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# REVIEW ON: VESICULAR CARRIERS FOR TOPICAL DELIVERY

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## Abstract:

The skin serves as both a prominent target and a primary barrier in the context of topical/transdermal (TT) drug delivery. Topical drug delivery plays a crucial role in the treatment of skin disorders, ocular conditions, rectal ailments, vaginal issues, as well as systemic disorders that manifest on the skin. The stratum corneum, a vital component of the skin, plays a pivotal role in acting as a barrier to the delivery of drugs via topical routes.

The development of topical drug delivery systems is specifically aimed at achieving effective transportation of therapeutically active drugs across the skin. Vesicular carriers have gained significant prominence in the field of topical drug delivery due to their biocompatible, biodegradable, non-toxic, and non-irritating properties, as well as their ability to achieve nanoscale dimensions, enabling penetration into the deeper layers of the skin.

However, the limited permeability of the stratum corneum poses a challenge as it acts as an effective barrier for drug penetration. To overcome this obstacle, various carrier systems have been developed. Vesicular carriers, including liposomes, niosomes, transferases, and ethosomes, have emerged as recently invented carriers that have been widely employed in the treatment of various topical skin diseases. This review article aims to focus on the topical delivery facilitated by these vesicular carriers, with an emphasis on future prospects and various aspects of these carriers.

***Keywords:*** *Vesicular carriers, Liposomes, Niosomes, Cryptosomes, Ethosomes*

## Introduction:

The skin is a vital organ in the human body, and research has focused on developing effective methods for delivering drugs through it. Topical drug delivery involves applying a medication to the skin or mucous membrane to treat skin conditions or manifestations of a disease. The purpose of topical drug delivery is to restrict the pharmacological effects of the drug to the surface or layers of the skin or mucous membrane, rather than allowing it to be absorbed into the bloodstream and affect the entire body. This approach is often used to treat specific cutaneous disorders or manifestations of a disease that appear on the skin or mucous membranes. (1)

Novel drug delivery systems are created to enhance the therapeutic advantages of current medications by targeting the drug to a specific site for a specific duration. The primary motivation for developing these innovative delivery systems is to either extend the drug's release period or sustain an effective concentration of the drug while minimizing adverse effects. (2)

In 1909, Paul Ehrlich developed targeted drug delivery systems, which delivered therapeutic agents specifically to diseased cells. Since then, a variety of carriers have been employed to transport drugs to their intended targets, including immunoglobulins, serum proteins, synthetic polymers, microspheres, liposomes, niosomes, erythrocytes, and others. (3)

The topical/transdermal (TT) route of drug administration offers several advantages over other routes. By avoiding the hepatic first-pass effect, the drug can enter the systemic circulation directly, resulting in improved bioavailability. Additionally, continuous drug delivery can be achieved through the TT route, which is especially useful for drugs that require long-term therapy.

There are various vesicular systems available for skin application, with the majority of lipid-based delivery systems being categorized as either vesicular carriers or lipid particulate systems. Vesicular carriers include liposomes, ethosomes, deformable vesicles, and other specialized novel vesicular carriers. However, the efficacy of conventional liposomes for skin delivery has been limited, leading to recent research focused on polymeric and elastic vesicles such as ultra-deformable vesicles, ethosomes, and transethosomes. The choice of vesicular system depends on the pharmaceutical and dermatological factors involved. The effectiveness of vesicles as topical delivery systems remains a topic of debate, with varying effects reported depending on the type of vesicles and their composition. (4)

liposomes were used for topical drug delivery. Liposomes are commonly hollow spheres surrounded by a lipid double layer. (5) After application to the skin, liposomes tend to stay in the upper layer of the Stratum Corneum and function as a reservoir for drugs. However, due to their instability and limited ability to penetrate the skin, they are only useful for delivering drugs topically. To address these challenges, a new type of lipid vesicles called deformable or elastic liposomes, also known as ultra deformable vesicles (UDV), were developed in the early 1990s. Compared to conventional liposomes, UDV are more flexible, which allows them to cross the skin barrier more effectively. (6)

Elastic vesicles are similar to conventional liposomes but except for the inclusion of an edge activator in their lipid bilayer structure to provide elasticity. These vesicles are applied to the skin without being occluded and have demonstrated the ability to permeate through the lipid lamellar regions of the stratum corneum. (7)

Niosomes are a type of vesicle created using non-ionic surfactants, including polyglycerol alkyl ethers, glucosyl dialkyl ethers, polyoxyethylene alkyl ether, brij, span series, and tween series. They are considered second-generation vesicles, as they offer enhanced chemical stability, improved entrapment efficiency, better penetration, and lower production costs when compared to liposomes. (8)

Ethosomes are elastic nanovesicles made up of phospholipids and a high concentration of ethanol (20-45%). Ethanol is a potent permeation enhancer, and it has been incorporated into these vesicular systems to create elastic nanovesicles. (9)

Transferosomes are a type of drug delivery carrier that can penetrate intact deeper regions of the skin after topical administration, delivering higher concentrations of active substances. This makes them an effective drug delivery option for transdermal applications. Transethosomes are composed of ethanol, phospholipids, and an edge Ethanol and edge activator help to enhance the skin permeation of Transethosomes. This non-invasive technique improves patient compliance while also increasing drug entrapment efficiency. (10)

**Advantages**

Topical vesicular systems offer several advantages for improved skin drug delivery. These include enhanced patient compliance due to their easy application and removal. These systems are also easily retractable, allowing drug therapy to be terminated if toxic effects are observed. Topical systems provide sustained and controlled drug levels in the bloodstream, reducing the risk of over or under-dosing and decreasing the frequency of drug administration. Additionally, topical systems bypass hepatic first-pass metabolism, eliminating the need for pleasant-tasting medications and avoiding gastrointestinal side effects.

**Disadvantages**

Despite their many advantages, topical drug delivery systems do have some disadvantages. These systems can be relatively expensive compared to conventional drug delivery methods. Additionally, this route is not suitable for drugs that have the potential to irritate or sensitize the skin. Many drugs have high molecular weights and poor lipid solubility, making them difficult to absorb through the skin or mucous membranes.

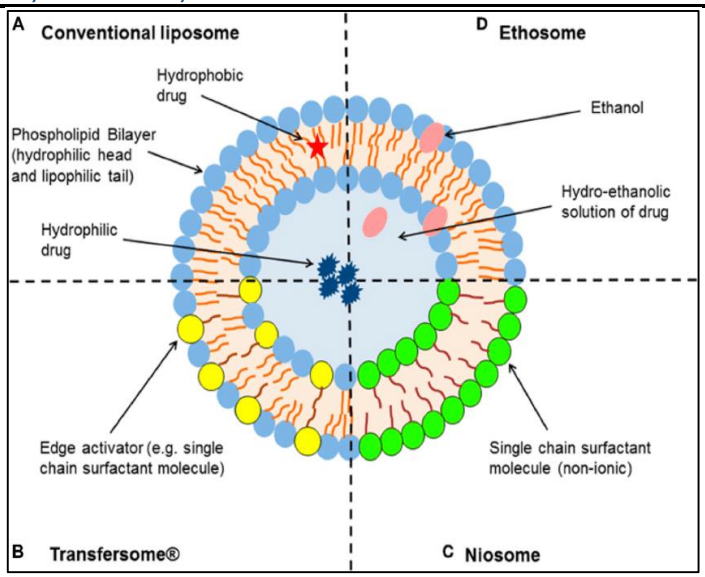


**Figure 1: Various types of vesicular carrier**

**Table 1: Topical delivery of variety of drugs via different list of vesicular carriers.**

| Vesicular Carrier | Drug | Therapeutic Category | Inference | References |
|---|---|---|---|---|
| liposomes | Paromomycin | Antibiotic | sustain and control drug delivery with enhanced permeation | (11) |
| Liposome | Miconazole nitrate | Antifungal | Targeted drug delivery and improved bioavailability | (12) |
| Ethosomes | Fluconazole | Antifungal | Provides better remission from disease | (13) |
| Ethosomes | Acyclovir | Anti-viral | Increased antiviral activity | (14) |
| Niosomes | Methotrexate | Anti-neoplastic | Sustained drug release | (15) |
| Niosomes | Doxorubicin | Anti-tumour | Decreases rate of sarcoma proliferation | (15) |
| Transferosomes | Zidovudine | Anti-HIV | Enhanced delivery across the skin | (16) |
| Transferosomes | Ibuprofen | Non-steroidal anti-inflammatory | Enhanced penetration | (1) |
| Penetration enhancing vesicles | Minoxidil | Anti-hypertensive | Potential innovative carrier for improved drug delivery | (17) |
| Niosomes | Itraconazole | Anti-mycotic | Effective anti-mycotic activity | (18) |

| | | | | |
|---|---|---|---|---|
| Ethosome | Benzocaine | Local Anaesthetic | Enhanced clinical effectiveness in topical anaesthesia | (19) |
| Niosomes | Lidocaine | Local anaesthetic | Higher flux as compared to liposomes | (20) |
| Transferosomes | Diclofenac | Non-steroidal anti-inflammatory | Improved penetration directly into the depth of soft tissues | (1) |
| Transethosomal | ketokonazol | Antifungal | Enhance the drug ocular permeation | (21) |
| Liposome | Tamoxifen | Anti-estrogen | Enhanced permeation and retention in the skin | (22) |

**Liposomes:**

The development of Banghman's vesicles, also known as liposomes, in 1960 marked a breakthrough in the field of drug delivery systems. (23)

Liposomes were first described by Banghman and colleagues over 40 years ago. They are small, spherical vesicles that can be made from a variety of substances, including cholesterol, non-toxic surfactants, Sphingolipids, glycolipids, long-chain fatty acids, and even membrane proteins. (24)

Liposomes may consist of naturally derived phospholipids containing various lipid chains, or they could incorporate other surfactants. Liposomes are tiny vesicles composed of a lipid bilayer that encloses an aqueous volume. They consist mainly of phospholipids and cholesterol, but may contain other components as well. One type of liposome, the stratum corneum lipid liposome (SCLL), is made up of lipids that have a composition similar to those found in the outermost layer of human skin, known as the stratum corneum. These liposomes typically contain phospholipids as the major components, but an additional surfactant may be added as an edge activator to alter their elasticity and enhance their ability to deform. (2)

Liposomes are composed of a hydrophobic membrane that encloses a region of aqueous solution. Hydrophilic solutes are unable to pass through the lipid membrane, but hydrophobic molecules can dissolve into the membrane, allowing liposomes to carry both hydrophilic and hydrophobic molecules. In order to deliver these molecules to their target site, the lipid bilayer of the liposome can fuse with other lipid bilayers, such as those found in cell membranes, thereby releasing the contents of the liposome. (25) According to Jung et al, (2011) developed liposomes specifically for delivering adenosylcobalamin (AdCbl) topically. Their research demonstrated a 17-fold increase in AdCbl permeation when compared to using plain AdCbl gel without liposomes. (26)

Touitou et al, have extensively reviewed the use of liposomes as carriers for topical and transdermal delivery. One of the earliest reported applications of topically administered liposome-entrapped triamcinolone was by Mezei et al, since then, the use of liposomes for topical delivery has been investigated for a variety of drug categories, including steroids, non-steroidal anti-inflammatory drugs, local anesthetics, and antimicrobial agents. (27)

Verma et al, (2003) used confocal laser scanning microscopy with entrapped and unentrapped carboxyfluorescein to investigate the kinetics of liposome penetration. They discovered that there was improved penetration into the stratum corneum (SC) and possibly even deeper skin layers. The drug that is entrapped in liposomes can become bioavailable only when it is released at an optimal rate and for an adequate period of time to produce the desired therapeutic effect. (26)

The use of liposomes for topical ocular drug delivery has also received significant attention. Liposomes have advantages over most ophthalmic preparations in that they are completely biodegradable and non-toxic. Liposomes can make intimate contact with the corneal and conjunctival surfaces, and thereby increase the ocular drug absorption. (27)

Research has shown that positively-charged acetazolamide liposomes have higher entrapment efficiency compared to negatively-charged or neutral liposomes. Additionally, positively-charged liposomes have produced a strong and sustained reduction in

intraocular pressure (IOP) in rabbits. Incorporating acetazolamide into a liposomal preparation for ocular drug delivery can be valuable in minimizing the side effects associated with oral administration of the drug. (28)

To further improve the penetration of these vesicles over the skin, charged liposomes have been produced for topical distribution in the nascent field of liposomal research. This is an ongoing area of study and development, with the goal of improving the efficacy and safety of topical drug delivery. (1)

Liposomes have highly promising properties for skin delivery compared to conventional non-vesicular formulations. Vesicle systems can improve drug penetration, increase pharmacological effect, reduce side effects, enable controlled drug release, and provide drug protection. As such, liposomes have the potential for numerous applications in skin delivery.

## Advantages of Liposomes

Liposomes offer numerous advantages as a vesicular carrier for drug delivery. They are biocompatible, biodegradable, non-toxic, and flexible, making them safe for use in humans. Liposomes can enhance the therapeutic index and efficacy of drugs, and can protect the encapsulated drug from the external environment. They can exhibit sustained release of drugs, and can be formulated in a variety of dosage forms, including suspensions, aerosols, and semisolid forms such as gels, creams, and lotions. Liposomes can be administered through various routes, including ocular, pulmonary, nasal, oral, intramuscular, subcutaneous, topical, and intravenous routes. They are suitable for the delivery of both hydrophobic and hydrophilic drugs, with reduced toxicity and increased stability of the entrapped drug.

**Classification:**

Liposomes may be produced by a variety of methods. Their name is also influenced by the preparation process, structural characteristics, or unique roles that are given to them.

**Table 2: Classification according to size:**

| Type | Specifications |
|---|---|
| MLV | Multilamellar large vesicles- >0.5µm |
| OLV | Oligolamellar vesicles- 0.1-1µm |
| UV | Unilamellar vesicles (all size range) |
| SUV | Small Unilamellar vesicles- 20-100nm |
| MUV | Medium sized Unilamellar vesicles |
| GUV | Giant Unilamellar vesicles- >1µm |
| MV | Multivesicular vesicles- 1µm |
| LUV | Large Unilamellar vesicles- >100 |

**Mechanism of Penetration**

Regarding the permeation mechanism of drug-loaded liposomes through skin, different interpretations have been proposed. Liposomes release drugs into the skin by penetrating the epidermal layers. During this process, they lose their bilayer membrane, allowing the lipids to adhere to the skin surface and fuse with the lipid matrix. These fusion releases the enclosed drug. However, it has been recently reported that the drug can permeate the skin after being released from the vesicles. On application of vesicles, transformation in the ultra-structures of the intercellular lipids was observed which demonstrates 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 partioning into the skin. (1)

For example, Cationic liposomes are a specific type of liposomal vesicles that act as penetration enhancers by utilizing the interactions between their positively charged components and the negatively charged components of the Stratum corneum. This interaction induces a transfer between the liposomes and the skin. This mechanism has shown that cationic liposomes can enhance the delivery of various drugs into the skin, including retinoic acid, heparin, meloxicam, acyclovir, and most recently, minoxidil. (29)

The penetration behaviour of active substances through the skin can be affected by various parameters, such as the method of preparation, vesicle-membrane structure, lipid composition, mean sizes, and physicochemical properties of the drug. For example, depending on their composition, liposomal bilayers can exist in either a gel state or a liquid crystalline state. The gel state is characterized by rigid and inflexible bilayers, leading to drug accumulation in the upper layers of the skin and reduced transdermal drug penetration. On the other hand, a liquid crystalline state of phospholipid bilayers is preferred for transdermal drug delivery as they are relatively flexible and accommodating. (30)

In addition to the parameters mentioned previously, the inclusion of an edge activator (EA), such as Tween 80, in the standard composition of liposomes has been shown to enhance the deformability of the systems. This increased deformability improves the penetration of loaded drugs into deeper epithelial layers. An example of this is the ultra-deformable liposomes developed by Perez et al. (31)

Noisome

Niosomes are vesicular structures that create a closed bilayer structure in aqueous conditions and are composed of cholesterol and a single nonionic surfactant in the alkyl chain. Nonionic surfactants like sorbitan esters, polysorbates, and span60 and span80 are employed. Niosomes have a structure similar to liposomes but their membranes are made of one or more nonionic surfactants and cholesterol. (32)

The application of noisome as dermal/transdermal delivery systems is receiving an increasing attention due to their outstanding characteristics. They are capable of increasing drug penetration and offering controlled or sustained drug release. In addition, the use of non-ionic surfactants in niosomes is advantageous for topical and transdermal delivery because they are generally considered to be safe, non-toxic, and non-irritating, unlike cationic and anionic surfactants. (33)

Niosomes have several advantages over liposomes. They are able to encapsulate both hydrophilic and lipophilic drugs, and are also more cost-effective and stable than liposomes. This is because surfactants used in niosomes are generally less expensive than pure phospholipids and are more resistant to hydrolytic degradation.

Niosomes function as a reservoir system, and their release kinetics can be adjusted by altering their composition. When selecting surfactants for pharmaceutical applications, it is important to choose those that are biocompatible, biodegradable, non-immunogenic, and noncarcinogenic. Examples of suitable surfactants include polyglycerol alkyl ethers, glucosyldialkyl ethers, crown ethers, and some varieties of Tween®. However, the most commonly used surfactants in niosomes are Brij® and Spans.

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. (1)

Niosomes have been extensively studied as vesicular carriers for a wide range of drugs and cosmetics for topical use. They have been found to be effective in the treatment of various dermatological disorders. Niosomes are considered to be highly efficient in topical drug delivery, as they can enhance the residence time of drugs in the stratum corneum and epidermis, while also reducing systemic drug absorption. (1)

When using vesicular carriers for topical drug administration, it is important to investigate the safety of the carrier components. Since niosomal drugs are likely to be used on damaged skin, any potential local and/or systemic effects of the carriers must be addressed before in vivo testing. However, it has been found that vesicle formation tends to decrease surfactant toxicity. Recent studies have confirmed the good safety profile of Span and Tween niosomes on the skin.(34)

In a recent study, fluconazole-loaded niosomes were created using the film hydration method with various surfactants, such as Span and Brij series. The niosomes were characterized for various parameters and incorporated into a gel for sustained release and site specificity. In vitro and in vivo studies demonstrated that the skin retention of fluconazole was 14.2 and 3.3 times higher, respectively, when using niosomal gels compared to plain gel. Similar studies also revealed the presence of localized depots of fluconazole, indicating sustained drug release and enhancement in cutaneous drug retention. (35) A recent study explored different types of surfactants, bearing different numbers and natures of alkyl chains, for formulating Acetazolamide -loaded niosomes to improve its penetration and bioavailability.

**Table 3: Various Non-ionic surfactants used for topical drug delivery by noisome:**

| Drug used | Non-ionic surfactant used | Application | Method | Reference |
|---|---|---|---|---|
| Acetazolamide | Span 40, 60 | Ocular delivery to improve the low corneal penetration and bioavailability | Reverse phase evaporation, thin film hydration technique | (36) |
| Acyclovir | Sorbitan monostearate | Prolong the drug release | Thin film hydration technique | (37) |
| 5-fluorouracil | Bola surfactant, Span 80 | Topical drug delivery carrier for treatment of cance | Thin film evaporation technique | (38) |
| Rofecoxib | Span 20, 40, 60 | Sustained therapeutic action | Thin film hydration technique | (29) |
| Gallidermin | Tween 61 | Transdermal drug delivery system | Freeze dried method | (39) |
| Capsaicin | Span 80, Tween 80 | Transdermal drug delivery system | Thin film hydration technique | (40) |

In recent years, there has been a growing interest in the use of niosomal formulations to treat skin cancer and psoriasis. Niosomes have shown promising results as drug delivery systems for cancer therapy by targeting drugs to cancer cells, increasing treatment duration, reducing severe side effects, and improving drug stability. Psoriasis, on the other hand, is a life-threatening autoimmune inflammatory skin disease triggered by T lymphocytes. It is a noncontagious skin condition that results in plaques of thickened, scaling skin due to the rapid proliferation of skin cells. Although psoriasis is considered an incurable, long-term skin condition, great attention is being paid to developing effective treatments to control psoriasis symptoms. (41) Recently, the drugs most commonly used for the treatment of psoriasis include methotrexate (MTX), cyclosporine (CsA), acitretin, dexamethasone, and salicylic acid.

Niosome technology has been used to develop a delivery system for PUVA therapy with 8MOP. The niosomes were prepared using the thin-film hydration method with cholesterol and had a high entrapment efficiency ranging from 83% to 90%. The size of the vesicles ranged from 111.1 to 198.8 nm. The niosome formulations were incorporated into a hydrogel matrix, which resulted in a slower release of 8MOP compared to the niosomal vesicles alone. In vivo studies using confocal laser scanning microscopy showed that the niosomes penetrated the skin better than plain hydrogel. In vitro studies using rat skin also demonstrated improved penetration and accumulation of 8MOP after 8 hours. (42)

Melanoma is a type of skin cancer that begins in the cells that produce melanin, which is responsible for the color of your skin. It can also develop in the eyes or other parts of the body. Researchers, including Dwivedi et al, have created a new way to deliver a drug called Artemis one using tiny bubbles called niosomes. When tested, these niosomes showed a strong ability to kill melanoma cells specifically, while having little to no harmful effects on healthy skin cells. (43)

The researchers examined the ability of artemisone MM-loaded formulations to kill human melanoma cells (A-375) and human keratinocytes (HaCaT). The study found that both formulations effectively reduced the number of melanoma cells in a dose-dependent manner. The niosomes were made using the chloroform film method and a combination of non-ionic surfactant (span 60), cholesterol, and artemisone in a specific ratio (3:1:4, w/w/w). Encapsulating artemisone in nanovesicle formulations greatly enhanced its potency against cancer cells, indicating its potential use in cancer chemotherapy. (44) The niosomal vesicular drug delivery system has the ability to penetrate the skin effectively, making it a promising technique for delivering drugs to the skin. As a result, it is considered as a potential method for dermal drug delivery.

**Table 4: Niosomes as a drug carrier for skin cancer treatment using different methods with their results.**

| Drug | Dosage form | Method | Result | References |
|---|---|---|---|---|
| 5-fluorouracil | Niosomes | thin layer evaporation technique | In comparison to the free drugs, 5-FU-loaded bola-niosomes showed an improvement in the cytotoxic impact. | (38) |
| 5-Fluorouracil | PEG-coated Niosomes | thin layer evaporation technique | PEGylated niosomal 5-FU has more potent antitumoral action. | (45) |
| Paclitaxel and curcumin | cationic PEGylated niosomal | thin-film hydration method | An entrapment Efficiency, controlled release and exhibit enhanced synergistic antitumor efficacy. | (46) |
| Cyclophosphamide | Niosomal gel | solvent injection method | For skin therapy, a good formulation approach design was developed. | (42) |

**Advantages of Niosomes**

Niosomes, being a carrier system, offer various benefits such as greater chemical stability when compared to traditional liposomal carriers. The surfactants used to prepare niosomes are often biocompatible and biodegradable, making them a safe and non-toxic carrier with no risk of causing immune reactions. The unique structure of niosomes allows them to entrap a wide range of chemicals, including hydrophilic, lipophilic, and amphiphilic drugs. Moreover, niosomes can encapsulate significant amounts of materials in a small volume of vesicles.

**Mechanism of Penetration**

Niosomes act as permeation enhancers and directly fuse with the stratum corneum and diffuse as a whole (Marianeccia et al., 2014) Niosomes have been utilized to deliver peptide drugs and have found application in the cosmetics industry. Topical application of niosomes increases the drug's residence time in the stratum corneum and epidermis while minimizing systemic absorption. In addition, niosomes are thought to enhance the horny layer's properties by reducing water loss and replenishing lost skin lipids, resulting in smoother skin. (47)

The transfer of drugs through the stratum corneum is typically passive and can occur through three pathways: intercellular, transcellular (paracellular), and transappendageal. Once a compound crosses the epidermis, it may be eliminated by dermal circulation or transported to deeper tissues. Several strategies have been evaluated to improve drug transport through the skin by overcoming the barrier function of the stratum corneum. Penetration enhancers can act by altering the intercellular lipid structure between corneocytes to increase diffusivity or modifying intracellular protein domains within the horny layer to enhance drug partitioning into the skin tissue, based on the lipid-protein-partitioning theory. Niosomes have been extensively investigated in the last decade for transdermal drug delivery and appear to be promising carriers for active substances and targeted delivery to the skin layer. (48)

There are different mechanisms that contribute significantly to the interaction between niosomes and skin, resulting in improved drug permeation. These include the surfactant molecules' penetration-enhancing effect and the impact of vesicular structures, which is likely due to the vesicles adsorbing at the stratum corneum suspension interface. (49)

In areas of the stratum corneum with high water content, the reformation of large niosomes into smaller vesicles occurs, creating new small niosomal vesicles. This phenomenon is thought to occur due to the smaller diameter of the lipid lamellar spaces in the stratum corneum, which is smaller than the size of niosome vesicles, making this mechanism more significant.

Niosomes interact with the stratum corneum through processes such as aggregation, fusion, and adhesion to the cell surface. This creates a significant thermodynamic activity gradient of the drug at the interface between the vesicle and the stratum corneum, which acts as a driving force for the penetration of lipophilic drugs across the stratum corneum. (50)

Furthermore, study examined the ability of various proniosome gel formulations to improve the permeation of ketorolac, a nonsteroidal anti-inflammatory drug, through excised rabbit skin using Franz diffusion cells. The results showed that the prepared proniosomes were effective in enhancing drug permeation and decreasing lag time. The simplicity of proniosome production and scalability make them a promising carrier option for ketorolac and other drugs. (51)

**Ethosomes:**

Ethosomes are phospholipid nanovesicles that contain ethanol, phospholipids, and water. They were created by Touitou and colleagues in 1997 and are used for the delivery of molecules through the skin and into the body. Ethosomes have been shown to enhance the transport of drugs and other substances through the skin. (52)

Ethosomes are modified versions of liposomes, which have been shown to be effective transdermal carriers. The drug's ethanolic solution is housed in the aqueous core of ethanolosomes, and a lipid bilayer makes up the outer layer. The fluidization of the phospholipid bilayers by ethanol results in the development of vesicles with a malleable structure that makes it possible to deliver molecules (drugs, pharmaceuticals, or active agents) to the deeper layers of the skin. (48)

Ethosomal systems are vesicles made primarily of phospholipids, water, and a significant amount of ethanol, and 50% of ethanol to the aqueous phase of liposomes has shown a substantial improvement in dermal transport. This concept was elaborated by Touitou et al. (32) Ethanol is known to act as a skin penetration enhancer at concentrations up to approximately 60% and Enhanced penetration to deep tissues and the systemic circulation has been reported for a range of drugs encapsulated in ethosomes.

To create vesicles with a flexible and pliable structure, ethanol is known to cause fluidization of phospholipid bilayers. Phosphorus-31 nuclear magnetic resonance (P-NMR) studies have revealed that when ethanol concentrations are within 45%, phosphatidylcholine adopts an organized bilayer structure, forming closed vesicles.(53) Moreover, when compared to commercially available patches, the delivery of testosterone through the skin using an ethosomal patch was found to be greater both in vitro and in vivo. (54)

Touitou E. et al comprehensively reviewed the potential of ethosomal delivery systems for transdermal drug delivery, which included in vitro and in vivo studies in animals and humans using various drugs. Ethosomes, due to their unique structure, have the ability to encapsulate and deliver highly lipophilic molecules, such as cannabinoids, testosterone, and minoxidil, as well as cationic drugs, such as propranolol and trihexyphenidyl, through the skin. In a double-blind two-armed randomized clinical study, the ethosomal acyclovir formulation significantly improved all evaluated parameters. (53)

The use of an ethosomal carrier system provides protection for nutraceuticals located in the lipid core, while also delivering lipophilic molecules to the targeted site. In comparison to traditional liposomes and ethanolic drug solutions, ethosomes are believed to enhance the transdermal permeability of the incorporated drug. This is due to the negative charge generated by higher ethanol concentrations, which promotes steric stabilization and deeper penetration of the drug into the skin, resulting in a consistent high transdermal flux. (55)

Comparison of liposomes and ethosomes for the topical administration of psoralen for the treatment of psoriasis. In the study, ethosomes—flexible vesicles that can penetrate the stratum corneum and target deep skin layers—were used to construct a new psoralen transdermal delivery method. Psoralen-loaded ethosomes had more skin permeability than liposomes, according to an in vitro investigation on skin permeation. When compared to a comparable ethanol solution, the ethosomes demonstrated greater biocompatibility with human embryonic skin fibroblasts, proving that the phosphatidylcholine in the ethosome vesicles enhanced their biocompatibility. These results suggested that the transdermal distribution of psoralen and probably other medications needing deep skin penetration could be enhanced by ethosomes. (56)

The development of herbal ethosomes for the delivery of herbal drugs is a novel step in the field of herbal drug technology. While herbal treatments have long been thought to be safe and free of side effects, synthetic pharmaceuticals have the drawback of having

poisonous or undesirable consequences. Herbal ethosomal medication delivery has various benefits. It can therefore entrap all pharmacological molecules, whether they are hydrophilic, lipophilic, or amphiphilic. Proteins and peptide molecules are examples of large molecules. It is non-invasive, passive, and non-toxic and has a wide range of applications in the fields of cosmetic, veterinary, and herbal medication technology. (57)

This study compared two different transdermal testosterone formulations: a Testoderm patch and an ethosomal patch called Testosome. Both formulations contained the same amount of testosterone, and the experiment was conducted in vitro using rabbit pinna skin in Franz diffusion cells. The amount of testosterone trapped in the ethosomes was measured and found to be 90 ± 3.5%. The experiment lasted for 24 hours, and HPLC was used to measure the amount of the drug in the receiver and in the skin. The results showed that the ethosomal patch allowed 30 times more testosterone to permeate the skin compared to Testoderm. Additionally, the amount of the drug found in the skin at the end of the experiment was approximately seven times greater than the Testosome. (53) There are several ways to make ethosomes, but the most popular ones include the hot technique, cold method, traditional mechanical dispersion method, and classic method. benefits of ethosome. Large molecules (peptides, protein molecules) can be delivered. improved medication delivery through the skin using transdermal technology. High patient compliance is achieved since the ethosomal medication is administered in semisolid form (gel or cream). The Ethosomal system may be immediately commercialized and is passive and non-intrusive.

**Table 5: Various ethosome base product are available in the market**

| Name of product | Manufacturer | Applications |
|---|---|---|
| Skin genuity | Physonics, Nottingham, UK | Powerful cellulite buster, reduces orange peel |
| Noicellex | Novel Therapeutic Technologies, Israel | Topical anti-cellulite cream |
| Decorin cream | Genome Cosmetics, Pennsylvania, US | Anti – aging cream that reduces the visible ageing signs of skin which includes wrinkle lines, sagging, age spots, and hyper pigmentation. |
| Cellutight EF | Hampden Health, USA | Topical cellulite cream, contains a powerful combination of ingredients to enhance metabolism and breakdown of the fat |
| Skin genuity | Physonics, Nottingham, UK | Powerful cellulite buster, reduces orange peel |
| Nanominox | Sincere, Germany | Minoxidil 4% containing product, for hair growth |
| Supravir cream | Trima, Israe | For the treatment of herpes virus, the formulation of acyclovir drug has a long shelf life with no stability problems, stable for 3 yrs, at 25o C. Skin permeation experiments showed that the cream retained its initial penetration enhancing properties even after 3 years. |

**Mechanism of penetration**

The enhanced permeability of ethosomes is due to their structure and high alcohol concentration. Ethosomes can permeate the skin by fusing with the upper stratum corneum or passing through the intercellular space and rupturing during penetration to release the drug. Ethosomes are highly flexible and deformable, which allows them to deliver drug molecules more effectively through the

skin's layers than traditional liposomes. This property enables them to penetrate the stratum corneum and reach deeper layers of the skin. (52)

The increased concentration of alcohol boosts the movement of the polar lipid heads in the lipid molecules, which results in greater flexibility and fluidity of the membranes. It also lowers the density of the intercellular lipid domains, causing the ethosomes to bend and deform during transmission. Ethosomes then interact with the altered stratum corneum, changing the intercellular lipid layers and creating their own paths to pass through the disturbed stratum corneum. This allows them to penetrate deeper into the skin and increase permeability. (58)

Secondly, the concentration of alcohol plays a crucial role in promoting drug solubility in the lipid layer and dehydrating and defatting the stratum corneum. As a result, it enhances permeation for an extended period. Moreover, it can alter the tight arrangement of lipid bilayers in the stratum corneum, reduce the phase-transition temperature, and promote the fusion of ethosomes with the skin's lipid, thereby facilitating transdermal drug absorption. Hence, higher alcohol concentrations increase permeation rates. The fusion of ethosomes with the skin's lipids during the entire transdermal process leads to the release and absorption of the drug in the deep skin. (59)

**Table 6: Effect of ethanol concentration in different ethosomal reports.**

| % ethanol concentration | Study | Results/conclusion | References |
|---|---|---|---|
| 30% ethanol | a comparison of the transdermal administration of the testosterone ethosomal patch and other commercially available patches, as well as a study of the minoxidil ethosomes in comparison to other ethanolic hydroethanolic solutions or phospholipid ethanolic micellar solutions of minoxidil. | Enhancement the delivery of minoxidil and increased entrapment efficiency of testosterone | (60) |
| 40% ethanol | A comparison of the dermal delivery of the lipophilic drug minoxidil (Mx) using ethosomes versus conventional liposomes was made using TEM and CLSM to characterize the liposomes' shape, lamellarity, particle size, and entrapment efficiency percentage (EE). | more effective than liposomes or hydroalcoholic solutions in terms of quantity and depth of delivery of a fluorescent substance into the skin. | (61) |
| 30% ethanol | Ketotifen (KT) skin delivery using deformable liposomes, under non-occlusive conditions. | improved non-entrapped KT skin delivery. The skin deposition on ethosome with KT both inside and outside the vesicles was superior. | (62) |

**Transferosome**

Gregor Cevc introduced transfersomes and the underlying idea of transfersomes in 1991. Transfersomes are better suited for the transportation of therapeutic agents across the skin than standard liposomes due to their increased elasticity. (63) In the class of ultra-elastic nanovesicles are transferosomes. They are formed of phospholipids and EAs such as Tween 20, Tween 60, Tween 80, sodium cholate, sodium deoxycholate, Span 60, Span 65, and others. (64)

The unique advantage of transferosomes as modern vesicular drug delivery systems is a highly flexible vesicle. Its flexibility allows it to fit through a pore that is considerably smaller than itself. As a result, it can increase skin penetration and deliver drugs through the skin barrier without suffering any noticeable loss. (65)

Transferosomes are an effective carrier for transdermal applications because they can transfer larger concentrations of active compounds to deeper regions of the skin after topical drug administration. These vesicular systems are capable of delivering molecules with both low and high molecular weights. (66) Due to the presence of "edge activators" in the vesicular membrane, each transfersome has at least one inner aqueous compartment that is surrounded by a lipid bilayer that has been carefully modified in terms of its properties. As edge activators, surfactants like span 80, tween 80, sodium cholate, and sodium deoxycholate have been utilized.

Adventures of transferosome are biocompatible, and biodegradable, and they can protect the drug from metabolic degradation. They can also transport therapeutic agents through most skin cells' extremely small communication channels, which are five to ten times narrower than their own diameter, without suffering significant loss. Transfersomes can be applied without the need for a complicated procedure using a non-occluded technique, in which they pass through the stratum corneum's multilayered lipid matrix as a result of the skin's moisture or osmotic force. (63)

Numerous investigations have demonstrated the ultra-deformability and skin-crossing capacity of transferosomes. Gabriele et al., 2001 made an effort to clarify in studies on animals, that the ultradeformable vesicle-based diclofenac lotion Transferosome has shown to be superior to the best commercial diclofenac gel for topical delivery. Transferosome was demonstrated to be significantly more site-specific and at least five times more efficacious than the 'competing' topical diclofenac formulations when administered to mice at a range of dosages that was appropriate. (67)

Cosco and Donatella Paolino produced yet another intriguing piece of work. They are looking at multi-drug drug delivery systems using extremely deformable vesicles. In this work, the possibility of treating non-melanoma skin cancer with resveratrol and 5-fluorouracil-loaded ultradeformable liposomes was examined. In comparison to the free drug form and the separately entrapped agents, the co-encapsulation of resveratrol and 5-fluorouracil (multi-drug carrier) in ultradeformable liposomes enhanced their anticancer effect on skin cancer cells. These multi-drug ultradeformable liposomes stop cell division in the G1/S phase, changing the way 5-fluorouracil works and boosting the activity of resveratrol. In order to treat squamous cell carcinoma, the scientists demonstrated that encapsulating 5-FU and RSV in transferosomes had a strong synergistic antitumor effect on skin cancer cells. (66)

The process by which the lipid suspension (Transferosomes) penetrates the skin is through the creation of an "osmotic gradient" caused by the evaporation of water during application.

The high rate of penetration is due to the presence of naturally occurring "transdermal osmotic gradients", which refers to a more prominent gradient across the skin. As a result, concentration has no bearing on how these elastic vesicles move. The vesicles are transported by trans-epidermal hydration, which acts as a driving force. Despite the stratum corneum pores' size being less than one-tenth of the vesicle's diameter, the vesicles' elastic nature allows them to pass through them. (68) For topical skin cancer chemoprevention, Mengbing Chen and colleagues (2018) tested carvedilol-loaded Nano-transfersomes. Both in vivo and in vitro studies have shown the beta blocker carvedilol helps prevent skin cancer. The cardiovascular system may have problems as a result of beta blockers, hence carvidilol-loaded transfersomes are used as target sites. The ratio of Carvedilol, Tween 80, and Soyphosphatiolycholine is 1:0.5:3. Apoptosis and DNA damage are stopped. For the purpose of chemoprevention of skin tumors, carvedilol is applied topically. Transfersomes that have been loaded with carvedilol cause slower medication release and fewer systemic side effects when applied topically. For topical administration, a loaded carvedilol formulation containing suspending agents and surfactants was adopted. This is advised because the drug is more thoroughly absorbed into the skin, producing beneficial pharmacological effects and fewer adverse reactions.

Transferosomes are prone to oxidative destruction, which makes them chemically unstable. Another factor that works against the use of transferosomes as drug delivery systems is the purity of natural phospholipids. The cost of transferosome formulations is high. (25)

The use of elastic vesicles as transdermal drug delivery systems is a significant scientific step and provides the following benefits: They allow for increased drug penetration through the skin; their composition is safe, and their ingredients are accepted for use in

pharmaceutical and cosmetic products; they can increase transdermal flux, prolong the release of bioactive molecules, and enhance site specificity; and they can accommodate drug molecules with a wide range of solubility. As a result, the increased distribution of bioactive compounds through the skin using an ultra-deformable vesicular carrier creates new difficulties and potential for the creation of newer, improved therapeutics. (25)

**Table 7: Components used for the preparation of transferosomes**

| Type of material | Example | Functions |
|---|---|---|
| Phospholipids | Soya phosphatidylcholine, Dipalmitoylphosphatidyl choline, Distearoylphosphatidyl choline. | Vesicles forming component |
| Surfactant | Sodium cholate, Sodium deoxy cholate, Tween 80, Span 80 | For providing flexibility |
| Alcohol | Ethanol, Methanol | As a solvent |
| Dye | Rhodamine-123, Fluorescein, Nile red | For CSLM (confocal scanning laser microscopy) study |
| Buffering agent | Saline Phosphate buffer (6.4) | As a hydrating medium |

## Challenges and Future Prospects

The therapeutic benefits and precise targeting of bioactive peptides have captured the attention of both researchers and industry professionals, making them an appealing option for the development of new biopharmaceuticals or cosmeceuticals. However, their use presents certain difficulties, such as instability when stored in different conditions and degradation when ingested orally. In addition, parenteral administration can be invasive and painful, causing patients to be less compliant. One solution to these challenges is to deliver bioactive peptides topically, which is a noninvasive and painless method that reduces peptide degradation, provides localized effects, and enhances patient adherence. (69)

Topical drug treatments are available for various disorders, but their effectiveness is often limited by physicochemical properties and toxic side effects. One promising solution to these issues is vesicular delivery systems, which have high biocompatibility, can be easily modified, and can provide controlled delivery. However, the therapeutic potential of these systems can be further enhanced by combining them with environmentally responsive dispersants such as hydrogels, ionic liquids, and deep eutectic solvents. By using a combination of these formulation approaches, it is possible to achieve improved vesicular drug delivery for topical treatments. (70)

**Aquasomes:** Ceramics carbon nanocrystalline particle cores covered with glassy cellobiose-specific targeting and molecular shielding are used in three-layered self-assembly compositions.

**Cryptosomes:** Lipid vesicles containing a polyoxyethylene derivative of phosphatidyl ethanolamine that is appropriate for pc and capable of ligand-mediated drug targeting.

**Discosomes:** Niosomes were solubilized in polyoxyethylene cetyl ether-class non-ionic surfactant solutions. Display drug targeting mediated by ligands.

**Photosomes:** As a result of photo-activated charges in the membrane's permeability characteristic, photolyase contained in liposomes releases its content.

**Virosomes:** Virus glycoprotein-infused liposomes that were inserted into the liposomal bilayers based on lipids produced from retroviruses.

**Genosomes;** Functional gene transfer using synthetic macromolecular complexes. Since they have a high rate of biodegradation and blood-stream stability, cationic lipids are the most suited. Gene transfer that is cell-specific.

**Enzymosomes:** On the surface of liposomes, enzymes are covalently immobilized or linked.

**Vesosomes:** Interdigested bilayer phase generated by adding ethanol to a variety of saturated phospholipids results in nested bilayer compartments in vitro. Vesosomes with many compartments provide serum inner contents with more protection.

**Photosomes:** Liposome-encapsulated photolysase releases its content when light strikes charges that are associated with membrane permeability.

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