REVIEW ARTICLE

Vesicles as a Tool for Enhanced Topical Drug Delivery

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Abstract

Designing of a drug in the vesicular system has brought a new life to the old pre-existing drug and thus has improved its therapeutic efficacy by controlling and sustaining the actions. As skin is one of the crucial and important organs of the human body, delivering the drug across it requires an effective development in the field of research. Topical drug delivery system is specifically designed with the objective to accomplish the delivery of therapeutically active drugs across the skin. Vesicular carriers are one of the recently invented carriers. Liposomes, niosomes, transfersomes, and ethosomes constitute the major part of these vesicles that have been sufficiently employed for the treatment of variety of topical skin diseases. In the past few years, various research reports on the development of topical carrier systems showed that these carriers have emerged as a novel vesicular carrier. The present review focuses on the topical delivery via these vesicles, emphasizing on various aspects of all these carriers.

Key words: Drug, permeation, skin, topical, vesicles

INTRODUCTION

Novel drug delivery systems are designed with an intend to deliver drugs to the specific site at a rate and extent directed by the needs of the body and it directs an active entity to specific site of action during the period of treatment,[1] whereas a drug delivery system is considered to be the one which delivers the drug to the targeted site for a specific period of time.[2] The main rationale behind the development of novel delivery systems is either to sustain the drug release or to maintain the effective drug concentration with reduced adverse effects.[3] A variety of carrier systems has been developed for drug delivery by means of miscellaneous routes so as to achieve controlled and targeted drug delivery.[4] Numerous techniques implicated in drug delivery are the patented technologies that affect drug release profile, pharmacokinetics for the purpose of improving product's safety and efficacy. Thereby, this approach culminated in improved patient compliance.[5] In the process of drug transport across the skin, the skin acts as a portal of entry for drugs to achieve localize and systemic effects in dermal and transdermal delivery.[6] The topical site of drug application is considered to be one of the most relevant routes for treating skin diseases efficaciously. Thereby, a wide variety of drugs have been applied topically to the skin to treat various fungal infections.[7] When compared with conventional formulation (creams and ointments), novel dermal systems possess different structure and compositions exteriorly as well as interiorly, and it has been developed as possible carriers to deliver antifungal drugs to the target site and to enhance an epidermal permeation across the skin.[8] To improve drug delivery via topical route, lots of approaches have been made in inventing lipid based vesicular carriers.[9] A number of vesicular drug delivery systems such as liposomes, niosomes, transfersomes, and ethosomes have been emerged and choice of selection among these systems depends on the pharmaceutical and dermatological factors.[8] Entrapment of drug in a vesicle is considered to be an efficient transporter system with prolonged systemic circulation and reduced toxicity.[4] These vesicles are also gaining prominent importance as a carrier in exhibiting immune response and can also be used for topical immunization.[8] Different reports

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Received: 18-05-2016
Revised: 05-07-2016
Accepted: 13-07-2016

have revealed a promising future of these vesicles in making topical delivery of various drugs more effective and will provide better *in vivo* drug release.[10]

TOPICAL DRUG DELIVERY SYSTEM

Topical delivery system represents a system that is meant to be applied to the skin. These preparations on application exert physical effect on skin, i.e., they act as skin protectant, lubricant, emollient, drying agent, etc.[11] It is a localized drug delivery system acting through the ophthalmic, rectal, vaginal, and skin as topical routes.[12]

Advantages of topical systems

Topical systems have the following advantages associated with its usage. These include improved patient compliance as these systems are easy to apply and remove.[13] It avoids risk and inconvenience associated with intravenous therapy and eliminates the variables, which influence gastrointestinal absorption such as food intake, stomach emptying, intestinal motility, and transit time. A topical system exhibits sustained and controlled level of drug in plasma and thus reduces the chance of over or under dosing. Thereby, also reducing frequency of drug administered.[14] Topical systems are easily retractable, thereby the drug therapy can be terminated, if toxic effects are observed cells.[15,16]

Limitation of topical systems

In spite of possessing numerous advantages as a drug delivery system, it has the following disadvantages, i.e., this route is not suitable for such type of drugs that irritate or sensitize the skin. Topical drug delivery systems are relatively expensive as compared to conventional dosage forms.[11]

SKIN AS A BARRIER TO THE PERMEATION

Skin is one of the most extensive and readily accessible organs of the human body, exhibiting an extremely good barrier to the penetration of drugs.[17] It is considered to be a prominent organ for the drug application for topical delivery.[18] From several decades, it has been studied as an effective route of administration of various drugs and till now numerous drug delivery technologies have been developed to facilitate the delivery of drugs across the skin.[19] It is the largest organ of the body, covering every part of the body. Its characteristics include elasticity, ruggedness, and self-regenerating and have a thickness of 2.97 ± 0.28 mm.[17] It covers a total surface area of about 1.8 m and serves as a medium of contact between human body and an existing environment.[20] It is mainly acting as a protective layer providing protection against heat, light, injury and infection, inspite of performing a protective action; it also regulates the temperature of the body, prevents loss of water, and also inhibits the bacterial entry. It is considered as a site of drug application for both local and systemic effects,[18] acting as an optimum interface for systemic drug delivery.[21] The human skin consists of mainly three layers, i.e. epidermis, dermis, subcutaneous fat layer.[7] Stratum corneum, the uppermost layer signifies the barrier nature of the skin[22] and thus limiting both topical and transdermal bioavailability.[18]

APPROACHES FOR OPTIMIZING SKIN PENETRATION

To optimize the penetration of diverse nature of drug molecules via skin for both topical and transdermal delivery, different methods such as vehicle-drug interactions, use of vesicular carriers, nanoparticles, modification of stratum corneum, bypassing or removal of stratum corneum (including tape stripping, stratum corneum ablation, microscissioning, micro needle array), and energy-driven methods have been used.[23] Various attempts have also been made to undergo cutaneous resurfacing, as after the age of 28 years, skin shows the sign of aging such as reduced elastic capacity, decreased collagen production, lesser number of dermal elastic fibers, and decrease production of sebum.[24,25] Cutaneous resurfacing or skin resurfacing is a process that causes controlled injury to the skin, thus stimulating the wound healing. It may be accomplished by the methods such as chemical peeling, use of topical preparations, microderma abrasion, radiofrequency coblation, and thermal resurfacing.[26]

Nowadays, topical delivery has gaining renowned importance, and scientists are working with keen interest in developing this system.[27] Treatment of skin cancer has also become possible by the radiation therapy, which uses high energy rays such as X-rays or particle mainly photons, electrons, or protons to kill the cancer cells. The beam of electrons penetrates the skin to treat cancer cells.[28]

VESICLES AS SKIN DELIVERY SYSTEM

General

Many skin diseases are found to be deeply located indermal layers of the skin such as acne, alopecia, and psoriasis.[29] Conventional dosage forms are seemed unable to be effective in treating these conditions because of poor retention in the skin. Therefore, there has been a need to explore a new system for the management of such topical diseases.[30] Asa currently flourished novel carrier system, the use of vesicles, i.e. lipid-based vesicular carriers have gained increased consideration in the new era of treating deep seated fungal infections.[31] For topical delivery, vesicular approach is one

of the most illustrious methods of delivery. Drug delivered via encapsulating in the vesicle being prepared by using phospholipids and non-ionic surfactants is known to transport the drug into and across the skin.[32] Vesicles are considered as water-filled colloidal particles. The walls of these vesicles consist of amphiphilic molecules in a bilayer conformation. In the presence of large amount of water, these vesicles can form unilamellar or multilamellar concentric bilayer vesicles.[33] These vesicular carriers minimize the cost of therapy by improving the bioavailability of medication specifically in case of poorly soluble drugs.[34] Hydrophilic drugs can be enclosed within an internal aqueous region, while lipophilic drugs are enclosed within the vesicular bilayer[35] [Figure 1].

These vesicles can act either as carrier system or as penetration enhancer. If vesicles act as carrier system, they might be able to transport large molecular weight drugs, such as proteins into the skin or even into systemic circulation. If they act as penetration enhancers, however, the main mode of action is perturbation of lipid organization in the stratum corneum, thereby increasing the transport rate across the skin.

The latter is only efficient for low molecular weight drugs. One of the most important characteristics of drug carrier system is that the drug and carrier should permeate along the same route across the skin.[33] Many cosmetics have also been reported to be delivered via enclosing them in vesicles such as humectants, sun screening, and tanning agents.[18]

A number of vesicular drug delivery systems such as liposomes, niosomes, transfersomes, and pharmacosomes were developed as an alternative for improved skin drug delivery [Figure 2]. The biological origin of these vesicles was first reported in 1965 by "Bangham." Vesicles act as drug carrier in controlled drug release.[9] In past, topical delivery via liposomes has gained notable interest. Deformable liposomes and transfersomes were the first generation elastic vesicles i ntroduced by Ceve and Blume in 1992 and were reported to penetrate the skin under non-occluded conditions.[36] Vesicles containing penetration enhancers have also been reported nowadays. Whereas niosomes are the type of vesicles prepared with non-ionic surfactants that have been came into existence for drug delivery into or across the skin. Various drugs have been reported in the literature that has been delivered via these carriers [Table 1].

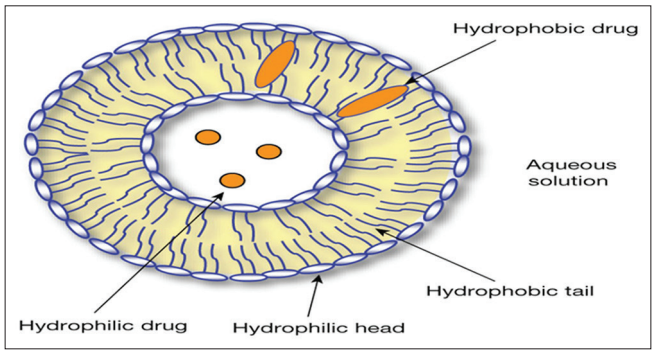

Figure 1: Diagrammatic view of a vesicle

LIPOSOMES

Liposomes were first discovered by "Bangham" *et al*.[57] and were widely investigated since 1970 as drug vesicular carrier for improving the delivery of variety of therapeutic agents to the specific sites in the body.[58] These are microscopic vesicles comprising phospholipid bilayer, which when comes in contact of water, gets hydrated and results in the formation of liposomes.[57,59] It contains one or more concentric lipid bilayer enclosing aqueous compartment within its inner region.[60]

These lipid vesicles are composed of mainly phospholipids with or without using additives. Cholesterol is also included in the preparation to modify the bilayer properties, stabilizing vesicular membrane, and increasing the rigidity of the vesicles.[61]

It can efficiently encapsulate both hydrophilic and lipophilic drugs. They are available in various sizes varying from 20 nm to 1 μm. Liposomes are observed to carry the drug in different compartments such as water soluble drugs enclosed in the central aqueous core, lipid soluble drugs in lipid phase and peptide and small proteins at aqueous-lipid interface.[57] In the novel span of liposomal research, charged liposomes have also been developed for topical delivery to further modify the penetration of these vesicles across the skin.[62]

Advantages of liposomes

Advantages of liposome as a vesicular carrier are numerous. These are as follows; liposomes are biocompatible, completely biodegradable, non-toxic, and flexible vesicles. These carriers enhance the therapeutic index of drug and its therapeutic efficacy. Liposomes have an ability to protect the encapsulated drug from external environment, exhibits sustained release of drugs.

It can be formulated as a dosage form in the form of suspension, as an aerosol, or in a semisolid form such as gel, cream, and lotion, can be administered through ocular, pulmonary, nasal, oral, intramuscular, subcutaneous, topical, and intravenous routes. Suitable for delivery of hydrophobic and hydrophilic drugs with reduced toxicity and increased stability of entrapped drug.[57]

Limitation of liposomes

The various disadvantages associated with liposomes are its high production cost, leakage, and fusion of encapsulated drug/molecules. The phospholipids present may undergo oxidation or hydrolysis, thus affecting stability of liposomes.[63] The

Table 1: Topical delivery of variety of drugs via different novel vesicular carriers

Drug	Therapeutic category	Vesicular carrier	Inference	References
Fluconazole	Antifungal	Ethosomes	Provides better remission from disease	[1]
Diclofenac	Non-steroidal anti-inflammatory	Transfersomes	Improved penetration directly into the depth of soft tissues	[3]
Ibuprofen	Non-steroidal anti-inflammatory	Transfersomes	Enhanced penetration	[3]
Econazole nitrate	Antifungal	Ethosomes	Improved therapeutic efficacy	[37]
Miconazole nitrate	Antifungal	Liposome	Localized drug delivery and improved bioavailability	[38]
Tamoxifen	Anti-estrogen	Liposomes	Enhanced permeation and retention in the skin	[39]
Acyclovir	Anti-viral	Ethosomes	Increased antiviral activity	[40]
Benzocaine	Local Anaesthetic	Liposomes	Longer duration of action with slow release of drug	[41]
Doxorubicin	Anti-tumour	Niosome	Decreases rate of sarcoma proliferation	[42]
Methotrexate	Anti-neoplastic	Niosomes	Sustained drug release	[42]
Triamcinolone	Anti-inflammatory	Liposome	Five-times higher epidermal concentration	[43]
Linoleic Acid	Anti-hyperpgmentation agent	Transfersome	Effective in the treatment of melasma	[44]
Lidocaine	Local anesthetic	Niosomes	Higher flux as compared to liposomes	[45]
Rofecoxib	Non-steroidal anti-inflammatory drug	Niosomes	Prolonged drug release with higher retention	[46]
Paromomycin	Antibiotic	liposomes	Controlled drug delivery with enhanced permeation	[47]
Itraconazole	Anti-mycotic	Niosomes	Effective anti-mycotic activity	[48]
Buflomedil Hydrochloride	Anti-wound	Liposomes	Enhanced wound healing	[49]
Minoxidil	Hair-growth stimulant	Niosomes	Effective in hair loss treatment	[50]
Cypoterone Acetate	Anti-androgen	liposomes	Better penetration than conventional dosage form	[51]
Benzocaine	Local Anaesthetic	Ethosome	Enhanced clinical effectiveness in topical anesthesia	[52]
Clotrimazole	Antifungal	Ethosomes	Uniform deeper penetration across the skin	[53]
Minoxidil	Anti-hypertensive	liposomes	Potential innovative carrier for improved delivery	[54]
Temoporfin	Photo sensitizer	Invasomes	Effective drug carrier system deep into the stratum corneum	[55]
Tacrolimus	Anti-inflammatory	Transfersome	Improved Skin Permeation	[56]

major disadvantage that liposome possesses is that they have little or no value as a carrier, as these carriers do not deeply penetrate into the skin and remain confined to the upper layers of the stratum corneum, ineffective for efficient topical delivery.[20] This characteristic of liposomes makes their application very limited across the globe. However, various modifications have been made in them to improve the delivery via these vesicles, by the use of non-ionic surfactant or ethanol as permeation enhancer etc.

Mechanism of penetration

Liposomes act by penetrating the epidermal layers releasing drug into the skin [Figure 3]. They lose their bilayer membrane

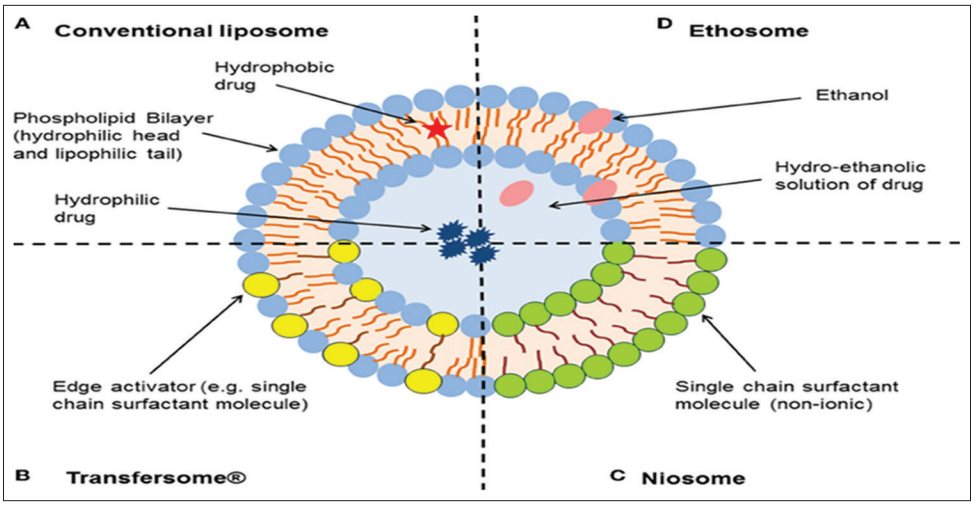

Figure 2: Difference in different vesicular system

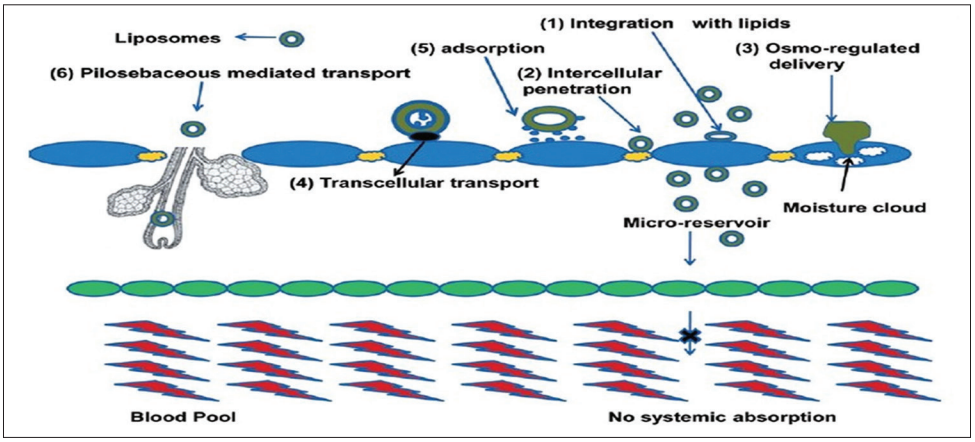

Figure 3: Mechanism of drug penetration through liposome

during the penetration and thus, these lipids penetrate into the stratum corneum by adhering to the skin surface and finally fusing with the lipid matrix and releasing the drug enclosed in it.[61] However, it has been reported recently that the drug undergoes permeation across the skin after releasing from the vesicles. On the application of vesicles, transformation in the ultra-structures of the intercellular lipids was observed which demonstrates the penetration enhancing effect. Upon fusing with the stratum corneum, these vesicles may adsorb onto the surface of the stratum corneum, transferring drug directly from vesicles to the skin or vesicles may undergo fusion and get mix with the stratum corneum lipid matrix, enhancing the drug partitioning into the skin. The interaction of liposomes with human skin has been evaluated by various researchers and it was concluded that they can be taken into the skin but cannot be easily penetrated through intact healthy stratum corneum. Thus, it was reported that traditional liposomal vesicles cannot penetrate the human skin effectively.[20]

Method of preparation of liposomes

Liposomes are prepared by various methods. These are described as follows.

Lipid hydration method (hand shake vesicles)

Drug is dissolved in a solution of lipid and is then dried to get a thin film at the bottom of round bottom flask. This film is hydrated by using an aqueous buffer and subjected to vortex shaker for homogeneous mixing for some time, at the temperature above gel-liquid crystalline transition temperature.[57]

Ether injection method

A solution of phospholipid in diethyl ether or in a mixture of ether/methanol is injected slowly in an aqueous solution of drug at 55-65°C or under reduced pressure. The removal of solvent under vacuum resulted in the formation of liposomes.[57]

Lyophilization method

By this method, liposomes are formed by removing water from the product in the frozen state at extremely low pressure. The process is generally used to dry thermolabile products and also for the products that can be destroyed by heat drying.[64]

Applications

The application of liposome on skin surface proved to be effective in topical delivery of variety of drugs. Liposome enhances the skin permeation and reduces the side effect associated with the use of drug as low dose of drug is required.[57] They are widely used in delivering drugs as well as antigens. They are also used for site-specific drug delivery.[65] As a topical carrier for topical drug delivery, it exhibits various applications such as in providing effective skin targeting, as it enhances the penetration of drugs across the stratum corneum and deposited in epidermal as well as dermal layers.

The approach for drug targeting via liposomes involves the use of ligands (e.g., antibodies, sugar residues, apoproteins, or hormones), which are tagged on the lipid vesicles. The ligand recognizes specific receptor sites and, thus, causes the lipid vesicles to concentrate at such target sites. By this approach the otherwise preferential distribution of liposomes into the reticuloendeothelial system RES (liver, spleen, and bone marrow) is averted or minimized.[29]

NIOSOMES

Niosomes are the vesicles devised by using non-ionic surfactants.[66] It consists of hydrophilic tails of monomers of surfactant shielded away from the central aqueous core and hydrophilic head zone. Addition of cholesterol in the formation of niosomes provided the rigidity to the bilayer and thus results in limited drug leakage from them.[34] These vesicles are generally referred to as second generation vesicles possessing improved chemical stability, better entrapment efficiency, enhanced penetration as well as lower production cost as compared to liposomes.[67] These have been evaluated as vesicular carriers for variety of drugs and cosmetics topically. Niosomes are found to be effective in the treatment of various dermatological disorders. These vesicles are found to be efficient in topical drug delivery as it can enhance residence time of drugs in the stratum corneum as well as epidermis, and on the other hand, also reduce the system absorption of drug.[66] Niosomes have been reported to serve as drug depot in the body releasing drug in a controlled manner. Targeted drug delivery can also be achieved by using niosomes as drug is directly delivered to the specific site where therapeutic effect is desired.[68]

It consists of cholesterol to provide rigidity to the vesicles and proper shape.[69] They are prepared by using non-ionic surfactants such as polyglycerol alkyl ethers, gluosyl dialkyl ethers, polyoxyethylene alkyl ether, brij, span series, and Tween series.[34]

Advantages of niosomes

As a carrier system, niosomes have several advantages such as these are chemically more stable as compared to conventional liposomal carriers. These vesicles have low production and various classes of surfactants are available for their development. They are potentially capable for both controlled and targeted drug delivery, possess high patient compliance, osmotically active, and stable. Handling and storage of surfactants is easy. Niosomes showed improved oral bioavailability as well as enhanced skin penetration and improved therapeutic performance of the drug.[66]

Limitation of niosomes

Niosomal aqueous suspensions owe limited shelf life due to fusion, aggregation, leaking of entrapped drugs, and hydrolysis of encapsulated drugs. The techniques involved in the niosomal formulation such as extrusion, sonication are time consuming and requires specialized 5 equipment for processing.[66,68]

Mechanism of penetration

Several mechanisms of permeation have been proposed to understand the effectiveness of niosomes for topical drug delivery. The permeation via niosomes occurs via diffusion from the stratum corneum layer of skin as a whole. The water content present in the skin is one of the crucial factors for interpreting [Figure 4].

The diameter of lipid lamellar spaces of the stratum corneum is smaller than the noisomal vesicles which makes this pathway more beneficial.[70] Niosomes are also reported to exert their action by interacting with the stratum corneum with aggregation, fusion, and adhesion to the cell surface result in high thermodynamic activity gradient of the drug at the vesicle-stratum corneum surface, which is the driving force for the penetration of lipophilic drugs across the stratum corneum.[71] They also modify the structure of stratum corneum, which loosen an intercellular lipid barrier of the stratum corneum making them more permeable.[72] The presence of non-ionic surfactant in niosomes, acts like a permeation enhancer and improves drug permeation from niosomes.[73]

Method of preparation

Niosomes are now broadly employed as an alternative to liposomes and are observed to be similar to liposomes in terms of their physical properties, also being prepared in the same way as that of liposomes.[72]

Applications

Niosomes have widespread utility as a vesicular carrier not only in topical delivery, but also in transdermal as well as in ocular drug delivery. These are also used for drug targeting,

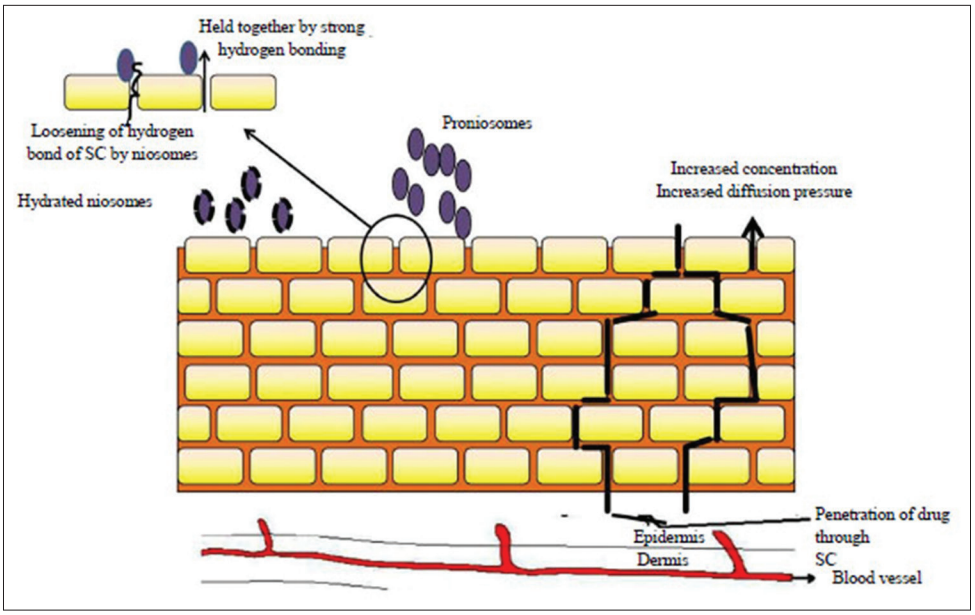

Figure 4: Mechanism of drug penetration through niosomes

in the treatment of various topical diseases as a novel drug delivery system. Niosomes containing anti-cancer drugs, like methotrexate and doxorubicin can efficiently enhances drug delivery to the tumor cells. Apart of this, multiple dosing with sodium stibogluconate-loaded niosomes was found to be effective against parasites in liver, spleen, and bone marrow as compared to simple solution of sodium stibogluconate.[69,74]

TRANSFERSOMES

Transfersomes are an outcome of the past 15 years of experimentation in the world of developing highly deformable form of liposomes.[75] These are an ultra-deformable lipid aggregates,[34] composed of lipids and biocompatible membrane softeners.[75] Theses vesicles are capable of penetrating the skin and have an inner aqueous region surrounded by a lipid bilayer containing edge activators such as sodium cholate, sodium deoxycholate, span 80, and Tween 80.[34] Wide range of phospholipids that can be used in formulating transfersomes includes soya phosphatidylcholine, dipalmitoyl phosphatidylcholine, and surfactants (Tween 80, span 80, etc.).

Alcohol is used as a solvent and buffering agent such as saline phosphate buffer can also be used as a hydrating medium.[76] These are quiet similar to liposomes in various aspects, but differ by the fact that they are more deformable and have better membrane integrity. Transfersomes are effective enough for the transport of large molecular drugs.[75] Characterization of vesicular system is important for desired results, there are different methods for the characterization of transfersomes and others [Table 2].

Advantages of transfersomes

The benefits of transfersomes are as follows; the presence of highly flexible membrane permits transfersomes to squeeze through the pores smaller than their own diameter. They can accommodate drug molecule with wide range of solubility and high deformability nature of these carriers result in better penetration. It can act as a porter for both low and high molecular weight drugs, also have higher percent entrapment efficiency.

Limitation of transfersomes

Like liposomes, transfersomes also have several restrictions associated with its use such as these are chemically unstable as drug delivery vehicle; lack of purity of the natural phospholipids affect their role. Transfersomal formulations are expensive to prepare as compared to other vesicular preparations.

Mechanism of penetration

Transfersomes act by penetrating the stratum corneum by either intracellular or transcellular route producing an "osmotic gradient." These vesicles migrate into the hydrated deeper layers as they can easily squeeze through pores of stratum corneum due to its elastic nature [Figure 5].[75]

However, it has been reported that these vesicles mainly follow two major mechanisms; first by acting as a drug carrier, they can directly enter the stratum corneum carrying vesicle - bound drug molecules into the skin. Second, these can work as penetration enhancers, where vesicular bilayers enter the stratum corneum and subsequently modify the

Table 2: Characterization of vesicular system[90-96]

Biological characterization	
Characterization parameters	Instrument for analysis
Sterility	Aerobic/anaerobic culture
Pyrogenicity	Rabbit fever response
Animal toxicity	Monitoring survival rats
Physical characterization	
Characterization parameters	Instrument for analysis
Vesicle shape and surface morphology	TEM and SEM
Vesicle size and Size distribution	Dynamic light scattering TEM
Surface Charge	Free flow electrophoresis
Electrical surface potential and surface	pH zeta potential measurement and pH sensitive probes
Entrapment	Dialysis bag/centrifugation method
Lamellarity	P-NMR
Phase behavior	DSC, freeze fracture electron microscopy
Percent capture	Mini column centrifugation
Drug release	Diffusion cell/dialysis
Chemical characterization	
Characterization parameters	Instrument for analysis
Phospholipids concentration	HPLC/Barrlet assay
Cholesterol concentration	HPLC/cholesterol oxide assay
Phospholipids per-oxidation	UV observation
pH	pH meter
Osmolarity	Osmometer

TEM: Transmission electron microscopy, SEM: Scanning electron microscopy, DSC: Differential scanning calorimetry, HPLC: High performance liquid chromatography, UV: Ultraviolet

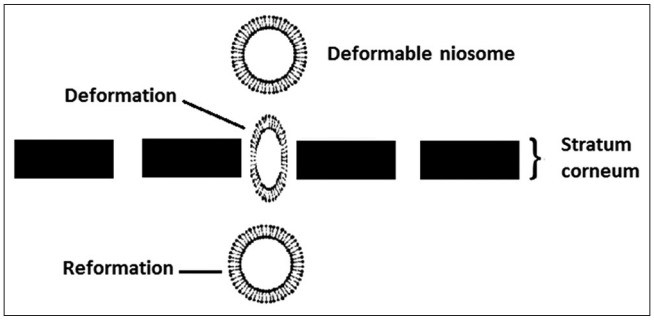

Figure 5: Mechanism of penetration through transfersome

intercellular lipid lamellae. This will facilitate the penetration of free drug molecules into and across the stratum corneum.[20]

Method of preparation

A thin film is prepared by hydration and then brought to the desired size by sonication. These sonicated vesicles are then homogenized by extrusion using a polycarbonate membrane. The mixture of phospholipids and surfactant is dissolved in volatile organic solvent (chloroform-methanol). The organic solvent is evaporated above the lipid transition temperature using rotary evaporator. Final traces of solvent are removed under vacuum for overnight. The deposited lipid films are then hydrated with buffer (pH 6.5) by rotation at 60 rpm at the corresponding temperature. The resulting vesicles are swollen for 2 h at room temperature.[76]

APPLICATION

Transfersomes as a vesicle exemplify various applications both in topical as well as transdermal drug delivery. These vesicles are reported to be used in the transport of tremendous very small molecular drugs which have difficulty in diffusing across the stratum corneum barrier. They can be used to target peripheral subcutaneous tissues.[75,77]

ETHOSOMES

Ethosomes are the ethanolic phospholipid vesicular carriers[76] developed by Touitou *et al*.[36] These are mainly designed to overcome the limitation being possessed by the liposomes. It was observed that liposomes remain restricted to the upper layers of the skin. Incorporation of high alcohol content in liposomes is found to be capable of enhancing penetration

to deep tissues and the systemic circulation. Ethosomes are the soft, malleable vesicles tailored for enhanced delivery of active agents, composed mainly of phospholipids, high concentration of ethanol and water. The size range of ethosomes may vary from tens of nanometers to microns.[78] It has been reported that physicochemical properties of these carriers allow them to transport drug more effectively into the deeper layers of the skin.[79] The presence of high concentration of ethanol makes ethosomes an innovative and a novel carrier for topical drug delivery. Ethanol present in ethosomes acts by causing disturbance of skin lipid bilayer organization, hence when incorporated into a vesicle membrane, it enhances the vesicle's ability to penetrate the stratum corneum. Moreover, because of their high ethanol concentration, lipid membrane is packedless tightly than conventional vesicles but has equivalent stability, allowing more malleable structure and improves drug distribution ability in stratum corneum lipid.[78]

Topically applied ethanol acts as skin penetration enhancer and may increase topical delivery.[80] Typically, ethosomes may contain phospholipids with various chemical structures such as phosphatidylcholine (PC), hydrogenated PC, alcohol (ethanol or isopropyl alcohol), water, and propylene glycol (or other glycols).[81]

These vesicles are evaluated for various parameters such vesicular characterization such as vesicle shape can be visualized by scanning electron microscopy (SEM) or transmission electron microscopy (TEM), vesicle size, zeta potential, and polydispersity index is measured by using Zeta meter. Entrapment efficiency can be determined by using ultracentrifugation technique and *in vitro* permeation study by using Franz diffusion cell where as *in vivo* permeation may be observed through confocal laser scanning microscopic study.[36]

Advantages of ethosomes

There are numerous advantages of ethosomes as a novel lipid carrier over other vesicular carriers such as enhanced permeation of drug through the skin for dermal and transdermal drug delivery. Delivery of large molecules (peptides, protein molecules) is possible. These vesicles contain nontoxicraw materials in formulation. High patient compliance in ethosomes drug is administered in semisolid form (gel or cream); hence producing high patient compliance. Ethosomal system is passive, non-invasive, and it is available for immediate commercialization and can be applied widely in pharmaceutical, veterinary, and cosmetic fields.[78]

Limitation of ethosomes

Drugs that require high blood levels cannot be administered - limited only to potent molecules, those requiring a daily dose of 10 mg or less. Ethosomal administration is not a means to achieve rapid bolus type drug input, rather it is usually designed to offer slow, sustained drug delivery. Adequate solubility of the drug in both lipophilic and aqueous environments to reach dermal microcirculation and gain access to the systemic circulation.[75,78]

Mechanism of drug penetration

The formulations developed by using ethosomes as a carrier contain ethanol as one of its important content which have the property to interact with the lipid molecules, resulting in increasing the stratum corneum fluidity and thereby enhances the inter- and intra-cellular permeability of the ethosomes. Ethanol not only imparts fluidity, but also provides flexibility to the ethosomal membrane that enhances the skin permeation across the skin [Figure 6].[81]

The penetration of drug delivered via ethosomal carrier across the stratum corneum is reported to be due to two predominant effects, i.e., ethanol effect and ethosomes effect. These two effects dictate the mechanism of drug penetration.

Ethanol effect

Ethanol present in ethosomes acts as a penetration enhancer through the skin. It exerts its action by penetrating into the intercellular lipids and increasing the fluidity of lipids present in cell membrane and decreases the density of lipid multilayer of cell membrane.

The fluidizing effect exerted by ethanol result in disturbance of the skin lipid bilayer organization and this in turn leads to the penetration of soft vesicles through the disorganized stratum corneum lipid bilayer more easily.

Ethosome effect

Increased cell membrane lipid fluidity caused by the ethanolic content of ethosomes result in increasing skin permeability. Hence, ethosomes can permeate very easily inside the deep skin layers, where it undergoes fusion with skin lipids and releases the drug into the layers of the skin.[78]

Method of preparation of ethosome

Various methods involve in preparing the ethosomes are as follows.

Hot method

Drug is dissolved in ethanol and propylene glycol mixture and is then added to the phospholipid dispersion of water at 40°C on magnetic stirrer and mixing for 5 min. The preparation is sonicated at 4°C for 3 cycles of 5 min each with rest of 5 min between each cycle using probe sonicator. The formulation

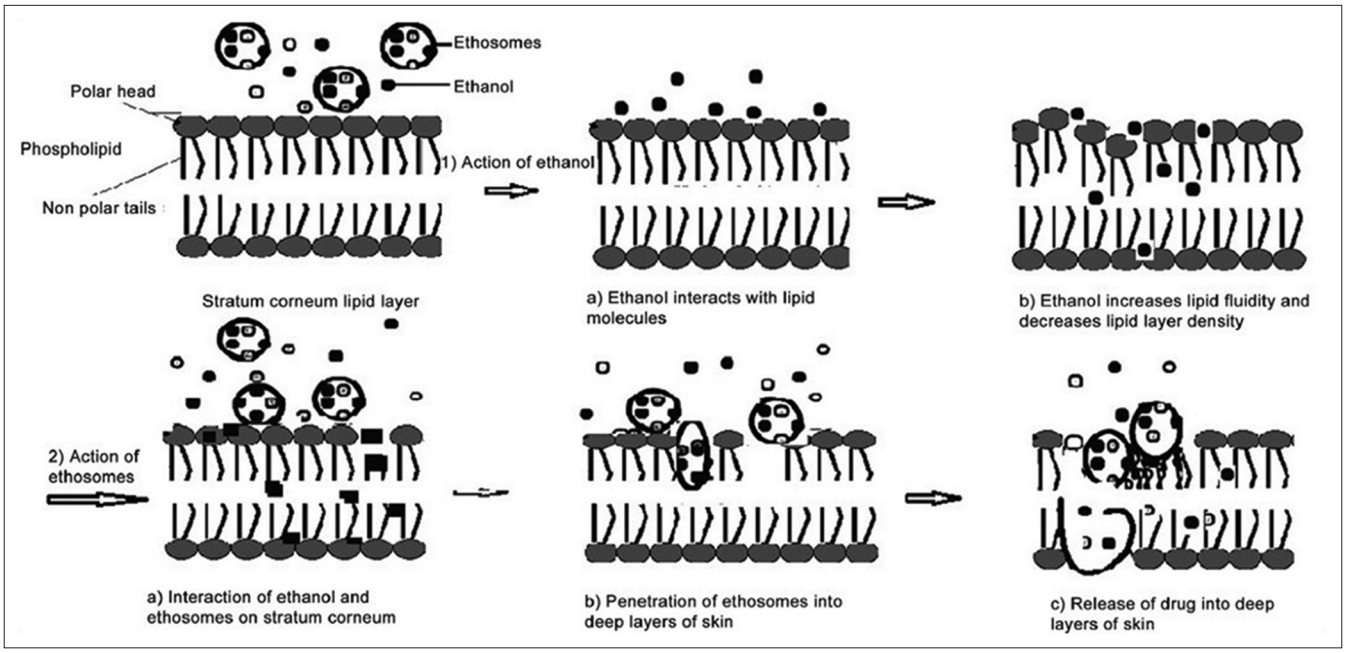

Figure 6: Mechanism of penetration through ethosome

was homogenized at 15,000 psi pressure in 3 cycles using high pressure homogenizer to get nano-sized ethosomes.[1]

Cold method

Phospholipid and drug are dissolved in a solution of ethanol and propylene glycol. The mixture is heated to 30°C ± 1°C in a water bath. Double distilled water is heated to 30°C ± 1°C, and added slowly as a fine stream to lipid mixture at constant stirring at 700 rpm in a closed vessel. The mixing is continued for additional 5 min, while maintaining the system at 30°C ± 1°C. The solution of ethosomes is left to cool at room temperature. Preparation is then homogenized by using vertex shaker for 15 min.[36,40]

Thin film hydration method

Phospholipid is dissolved in chloroform and methanol (2:1, v/v) in a 250 ml round-bottom flask. The mixture is evaporated in a rotary evaporator above the transition temperature of the phospholipid, at 60°C and solvent traces are removed under the vacuum overnight. The film is then hydrated with drug dissolved in ethanolic solution, above the lipid transition temperature for 30 min. The vesicle suspension is dispersed by a probe sonicator at 25 W for 1 min to prepare ethosomes.[82]

Application

Ethosomes exhibited widespread utility in delivering the variety of antiviral, antifungal, antibacterial, anti-inflammatory drugs topically, dermally as well as transdermally.[83] Both hydrophobic and hydrophilic molecules were reported to be delivered through ethosomal vesicles across the skin. *In vitro* and *in vivo* permeability studies clarified the fact that these vesicles exhibited enhanced permeability of both hydrophobic and hydrophilic drugs.[84,85]

FUTURE PROSPECTS

Innovative instigation in the sphere of vesicular investigation has immensely gain importance. Skin diseases nowadays are increasing day by day across the globe. Thus, there is a need of development of a carrier that reaches deep into the skin.[86] Hence,enceH various new carriers have been in progress, among these are the penetration enhancers containing vesicles, in which the use of penetration enhancer such as transcutol, labrasol, and cineole can improve the penetration as compared to conventional vesicles.[87] Invasomes are among the class of the newly developed carriers which have been employed for enhanced topical delivery across the skin. These are vesicles that have been composed of using specifically terpenes as the penetration enhancer. Invasomes prepared by using phosphatidylcholine, ethanol, and a mixture of terpenes have been developed by Verma and Fahr's group. The mechanism of penetration via these vesicles is contemplated to be by disrupting lipid packaging of stratum corneum and/or disturbing the stacking of the bilayers.[20]

Further, introduction of ethosomes has initiated a new area in vesicular research for topical drug delivery. Different reports show a promising future of ethosomes in making topical delivery of various agents more effective. Furthermore, research in this area will allow better control over drug release *in vivo*, allowing physician to make the therapy more effective. Ethosomes offers a good opportunity for the

noninvasive delivery of small, medium, and large sized drug molecules. Milliliter quantities of ethosomal formulations can be prepared more easily. It therefore should be not before long that the corresponding drug formulation would have found their way into clinics to be tested for wide spread usage.[10] There is an increasing need to target the drugs to the deeper layers of the skin to achieve efficient dermal therapy.[88,89]

Vesicular system was introduced first in 1980 for topical drug delivery and since then have attracted considerable interest and generated many speculative claims concerning their potential utility both as a drug carrier and reservoir for controlled release of drugs within various layers of the skin. A number of clinical studies have now demonstrated the superiority of vesicular drug formulations over conventional delivery systems. In this respect, vesicular formulations have been successful in the treatment of a number of dermatological diseases and disorders such as psoriasis, mycoses, idiopathic hirsutism, and cutaneous infections.

CONCLUSION

The attempt to article gives an outline about the various vesicular systems with their importance, the system discussed provides flexibility for drug design, overcoming various solubility, and bioavailability problems. The significance of the vesicular system lies in controlling and sustaining of drug action. There are number of problems associated with vesicular delivery, still they will continue to play an important role in breathing new life to the old pre-existing drugs. Upcoming new systems are predicted to bring forward the new era of drug delivery.

REFERENCES

1. Bhalaria MK, Naik S, Misra AN. Ethosomes: A novel delivery system for antifungal drugs in the treatment of topical fungal diseases. Indian J Exp Biol 2009;47:368-75.
2. Aggarwal S, Singh PN, Mishra B. Studies on solubility and hypoglycaemic activity of gliclazide beta-cyclodextrin-hydroxyl propyl methyl cellulose complexes. Pharmazie 2001;57:191-3.
3. Jadhav SM, Morey P, Karpe M, Vilasrao K. Novel vesicular system: An overview. J Appl Pharm Sci 2012;2:193-202.
4. Biju SS, Talegaonkar S. Vesicular systems. Indian J Pharm Sci 2006;68:141-53.
5. Sharma SK, Chauhan M, Kumar NA. SPAN-60 niosomal oral suspension of fluconazole: Formulation and evaluation. J Pharm Res Healthc 2009;1:142-56.
6. Touitou E. Drug delivery across the skin. Expert Opin Biol Ther 2002;2:723-33.
7. Katare OP, Raza K, Singh B, Dogra S. Novel drug delivery systems in topical treatment of psoriasis: Rigors and vigors. Indian J Dermatol Venereol Leprol 2010;76:612-21.
8. Gupta PN, Singh P, Mishra V, Jain S, Dubey PK, Vyas SP. Topical immunization: Mechanistic insight and novel drug delivery. Ind J Biotechnol 2003;3:9-21.
9. Sinico C, Fadda AM. Vesicular carriers for dermal drug delivery. Expert Opin Drug Deliv 2009;6:813-25.
10. Jerajani HR, Amladi ST, Bongale R, Adepu VT. Evaluation of clinical efficacy and safety of once daily topical administration of 1% oxiconazole cream and lotion in dermatophytosis: An open label, non-comparative multicentre study. Indian J Dermatol Venereol Leprol 2000;66:188-92.
11. Reddy GS, Reddy BA, Jotish M, Pranitha CN, Suryadevara H. Organogels - A review. Int J PharmTech 2011;2:584-602.
12. Purohit DK, Nandgude TD, Poddar SS. Nano-lipid carriers for topical application: Current scenario. Asian J Pharm 2016;Suppl 9:1-9.
13. Dayan N. Pathways for skin penetration. Cosmet Toilet Mag 2005;120:67-76.
14. Jacobi U, Toll R, Sterru W, Lademan NJ. Do follicles play a role as penetration Pathways in *in vitro* studies on porcine skin an optical study. Laser Phys 2005;15:1594-8.
15. Patel HJ, Trivedi DG, Bhandari AK, Shah DA. Penetration enhancers for transdermal drug delivery system: A review. IJPI's J Pharm Cosmet 2011;1:68-80.
16. Lauer AC, Elder JT, Weiner ND. Evaluation of the hairless rat as a model for *in vivo* percutaneous absorption. J Pharm Sci 1997;86:13-8.
17. Bendas ER, Tadros MI. Enhanced transdermal delivery of salbutamol sulfate via ethosomes. AAPS PharmSciTech 2007;8:E107.
18. Benson HA. Transdermal drug delivery: Penetration enhancement techniques. Curr Drug Deliv 2005;2:23-33.
19. Dixit N, Bali V, Baboota S, Ahuja A, Ali J. Iontophoresis - An approach for controlled drug delivery: A review. Curr Drug Deliv 2007;4:1-10.
20. Prasanthi D, Lakhshmi PK. Vesicles: Mechanism of transdermal permeation: A review. Asian J Pharm Clin Res 2012;5:18-25.
21. Thong HY, Zhai H, Maibach HI. Percutaneous penetration enhancers: An overview. Skin Pharmacol Physiol 2007;20:272-82.
22. Godin B, Touitou E. Transdermal skin delivery: Predictions for humans from *in vivo*, *ex vivo* and animal models. Adv Drug Deliv Rev 2007;59:1152-61.
23. Morrow DI, McCarron PA, Woolfson AD, Donnelly RF. Innovative strategies for enhancing topical and transdermal drug delivery. Open Drug Deliv J 2007;1:36-59.
24. Kilpatric-Liverman L, Mattal J, Tinsly R, Wu J. Mechanisms of skin hydration. In: Barel AO, Paye M, Maibach HI, editors. 3rd ed. New York: Informa Healthcare; 2009. p. 91-2.
25. Trommer H, Neubert RH. Overcoming the stratum

corneum: The modulation of skin penetration. A review. Skin Pharmacol Physiol 2006;19:106-21.
26. Hirsch RJ, Dayan SH, Shah AR. Superficial skin resurfacing. Facial Plast Surg Clin North Am 2004;12:311-21, v-vi.
27. Cross SE, Roberts MS. Physical enhancement of transdermal drug application: Is delivery technology keeping up with pharmaceutical development? Curr Drug Deliv 2004;1:81-92.
28. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. N Engl J Med 2005;353:2262-9.
29. Liu X, Liu H, Liu J, He Z, Ding C, Huang G, *et al.* Preparation of a ligustrazine ethosome patch and its evaluation *in vitro* and *in vivo*. Int J Nanomedicine 2011;6:241-7.
30. Arora S, Lamba HS, Tiwari R. Dermal delivery of drugs using different vesicular carriers: A comparative review. Asian J Pharm 2012;6:237-44.
31. Kumar R, Aslam MD, Tripathi A, Prasad D, Chaudhary V, Jain V, *et al*. Ethosomes: Novel vesicular carriers in transdermal drug delivery. J Glob Pharm Technol 2010;2:1-7.
32. Nikalje AP, Tiwari S. Ethosomes: A novel tool for transdermal drug delivery. Int J Res Pharm Sci 2012;2:1-20.
33. Honeywell-Nguyen PL, Bouwstra JA. Vesicles as a tool for transdermal and dermal delivery. Drug Discov Today Technol 2005;2:67-74.
34. Chiranjeevi C, Muthukumaran M, Krishnamoorthy B. A review on potency of vesicular systems in targeting drug delivery. Res J Pharm Bio Chem Sci 2013;4:156-70.
35. Pouillot A, Dayan N, Polla AS, Polla LL, Polla BS. The stratum corneum: A double paradox. J Cosmet Dermatol 2008;7:143-8.
36. Verma P, Pathak K. Therapeutic and cosmeceutical potential of ethosomes: An overview. J Adv Pharm Technol Res 2010;1:274-82.
37. Verma P, Pathak K. Nanosized ethanolic vesicles loaded with econazole nitrate for the treatment of deep fungal infections through topical gel formulation. Nanomedicine 2012;8:489-96.
38. Agarwal R, Katare OP. Preparation and *in vitro* evaluation of miconazole nitrate-loaded topical liposomes. PharmTech 2002;10:48-60.
39. Bhatia A, Kumar R, Katare OP. Tamoxifen in topical liposomes: Development, characterization and *in-vitro* evaluation. J Pharm Pharm Sci 2004;7:252-9.
40. Jain S, Umamaheshwari RB, Bhadra D, Jain NK. Ethosomes: A novel vesicular carrier for enhanced transdermal delivery of an anti - HIV agent. Indian J Pharm Sci 2004;66:72-81.
41. Singh R, Vyas SP. Topical liposomal system for localized and controlled drug delivery. J Dermatol Sci 1996;13:107-11.
42. Keservani RK, Sharma AK, Ayaz MD, Kesharwani RK. Novel drug delivery system for the vesicular delivery of drug by the niosomes. Int J Res Control Release 2011;1:1-8.
43. Mezei M, Gulasekharam V. Liposomes – a selective drug delivery system for the topical route of administration: Gel dosage form. J Pharm Pharmacol 1982;34:473-4.
44. Celia C, Cilurzo F, Trapasso F, Cosco D, Fresta M, Paolino D. Ethosomes® and transfersomes containing linoleic acid: Physicochemical and technological features of topical drug delivery carriers for the potential treatment of melasma disorders. Biomed Microdevices 2012;14:119-30.
45. Carafa M, Santucci E, Lucania G. Lidocaine-loaded non-ionic surfactant vesicles: Characterization and *in vitro* permeation studies. Int J Pharm 2002;231:21-32.
46. Das MK, Palei NN. Sorbitan ester niosomes for topical delivery of rofecoxib. Indian J Exp Biol 2011;49:438-45.
47. Ferreira LS, Ramaldes GA, Nunan EA, Ferreira LA. *In vitro* skin permeation and retention of paromomycin from liposomes for topical treatment of the cutaneous leishmaniasis. Drug Dev Ind Pharm 2004;30:289-96.
48. Wagh VD, Deshmukh OJ. Itraconazole niosomes drug delivery system and its anti-mycotic activity against *Candida albicans*. ISRN Pharm 2012;18:1-7.
49. Roesken F, Uhl E, Curri SB, Menger MD, Messmer K. Acceleration of wound healing by topical drug delivery via lipoosmes. Arch Surg 2000;385:42-9.
50. Balakrishnan P, Shanmugam S, Lee WS, Lee WM, Kim JO, Oh DH, *et al*. Formulation and *in vitro* assessment of minoxidil niosomes for enhanced skin delivery. Int J Pharm 2009;377:1-8.
51. Soleiman MS, Hashem M, Minoo J. Preparation and evaluation of cypoterone acetate liposomes for topical drug delivery. Iran J Drug Del 2009;5:199-204.
52. Maestrelli F, Capasso G, González-Rodríguez ML, Rabasco AM, Ghelardini C, Mura P. Effect of preparation technique on the properties and *in vivo* efficacy of benzocaine-loaded ethosomes. J Liposome Res 2009;19:253-60.
53. Akhtar N, Pathak K. Cavamax W7 composite ethosomal gel of clotrimazole for improved topical delivery: Development and comparison with ethosomal gel. AAPS PharmSciTech 2012;13:344-55.
54. Mura S, Manconi M, Sinico C, Valenti D, Fadda AM. Penetration enhancer-containing vesicles (PEVs) as carriers for cutaneous delivery of minoxidil. Int J Pharm 2009;380:72-9.
55. Dragicevic-cevic N, Scheglmann D, Albrecht V, Fahr A. Temoporfin - Loaded invasomes: Development, characterization and *in vitro* skin penetration studies. J Control Release 2008;127:59-69.
56. Lei W, Yu C, Lin H. Development of tacrolimus-loaded transfersomes for deeper skin penetration enhancement and therapeutic effect improvement *in vivo*. Asian J Pharm Sci 2013;8:336-45.
57. Sipai AB, Yadav V, Mamatha Y, Prasanth VV. Liposomes: An overview. J Pharm Sci Innov 2012;1:13-21.
58. Goyal P, Goyal K, Vijaya Kumar SG, Singh A, Katare OP,

Mishra DN. Liposomal drug delivery systems – clinical applications. Acta Pharm 2005;55:1-25.
59. Brown MB, Martin GP, Jones SA, Akomeah FK. Dermal and transdermal drug delivery systems: Current and future prospects. Drug Deliv 2006:175-87.
60. Maurer N, Fenske DB, Cullis PR. Developments in liposomal drug delivery systems. Expert Opin Biol Ther 2001;1:923-47.
61. Dhamecha DL, Rtahi AA, Saifee M, Kahoti SR, Dehgan MH. Drug vehicle based approaches of penetration enhancement. Int J Pharm Pharm Sci 2009;1:24-46.
62. González-Rodríguez ML, Rabasco AM. Charged liposomes as carriers to enhance the permeation through the skin. Expert Opin Drug Deliv 2011;8:857-71.
63. Verma S, Singh SK, Syan N, Mathur P, Valecha V. Nanoparticle vesicular tool for drug delivery. J Chem Pharm Res 2010;2:496-509.
64. Dua JS, Rana AC, Bhandari AK. Liposomes: Method of preparation and application. Int J Pharm Stud Res 2012;3:14-20.
65. Crommelin DJ, Bos GW, Storm G. Liposomes - Successful carrier system for targeted delivery of drugs. Drug Del 2003;10:209-13.
66. Singh A, Kumar SP, Kumar GV, Garima G. Approaches used for penetration enhancement in transdermal drug delivery. Int J Pharm Sci 2010;2:708-16.
67. Atrux-Tallau N, Denis A, Padois K, Bertholle V, Huynh TN, Haftek M, *et al*. Skin absorption modulation: Innovative non-hazardous technologies for topical formulations. Open Dermatol 2010;4:3-9.
68. Sankhyan A, Pawar P. Recent trends in noisome as vesicular drug delivery system. J Appl Pharm Sci 2012;2:20-32.
69. Tangri P, Shaffi K. Niosomes: Formulation and evaluation. Int J Biopharm 2011;2:47-53.
70. Sahin NO. Niosomes as nanocarrier systems. Nanomater Nanosyst Biomed Appl 2007;8:67-81.
71. Ogiso T, Niinaka N, Iwaki M. Mechanism for enhancement effect of lipid disperse system on percutaneous absorption. J Pharm Sci 1996;85:57-64.
72. Fang JY, Hong CT, Chiu WT, Wang YY. Effect of liposomes and niosomes on skin permeation of enoxacin. Int J Pharm 2001;219:61-72.
73. Javadzadeh Y, Shokri J, Hallaj-Nezhadi S, Hamishehkar H, Nokhodchi A. Enhancement of percutaneous absorption of finasteride by cosolvents, cosurfactant and surfactants. Pharm Dev Technol 2010;15:619-25.
74. Gandhi A, Oomensen S, Paul A. Current trends in niosome as vesicular drug delivery system. Asian J Pharm Life Sci 2012;2:33.
75. Soumya S, Doney AB, Sabitha M. Current trends in lipid based delivery systems and its application in drug delivery. Asian J Pharm Clin Res 2012;3:4-9.
76. Kombath RV, Kumar MS, Sockalingam A, Subadhra S, Parre S, Reddy TR, *et al*. Critical issues related to transferosomes - Novel vesicular system. Acta Sci Po Technol Aliment 2012;11:67-82.
77. Ravi K, Singh M. Transfersomes: Novel approach for transdermal drug delivery. IRJP 2012;3:20-4.
78. Gangwar S, Singh S, Garg G. Ethosomes: A novel tool for drug delivery through the skin. J Pharm Res 2010;3:688-91.
79. Dave V, Pareek A, Paliwal S. Ethosome: A novel approach of transdermal drug delivery system. Int J Adv Res Pharm Bio Sci 2012;1:439-52.
80. Lachenmeier DW. Safety evaluation of topical applications of ethanol on the skin and inside the oral cavity. J Occup Med Toxicol 2008;3:26.
81. Aggarwal G, Goel A, Dhawan S, Shama A. Carriers/vesicles based approaches for penetration enhancement in transdermal drug delivery. Latest Rev 2010;8:1-15.
82. Fang YP, Huang YB, Wu PC, Tsai YH. Topical delivery of 5 - Aminolevulinic acid - Encapsulated ethosomes in a hyperproliferative skin animal model using the CLSM technique to evaluate the penetration behaviour. Eur J Pharm Biopharm 2009;73:391-8.
83. Akhtar N, Pathak K. Preclinical and clinical aspects of antimicrobial drugs delivered through ethosomal vesicles. Anti Infect Agent 2012;10:15-25.
84. Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M. Ethosomes - Novel vesicular carriers for enhanced delivery: Characterization and skin penetration properties. J Control Release 2000;65:403-18.
85. Vijayakumar KS, Parthiban S, Senthilkumar GP, Mani TT. Ethosomes - A new trends in vesicular approaches for topical drug delivery. Asian J Res Pharm Sci Biotechnol 2014;2:23-30.
86. Girhepunje K, Pal R, Gevariya H, Behera A. Ethosomes: A novel vesicular carrier for enhanced dermal delivery of ciclopiroxolamine. Der Pharm Lett 2010;2:360-7.
87. Hire NN, Gudsoorkar VR, Bhise KS, Upasani CD, Nandgude TD, Dalvi H. Microparticulate drug delivery system for topical administration of ITR. Asian J Pharm 2007;1:83-8.
88. Bhise KS, Nandgude TD, Bhura RG, Shah SK, Subburaju T. Advances in nanoscience and nanotechnology in treatment of cancer. J Curr Res Ayurvedic Pharm Sci 2011;2:2.
89. Muzzalupo R, Tavano L. Niosomal drug delivery for transdermal targeting recent advances. Res Rep Trans Drug Deliv 2015;4:23-33.
90. Pandita A, Sharma P. Pharmacosomes: An emerging novel vesicular drug delivery system for poorly soluble synthetic and herbal drugs. ISRN Pharm 2013;2013:Article ID: 348186, 1-10.
91. Nandgude TD, Bhise KS, Gupta VB. Characterization of hydrochloride and tannate salts of diphenhydramine. Indian J Pharm Sci 2008;70:482-6.
92. Laouini A, Maalej CJ, Blouza IL, Sfar S, Charcosset C, Fessi H. Preparation, characterization and applications of liposomes: State of the art. J Colloid Sci Biotechnol 2012;1:147-68.
93. Lohumi A, Rawat S, Sarkar S. A novel drug delivery

system: Niosomes review. J Drug Deliv Ther 2012;2:129-35.
94. Semalty A, Semalty M, Rawat BS, Singh D, Rawat MS. Pharmacosomes: The lipid-based new drug delivery system. Expert Opin Drug Deliv 2009;6:599-612.
95. Jain S, Jain P, Umamaheshwari RB, Jain NK. Transfersomes – A novel vesicular carrier for enhanced transdermal delivery: Development, characterization, and performance evaluation. Drug Dev Ind Pharm 2003;29:1013-26.
96. Muller-Goymann CC. Physicochemical characterization of colloidal drug delivery systems such as reverse micelles, vesicles, liquid crystals and nanoparticles for topical administration. Eur J Pharm Biopharm 2004;58:343-56.

Source of Support: Nil. **Conflict of Interest:** None declared.