered by transfersomes like biocompatible, biodegradable, possess high entrapment efficiency, act as depot so releasing their contents slowly



and gradually, ability to deform and pass through narrow constriction, can be used for systemic as well as topical drug delivery. Apart from their benefits, transfersomes are associated with some drawbacks such as: chemical instability, expensive to formulate and purity of natural phospholipids.^{49, 50} Transfersomes are evaluated with

respect to various parameters like surface morphology, vesicle size and size distribution, number of vesicles per cubic mm, surface charge and charge density, penetration ability, entrapment efficiency, in vitro drug release profile etc.⁵⁰

Table 2: Evaluation parameters of niosomes^{22, 23}

Parameters	Techniques and instrument
Vesicle Size And Surface Morphology	Transmission electron microscopy(TEM), freeze fracture microscopy, optical microscopy
Vesicle Size And Size Distribution	Dynamic light scattering, TEM, Zetasizer, gel permeation, gel exclusion
Electric Surface Potential And Surface pH	Zeta potential measurements and pH sensitive probes
Lamellarity	Small angle X-Ray scattering, ³¹ P-NMR
Phase Behaviour	Differential scanning calorimetry
<i>In Vitro</i> Release Study	Dialysis tube
<i>In Vivo</i> Study	Animal model
Stability Study	By storing formulations at different temperature and humidity conditions
Entrapment Efficiency	Centrifugation method (below 7000x g), Ultracentrifugation method (15000X g), Exhaustive dialysis method, gel permeation

Table 3: Effect of HLB value of surfactants on the formation of niosomes²³

HLB value	Impact on formulation
Very low	Needs to add cholesterol to increase stability
1.7 to 8.6	Decreases entrapment efficiency
<6	Needs to add cholesterol in formation of bilayer vesicle
8.6	Increase entrapment efficiency of niosomes
14–16	Does not produce niosomes

Table 4: Application of niosomes for topical delivery of drugs

Drug	Formulation and Composition	Reference
Aceclofenac	Niosomal gel- Carbopol 980, Span 60	29
Nimesulide	Niosomal gel- Carbopol 934, Span 20,60,80 and 85, Tween 20,60 and 80	30
Rofecoxib	Niosomal gel- Carbopol 940, Span 20,40 and 60	31
Ibuprofen	Niosomal gel- Carbopol 934, Tween 40,60 and 80	34
Lornoxicam	Niosomal gel- Carbopol 940, Span 40,60 and 80	35
Erythromycin	Niosomal gel- Carbopol 934, Span 20,60 and 80	36
Tretinoin	Niosomal gel- Carbopol 971, Span 60	37
N-acetyl glucosamine	Niosomes - Span 40,60 and 80	38
Minoxidil	Niosomes- Span 20,40,60 and 80, Brij 52,76	40
Ellagic acid	Niosomes- Span 60, Tween 60	41

Application of Transfersomes

Transfersomes are used as a carrier for protein and peptides like insulin, bovine serum albumin, vaccines, etc. They improve the site specificity, overall drug safety and lower the doses several times than the currently available formulations for the treatment of skin diseases.

Transfersomes of telmisartan were prepared by conventional rotary evaporation sonication method for

enhanced skin absorption. The optimized transfersomal gel shows high entrapment efficiency and high transdermal flux and thus proves to be novel approach for the transdermal delivery of telmisartan.⁵¹ Transfersomal gel containing insulin is formulated by reverse phase evaporation method. The study of optimized transfersomal gel has demonstrated prolonged hypoglycemic effect and it is suggested that optimized transfersomal gel containing insulin can be transdermally

administered in the treatment of insulin dependent diabetes mellitus with maintaining lower blood glucose level and improved patient compliance.⁵² Transfersomal formulation with respect to dermal delivery of paromomycin sulfate (PM) was prepared for possible topical therapy of cutaneous leishmaniasis (CL). The results of this study showed that PMTFs (paromomycin sulphate transfersomal formulations) prepared with 2% of sodium cholate (Na-Ch) with and without 5% ethanol might be useful as a candidate for the topical treatment of cutaneous leishmaniasis.⁵³ Maurya et al. (2010) formulated transfersomal gel of indinavir sulphate. Transfersome of indinavir sulphate was prepared by conventional rotary evaporation method and then incorporated into a gel base. The study suggest that the optimized formulation shows decreased lag time and high transdermal flux of nearly 7.5 and 12.04 times, as compared to conventional liposomal formulation bearing indinavir sulfate and plain drug solution⁵⁴. Curcumin when given orally posses poor bioavailability because of its less GI absorption. Nearly 25 to 85% of orally administered curcumin is eliminated unabsorbed by faeces. Transfersomes containing curcumin for transdermal delivery was formulated and optimized. The optimized formulation showed higher entrapment efficiency, provides higher permeation of drug from transfersomal gel and can be used as a promising approach to improve the permeability of curcumin in period of time.⁴⁸ Transfersomes have also been used as a carrier for interferons, for example leukocytic derived interferon- α (INF- α) is a naturally occurring protein having antiviral, antiproliferative and some immunomodulatory effects. Transfersomes 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. (1999) studied the formulation of interleukin-2 and interferon- α containing transfersomes for potential transdermal application. They reported delivery of IL-2 and INF- α trapped by transfersomes in sufficient concentration for immunotherapy.⁵⁵ Transfersomes have also used for the delivery of corticosteroids. Transfersomes improves the site specificity and overall drug safety of corticosteroid delivery into skin by optimizing the epicutaneously administered drug dose. Transfersomes based corticosteroids are biologically active at dose several times lower than the currently used formulation for the treatment of skin diseases.⁴⁵ Cationic transfersomes is a modified version of transfersomes, composed of cationic lipid DOTMA and sodium deoxycholate as constitutive lipids. Plasmid DNA encoding hepatitis B surface antigen (HBsAg) was loaded in the cationic transfersomes using charge neutralization method for topical application and compared with naked DNA. Study revealed that DNA loaded cationic transfersomes elicited significantly ($P < 0.05$) higher anti-HBsAg antibody titer and cytokines level as compared to naked DNA and showed the potential of cationic transfersomes as DNA vaccine carriers for effective topical immunization.⁵⁶

ETHOSOME

Ethosomes are novel lipidic carriers that are the modified forms of liposomes containing high ethanol content. This lipidic vesicular system containing ethanol has been developed by Touitou. Ethosomes contains phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water having a size range from tens of nanometers to microns. Size of ethosomes depends upon the method of preparation and application of techniques like sonication.^{57, 58} Ethosomes are mainly used for the delivery of drugs through transdermal route. These vesicular systems have higher penetration rate through the skin as compared to liposomes. Unlike liposomes, which are mainly known for the delivery of drugs to the outer layers of skin, ethosomes have been shown to enhance permeation of drug through the stratum corneum barrier. The main reason suggested to be responsible for deeper distribution and penetration in the skin was might be due to the synergistic effects of combination of phospholipids and high concentration of ethanol in ethosomes.^{57, 59} Ethosomes as a carrier of drugs offers a number of advantages like, high patient compliance as the ethosomal drug is administered in semisolid form (gel or cream), non-invasive and can be widely used in pharmaceutical, veterinary, cosmetic fields.⁶⁰ Ethosomes can be prepared by two methods such as hot and cold method and characterized mainly for its vesicle shape, size, zeta potential, surface tension, transition temperature, penetration and permeation studies, drug content and vesicle stability etc.³ Ethosomes can entrap wide variety of drugs viz. hydrophilic, lipophilic, or amphiphilic. Different reports show a promising future of ethosomes in making transdermal delivery of various agents more effective. Ethosomes also offers good opportunity for the non-invasive delivery of small, medium, and large sized drug molecules.^{61, 62}

Application of Ethosomes

Ethosomes can be used for many purposes in drug delivery. Ethosomes are mainly used as replacement of liposomes. Various applications of ethosomes as a carrier of wide range of drugs are discussed below:

Delivery of HIV drugs

Conventional topical cream containing 5% acyclovir (Zovirax cream) an antiviral drug for treatment of herpes labials show low therapeutic efficiency due to poor permeation through skin as replication of virus take places at the basal dermis. In comparison with conventional Zovirax, ethosomal formulation of acyclovir show high therapeutic efficiency with shorter healing time in the treatment of recurrent herpes labialis.⁶³ Jain et al (2007) prepared ethosomal formulations of lamivudine as model drug. They found that optimized ethosomal formulation showed 25 times higher transdermal flux ($68.4 \pm 3.5 \mu\text{g}/\text{cm}^2/\text{h}$) across the rat skin as compared with that of lamivudine solution ($2.8 \pm 0.2 \mu\text{g}/\text{cm}^2/\text{h}$). The results of the characterization studies indicate that lipid perturbation along with elasticity of

ethosomes vesicles seems to be the main contributor for improved skin permeation.⁶⁴ Ethosomes of stavudine have been prepared and incorporated into HPMC gel. The optimized ethosomal formulation showed 8 times greater transdermal flux across rat skin as compared to plane drug solution. Ethosomes containing zidovudine were prepared by Jain et al., (2004) for the transdermal delivery of the model drug as orally administered zidovudine has strong side effects. The optimized ethosomal formulation showed high transdermal flux across the rat skin as compared to control hydroethanolic solution of drug and ethanolic drug solution. From these reported studies it revealed that ethosomes can increase the transdermal flux, prolong the release and present an attractive route for the sustained delivery of zidovudine.^{65, 66}

Delivery of NSAID drugs

Ethosomes containing Diclofenac potassium were formulated and incorporated in carbopol gel base and its anti-inflammatory efficiency was compared with the marketed diclofenac gel. The ethosomal vesicles were incorporated in carbopol gel base showed higher cumulative percentage of drug permeation and more skin retention as compared to liposomal formulation, hydroethanolic drug solution and phosphate buffer saline (pH7.4) drug solution. The ethosomal vesicles were compared with marketed diclofenac gel for its anti-inflammatory activity and results showed the enhanced anti-inflammatory activity of ethosomal gel than marketed gel formulation.⁶⁷ Garg et al. (2010) were formulated aceclofenac containing ethosomes and converted to ethosomal gel using different concentrations of carbopol, and evaluated for in vitro and in vivo. Efficiency of aceclofenac ethosomal gel was found to be significantly higher than plain aceclofenac gel and marketed aceclofenac gel (Hifenac).⁶⁸ Ketoprofen loaded ethosomal formulation were prepared and evaluated. Results of the in vitro release study through the skin revealed higher transdermal flux with ethosomal formulation compared to hydroalcoholic drug solution and it is concluded from the results that ethosomal formulation is a potentially useful vehicle for transdermal delivery of ketoprofen.⁶⁹ Ibuprofen loaded ethosomal gel was formulated and evaluated by Shumilov et al, (2010). The drug, applied transdermally from the ethosomal gel was present in plasma for a longer period of time as compared to the oral administration and showed a high relative bioavailability. The ibuprofen ethosomal gel had an efficient antipyretic effect in fevered rats.⁷⁰

Delivery of Anti-Fungal drugs

Ethosomes and ultradeformable liposomes of clotrimazole were compared for the transdermal potential. Ethosomal formulation provided enhanced transdermal flux and greater penetration as compared to ultradeformable liposomes. Formulation also had the highest zone of inhibition in contrast to ultradeformable liposomes formulation.⁷¹ Fluconazole encapsulated

ethosomes was formulated and incorporated in suitable dermatological base and compared with liposomal gel and hyperethanolic solution of drug. The results revealed that drug diffuses from the ethosomes was twice than liposomal and nearly thrice than hyperethanolic solution of drug.⁶² Transethosome, for enhanced skin delivery of voriconazole, was formulated and compared with ethosomes, deformable liposomes and conventional liposomes. Transethosome dramatically enhanced the skin permeation of voriconazole compared to the control and other vesicles. Moreover, the transethosome enhanced both in vitro and in vivo skin deposition of voriconazole in the dermis/epidermis region compared to ethosomes, deformable liposomes and control.⁷²

Delivery of Other drugs

Pilosebaceous units have been used for localized therapy, particularly for the treatment of follicle related disorders such as acne or alopecia. Ethosomal formulation of minoxidil, a lipid soluble drug used for baldness, accumulates into nude mice skin. The ethosomal system dramatically enhanced the skin permeation of minoxidil in vitro compared with either ethanolic or hydroethanolic solution or phospholipid ethanolic micellar solution of minoxidil, and can be used for pilosebaceous targeting for better clinical efficacy.⁵⁸ Melatonin, an anti-jet lag agent associated with poor skin permeation and long lag time was loaded in ethosomes and evaluated. The study revealed that melatonin loaded ethosomes provided an enhanced transdermal flux, lower lag time, higher entrapment efficiency and low skin irritancy potential, thus leading to the generic conclusion that this approach offers a suitable approach for transdermal delivery of melatonin.⁷³ Paclitaxel-loaded ethosomes were prepared as topical drug delivery systems. The results showed that improve permeation of paclitaxel in a stratum corneum-epidermis membrane model and increased its anti-proliferative activity in a squamous cell carcinoma model as compared to the free drug, thus it can be used as a potential treatment of squamous cell carcinoma, a malignant transformation of actinic keratoses.⁷⁴ Tacrolimus is an immunosuppressant treating atopic dermatitis, was loaded in ethosomes to investigate inhibitory action upon allergic reactions of mice aiming at improving pharmacological effect for tacrolimus. The results indicated that the ethosomes showed lower vesicle size and higher encapsulation efficiency and more effective retention in the epidermis.⁷⁵ Methotrexate (MTX) was encapsulated in ethosomes. MTX is an anti-psoriatic, anti-neoplastic, highly hydrosoluble agent which have limited transdermal permeation. MTX loaded ethosomal carriers provided an enhanced transdermal flux and decreased lag time across human cadaver skin. The formulation retained its penetration power after storage and the vesicle interaction study also highlighted the penetration enhancing effect of ethosomes, with some visual penetration pathways and corneocyte swelling.⁷⁶ Gold Nanoparticle was loaded in ethosomes, high entrapment efficiency was achieved and the results

showed enhancement of pharmacological efficacy in transdermal and dermal delivery systems.⁷⁷

CONCLUSION

It can be concluded from the review of research works carried out in the field of vesicular carriers that they prove to be very promising novel drug delivery units with respect to biocompatibility, reduced toxicity and enhanced controlled release quality that would be essential to address issues pertaining to compromised therapeutic efficacy of the bio-actives especially through topical route of administration. Diversity of vesicular based topical and transdermal technology renders variety of critical properties that can be exploited by the formulator on the basis of the challenges imposed by the active moiety via this route. Vesicular formulations shows better therapeutic results as compared to conventional formulations and it has been expected that in upcoming years more vesicular formulations would find their place in therapeutic world.

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Source of Support: Nil, Conflict of Interest: None.