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Review Article

Recent Advancements in Transdermal Drug Delivery System

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Abstract

For improved transdermal delivery and therapeutic effectiveness, drugs must possess a low molecular weight (under 1 kDa), an affinity for both lipophilic and hydrophilic phases, a brief half-life, and be non-irritating to the skin. Many factors affect drug penetration through the skin, such as species differences, skin age and site, skin temperature, state of t the skin, area of application, duration of exposure, moisture content of the skin, pre-treatment methods, and physical characteristics of the penetrant. Recent research has concentrated on various elements of transdermal drug delivery technologies, including the creation of chemical enhancers that improve drug diffusion through the skin or boost the solubility of drugs, or increase the solubility of drugs in the skin to novel innovative approaches that extend this concept to the design of super strong formulations, microemulsion, and vesicles. This article majorly focus on recent advancements in transedermal drug delivery

Keywords: health facility; governing committees; and accountability

Vesicles

Vesicles are colloidal patches filled with water and correspond to amphiphilic molecules in a bilayer arrangement. Under redundant water conditions, these amphiphilic molecules form concentric bilayers with one or further shells (multilayer vesicles). Vesicles can carry water-soluble and fat-soluble drugs to attain transdermal absorption. When employed for topical operations, vesicles can be used to achieve sustained release of stored medicines. It's also possible to employ vesicles in TDDS to control the immersion rate through a multi-layered structure owing to the presence of different factors, vesicle systems can be divided into several types, such as liposomes, transferosomes, and ethosomes, depending on the properties of the constituent substances.

Liposomes

Liposomes are round, flexible vesicles created by one or more bilayer membranes that divide an aqueous environment from another. Typically, their primary components consist of phospholipids, either containing cholesterol or lacking it. The formation of liposomes occurs spontaneously upon reconstitution of a dry lipid film in an aqueous solution, this unique structure allows liposomes to be both hydrophilic and hydrophobic and allows for the encapsulation of both water-soluble and fat-soluble compounds. [1,2]

Liposomes showcase significant promise as drug delivery systems, functioning not just intravenously but also as vehicles for drugs intended for effective administration on and through the skin. Their topical use for transdermal delivery depends on characteristics such as size, face, charge, and chemical composition Dermal or transdermal drug delivery routes of liposome-meshed drugs have some advantages when compared to systemic operation. They are;

(a) analogous to natural membranes, liposomes are suitable to store water-soluble or amphiphilic and lipophilic substances in their interior or membranes, independently.

(b) Most traditional vehicles do not effectively deliver the active ingredients into the skin as they cannot penetrate the stratum corneum. Interacting with the alike skin lipids, liposome bilayers may fluently improve local drug concentrations;

(c) Liposomes can function as a novel reservoir (force effect) for the prolonged release of dermatological active ingredients such as antibiotics, corticosteroids, and retinoic acid, thanks to the ability of individual phospholipid molecules to penetrate the lipid layers of the stratum corneum (SC) and epidermis.

(d) Liposomes can lower systemic absorption and minimize collateral symptoms due to a reservoir effect.

(e) Liposomal formulations that contain phospholipids can serve as penetration enhancers and support dermal delivery. By interacting with the SC, they destabilize the lipid matrix by fusing or mixing and increase the drug flux through the skin;

(f) Liposomes may act as rate-limiting membrane walls for the modulation of systemic absorption, i.e. they constitute a controlled transdermal delivery system.

Drug-containing liposomes when applied to the skin begin to combine with the cellular membranes and a load of active materials is released into

the cells. Thus, it isn't only a direct delivery system into the intended cells, but also one active for a long period of time. Drugs may also be released at target spots in skin appendages, adding systemic absorption. Liposomes have been constantly used in attempts to enhance the percutaneous absorption of several compounds like diclofenac, beta histidine, tetracaine, and triancinolone. It has been proposed that a follicular pathway contributes to the liposomal delivery of drugs into the deeper skin strata. Liposome delivery through the skin is veritably dependent on size. Schramlova et al. reported that liposomes up to 600 nm in diameter penetrate through the skin rather fluently, whereas liposomes with 1,000 nm and more remain interiorized in the stratum corneum. Studies considering liposomes as carriers for targeted drug delivery into pilosebaceous structures have indicated that liposomal encapsulation could benefit the treatment of hair follicle-associated diseases such as acne and alopecia. In addition, the system may be a mediator in accelerated systemic delivery via transport through this pathway. In other studies, liposomes were developed as hair follicle-picky systems for large and small motes, including genes, opening the field of gene and/ or molecular remedy to restore hair growth or help hair loss in androgenic alopecia.

Drugs prepared and marketed by using this technique are: Lipo-Active gel (Vit C)

II. Transferosomes

Transferosomes are vesicular carrier systems that are specially designed to have at least one inner aqueous compartment that is enclosed by a lipid bilayer, together with an edge activator. [3,4]

Transferosomes are deformable Liposomes that can permeate into the deeper layers of the skin. These carriers are characterized by two crucial features high elasticity of the lipid bilayer (ultra-flexibility and ultra-deformability), and osmotic grade around the skin.

These features result in better permeation into the deeper layers of skin through the SC, better entrapment of API, and controlled release at the target location. These properties make transferosomes a better carrier for TDD as they can travel through pore sizes much lower than their size. As a result, transferosomes undergo a series of reversible stress-dependent adaptations through intercellular lipidic channels. This convoluted transport of transferosomes results in the delivery of drugs across the skin readily and reproducibly. Unlike solid lipid nanoparticles and liposomes, which affect advanced drug deposition in the skin layer due to a burst effect, transferosomes show controlled release due to the generation of an osmotic grade. This avoids the accumulation of toxic substances in the body tissues.

Transferosomes, unlike solid LNPs (Lipid Nanoparticles) and liposomes, have advanced surface hydrophilicity and in addition to the transcutaneous route followed by liposomes, transferosomes transport through what's known as transpore hydrotaxis[5,6].

Transferosomes are administered in a non-occlusive manner to induce an osmotic gradient across the skin, relying on the effects of hydration for effective delivery. The use of edge activators (EAs) aids in the generation of an osmotic grade. EAs assist transferosomes in penetrating the tight lipid junctions between SC cells. Due to their advanced surface hydrophilicity, these particles have an advanced tendency to bind and retain further water. Hence, dehydration of these particles rarely occurs. This prevents agglomeration and fusion of vesicles imparting further stability and increased shelf life. When the transferosome reaches the SC, it starts accumulating at the site and the particle starts to deform to fit into the pore. Even so, in the case of solid LNP, this property of deformability doesn't exist, and the particle stays dilated. This elasticity of transferosomes allows the atoms to pass through the tenuous pores in the SC. This transport is biased to the elasticity of the transferosomes and can be achieved by using suitable ratios of lipids and surfactants. The elasticity of transferosomes also reduces the threat of rupturing the particle and releasing the drug at off-target sites. The transport of transferosomes involves the principles of elasto- mechanics and transepidermal hydrotaxis. It is given as the following steps:

1. Transferosomes — SC interaction

2. Reversible deformation of transferosome to fit into the lipid channels between the corneocytes.

3. Hydrotaxis of transferosomes from lipophilic SC to aqueous viable epidermis.

4. conformation of osmotic grade and continued movement of transferosomes to largely perfused dermis rich in the capillary bed.

5. Controlled release of drug via osmosis into the microcirculation via capillaries and release into the systemic circulation.

The design of transferosomes is capable of penetrating skin pores 5 to 10 times smaller than their size to enable the delivery of skin-penetrating drugs with MW up to 1000 Da. Transferosomes are versatile tools for both local and systemic delivery of large macromolecules, including various steroids, proteins, insulin, corticosteroids, ketoprofen, anticancer drugs, and hydrophilic macromolecules. They are also important in the transport of genetic material and show potential for vaccine development[7,8].

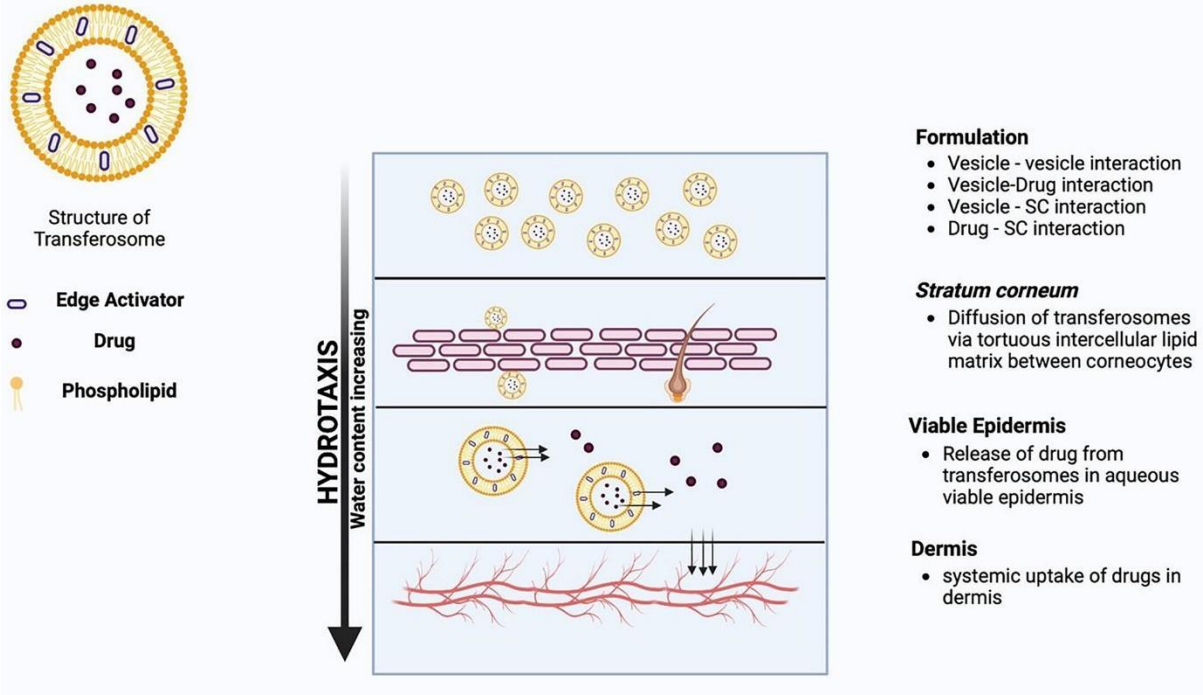

Figure 1: A schematic overview of different stages of the transferosomes when applied to the skin. The transferosome-skin interaction results in the diffusion of transferosome through the SC using an intercellular route. The diffusion of the transferosomes is driven by the water gradient in the skin layers (hydrotaxis). When the transferosome reaches the viable epidermis, the drug is released out of the transferosome into the aqueous environment. The released drug is then taken up into the systemic circulation by the capillary bed in the dermis.

Drugs prepared and marketed by using this technique are: Voltaren Emulgel (Diclofenac)

III. Ethosomes

Ethosomes are composed of phospholipids, alcohol, and water. In contrast to liposomes, ethosomes contain higher levels of alcohol. Ethosomes enhance the transdermal absorption of medications, with phospholipids further aiding this process. [4,5]

Ethosomes represent a sophisticated category of non-invasive delivery systems that facilitate the transport of pharmaceutical agents to the deeper strata of the skin and into the systemic circulation. Composed of soft and malleable lipid-based vesicles, these carriers are specifically designed to enhance the penetration and bioavailability of active compounds. The unique structural composition of ethosomes allows for seamless integration into lipid membranes, thereby optimizing transdermal drug delivery efficacy. By employing ethosomes, it is possible to achieve superior therapeutic outcomes while significantly reducing the reliance on invasive administration methods. This innovative approach not only maximizes the effectiveness of active agents but also underscores a patient-centered strategy in therapeutic interventions. They're composed substantially of phospholipids, (phosphatidylcholine, phosphatidylserine, phosphatidic acid), high concentrations of ethanol, and water. The high concentration of ethanol makes the ethosomes unique, as ethanol is known for its disturbance of skin lipid bilayer organization; thus, when integrated into a vesicle membrane, it gives that vesicle the capability to access the stratum corneum. The presence of high ethanol concentration in the lipid membrane results in a structure that is less tightly packed compared to traditional vesicles. Despite this looser arrangement, the membrane still exhibits a comparable level of stability. This unique characteristic contributes to a more flexible and adaptable structure that facilitates improved distribution of drugs within the lipid layers of the stratum corneum, enhancing their effectiveness in penetrating the skin barrier[6,7].

Types of ethosomal systems

There are three types of ethosomal systems grounded on their composition. They are Classical ethosomes, Binary ethosomes, and Transethosomes[8,9].

A.Classical ethosomes

Classical ethosomes are a revision of classical liposomes and are composed of phospholipids, a high concentration of ethanol up to 45 w/w, and water. Classical ethosomes have been demonstrated to possess advantages over traditional liposomes in the context of transdermal drug delivery. Their smaller size, negative ζ-potential, and superior entrapment efficiency contribute to their effectiveness. Furthermore, classical ethosomes exhibit enhanced skin permeation and improved stability profiles when compared to traditional liposomes. The molecular weights of medications incorporated in traditional ethosomes have varied from 130.077 Da to 24 kDa[10,11].

B.Binary ethosomes

Binary ethosomes were introduced by Zhou et al. They were primarily developed by incorporating an additional type of alcohol into the traditional ethosomes. The alcohols most frequently utilized in binary ethosomes are propylene glycol (PG) and isopropyl alcohol (IPA).

C.Transethosomes

Transethosomes represent an advanced category of ethosomal systems, initially described by Song et al. in 2012. This innovative ethosomal formulation encompasses essential characteristics of traditional ethosomes, while also integrating additional components, such as penetration enhancers or edge activators (surfactants). The development

of transethosomes serves to combine the beneficial properties of classical ethosomes, which are renowned for their enhanced capacity for skin permeation, with the unique features of deformable liposomes, or transferosomes, characterized by their flexible structure that allows adaptation to various skin microenvironments. The objective of creating transethosomes is to optimize drug delivery systems, thereby enhancing the efficacy and absorption of therapeutic agents through the skin. Different types of edge activators and penetration enhancers have been developed to produce ethosomal systems with better characteristics. Transethosomes are known to encapsulate drugs with molecular weights between 130.077 Da and 200 – 325 kDa.

Drugs prepared and marketed by using this technique are: Etoderm (Diclofenac).

Iv. Invasomes

Invasomes are flexible liposomes conforming to phospholipids, ethanol, and one terpene molecule or a mixture of terpenes. Ethanol increases the fluidity of lipids in the vesicle structure, creating a soft structure less rigid than conventional liposomes and, thus, enhancing its permeability into the skin. They serve as potential carriers with advanced skin penetration. Invasomes have an advanced rate of skin penetration than ethosomes and liposomes. Invasomes offer a number of benefits, such as enhancing patient comfort and compliance and promoting therapeutic efficacy. They constituted a small amount of ethanol, a minor amount of a blend of terpenes (cineole, citral, and d- d-limonene), and unsaturated soybean lecithin with a high percentage of phosphatidylcholine. [13,14]

When ethanol is integrated into a vesicle's membrane, it gives that vesicle the ability to penetrate the stratum corneum because ethanol is known for disrupting the organization of the skin's lipid bilayers. Due to the presence of ethanol, the lipid membrane is packed less tightly than usual vesicles while maintaining original stability, allowing for a further malleable structure, giving it more freedom and the capability to squeeze through tight spaces, such as the gaps created by disturbing the lipid in the stratum corneum. By interacting with lipid molecules in the polar head group region, ethanol causes the stiffness and fluidity of SC lipids to change. A regional application over the membrane may be encouraged by such an initial release of active ingredients on the skin's surface. With the release of trace quantities of ethanol through invasive dissipation, the SC lipids might fluidize (being outside vesicles). In addition, a significant portion of the invasomes is presumably broken to enter the upper SC layers, releasing terpenes, ethanol, and unsaturated phospholipids[15].

The invasome's reduced vesicle size aids in the drug's penetration as well. Moreover, since complete deformable, high hydrophilic vesicles appear to follow the skin hydration gradient, the transepidermal osmotic gradient's presence is essential (the driving force) for the diffusion of these vesicles. On the other hand, vesicles merging with the intercellular lipids of the SC may affect the drug being released into the skin layers.

Moreover, the pilosebaceous units constantly served as a substantial pathway for invasome penetration into the skin.

V.Niosomes

Niosomes represent an innovative vesicular drug delivery system that facilitates sustained, controlled, and targeted administration of pharmaceutical agents. Niosomes can be unilamellar, oligolamellar or multilamellar.

Niosomes are lipid-based carriers primarily composed of non-ionic surfactants, which contribute to their non-toxic nature. These surfactants help form a bilayer structure that encapsulates various compounds, making niosomes effective for drug delivery and other applications. In addition to non-ionic surfactants, niosomes can also include cholesterol or its derivatives, which play a crucial role in stabilizing the bilayer and enhancing the fluidity of the vesicle membrane. The incorporation of charged molecules can further modify the properties of niosomes, allowing for tailored functionalities depending on the intended use. Cholesterol adds rigidity to the structure, while the charged molecule helps maintain the stability of the preparation. The capability of niosomes to incorporate different drugs with a wide range of solubilities suggests that they have a high potential for future remedial operations. Niosomes can encapsulate aqueous solutions, effectively trapping both hydrophilic and hydrophobic substances. Niosomes have been used for encapsulating drugs, nutraceuticals, antioxidants, micronutrients, and other substances. Because of their implicit capability to carry a variety of therapeutics, these vesicles have been extensively used as drug delivery systems to achieve drug targeting, controlled release, and permeation enhancement.

There's no single mechanism that can sufficiently explain the capability of niosomes to increase drug transfer through the skin, and several mechanisms have been proposed, including:

i. Niosomes diffuse from the stratum corneum layer of the skin as a complete unit.

ii. New smaller vesicles are generated within the skin, resulting in the re-formation of problematic vesicles. The water content of the skin is a pivotal issue for interpreting and establishing this mechanism. The smaller diameter of lipid lamellar spaces in the stratum corneum compared to noisome vesicles makes this mechanism more significant.

iii. Niosomes interact with the stratum corneum with aggregation, fusion, and adhesion to the cell surface which causes a high thermodynamic activity gradient of the medicine at the vesicle- The surface of the stratum corneum serves as a key factor in the effective penetration of lipophilic drugs through this barrier. Scanning electron microscopy verified the emulsion of niosome vesicles of oestradiol on the face of the skin

iv. Niosomes may modify stratum corneum structure which makes the intercellular lipid barrier of the stratum corneum looser and further permeable

v. Non-ionic surfactant itself, the composing component of niosome, acts as a permeation enhancer and might partially contribute to the enhancement of drug permeation from niosomes

The type of surfactant plays an important part in the alteration of permeation using niosome vehicles.

New largely flexible niosomes, known as elastic vesicles, have been proposed and are reported to be effective at delivering molecules through the skin since edge activators (I.e., ethanol) give vesicles with elastic characteristics, which allow them to access more readily into the deeper layers of the skin[16].

The major limitation of niosomes is the liquid nature of the medication, because when applied they may leak from the application site. This challenge can be overcome by objectification of niosomes in an acceptable vehicle, which can be achieved by adding gelatinizing agents to niosomal dispersions, thereby forming a niosomal gel. Niosomal gels were developed to improve the retention of therapeutics within the skin and to achieve elevated and sustained concentrations of the drug in the dermal layers[17].

Proniosomes are non-ionic-based surfactant vesicles, they're known as ‘‘dry niosomes’’ because they may necessitate hydration before drug release and permeation through the skin. Proniosomal gels have been used in TDD because they act as penetration enhancers that enhance the drug saturation from the skin barrier. Upon hydration proniosomes are converted into niosomes which are able to diffuse across the stratum corneum and also adhere to the cell surface causing a high thermodynamic activity gradient of the drug at the vesicle/ stratum corneum surface,

therefore acting as the driving force for the penetration of lipophilic drugs across the skin[18].

Drugs prepared and marketed by using this technique are: Aceclofenac gel (ACEWELL HOT GEL)

VI . Phytosomes

Phytosomes, sometimes referred to as herbosomes, represent an innovative vesicular drug delivery system. Their primary function is to significantly enhance the absorption and bioavailability of drugs that are poorly soluble in water, which can often limit their therapeutic effectiveness. These specialized carriers consist of a sophisticated complex formed by phospholipids and natural active phytochemicals derived from plants. The process of creating phytosomes involves a specific reaction between phosphatidylcholine—an essential component that provides hydrophilic polar head groups—and plant extracts. This reaction takes place in an aprotic solvent, facilitating the integration of the plant's beneficial compounds into a stable, cell-like structure, thereby improving their delivery and efficacy in various medical applications. These formulations demonstrate enhanced pharmacological and pharmacokinetic properties when compared to existing preparations. The lipid-soluble phosphatidyl component fully envelops the hydrophilic phytoconstituent-choline complexes, ensuring optimal interaction and stability. Phytosomes have remarkable benefits such as high drug encapsulation, revealing a better stability profile (chemical bonds are formed among the polar head of the amphiphile molecule and phytoconstituent), and better bioavailability. Phytochemicals, or plant chemicals, consist of a variety of naturally occurring bioactive substances generated by plants. Phenolics, alkaloids, carbohydrates, lipids, terpenoids, and other nitrogen-containing compounds are the most structurally different major categories of phytochemicals. The proposed mechanism for phytosome creation illustrates the formation of hydrogen bonds between the phytochemical and the polar head of a phospholipid[19].

Drugs prepared and marketed by using this technique are: Ginkgoselect (Ginkgo biloba)

Conclusions

TDDs is increasingly favoured as a delivery method for multiple diseases, due to its advantages, including non-invasiveness and self-administration, which enable uniform drug distribution at set and controlled rates. Consequently, TDD technology is gaining popularity in the pharmaceutical sector. Nanoparticles, liposomes, niosomes, and nanoemulsions are examples of chemical transdermal delivery systems that have been employed to transport medications through the skin. These delivery systems, however, sometimes encounter the stratum corneum, which prevents hydrophilic molecules and macromolecules from penetrating unbroken skin. Techniques for physical enhancement have demonstrated an ability to improve drug delivery to the systemic circulation, facilitating the administration of various drugs, particularly those that are usually challenging to deliver with chemical penetration enhancement methods, including macromolecules. Nonetheless, at present, there are just a handful of products available that utilize this method. However, there are upcoming opportunities for the broader adoption of TDD as a viable approach for drug delivery systems.

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