Vesicles as a Tool for Enhanced Topical Drug Delivery

Suraj B. More, Tanaji D. Nandgude, Sushilkumar S. Poddar
Department of Pharmaceutics, Dr. D Y Patil Institute of Pharmaceutical Sciences and Research, Pune, Maharashtra, India

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.[10] 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

Address for correspondence:
Tanaji D. Nandgude, Department of Pharmaceutics, Dr. D Y Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune - 411 018, Maharashtra, India. Phone: +91-9096262509. E-mail: tanajinandgude@gmail.com

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,[16] 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.[17] 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, microcisioning, 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.\[14\] 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.\[39\] Many cosmetics have also been reported to be delivered via encapsulating 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 introduced 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].

**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
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

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<td>Provides better remission from disease</td>
<td>([1])</td>
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<td>Diclofenac</td>
<td>Non-steroidal anti-inflammatory</td>
<td>Transfersomes</td>
<td>Improved penetration directly into the depth of soft tissues</td>
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<tr>
<td>Ibuprofen</td>
<td>Non-steroidal anti-inflammatory</td>
<td>Transfersomes</td>
<td>Enhanced penetration</td>
<td>([3])</td>
</tr>
<tr>
<td>Econazole nitrate</td>
<td>Antifungal</td>
<td>Ethosomes</td>
<td>Improved therapeutic efficacy</td>
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<tr>
<td>Miconazole nitrate</td>
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<td>Tamoxifen</td>
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<tr>
<td>Acyclovir</td>
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<td>Benzocaine</td>
<td>Local Anaesthetic</td>
<td>Liposomes</td>
<td>Longer duration of action with slow release of drug</td>
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<td>Doxorubicin</td>
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<td>Methotrexate</td>
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<tr>
<td>Lidocaine</td>
<td>Local anaesthetic</td>
<td>Niosomes</td>
<td>Higher flux as compared to liposomes</td>
<td>([45])</td>
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<tr>
<td>Rofecoxib</td>
<td>Non-steroidal anti-inflammatory drug</td>
<td>Niosomes</td>
<td>Prolonged drug release with higher retention</td>
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</tr>
<tr>
<td>Paromomycin</td>
<td>Antibiotic</td>
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<td>Controlled drug delivery with enhanced permeation</td>
<td>([47])</td>
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<td>Itraconazole</td>
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<td>Buflomedi Hydrochloride</td>
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<td>Cypoterone Acetate</td>
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<tr>
<td>Benzocaine</td>
<td>Local Anaesthetic</td>
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<td>Enhanced clinical effectiveness in topical anesthesia</td>
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<tr>
<td>Clotrimazole</td>
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<td>Uniform deeper penetration across the skin</td>
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<tr>
<td>Minoxidil</td>
<td>Anti-hypertensive</td>
<td>liposomes</td>
<td>Potential innovative carrier for improved delivery</td>
<td>([54])</td>
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<tr>
<td>Temoporfin</td>
<td>Photo sensitizer</td>
<td>Invasomes</td>
<td>Effective drug carrier system deep into the stratum corneum</td>
<td>([55])</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Anti-inflammatory</td>
<td>Transfersome</td>
<td>Improved Skin Permeation</td>
<td>([56])</td>
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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. 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.

**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.

**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.

**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.
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.\textsuperscript{[57]} They are widely used in delivering drugs as well as antigens. They are also used for site-specific drug delivery.\textsuperscript{[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 reticuloendothelial system RES (liver, spleen, and bone marrow) is averted or minimized.\textsuperscript{[29]}

NIOSOMES

Niosomes are the vesicles devised by using non-ionic surfactants.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[69]}

It consists of cholesterol to provide rigidity to the vesicles and proper shape.\textsuperscript{[69]} They are prepared by using non-ionic surfactants such as polyglycerol alkyl ethers, glusoyl dialkyl ethers, polyoxyethylene alkyl ether, brij, span series, and Tween series.\textsuperscript{[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.\textsuperscript{[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 equipment for processing.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[71]} They also modify the structure of stratum corneum, which loosen an intercellular lipid barrier of the stratum corneum making them more permeable.\textsuperscript{[72]} The presence of non-ionic surfactant in niosomes, acts like a permeation enhancer and improves drug permeation from niosomes.\textsuperscript{[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.\textsuperscript{[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,
in the treatment of various topical diseases as a novel drug delivery system. Niosomes containing anti-cancer drugs, like methotrexate and doxorubicin can efficiently enhance 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]

**ADVANTAGES OF TRANSFERSONES**

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 TRANSFERSONES**

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 skin's barrier function.
intercellular lipid lamellae. This will facilitate the penetration of free drug molecules into and across the stratum corneum.\cite{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.\cite{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.\cite{75,77}

**ETHOSOMES**

Ethosomes are the ethanolic phospholipid vesicular carriers\cite{76} developed by Touitou et al.\cite{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

### Table 2: Characterization of vesicular system\cite{90-96}

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**Figure 5: Mechanism of penetration through transfersome**

Ethosomes are the ethanolic phospholipid vesicular carriers developed by Touitou et al. 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.
The presence of high concentrations of ethanol makes ethosomes an innovative and novel carrier for topical drug delivery. Ethanol present in ethosomal drug 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 packed less tightly than conventional vesicles but has equivalent stability, allowing more malleable structure and improves drug distribution ability in stratum corneum lipid.

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

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.

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 nontoxic raw materials in formulation. High patient compliance in ethosomal 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.

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.

Mechanism of drug penetration

The formulations developed by using ethosomal drug 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 ethosomal drug. Ethanol not only imparts fluidity, but also provides flexibility to the ethosomal membrane that enhances the skin permeation across the skin [Figure 6].

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 ethosomal effect. These two effects dictate the mechanism of drug penetration.

Ethanol effect

Ethanol present in ethosomal drug 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 ethosomal drug result in increasing skin permeability. Hence, ethosomal drug 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.

Method of preparation of ethosome

Various methods involve in preparing the ethosomal drug 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
was homogenized at 15,000 psi pressure in 3 cycles using high pressure homogenizer to get nano-sized ethosomes.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[82]}

**Application**

Ethosomes exhibited widespread utility in delivering the variety of antiviral, antifungal, antibacterial, anti-inflammatory drugs topically, dermally as well as transdermally.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[86]} Hence, a variety of 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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[10]} There is an increasing need to target the drugs to the deeper layers of the skin to achieve efficient dermal therapy.\textsuperscript{[18],[19]}

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.

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