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Recent Advances in Development of Vesicular Carrier for Transdermal Drug Delivery: A Review

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ABSTRACT

Transdermal drug delivery has gained significant attention as a non-invasive and convenient method for administering drugs. However, the stratum corneum, the outermost layer of the skin, poses a significant barrier to drug permeation. To overcome this challenge, vesicular carriers have emerged as promising systems for enhancing drug delivery through the skin. This review highlights recent advances in the development of vesicular carriers for transdermal drug delivery. Liposomes, niosomes, transfersomes, ethosomes, and solid lipid nanoparticles are among the commonly used vesicular carriers. These carriers offer advantages such as improved drug solubility, prolonged drug release, and enhanced drug stability. Additionally, they can encapsulate a wide range of drugs, including hydrophilic and lipophilic compounds. Various strategies have been employed to optimize vesicular carriers for transdermal drug delivery. These include modifying the vesicle composition, size, and surface charge to enhance skin penetration. The incorporation of penetration enhancers, such as surfactants, has also been explored to improve drug permeation across the skin. Furthermore, advancements in nanotechnology have led to the development of novel vesicular carriers, such as nanostructured lipid carriers and elastic liposomes. These carriers offer improved drug loading capacity, sustained release profiles, and enhanced skin penetration. Moreover, the use of vesicular carriers has shown promise in delivering a wide range of therapeutic agents, including small molecules, peptides, proteins, and genetic material. The ability to encapsulate and deliver these diverse drug entities opens new possibilities for transdermal drug delivery in various therapeutic areas.

Keywords: Transfersomes, liposomes, niosomes, ethosomes, ufasomes, sphingosomes and cubosomes, transdermal drug delivery, vesicular formulation.

I. INTRODUCTION

From 2021 to 2030, the global transdermal drug delivery systems market is expected to increase at a compound annual growth rate (CAGR) of 4.9 percent, rising from $52,476.50 million in 2020 to $87,322.40 million in 2030[(1)]. Transdermal drug delivery systems, which transport medications through the skin for therapeutic purposes, serve as an alternative to oral, intravascular, subcutaneous, and transmucosal routes. Transdermal drug delivery systems provide a painless, systematic form of medication delivery by applying the medicine to healthy, unbroken skin [(1-2)].

The skin serves as a popular site for drug administration for both local and systemic effects since it is the largest organ of the body and provides a direct entrance for medication into the systemic circulation. This bypasses all of the issues associated with the oral and parenteral routes. However, due to its nature as a barrier, the skin presents a significant obstacle to drug penetration, reducing transdermal bioavailability. Several approaches have been employed to improve drug penetration through the skin, and ongoing research has led to the development of newer vehicles/carriers, specifically vesicular carriers, lipid-

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microemulsions, and other systems [2].

Furthermore, the development of newer technologies for delivering drug molecules along with safe penetration enhancers and the utilization of vesicular carriers have reignited interest in constructing transdermal drug delivery systems for medications previously deemed unsuitable [3].

Drug delivery from vesicle carriers, such as liposomes and niosomes, in transdermal formulations has been studied for a variety of purposes. However, both are inherently unstable, exhibit poor skin permeation, and lower entrapment efficiency. In addition, they increase Trans Epidermal Water Loss (TEWL), so they are mostly used in topical delivery in limited amounts [4].

According to recent studies, traditional vehicles such as suspensions and emulsions and traditional carriers such as liposomes and niosomes, can cause potential damage to the stratum corneum and reduce its thickness. They can also lead to skin dryness, demonstrate low penetration through the stratum corneum, and exhibit low entrapment efficiency [5]. However, some of these issues can be overcome by designing a unique vehicle or vesicular carrier.

The stratum corneum (SC), viable epidermis, dermis, and the subcutaneous tissue constitute the four primary layers of human skin. They are, on average, 0.5 mm thick (varying from 0.05 mm to 2 mm). The SC is a thick (10–20 µm) hydrophobic surface layer that contains 10–15 layers of interdigitated corneocytes that are regularly shed and replaced. Extracellular lipid constitutes 10% of the dry weight of this layer, while intracellular protein accounts for the remaining 90% (mainly keratin). As the cells differentiate during their migration to the surface, the phospholipid content decreases, and the sphingolipid (glucosylceramide and ceramide) and cholesterol content simultaneously increases. The SC is devoid of phospholipids but is enriched with ceramides and neutral lipids (cholesterol, fatty acids, cholesteryl esters). The skin's barrier lipids are tightly regulated, and any damage to them prompts active synthetic processes to replenish them [4, 6].

The relative humidity of the surroundings significantly impacts the skin's barrier function. When transitioning from a humid to a dry environment, transepidermal water loss can increase by 6–7 times. The reduction of lamellar bodies in the outermost stratum granulosum, the deposition of lamellar body contents at the stratum granulosum-stratum corneum interface, and the decrease in the amount of intercellular lamellae in the stratum corneum all could affect the barrier function. Conversely, transitioning from a wet environment to a dry one quickly stimulates epidermal growth, and vice versa [6, 7, 8].

The stratum corneum is a complex tissue due to the presence of multiple self-regulating enzymatic systems. It is metabolically active and undergoes dynamic structural alterations. This tissue encompasses numerous defensive (protective) functions, each with its structural and metabolic foundation. Newer metabolically-based methods have shown promise in broadening the range of drugs that can be delivered transdermally in hairless mouse epidermis when used alone or in conjunction with traditional methods. While these new approaches are highly promising, they may raise concerns about the risks associated with a significantly permeabilized stratum corneum, should they prove equally effective in human skin [6][8].

Instruments like the Vapometer, which detects transepidermal water loss, are utilized to determine the permeability barrier function (TEWL). The accuracy of TEWL measures has been verified both in vivo and ex-vivo using human and rodent models [9,10].

When salicylic acid (SA) penetration was evaluated in barrier-perturbed skin compared to unmodified skin in the same individual, the average increase was 2.2-fold in acetone-treated skin, 46-fold in moderate dermatitis, and 146- and 157-fold in severe dermatitis and tape-stripped skin, respectively. SA penetration was shown to be highly correlated with TEWL measurements of barrier disruption [7].

Hydration and chemical enhancers can also be used to modify the stratum corneum, or it can be bypassed/

eliminated via microneedles, ablation, and follicular administration. Examples of electrically assisted procedures include ultrasound, iontophoresis, electroporation, magnetophoresis, and photomechanical waves. The interaction of chemical enhancers, ultrasound, iontophoresis, and electroporation is particularly fascinating[11].

A novel high throughput (HTP) method for formulation screening is proposed, which is at least 50-fold more efficient in terms of skin utilization and up to 30-fold more efficient in terms of hold-up times than current methods (Franz diffusion cells). It is based on the conductivity of the skin and the penetration of mannitol into the skin. This strategy was used to conduct at least 100 tests in a single day [12].

This article provides a detailed account of various vesicular carriers, their formulation characteristics, pros and cons, along with a compilation of recent trends in transdermal drug delivery technology with respect to vesicular carriers.

II. VESICULAR CARRIERS

Mezei and Gulasekharam were the first to demonstrate that liposomes could be useful for topical therapy in 1980(13). Vesicles are known as water-filled colloidal particles. The walls of these capsules are made up of bilayers of amphiphilic molecules. In the presence of excess water, these amphiphilic compounds can form either one (unilamellar vesicles) or multiple (multilamellar vesicles) concentric bilayers [14]. Hydrophilic drugs can be enclosed in the internal aqueous compartment, whereas the vesicle bilayer can bind amphiphilic, lipophilic, and charged hydrophilic drugs through hydrophobic and/or electrostatic interactions [15].

The vesicles are predominantly composed of phospholipids or non-ionic surfactants [15, 16]. These two types of vesicles are referred to as liposomes and niosomes. The size, charge, thermodynamic phase, lamellarity, and bilayer elasticity of vesicles are all influenced by the composition of the vesicles. These physicochemical properties significantly impact vesicle behavior and, consequently, their effectiveness as a drug delivery method. They can be classified into the following roles:

1. Serve as drug carriers to transfer entrapped drug molecules into or across the skin.
2. Act as penetration enhancers by allowing individual lipid components to penetrate the stratum corneum, leading to alterations in the intercellular lipid lamellae within this skin layer.
3. Act as a depot for the sustained release of dermally active compounds over time.
4. Provide a regulated transdermal delivery method by acting as a rate-limiting membrane barrier for modulating systemic absorption.

In vitro permeation studies have demonstrated that liquid-state vesicles are more successful at increasing drug transport than gel-state vesicles [17, 18, 19, 20]. In vivo confirmation of these findings has been recently published [21].

1. Conventional Liposomes: The first generation of liposomes is termed conventional liposomes. They are a type of vesicle composed of a lipid bilayer that surrounds aqueous compartments and can be composed of cationic, anionic, or neutral (phospholipid) lipids, as well as cholesterol. Natural phospholipids or lipids, such as 1,2-distearyl-sn-glycerin-3-phosphatidylcholine (DSPC), sphingomyelin, lecithin, and monosialoganglioside, have been used in traditional liposome formulations. They have been widely used to transport hydrophilic and lipophilic compounds [22, 23, 24, 25, 26].

Table 1: Methods of separating carriers for transdermal drug delivery

S.No.	Carriers	Method Name	Reference
1	**Liposomes**	• Thin-film hydration process • Reverse-phase evaporation process • Solvent injection process	(27)
2	**Transfersomes**	• Thin film hydration technique/rotary evaporation-sonication method • Vortexing-sonication method • Modified handshaking process • Suspension homogenization process • Reverse-phase evaporation method • High-pressure homogenization technique	(28)
3	**Ethosomes**	• Cold method • Hot method • Mechanical dispersion method	(29)
4	**Niosomes**	• Ether injection method • Sonication • Multiple membrane extrusion method • Reverse phase evaporation technique (REV) • G.Trans membrane pH gradient (inside acidic) drug uptake process	(30)
5	**Ufasomes**	• Thin film hydration method • By addition of alcohol • Autopoeticprocess	(31)
6	**Sphingosomes**	• Lipid flimformation (hand shaking method) • Solvent spherule method • Calcium induced fusion method	(32)
7	**Cubosomes**	• Top-down approach • Bottom-up approach	(33)

Table 2: Carriers composition

Carriers	Class	Example	Use	Reference
Liposomes	Phospholipids	Soya phosphatidyl choline, egg phosphatidylcholine, dipalmitoylphosphatidyl choline	Vesicles forming component	**(8, 23, 24, 25)**
	Polyglycol	Propylene glycol, Transcutol RTM	Skin penetration enhancer	
	Cholesterol	Cholesterol	Provides stability to the vesicle membrane	
Transfersomes	Phospholipids	Soya phosphatidyl choline, egg phosphatidylcholine, dipalmitoylphosphatidyl choline	Vesicles forming component	**(34, 35)**
	Surfactants	Sodium cholate, Sodium deoxycholate, Tween-80, Span-80, Tween 20	Vesicles forming component	
	Solvents	Ethanol, methanol, isopropyl alcohol, chloroform	As Solvents	
	Buffering agents	Saline phosphate buffer (pH 6.4), phosphate buffer pH 7.4	As hydrating medium	
Ethosomes	Phospholipids	Soya phosphatidyl choline, egg phosphatidylcholine, dipalmitoylphosphatidyl choline	Vesicles forming component	(36, 37, 38, 39, 40, 41)
	Polyglycol	Propylene glycol, Transcutol RTM	Skin penetration enhancer	
	Alcohol	Ethanol, isopropyl alcohol	Provides softness to the vesicle membrane, as a penetration enhancer	
	Cholesterol	Cholesterol	Provides stability to the vesicle membrane	
	Dyes	Rhodamine -123, Rhodamine red, Fluorescence isothiocyanate,	For characterization study	
	Vehicle	Carbopol 934	As a gel provider	
Niosomes	Nonionic surfactants	Alkyl glycerol, alkyl glycosides, polysorbate 60,	Vesicles forming component	(42, 43, 44, 45)
	Cholesterol	Cholesterol	Provides stability	
	Charge inducer	diacetyl phosphate (DCP) and phosphotidic acid.	Increases stability	
	Hydrating medium	phosphate buffer	Buffering agent	
Ufasomes	Fatty acids	10% oleic and linoliec acid	Vesicle forming component	(46, 47, 48)
	Solvents	Chloroform, stream of nitrogen	membrane permeability	
	Buffering agent	Tris-hydroxymethyl aminomethane buffer (pH 8-9)	Hydrating medium	
Sphingosomes	Sphingolipids	Egg, brain, milk, soybean, plant yeast	Vesicle forming component	(49, 50)
	Cholesterol	Cholesterol	membrane stability	
Cubosomes	Amphiphilic lipids	glyceryl monooleate	Vesicle forming component	(51, 52, 53)
	Stabilizers	Poloxamer 407, polyethylene glycol 400	Membrane stability	

Table 3: Advantages and disadvantages of liposomes[54, 55]

Advantages	Disadvantages
Liposomes have the ability to form complexes with both negatively and positively charged substances.	The expense of production is high.
Liposomes provide some protection for DNA from degradative processes.	Encapsulated drug/molecule leakage and fusion
Liposomes have the ability to carry huge amounts of DNA, maybe as large as a chromosome.	Oftentimes, phospholipids are subjected to oxidation and hydrolysis-like processes.
Liposomes have the ability to target specific cells or regions.	Short half-life
Effects of improved pharmacokinetics	Low solubility
Increase in the drug's effectiveness and therapeutic index	Fewer stables

The key goals of a method for liposome nanoformulation formation are the generation of monodispersed particles with the desired degree of lamellarity, efficient drug inclusion, and long-term colloidal stability of products [13, 27, 55]. The primary processes involved in traditional liposome preparation methods include:

1. Dissolution of lipids in an organic solvent;
2. Drying down the resultant lipid solution to remove the organic solvent;
3. Hydrating the lipid with an aqueous media (followed by agitation/stirring);
4. Downsizing (and/or changing the lamellarity);
5. Post-formation processing (purification, sterilization)[56].

Mechanism of Action of Liposomes:

A liposome consists of a region of aqueous solution inside a hydrophobic membrane. Hydrophobic chemicals can easily dissolve into the lipid membranes. In this way, liposomes can carry both hydrophilic and hydrophobic molecules, although the extent of the location of the drug will depend on its physicochemical characteristics and the composition of the lipid. For the delivery of necessary drug molecules to the site of action, the lipid bilayers can fuse with other bilayers of the cell (cell membrane), which would release the liposomal contents.

Adsorption

(Interaction of liposomes within cell membrane)

↓

Endocytosis

(Cell surface membrane is engulfed and internalised into the liposomes)

↓

Fusion

(Liposome lipid bilayers fuse with the lipoidal cell membrane, resulting in direct delivery of liposomal contents into the cytoplasm.)

↓

Lipid exchange

(Lipid transfer proteins in the cell, recognizes liposomes and cause lipid exchange)

For instance, cancer cells consume vast amounts of fats to meet their rapid growth requirements, and they perceive liposomes (laden with anti-cancer drugs) as a potential source of nutrients. When targeted by liposomes, they are absorbed. Once the anti-cancer medications are released from the liposome into the tumor site, they destroy the cancer cells [57, 58].

Transfersomes: Transfersomes are a specific type of liposome composed of phosphatidylcholine and an edge activator (e.g., sodium cholate, sodium deoxycholate, span 80, and Tween 80). They are soft, malleable vesicles designed to deliver active substances more effectively [59]. The name is derived from the Latin word 'transfere,' meaning 'to carry across,' and the Greek word 'soma,' meaning 'body.' The pros and cons of transfersomes are outlined below (Table 4) [60, 61, 62, 63].

Table 4: Advantages and disadvantages of transfersomes [64]

Advantages	Disadvantages
A constant infusion of a substance is delivered via transdermal medication over a long period of time.	Drugs having hydrophilic structures pass through the skin too slowly to be of therapeutic value.
These systems allow for self-administration.	Because the patch size limits the amount that can be administered, the drug molecule must be powerful.
They are appropriate for medications having a limited therapeutic window.	High medication doses are not recommended.
Dosing frequency is reduced due to a longer duration of effect.	It is possible that skin irritation and hypersensitivity reactions will occur.
Bioavailability has improved.	It is not possible to deliver drugs that require high blood levels.
Improved therapy and fewer side effects	Because to oxidative breakdown, it is chemically unstable.

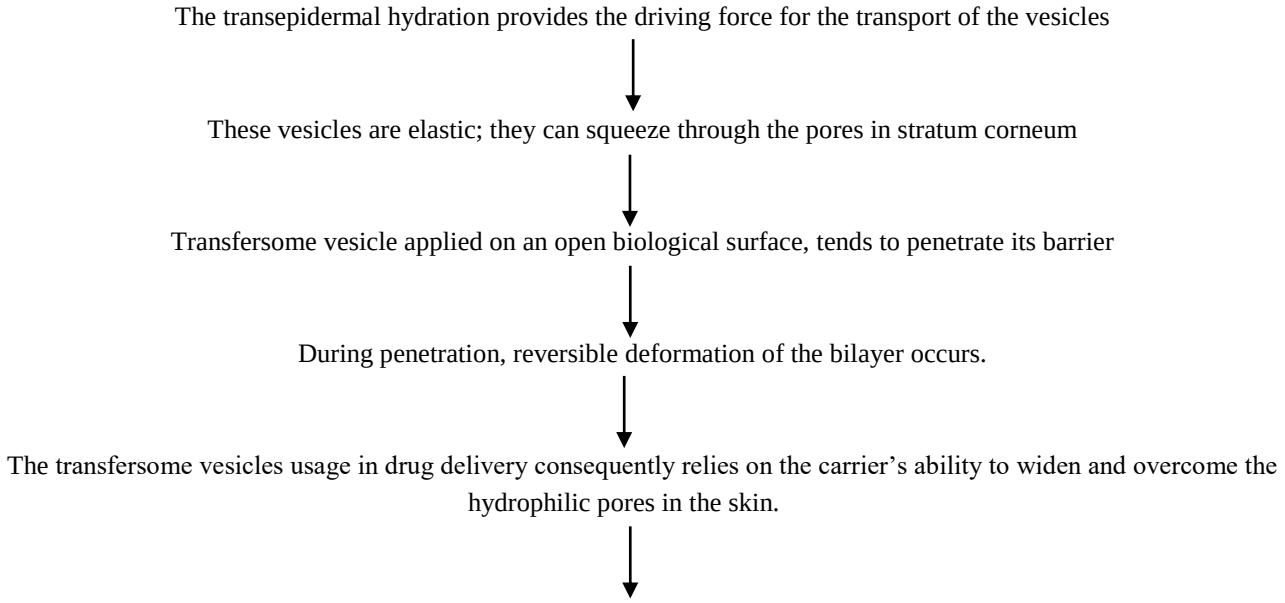
2.1 Mechanism of penetration of transfersomes

Transferosomes overcome the skin penetration difficulty Transferosomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipids of the stratum corneum. Two mechanisms of action have been proposed.

1. Transferosomes act as drug vectors, remaining intact after penetrating the skin.

2. Transferosomes act as penetration enhancers, disrupting the highly organized intercellular lipids from the stratum corneum, thereby facilitating drug molecule penetration into and across the stratum corneum. (Patel R., Singh S.K., Singh. S, Sheth N.R., Gendle R. "Development and Characterization of Curcumin Loaded Transferosome for Transdermal Delivery" Journal of Pharmaceutical Research and Science, 2009; 1(4): 71-80).

The formation of an "osmotic gradient" due to the evaporation of water on the skin surface is the mechanism for penetration [65].



3. Ethosomes: Ethosomes are soft, flexible lipid vesicles primarily composed of phospholipids, a high concentration of alcohol (20-45%), and water. Touitou and her colleagues initially developed ethosomes in 1997 [66, 67]. Owing to their high deformability, these carriers possess fascinating properties connected to their capacity to fully permeate human skin. The physicochemical properties of ethosomes allow these vesicular phospholipids to function as the vesicle-forming component of the ethosomal system. Phospholipids with various chemical structures such as phosphatidyl choline and phosphatidyl ethanolamine are utilized at concentrations ranging from 0.5 to 10%.

Table 5: Advantages and disadvantages of ethosomes

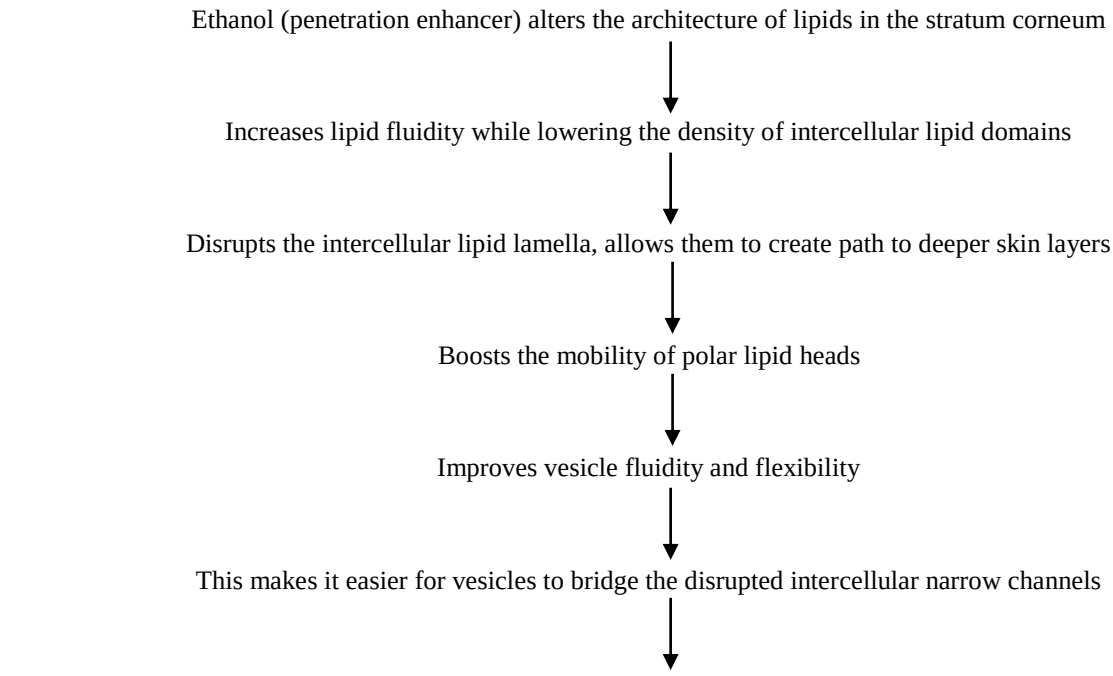
Advantages	Disadvantages
In its formulation, it uses non-toxic raw materials.	Poorly shelled ethosomes may clump together, resulting in precipitation.
Large molecule delivery.	Excipients and enhancers in drug delivery systems cause skin irritation or dermatitis.
Drug permeability through the skin is improved for transdermal drug delivery.	The loss of product occurs when ethosomes are transferred from the organic to the aqueous layer.
Ethosomes have the highest transdermal flux, which improves drug diffusion through deeper layers of skin.	The drug's molecular size should be small enough to be absorbed via the skin.
Under both occlusive and non-occlusive situations, ethosomes improve skin delivery.	The practical yield is poor.

3.1 Mechanism of skin penetration

The main advantage of ethosomes over liposomes is the increased permeation of the drug. The mechanism of drug absorption from ethosomes is not fully understood, but it likely occurs in two phases:

1. Ethanol Effect: Ethanol acts as a penetration enhancer through the skin. The mechanism of its penetration-enhancing effect is well established. Ethanol penetrates into intercellular lipids, increases the fluidity of cell membrane lipids, and decreases the density of the lipid multilayer of the cell membrane.
2. Ethosome Effect: The increased cell membrane lipid fluidity caused by the ethanol in ethosomes results in increased skin permeability. As a result, the ethosomes permeate very easily into the deep skin layers, where they fuse with skin lipids and release the drugs into the deeper layer of the skin.

The mechanism is illustrated below [68, 69].



4. Niosomes: Niosomes are a unique drug delivery technology that encapsulates drugs in a vesicle. The term niosome derives from the formation of the vesicle, which is composed of a bilayer of non-ionic surface-active chemicals. Niosomes are small, microscopic particles. Their size, on the nanometric scale, is misleading. Although niosomes are physically similar to liposomes, they have a few advantages. Recently, niosomes have been demonstrated to improve transdermal drug delivery and can also be employed in targeted drug delivery. Therefore, further research into these structures could lead to new drug delivery systems [70].

Niosomes are non-ionic surfactant-based vesicles made by hydrating synthetic nonionic surfactants, which can include cholesterol or other lipids. They are vesicular systems, similar to liposomes, that can transport both amphiphilic and lipophilic drugs. Since they are non-ionic, niosomes are a promising delivery route for drugs. By localizing the drug's effect to target cells, they are less hazardous and enhance the therapeutic index. The pros and cons of niosomes are outlined below [71].

Table 6: Advantages and disadvantages of niosomes

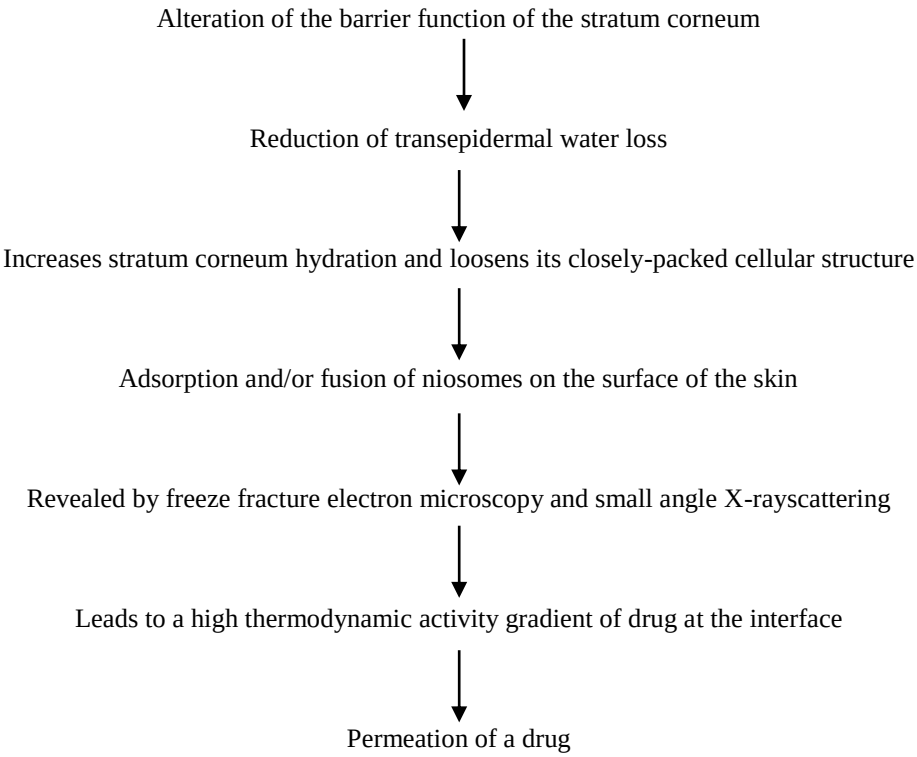
Advantages	Disadvantages
They are both osmotically active and osmotically stable.	Instability of the physical body
They improve the entrapped drug's stability.	Aggregation
Drug penetration through the skin can be improved.	Fusion
The surfactants are non-immunogenic, biodegradable, and biocompatible.	Entrapped drug leakage
Improve the drug's therapeutic performance by shielding it from the biological environment and limiting its effects to target cells, therefore lowering the drug's clearance.	Encapsulated medicines are hydrolyzed, reducing the shelf life of the dispersion[5-8]

4.1 Mechanism of skin penetration

Several mechanisms have been proposed to explain the ability of niosomes in transdermal and dermal drug delivery:

i) Niosomes diffuse from the stratum corneum layer of the skin as a whole. ii) New smaller vesicles are formed in the skin (re-formation of niosome vesicles). iii) Niosomes interact with the stratum corneum through aggregation, fusion, and adhesion to the cell surface, which causes a high thermodynamic activity gradient of the drug at the vesicle-stratum corneum surface. This is the driving force for the penetration of lipophilic drugs across the stratum corneum. iv) Niosomes may modify the stratum corneum structure, making the intercellular lipid barrier of the stratum corneum looser and more permeable. v) The non-ionic surfactant itself, the composing ingredient of niosome, acts as a permeation enhancer and might partially contribute to the improvement of drug permeation from niosomes [72].

The type of surfactant plays a significant role in modifying permeation using niosome vehicles. Niosomes fabricated from polyoxyethylene stearyl ether that exist in the gel state did not enhance estradiol permeation, whereas those prepared from polyoxyethylene lauryl ether and polyoxyethylene oleyl ether, both existing as liquid crystalline vesicles, significantly improved transport [73, 74]. Several mechanisms have been proposed, including:



5. OTHER NOVEL VESICULAR CARRIERS

5.1 Ufasomes: Ufasomes form when an evaporated film is physically agitated in the presence of a buffer solution. They are vesicles made up of long-chain unsaturated fatty acids. Colloidal suspensions of fatty acids and their ionized forms are referred to as fatty acid vesicles. It is an efficient way to deliver medications to an infection site quickly, with reduced opioid toxicity and side effects. Ufasome is a novel method to improve opioid absorption through the skin. Unsaturated fatty acids like linoleic and oleic acids are used as natural permeation enhancers in the production of ufasomes. Surfactants are often used with fatty acids to improve skin flexibility and medication transport across the skin membrane. Ufasomes enhance drug retention qualities inside the cell membrane of skin cells for an extended period. Ufasomes are soapy suspensions of closed lipid bilayers primarily composed of fatty acids [31, 75]. They typically maintain a narrow pH range of 7 to 9.1 in nature.

5.1.1 Mechanism of skin penetration[47, 76]

Fatty acid vesicles lower the phase transition temperature of lipids in biological membranes

↓

Bilayer membrane has a fusogenic tendency

↓

The vesicle membrane combines with skin lipids, allowing the contents of the vesicle to be released

↓

Fatty acid vesicles will serve as an effective carrier for increasing drug penetration into the stratum corneum

↓

resulting in lower toxicity

5.2 Sphingosomes: Sphingosomes are concentric, bilayered vesicles with an aqueous core surrounded by a membranous lipid bilayer primarily made up of natural or synthesized sphingolipids. Sphingosomes are composed of sphingolipids and cholesterol, with an internal aqueous environment that has a lower pH than the surrounding environment [77, 78, 79]. Sphingosomes are the key targeted lipid vesicular drug delivery method. They are constructed from a membranous lipid bilayer that surrounds an aqueous area in which the drug can be contained. Sphingosomes overcome the drawbacks of liposomes and niosomes due to their great resistance to acid hydrolysis and enhanced drug retention capabilities. Sphingosomes can be administered into the body via several routes, including parenteral, inhalation, oral, and transdermal. Sphingolipids, which are predominantly composed of amide and ester linkages, make up sphingosomes [32, 80, 81].

Table 7: Advantages and disadvantages of sphingosomes [82]

Advantages	Disadvantages
Provide tumor tissue with selective passive targeting.	Sphingolipids are more expensive.
Increase the therapeutic index and efficacy [89]	Entrapment efficacy is low.
The encapsulated agent's toxicity is reduced.	
Encapsulation improves stability.	

5.2.1 Mechanism of skin penetration [80]

There are various ways in which small unilamellar sphingosomal vesicles (SUSVs) interact with cells. These are as follows: stable adsorption, endocytosis, fusion, and lipid transfer.

Stable adsorption: Stable adsorption represents the association of intact vesicles with the cell surface. This process is mediated by non-specific electrostatic, hydrophobic or other forces present at the vesicles or the cell surface.

Endocytosis: Endocytosis is the uptake of intact vesicles into endocytotic vesicles and presumably results in their delivery to the lysosomal apparatus.

Fusion: Fusion is the simple merging of the vesicle's

bilayer with the plasma membrane bilayer, with the release of vesicle content into the cytoplasmic space.

Lipid Transfer: This involves the transfer of individual lipid molecules between vesicles and the cell surface without the cell association of aqueous vesicle content.

Stable adsorption

Adsorption of intact vesicles to the cell surface

(Non-specific electrostatic, hydrophobic, or other forces are involved in this process)

↓

Endocytosis

Intact vesiclestaken up by endocytotic vesicles and sent to the lysosomal apparatus.

↓

Fusion

Fusion of the bilayers of vesicles and plasma membranes

↓

with components releasing vesicle content into the cytoplasmic space.

↓

Lipid exchange

lipid molecules are transferred between vesicles and the cell surface without the need for aqueous vesicle content to be associated with the cell.

5.3 Cubosomes: Cubosomes are unique, sub-micron, nano-structured particles that represent a bicontinuous cubic liquid crystalline phase [(83)]. Cubosomes are self-assembled liquid crystalline particles of certain surfactants with a specific water-microstructure ratio and a solid-like rheology [(83)]. Cubosomes have the same microstructure as the parent cubic phase, but they possess a larger specific surface area and exhibit smaller viscosity dispersions than the bulk cubic phase [(84, 85, 86)]. The viscosity of the bulk cubic phases is higher than that of cubosomal dispersions [(87)]. Cubosomes are typically created by dispersing bulk cubic phase with high energy, then stabilizing the colloidal phase with polymeric surfactants. Cubic phase liquid crystals can be used for the controlled release of selected water-oil soluble compounds [(87, 88)]. Cubosomes comprise lipids, surfactants, and polymer molecules that have both polar and non-polar components.

Table 8: Advantages and disadvantages of cubosomes [89]

Advantages	Disadvantages
Hydrophilic and hydrophobic drugs, as well as amphiphilic drugs can be encapsulated.	In preparation, there is a low drug loading efficiency and drug leakage.
Have sustained drug delivery capabilities	Its stability acts as a deterrent, restricting their application.
Have qualities of biocompatibility and bioadhesivity	Because of the high viscosity, large-scale production can be challenging.

Table 9: Recent studies (Last 10 years) done in carriers for transdermal drug delivery

Carriers	Drug	Key findings	Indication	Reference
Liposomes	Econazole	Releases the drug at local sites of infection, may be through the action of lipase. Reduction of drug dosage and skin irritation	Anti-fungal	[90]
	Melanin	Deliver increased amounts of drugs to the site of action.	Hair growth	[91]
	Tetracaine	Delivery of drugs into the deeper skin strata.	Anaesthetic	[92]
	Tretinoin	Enhancing skin permeation in dermal delivery using different hydrophilic penetration enhancers. Increased cutaneous accumulation	Psoriasis	[93]
	Gentamycin	Drug showed increased survival rate of animal model and increased therapeutic efficacy	Pneumonia	[94, 95, 96]
	Vincristine	Enhanced vincristine cell uptake, penetration and concentration in tissues and organs and involved in the mononuclear phagocyte system	Leukemia	[96]

Carriers	Drug	Key findings	Indication	Reference
	Daunorubicin + cytarabine	Increased efficiency and target damaged cells, improved liposome pharmacokinetics,reduced toxicity and enhancing treatment efficacy	Acute myeloid leukemia	(97)
	Irinotecan + fluorouracil + foli nic acid	Increased the bioavailability. Maximum plasma concentration decreased, and half-life increased.	Pancreatic adenocarcinoma	(98)
	Ascorbic acid (Vitamin C)	**Liposomal encapsulation technology**. Therefore,it delivers maximized absorption via "Smart" nano spheres. Higher bioavailability and ability to reach cells	Ischemia	(99)
Transfersom es	Insulin	Increased in vitro skin permeation	Hypoglycemia	(100)
	Ketoconazole	Antibacterial action as well as a high potential for drug delivery	Antimicrobial	(101)
	Raloxifene hydrochloride	Great potential for transdermal delivery	Osteoporosis	(102, 103)
	Sildenafil citrate	Reduced dosage administration frequency improves transdermal permeability and bioavailability.	Sexual function	(104)
	Ovalbumin and saponin	Increased peptide permeation into the skin	Anti-OVA (Ovalbumin) antibody titer in serum	(105)

Carriers	Drug	Key findings	Indication	Reference
	Diclofenac sodium	Improvement of both the efficacy and the safety of localized therapy combining the performance of painless liquid injection devices	NSAID (Non-steroidal anti-inflammatory drugs)	(106)
	Meloxicam	Resulted in a high entrapment efficiency. Transfersomes provide greater MX skin permeation	relieve pain, tenderness, swelling, and stiffness caused by osteoarthritis	(107, 108)
	Curcuma longa extract	Better for improving skin properties. incorporated in the creams could be highly beneficial as enhanced skin hydration and sebum level	Photoprotective	(109)
	Itraconazole	Optimized nanotransfersomes with lecithin: Span®60, showed the best aerosolization efficiency	Anti-fungal	(110)
	Piroxicam	Improved stability and highest elasticity in its gel formulation	NSAID (Non-steroidal anti-inflammatory drugs)	(107)
Ethosomes	5-aminolevulivic acid (ALA)	Delivery of ALA in the inflammatory skin.	Anti- psoriasis	(68, 111)
	Erythromycin	Highly efficient in eradicating S. aureus-induced intradermal infections	Antibacterial	(37)
	Minoxidil	Enhance the penetration and accumulation of minoxidil in the skin	Hair growth promoter	(112)

Carriers	Drug	Key findings	Indication	Reference
Niosomes	Aceclofenac	Improves the penetration and therapeutic efficacy of the drug, acts as a reservoir for a prolonged period and serve as a penetration enhancer.	Pain management	(113)
	Ketoprofen	Prolonged drug release, encapsulated in niosomes containing Span 60 for topical application, and was released in a slow and sustained manner.	Anti-inflammatory	(114)
	Simvastatin	Improved not only the bioavailability of the drug but also its hypocholesterolemic effect	Hypercholesterolemia	(115)
	Flurbiprofen	Afforded high drug loading and skin permeation	Ulcer treatment	(116)
	Capsaicin	Better percutaneous permeation. Diffused faster from the niosomalmatrix than from the microemulsions	Pain relief	(117)
	Salidroside	Enhanced permeation and skin deposition. Good biocompatibility with skin tissue	Neuroprotective activities	(118)
	Baclofen	Improves the low skin penetration and poor bioavailability of conventional topical formulations	Muscle relaxant	(119)

Carriers	Drug	Key findings	Indication	Reference
Ufasomes	Clotrimazole	The drug's sustained release led to the conclusion that it could be useful in the treatment of skin infections such as candidiasis.	Anti-fungal	(120)
	Minoxidil	The concentration of minoxidil gel was ten times higher than the control, indicating that it is effective in delivering drugs to the skin and follicles.	Vasodilator	(121)
	Glucose amine sulphate	Can be used as an alternative to topical anti-osteoarthritis medication	Antiosteoarthritic	(122)
	Cinnarizine	Penetrates deep nasal mucosa layer and cinnarizine loaded ufasome vesicle is possible for intranasal delivery.	Nasal infection	(75)
	Fluconazole	Penetrate stratum corneum. Potential carrier topical targeted delivery.	Anti-fungal	(123)
Sphingosomes	Beclomethasone	Enhanced penetration of drug	Skin / dermal therapy	(124)
	Sphingosomes™ Moist	Improve the low skin penetration and poor bioavailability of formulations	Skin cleansing & make-up removal efficiency	(32, 125)
	Sphingosine and sphinganine, free sphingolipids of the stratum corneum	Releases the drug at local sites of infection, reduction of drug dosage and skin irritation	Anti-fungal	(126)
	Idoxuridine	Drug entrapped inside possess optimum corneal and increase contact time	Herpatiticskeatitis	(127)

Carriers	Drug	Key findings	Indication	Reference
	Topotecan	Increases efficiency and target damaged cells, improves pharmacokinetics,reduces toxicity and enhances treatment efficacy	Treatment of lung cancer	(128)
Cubosomes	Capsaicin	Capsaicin was released continuously, skin retention was prolonged with no irritation, and capsaicin was stable under intense light and high temperatures.	Psoriasis	(129)
	Silver sulfadiazine	When compared to commercially available products, this method produces great healing results with fewer adverse effects.	Treatment of infected burns.	(130)
	Erythromycin	Effective at delivering erythromycin to the skin in a non-invasive and long-lasting method	Treatment and prevention of several types of acne	(131)
	Cyclosporine A	Cubosomes showed low ocular irritation, improved ocular bioavailability and increased precorneal retention time of cyclosporine A.	Immunosuppressive agent	(132)
	Dapsone	Cubosomes enhance permeation of dapsone across the epidermal layers at the local site, reducing systemic side effects with higher transdermal flux value compared to marketed formulation.	Antiinflammatory agent	(133)

Carriers	Drug	Key findings	Indication	Reference
	Indomethacin	Prolong the anti-inflammatory activity of the loaded, depot effect on the epidermis	Anti-inflammatory	(86)
	Flurbiprofen	Showed low ocular irritation and improved transcorneal permeation of FB.	NSAID for occular irritation	(134)
	Metformin	The cubosomes formulation significantly lowered the concentration at which viable cells were destroyed compared to metformin alone.	Anticancer	(135, 136)
	Thymoquinone	A dose and time-dependent increase in apoptotic cells was observed when treated with thymoquinone-cubosome formulation against thymoquinone alone.	Anticancer	(137)
	Losartan-Amlodipine	Preparation, Characterization and Transdermal Permeation of Losartan-Amlodipine Molecular Sal	Hypertension	(138)
	Zinc Oxide	Development and Characterization of Anticancer Model Drug Conjugated to Biosynthesized Zinc Oxide Nanoparticles Loaded into Different Topical Skin Formulations	Anticancer	(139)

III. Conclusion

In recent years, vesicular carriers have shown promise as transdermal drug delivery platforms. Compared to conventional transdermal drug delivery methods, these carriers offer a number of advantages, including improved skin permeability, enhanced drug stability, and targeted drug administration. We have examined various vesicular carriers designed for transdermal drug delivery, such as liposomes, niosomes, ethosomes, and transfersomes. Each type of carrier possesses unique advantages and qualities. For instance, niosomes are less prone to degradation by skin enzymes than liposomes, which are renowned for their ability to encapsulate and deliver both hydrophilic and hydrophobic drugs. Ethosomes and transfersomes both incorporate permeation enhancers into their carrier structure to increase skin penetration. Researchers continue to innovate in the area of vesicular carriers for transdermal drug delivery. One notable recent advancement is the development of nanostructured lipid carriers, which can transport larger drug molecules than conventional vesicular carriers. NLCs are more optimal for long-term storage due to their higher stability compared to conventional vesicular carriers. While vesicular carriers for transdermal drug delivery require further research to perfect their design and formulation, they have the potential to revolutionize the way medications are administered through the skin. Areas for potential new studies to improve the efficacy and safety of vesicular carriers for transdermal drug delivery include: the creation of novel vesicular carriers with better targeting capabilities, higher drug loading capacities, and improved stability; enhancing vesicular carrier and formulation compatibility with skin and reducing skin irritation; investigating the use of vesicular carriers for the delivery of difficult-to-dissolve medications and those susceptible to skin degradation; and conducting clinical trials to evaluate the safety and efficacy of vesicular carriers for drug delivery to treat a variety of diseases.

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التطورات الحديثة في تطوير الناقل الحويصلي لتوصيل الأدوية عبر الجلد: مراجعة

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ملخص

بالنسبة للباحثين في مجال الأدوية، أثار أسلوب إعطاء الدواء عبر الجلد اهتمامهم. تعتبر الطبقة القرنية، وهي الطبقة الخارجية للجلد، عائقًا رئيسيًا أمام انتشار الأدوية والمواد النشطة بيولوجيًا عبر الطرق عبر الجلد. يتم الآن استخدام أساليب مختلفة، مثل الأساليب الفيزيائية، والطرق الكيميائية، وناقلات التسليم، لتحسين التوصيل عبر الجلد النشط بيولوجيًا. تقدم هذه المراجعة لمحة موجزة عن الجلد، وآليات نقل الأدوية عبر الجلد، بالإضافة إلى الأنظمة الحويصلية الدهنية المختلفة، مع التركيز على الأنظمة الحويصلية الدهنية مثل الجسيمات الناقلة، والجسيمات الشحمية، والنيوزومات، والإيثوسومات، والجسيمات اليوفا، والجسيمات السفينجوزومية، والجسيمات المكعبة، ومزاياها. في التسليم والبيانات الخاصة بالعديد من التركيبات الحويصلية للتوزيع عبر الجلد تم تلخيصها في هذه المراجعة بناءً على الأبحاث المنشورة في السنوات العشر الماضية. آفاق أحدث الأساليب القائمة على المواد الطبيعية في المستقبل.

الكلمات الدالة: الجسيمات الناقلة، الجسيمات الشحمية، النيوسومات، الإيثوسومات، الجسيمات اليوفا، الجسيمات السفينجوزومية والمكعبات، توصيل الأدوية عبر الجلد، التركيبة الحويصلية.

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