

Nanocarriers for transdermal drug delivery

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Abstract: Transdermal drug delivery offers an attractive alternative to the conventional drug-delivery methods of oral administration and injection. Apart from the convenience and noninvasiveness, the skin also provides a “reservoir” that sustains delivery over a period of days. It offers multiple sites to avoid local irritation and toxicity, yet it can also offer the option of concentrating drugs at local areas to avoid undesirable systemic effects. However, at present, the clinical use of transdermal delivery is limited by the fact that very few drugs can be delivered transdermally at a viable rate. This difficulty is because the stratum corneum of skin acts as an efficient barrier that limits penetration of drugs through the skin, and few noninvasive methods are known to significantly enhance the penetration of this barrier. In order to increase the range of drugs available for transdermal delivery, the use of nanocarriers has emerged as an interesting and valuable alternative for delivering lipophilic and hydrophilic drugs throughout the stratum corneum with the possibility of having a local or systemic effect for the treatment of many different diseases. These nanocarriers (nanoparticles, ethosomes, dendrimers, liposomes, etc) can be made of a lot of different materials, and they are very different in structure and chemical nature. They are too small to be detected by the immune system, and furthermore they can deliver the drug in the target organ using lower drug doses in order to reduce side effects.

Keywords: skin, transdermal drug delivery, transdermal nanocarriers, nanoparticles, dendrimers, liposomes, nanoemulsions, transfersomes

Introduction

Nanomedicine has become a very relevant topic nowadays. Since the last century, there has been a lot of new research and patents regarding nanomedicine in health sciences.¹ The main goal of nanomedicine is to diagnose and preserve health without side effects by using noninvasive treatments. The manipulation that nanomedicine provides to the drugs and other materials in the nanometer scale (1–500 nm) can change the basic properties and bioactivity of materials. The solubility, increment in surface area, control release, and site-targeted delivery are some characteristics that nanotechnology can manipulate in drug-delivery systems.²

Nanotechnology applied to health sciences contains new devices used in surgery, new chips for better diagnostics, new materials for substituting body structures, and some structures capable of carrying drugs through the body for the treatment of a lot of diseases. These structures can be made of a lot of different materials, and they are very different in structure and chemical nature. All these nanostructures are called nanocarriers, and they can be administered into the organisms by topical and transdermal routes.³ The idea for using these tiny systems is not new, but the use of

nanocarriers in pharmaceutical products is not frequent, since the technology is expensive for certain types of nanoparticles and because nanocarriers need to be evaluated to demonstrate they do not have toxic effects. Nowadays, the controversy of biological effects due to nanostructures is an open discussion: on one hand, nanotechnologists continue making new and more sophisticated nanocarriers, and on the other hand, toxicologists continue evaluating possible damaging effects.^{3,4} New nanocarriers will be created, and all scientists working in nanomedicine hope for this field to provide the cure for diseases that at this moment are difficult to deal with.⁴

Over time, the skin has become an important route for drug delivery when topical, regional, or systemic effects are desired.⁵ Nevertheless, skin constitutes an excellent barrier and presents difficulties for the transdermal delivery of therapeutic agents, since few drugs possess the characteristics required to permeate across the stratum corneum (SC) in sufficient quantities to reach a therapeutic concentration in the blood. In order to enhance drug transdermal absorption, different methodologies have been investigated, developed, and patented.^{6,7} Improvement in physical permeation-enhancement technologies has led to renewed interest in transdermal drug delivery. Some of these novel advanced transdermal permeation-enhancement technologies include iontophoresis, electroporation, ultrasound, microneedles to open up the skin, and more recently the use of transdermal nanocarriers.^{4,8–11}

A number of excellent reviews that have been published contain detailed discussions concerning many aspects of transdermal nanocarriers.^{12–18} The present article shows an updated overview of the use of submicron particles and other nanostructures in the pharmaceutical field, specifically in the area of topical and transdermal drugs. This focus is justified due to the magnitude of the experimental data available on the use of these nanocarriers. The development of submicron particles and other nanostructures in the pharmaceutical and cosmetic fields has been emerging in the last few decades for designing best formulations for application through the skin.^{19–22}

The skin

The skin is the largest organ of the body,^{23–25} accounting for more than 10% of body mass; it enables the body to interact more intimately with its environment. Essentially, the skin consists of four layers (Figure 1):

1. The SC, which is the outer layer of the skin. It forms the rate-controlling barrier for diffusion for almost

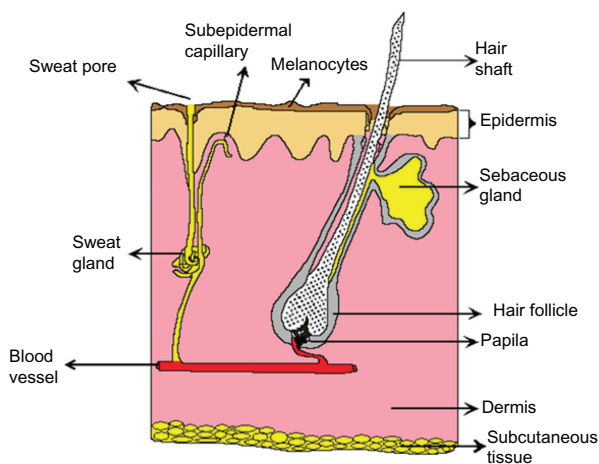


Figure 1 Schematic representation of skin layers.

all compounds. It is composed of dead, flattened, keratin-rich cells – the corneocytes. These dense cells are surrounded by a complex mixture of intercellular lipids: ceramides, free fatty acids, cholesterol, and cholesterol sulfate. Their most important feature is that they are structured as ordered bilayer arrays.²⁶ The predominant diffusional path for a molecule crossing the SC appears to be intercellular.^{27–29}

2. Remaining layers of the epidermis (viable epidermis).
3. The dermis.
4. Subcutaneous tissue.

There are also several associated appendages: hair follicles, sweat ducts, glands, and nails, but these occupy only about 0.1% of the total human skin surface.^{30,31}

The hair follicles are distributed across the entire skin surface, with the exception of the soles of the feet, the palms of the hand, and the lips. Each follicle is associated with a sebaceous gland that varies in size from 200 to 2000 μm in diameter. The sebum secreted by this gland, consisting of triglycerides, free fatty acids, and waxes, protects and lubricates the skin as well as maintaining a pH of about 5.5.³¹ The eccrine glands are epidermal structures that are simple, coiled tubes arising from a coiled ball, of approximately 100 μm in diameter, located in the lower dermis. It secretes a dilute salt solution with a pH of about 5; this secretion being stimulated by temperature-controlling determinants, such as exercise and high environmental temperature, as well as emotional stress through the autonomic (sympathetic) nervous system. Many things can interfere with the delicate structure of the skin's acid mantle (formed by the sebum and sweat of skin) externally and internally. As we age, our skin becomes more acidic in response to our lifestyle and

our environment. Everything that comes in contact with our skin (products, smoking, air, water, sun, pollution) contributes to the breaking down of the acid mantle and the skin's ability to protect itself.^{8,31} The acid mantle is a form of protection, but if our pH level is too alkaline or too acidic, this mantle is disturbed, skin conditions such as dermatitis, eczema, and rosacea may result, and skin drug permeability can change dramatically.

In a general context, the skin's functions may be classified as protective, homeostasis-maintaining, or sensing.^{30,31}

Many agents are applied to the skin either deliberately or accidentally, with either beneficial or deleterious outcomes. The main interest in dermal absorption assessment is related to:

1. Local effects in dermatology³²
2. Transport through the skin, seeking a systemic effect³²
3. Surface effects^{33,34}
4. Targeting of deeper tissues³⁵⁻³⁸
5. Unwanted absorption.^{39,40}

Routes of drug penetration through the skin

The permeation of drugs through the skin includes the diffusion through the intact epidermis through the skin appendages (hair follicles and sweat glands). These skin appendages form shunt pathways through the intact

epidermis, occupying only 0.1% of the total human skin.⁴¹ It is known that drug permeation through the skin is usually limited by the SC. Two pathways through the intact barrier may be identified (Figure 2).

The intercellular lipid route

Interlamellar regions in the SC, including linker regions, contain less ordered lipids and more flexible hydrophobic chains. This is the reason for the nonplanar spaces between crystalline lipid lamellae and their adjacent cells' outer membrane. Fluid lipids in skin barrier are crucially important for transepidermal diffusion of the lipidic and amphiphilic molecules, occupying those spaces for the insertion and migration through intercellular lipid layers of such molecules.^{42,43} The hydrophilic molecules diffuse predominantly "laterally" along surfaces of the less abundant water-filled interlamellar spaces or through such volumes; polar molecules can also use the free space between a lamella and a corneocyte outer membrane to the same end.⁴⁴

The transcellular route

Intracellular macromolecular matrix within the SC abounds in keratin, which does not contribute directly to the skin diffusive barrier but supports mechanical stability and thus intactness of the SC. Transcellular diffusion is practically unimportant for transdermal drug transport.^{45,46} The narrow

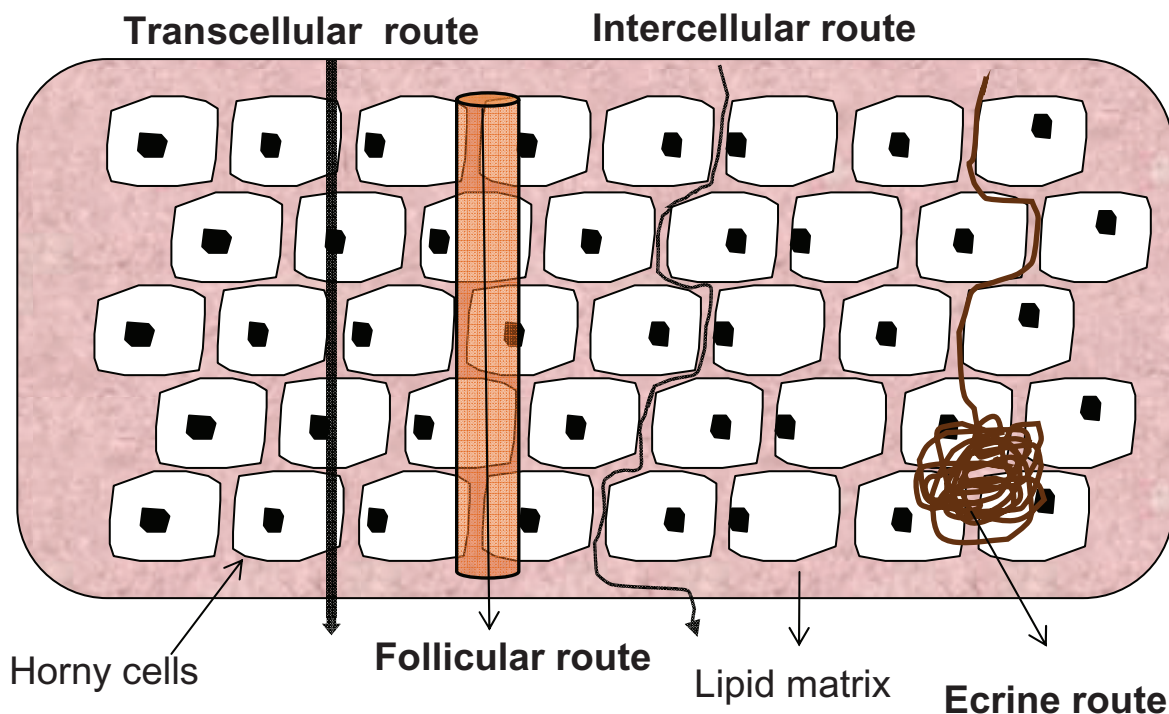


Figure 2 Processes of percutaneous absorption of drugs through the skin.

aqueous transepidermal pathways have been observed using confocal laser scanning microscopy. Here, regions of poor cellular and intercellular lipid packing coincide with wrinkles on skin surface and are simultaneously the sites of lowest skin resistance to the transport of hydrophilic entities. This lowest-resistance pathway leads between clusters of corneocytes at the locations where such cellular groups show no lateral overlap.⁴⁷⁻⁵¹

The contribution to transdermal drug transport can increase with pathway widening or multiplication, eg, that which is caused by exposing the SC to a strong electrical (electroporation/iontophoresis), mechanical (sonoporation/sonophoresis), or thermal stimulus, or suitable skin penetrants.⁵²

Recently, follicular penetration has become a major focus of interest due to the fact that drug targeting to the hair follicle is of great interest in the treatment of skin diseases. However, follicular orifices occupy only 0.1% of the total skin surface area. For this reason, it was assumed to be a nonimportant route for drug penetration. But a variety of studies have shown that hair follicles could be an interesting option for drug penetration through the skin.⁵³⁻⁵⁸ Such follicular pathways have also been proposed for topical administration of polystyrene nanoparticles. They were investigated in porcine skin (in vitro) and human skin (in vivo). Surface images revealed that polystyrene nanoparticles accumulated preferentially in the follicular openings. This distribution was increased in a time-dependent manner, and the follicular localization was favored by the smaller particle size.⁵⁹ The study also confirmed similarity in the penetration between both membranes (porcine and human skin).⁵⁷ In other investigations, the influence of microparticle size in skin penetration has been shown by differential stripping. Nanoparticles can act as efficient drug carriers or can be utilized as follicle blockers to stop the penetration of topically applied substances.^{58,60}

A number of methods are currently available for quantifying drugs localized within the skin.⁶¹ There is no direct, non-invasive technique to quantify penetrated drug into follicles, but the tape-stripping technique^{23,27,61} and cyanoacrylate skin surface biopsy⁶¹ have been used to remove layers of the SC containing dyes or drugs topically applied.⁶¹ Of the two techniques, tape stripping has been more successful due to non-invasiveness and selectivity to study penetration of skin-applied substances in the follicular infundibula.^{21,27,31,61,62}

Advantages and disadvantages of transdermal drug delivery

Transdermal drug-delivery systems offer several important advantages over more traditional approaches, in addition

to the benefits of avoiding the hepatic first-pass effect. Higher patient compliance and additional advantages and disadvantages⁶³⁻⁶⁵ that transdermal drug delivery offers is summarized in Table 1.

Transdermal nanocarriers

The types of nanocarriers that are used today have significantly increased in the last decades. These systems are designed around the two characteristics that are sought in the modern pharmacy: temporal delivery and spatial location.

It is hard to say what is the ideal nanocarrier, because every day new advantages and disadvantages of each are discovered.¹²⁻¹⁸ We can mention as general advantages improvements in drug solubility, permeability, half-life, bioavailability, and stability, among other properties,⁶⁶ and the main disadvantages are low load capacity in many cases and lack of stability of the system per se.⁶⁷

An important point highlighted by Panariti et al⁶⁸ is that physicochemical properties of nanocarrier systems determine the interaction with biological systems and nanocarrier cell internalization. The main physicochemical properties that affect cellular uptake are size, shape, rigidity, and charge in the surface of nanoparticles (see Table 2).

Nanoparticulated systems can be administered into organisms by almost all routes including transdermal,^{69,70} which offers several advantages over other delivery systems, but with its own limitations (see Table 1). The most used and investigated nanocarriers for topical/transdermal drug delivery in the pharmaceutical field,⁷¹ as a function of the material used to prepare them, are shown in Figure 3, and a

Table 1 Main advantages and disadvantages of transdermal drug delivery

Advantages of transdermal drug delivery	Disadvantages of transdermal drug delivery
Prolonged duration of action	Possibility of local irritation at the site of application
Reduction in the frequency of dosing	Skin irritation or contact dermatitis due to drug or excipients
More uniform plasma levels	Skin's low permeability limits the number of drugs that can be delivered in this manner
Useful for potent drugs	
Improvement in bioavailability	
Reduction of adverse effects	
Flexibility of terminating drug administration by simply removing the transdermal delivery system from the skin (patch)	

Table 2 Influence of main physicochemical properties of nanocarrier systems on cell uptake

Favors the uptake	Does not favor the uptake or decreases the uptake
Spherical shape	Large size
Positive surface charge	Negative surface charge
Small size	
Rigidity	

schematic representation of some nanocarriers is shown in Figure 4. This manuscript includes the most important carriers for transdermal drug delivery. Liposomes, transfersomes, ethosomes, niosomes, dendrimers, nanoparticles, and nanoemulsions are currently the main subjects when searching for transdermal drug delivery.

Liposomes

Liposomes are lipid bilayer systems that can carry hydrophilic drugs inside the core and lipophilic drugs between the bilayer. They were created by Alec Bangham. He realized that phospholipids in aqueous systems can form hollow, bilayered structures.⁴ Liposomes have become one of the pharmaceutical nanocarriers of choice for many purposes. In recent years, many liposome-based drugs and biomedical products have been approved for use as medicines.⁷²

In transdermal delivery, liposomes have been used widely. They are systems made of cholesterol and phospholipids.

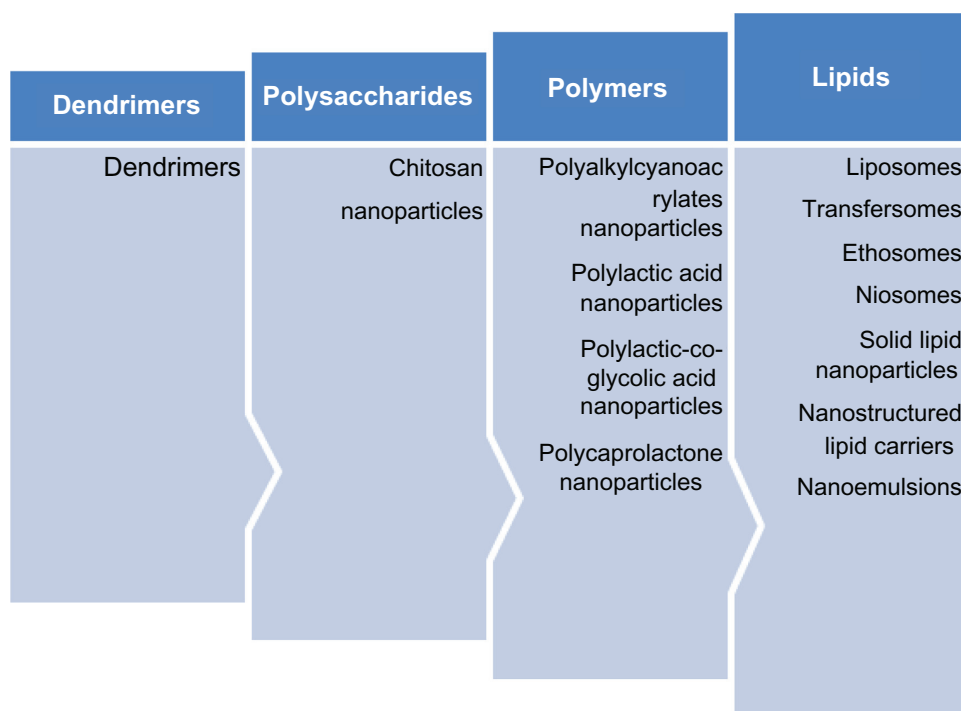
Their physicochemical properties depend on the materials used for their fabrication and the process performed. Liposomes are one of the best alternatives for drug delivery because they are nontoxic and remain inside the bloodstream for a long time.⁷³

Many factors can affect transdermal penetration of liposomes, eg, particle size and formulation, as well as the presence of penetration enhancers and the physical state of the SC, but there are other important variables like lamellarity, lipid composition, charge on the liposomal surface, mode of application, and total lipid concentrations. Liposomes have been used successfully to transport drugs across the skin.⁷⁴

The liposome lipid content makes the interaction of these entities with biological membranes easier. There has been research on the interaction between lipids present in the SC and liposome lipid bilayer, changing the structure of the upper skin. This interaction favors the penetration through the SC of lipophilic drugs.⁷⁵

Transfersomes

Some liposomes may have a deformable structure and pass through the SC or may accumulate in the channel-like regions in the SC, depending upon their composition. The driving force is nothing more than osmotic pressure; these liposomes are called transfersomes or transformable liposomes.⁷⁶

**Figure 3** Carriers commonly used in transdermal drug delivery as a function of material used to prepare them.

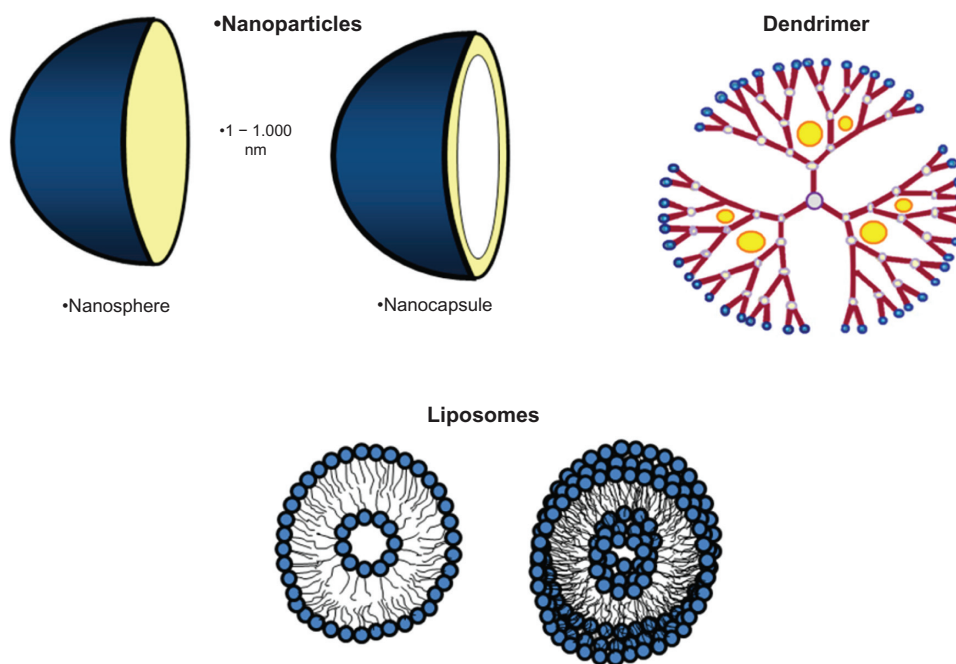


Figure 4 Schematic representation of some nanocarrier systems used for transdermal drug delivery.

The need to reach the narrow tubes that make up the skin (hair follicles and intercellular spaces between lipids), to deliver drugs, led to the invention of transfersomes. The original idea to use liposomes as drug delivery systems was very smart, as they are made of lipids similar to biological membranes, but they have rigid structure. The incorporation of elements in the lipid bilayer to make it flexible has made these carriers successful. Traditional transformable liposomes are made using surfactants in the lipid bilayer. In transdermal drug delivery, the paracellular and intercellular pathways are very important but appendage routes have been of increasing interest lately.⁷⁷ The use of flexible liposomes (transformable liposomes) is an invaluable strategy to reach the objective of drug delivery via the transdermal route. The use of these kinds of nanocarriers seems to be more effective than liposomes, and their flexibility allows the possibility of using them as transdermal vaccine vectors.

Ethosomes

The idea of making another kind of flexible liposome has been the goal of a lot of scientists. To that end, the ethosomes, which contain alcohol in the lipid bilayer to make them more flexible and be able to be deformed when pressure is applied,⁷⁸ were created.

These carriers allow drugs to reach deeper skin layers and systemic circulation. Ethosomes are easy to prepare, and they are considered safe and efficient. For these reasons, they could have wide future applications.⁷⁹ Their main characteristics

are softness and malleability, and they are considered good drug-delivery systems. Ethosomes are able to contain and deliver a lot of molecules because they can transport highly lipophilic drugs, eg, testosterone, minoxidil, and cationic molecules such as propranolol and trihexyphenidil.⁸⁰

Ethosomes can carry and deliver a lot of drugs, and in the future these systems offer a huge opportunity to make better therapies, besides which they can transport molecules through the skin and biological membranes. Examples of the application of these nanocarriers in transdermal delivery are widely described in the next section.

Niosomes

Niosomes are made of lipids (like cholesterol) and nonionic surfactants, which are biodegradable and minimally toxic. Niosomes were created with the same goal as transfersomes and ethosomes: to make liposomes less rigid and let these bilayer systems go where liposomes cannot go.⁸¹ In addition, the incorporation of nonionic surfactants let the liposomes be more stable. The niosomes were originally used in the cosmetics industry, and the versatility of these systems has allowed their use to spread to other areas. For example, in pharmaceutical products, they are formulated for drug delivery. They are used for many routes of administration: oral, parenteral, ocular, and vaginal, including transdermal.⁸² The application of niosomes in transdermal drug delivery has been very important, because they can carry anti-aging

agents and antifungal molecules, among other drugs. A more comprehensive review is in the applications section.

Dendrimers

Dendrimers are nonpeptidic fractal 3-D structures made of numerous small molecules. The term “dendrimer” is Greek: “dendra” means tree and “meros” means part. This name was coined in the late 1970s by a research group formed by Vögtle, Denkewalter, Tomalia, and Newkome. The structure of these molecules results in relatively uniform shapes, sizes, and molecular weights. They are a very good alternative for drug-delivery systems; dendrimers can be used in antiviral and anticancer pharmaceutical therapies, including vaccines.⁸³

The first material used and still most commonly used for dendrimer fabrication is poly(amidoamine), which was initially synthesized by Dow Laboratories between 1979 and 1985. In the context of controlled chemical delivery, dendrimers have been explored for drug delivery, gene therapy, and delivery of contrast agents.⁸⁴

The use of dendrimers to encapsulate hydrophobic and labile molecules has been a successful road. The permeability of dendrimers through the skin depends on physicochemical characteristics like generation size, molecular weight, surface charge, composition, and concentration.⁸⁵ Dendrimers as transdermal drug-delivery systems are relatively new, but there are numerous recent papers.^{2,4,8,83} These nanocarriers have been used to transport photosensitizers for photochemical therapy and antifungal molecules.

Nanoparticles

The main goal of delivery systems is to reach the organ of interest and often to go through it. The use of carriers like those previously mentioned in this text, in addition to the theme of this topic (nanoparticles), contributes to accomplishing this objective. Recently, scientists have developed lots of nanocarriers for helping to improve drug transport into the skin and through biological membranes.

As mentioned in previous paragraphs, the skin is an important route to go into the body, and with its larger contact area it can be very useful to administer drugs locally and systemically.⁸⁶ Nanotechnology in the pharmaceutical sciences opens a new avenue of therapies for the treatment of many diseases and represents hope that people may be helped to have a better life. Nowadays, it is possible to encapsulate a variety of molecules into nanoparticles like drugs, proteins, peptides, DNA, etc. Moreover, nanomaterial, such as gold nanoparticles, has been used for transdermal

delivery; for example, to encapsulate protein drugs to enable percutaneous delivery, the interaction between the gold nanoparticles and the skin barrier leads to an increase of skin permeability and effectively prompts percutaneous absorption of the coadministered proteins.⁸⁷ The main advantage of codelivery is that it does not require the loading of drugs into the nanoparticulate system. Therefore, compromise in activity can be minimized for both protein drugs and nanoparticles because of the exclusion of complicated drug-loading processes. This highlights a new strategy for percutaneous protein delivery, with obvious advantages in terms of simplicity and cost-effectiveness. Also, a combined multiphoton-pixel analysis method was developed for semiquantitation of gold nanoparticle penetration into different skin layers.⁸⁸ Gold nanoparticles are also commonly used in cosmetic products such as facial gold masks. Protein nanofiber gold nanoparticle creams and gold nanoparticle masks have been claimed to enhance the firmness of skin and to have a rejuvenating action.⁸⁹ Silver nanoparticles are similar to solid-drug nanoparticles in that the active agent appears to be the breakdown product of the particle. Silver nanoparticles exhibit minimal penetration into skin and are consequently considered safe. Studies of long-term occupational exposure to silver ions and silver nanoparticles have concluded that they are relatively nontoxic.⁹⁰ In many cases, lots of molecules have been difficult to administer using conventional therapeutic systems; in addition, the doses that need to be given to patients using conventional delivery methods reach toxic levels, or cause a lot of side effects.

Nanoparticles in a liquid form colloids due to their size and can be classified as nanospheres or nanocapsules. Nanospheres are solid-core structures, and nanocapsules are hollow-core structures.⁹¹ They can also be classified depending on the material from which they were made, eg, if they are made of lipids, polymers, polysaccharides, or proteins.

Nanoparticle-preparation techniques are based on their physicochemical properties. They are made by emulsification–diffusion by solvent displacement, emulsification–polymerization, in situ polymerization, gelation, nanoprecipitation, solvent evaporation/extraction, inverse salting out, dispersion polymerization, and other techniques derived from these.^{2,4}

Two of the main options for transdermal delivery are the solid-lipid nanoparticles and nanostructure lipid carriers. Aside from polysaccharide nanoparticles, polymeric nanoparticles are very good options for transdermal delivery because they can be tailor-made in different sizes and it is possible to modify their surface polarity in order to improve

skin penetration.⁹² From the upper skin, lipid nanoparticles can reach deeper skin regions because they exhibit mechanical flexion. Nanoparticles can even travel from the skin to lymph nodes, representing a promising tool for immunomodulation.⁹³

Nanoemulsions

Nanoemulsions are isotropic dispersed systems of two nonmiscible liquids, normally consisting of an oily system dispersed in an aqueous system, or an aqueous system dispersed in an oily system but forming droplets or other oily phases of nanometric sizes. They are thermodynamically nonstable systems, in contrast to microemulsions, because nanoemulsions need high energy to produce them. They are susceptible to Oswald ripening, and as a consequence susceptible to creaming, flocculation, and other physical instability problems associated with emulsions. Despite this, they can be stable (metastable) for long periods due to their extremely small size and the use of adequate surfactants. Hydrophobic and hydrophilic drugs can be formulated in nanoemulsions because it is possible to make water/oil or oil/water nanoemulsions.^{2,4,94} They are nontoxic and nonirritant systems, and they can be used for skin or mucous membranes and parenteral and nonparenteral administration in general, and they have been utilized in the cosmetic field. Nanoemulsions can be prepared by three methods mainly: high-pressure homogenization, microfluidization, and phase-inversion temperature. Transdermal delivery using nanoemulsions has decreased due to the stability problems inherent to this dosage form. Some examples of drugs using nanoemulsions for transdermal drug delivery are gamma tocopherol, caffeine, plasmid DNA, aspirin, methyl salicylate, insulin and nimesulide.^{2,4,95}

In general, the advantages and limitations of using nanocarriers for transdermal drug delivery are their tiny size, their high surface energy, their composition, their architecture, and their attached molecules. Table 3 shows advantages and disadvantages of these carrier systems.

Applications of nanocarrier systems for transdermal drug delivery

As has been mentioned before, the search for new strategies able to enhance the topical and transdermal penetration of drugs has become essential.^{2-4,8-11} Different carrier systems have been proposed in an attempt to favor the transport of drugs through the skin, enabling drug retention and in some cases allowing a controlled release. Table 4 summarizes the applications of nanocarrier systems for transdermal drug delivery. Skin penetration is essential to a number of

current concerns, eg, contamination by microorganisms and chemicals, drug delivery to skin (dermatological treatments) and through skin (transdermal treatments), and skin care and protection (cosmetics).^{58,60,76,82,84,85}

Liposomes have become one of the pharmaceutical nanocarriers of choice for many applications. Currently, many liposome-based drugs and biomedical products have been approved for use in clinic. They were used to study membrane processes and membrane-bound proteins. Liposomes were also proposed as drug carriers that reduce toxicity and increase efficacy. The nature of liposomes makes them one of the best alternatives for drug delivery because they are nontoxic and remain inside the bloodstream for a long time. They are being successfully used in cancer therapy and in skin melanoma.⁹⁶⁻⁹⁹ However, to date many liquid-type nanocosmetic carriers, such as liposomes, are structurally unstable. Specifically, when passing through the skin, they adhere to the inside walls of the skin cells, causing the collapse of phospholipid-association bodies and the leak of their encapsulated ingredients. As a result, their ability to transport active ingredients to deep skin is not likely good. For this reason, the use of flexible liposomes (transformable liposomes or transfersomes) has emerged as an invaluable strategy to reach the objective of drug delivery via the transdermal route. Table 4 shows some examples of drugs delivered through the skin by using liposomes and transfersomes.

The application of transformable liposomes, which are prepared using alcohol (ethosomes) in the lipid bilayer of SC, able to deform and penetrate throughout the skin when pressure is applied, has been increased. For example, tacrolimus-loaded ethosomes may be useful as a therapeutic agent for atopic dermatitis.¹⁰⁰ Skin permeation of ethosomal formulations assessed by confocal microscopy revealed enhanced permeation of Rhodamine 123-loaded formulation in comparison to the hydroalcoholic solution. Another ethosomal formulation has proved to be a potentially useful vehicle for transdermal delivery of ketoprofen.¹⁰¹ Furthermore, an ethosomal carrier (phosphatidylethanolamine) is an optional treatment for psoriasis that provides long-term therapeutic effects, is nontoxic, and has better compliance with patients. Application of ethosomal carriers with 5-aminolevulinic acid (ALA) in hyperproliferative murine skin can improve the penetration of ALA and the formation of protoporphyrin IX and significantly reduce tumor necrosis factor in this disordered skin compared to an ALA aqueous solution.¹⁰²

Ethosomes were used efficiently to enhance the anti-inflammatory activity of ammonium glycyrrhizinate compared to the ethanolic or aqueous solutions of this drug.¹⁰³

Table 3 Advantages and disadvantages of nanocarrier systems

Nanocarrier	Advantages	Disadvantages
Nanoparticles	<ul style="list-style-type: none"> They can be made of a lot of biodegradable materials. There are many ways to prepare them. They can include antibodies in their surface to reach target organs. Both hydrophilic and hydrophobic drugs can be loaded in a nanoparticle. They are able to avoid the immune system due to their size. 	<ul style="list-style-type: none"> Not enough toxicological assessment has been done. It is difficult to develop an analytical method for drug delivery. Some processes are difficult to scale up. Sometimes, the size they reach is not enough to avoid the immune system.
Nanoemulsions	<ul style="list-style-type: none"> They can be formulated as foams, liquids, creams, and sprays. They are nontoxic and nonirritant. Easily applied to skin and mucous membranes. 	<ul style="list-style-type: none"> They are susceptible to Oswald ripening. Surface charge has a marked effect on stability. Variable kinetics of distribution processes and clearance.
Liposomes	<ul style="list-style-type: none"> Control release based on natural lipids. High biocompatibility. Simple manufacture. Protein carriers increase their stability. High drug loads. 	<ul style="list-style-type: none"> When high-pressure homogenization is used, decreased stability of high-weight molecules. Lipid crystallization leads to a lot of polymorphic issues. Variable kinetics of distribution processes. They are susceptible to physical instability.
Dendrimers	<ul style="list-style-type: none"> They increase stability of therapeutic agents. They are easily prepared and functionalized. They increase bioavailability of drugs. They covalently associate drugs. Dendrimers also act like solubility enhancers, increasing the permeation of lipophilic drugs. 	<ul style="list-style-type: none"> They have shown cellular toxicity. Elimination and metabolism could be a problem depending on the generation and materials. Their synthesis costs are higher than other nanocarriers. Hemolytic effects can be found. They are not good carriers for hydrophilic drugs.
Niosomes, transfersomes, ethosomes	<ul style="list-style-type: none"> Biodegradable and low toxicity. Easy to prepare. Softness, malleability. They can encapsulate both hydrophilic and lipophilic moieties. Ability to target organs for drug delivery. Extremely high flexibility of their membrane. 	<ul style="list-style-type: none"> Predisposition to oxidative degradation. Purity of natural phospholipids. Formulations are expensive.

Moreover, the ethosomal system dramatically enhanced the skin permeation of minoxidil *in vitro* compared with either ethanolic or hydroethanolic solution or phospholipid ethanolic micellar solution of minoxidil. In addition, the transdermal delivery of testosterone from an ethosomal patch was greater both *in vitro* and *in vivo* than from commercially available patches.¹⁰⁴

Dendrimers have been utilized for transdermal drug delivery, as shown in Table 3. The main problems with this kind of transdermal carrier are their poor biodegradation and inherent cytotoxicity.¹⁰⁵ The main advantage of dendrimers is that they have multivalency,¹⁰⁶ and it is possible to precisely control the functional groups on the surface.¹⁰⁷ Due to their form and size, these molecules can carry drugs, imaging agents, etc. Dendrimers interact with lipids present in membranes, and they show better permeation in cell cultures and intestinal membranes. Dendrimers also act like solubility enhancers, increasing the permeation of lipophilic drugs. On the other hand, they are not good carriers for hydrophilic drugs and the

mechanisms underlying permeation enhancement and the interaction of dendrimers with skin are shown in Table 4.

Niosomes are versatile carrier systems that can be administered through various routes, including transdermal delivery.^{108,109} Particular efforts have been aimed at using niosomes as effective dermal and transdermal drug-delivery systems.^{110,111} In particular, niosomes are considered an interesting drug-delivery system in the treatment of dermatological disorders.

Niosomes have been reported to enhance the residence time of drugs in the SC and epidermis, while reducing the systemic absorption of the drug, and improve penetration of the trapped substances across the skin. In addition, these systems have been reported to decrease side effects and to give a considerable drug release.¹¹² Niosomes formed from sorbitan monoesters (Span) with cholesterol molar ratios of 1:1 are a promising approach for the topical delivery of minoxidil in hair-loss treatment.¹¹³ Junyaprasert et al demonstrated that the

Table 4 Summary of the applications of nanocarriers in transdermal drug delivery

Type of transdermal nanocarriers	Applications
Liposomes	Liposomes can encapsulate both lipophilic and hydrophilic drugs in a stable manner. Moreover, many liposome-based drugs have been approved for use in the clinic. Currently, positively charged liposomes have been used for DNA delivery in gene therapy. Also, liposomes are being used for many antifungal and anticancer applications. Examples of drugs delivered throughout the skin by using liposomes are melatonin, ¹¹⁶ indinavir, ¹¹⁷ methotrexate, ¹²⁶ amphotericin B, ¹²⁷ ketoprofen, ¹²⁸ estradiol, ¹²⁹ clindamycin hydrochloride, and lignocaine. ¹³⁰
Transfersomes	Several studies have reported that deformable liposomes were able to improve in vitro skin delivery of various drugs, ^{131–133} and to penetrate intact skin in vivo, transferring therapeutic amounts of drugs, ^{134–136} with efficiency comparable to subcutaneous administration. ¹³⁷ Examples of transdermal drug delivery using transformable liposomes (transfersomes) are diclofenac, insulin, tetanus toxoid, corticosteroids, superoxide dismutase, DNA, triamcinolone-acetonide, ketoprofen, interleukin-2, and ketotifen fumarate.
Ethosomes	At this time, ethosomes could be used in the treatment of atopic dermatitis. ¹⁰⁰ Furthermore, ethosomes can be used for Parkinsonian syndrome and for dystonia therapy. ¹³⁸ Examples of transdermal drug delivery using ethosomes are tacrolimus, ¹⁰⁰ clotrimazole, ¹³⁹ trihexyphenidyl HCl, ¹⁴⁰ ketoprofen, ¹⁰¹ and testosterone.
Niosomes	Niosomal formulations have greater potential for drug cutaneous targeting and could be used as a feasible cargo carrier for the topical delivery of minoxidil in skin diseases such as hair loss. Moreover, topical application of niosomes can increase the residence time of drugs in the stratum corneum and epidermis, while reducing the systemic absorption of the drug. ¹¹⁴ Examples of transdermal drug delivery using niosomes are minoxidil and ellagic acid.
Dendrimers	Dendrimers have been used in numerous applications such as gene therapy, ¹⁴¹ delivery of contrast agents, ¹⁴² controlled drug delivery, ^{138,144} light-harvesting agents, ^{143,144} catalysts, ¹⁴⁵ chemical sensors, ¹⁴⁶ and cross-linking agents. Additionally, dendrimers can be used in antiviral and anticancer pharmaceutical therapies, including vaccines. ^{147,148} Dendrimers also act like solubility enhancers, increasing the permeation of lipophilic drugs. Finally, dendrimers have been studied to assess biocompatibility and toxicity. ¹⁴⁹ Examples of drugs delivered throughout the skin by using dendrimers are tamsulosin, ¹⁵⁰ indomethacin, ¹⁵¹ ketoprofen, diflunisal, ¹⁵² 5-fluorouracil, ¹⁵³ and peptides. ¹⁵⁴
Nanoparticles	Nanoparticles have been used successfully in the treatment of diseases such as cancer and diabetes. ¹⁵⁵ Furthermore, polymeric nanoparticles are used to deliver therapeutic agents for various types of tumors, bone healing, and vaccination. Examples of drugs delivered throughout the skin by using nanoparticles are minoxidil, ¹⁵⁶ triptolide, ¹⁵⁷ DNA, ¹⁵⁸ triamcinolone acetonide acetate, ¹⁵⁹ dexamethasone phosphate, ¹⁶⁰ cyclosporin A, ¹⁶¹ flufenamic acid, ¹⁶² testosterone, ¹⁶² caffeine, ¹⁶² 5-fluorouracil, ¹⁶³ arthemeter, ¹⁶⁴ chlorhexidine, ¹⁶⁵ econazole nitrate, ¹⁶⁶ insulin, ¹⁶⁷ celecoxib, ¹⁶⁸ coenzyme Q ₁₀ ¹⁶⁹ and triclosan. ¹⁷⁰

Span 60 and Tween 60 niosomes may be a potential carrier for dermal delivery of ellagic acid.¹¹⁴

Nanoparticles have been successful in the therapy and diagnosis of cancer; this disease causes many deaths in developed countries every year.¹¹⁵ While many cancer drugs destroy both cancer and healthy cells, nanoparticles represent a more targeted solution to drug delivery. Nanoparticles have also been used for vaccine development because they offer features not found in other carriers: they are chemically stable and reproducible. As peptide vectors, nanoparticles have shown much better performance than traditional adjuvants in vaccine development.¹¹⁶ Nanoparticles are important because many recently developed drugs are insoluble, and they offer a lot of types, eg, solid lipid

nanoparticles and nanostructured lipid carriers. One of the most helpful recent developments involves pH-sensitive nanoparticles.¹¹⁷ Moreover, polymeric nanoparticles are used to deliver therapeutic agents for various types of tumors, diabetes, bone healing, and vaccination (Table 4).

At present transdermal delivery using nanoemulsions is not used as much as nanoparticle or liposome delivery, due to the stability problems inherent to this dosage form. Nevertheless, gamma tocopherol, caffeine, plasmid DNA, aspirin, methyl salicylate, insulin, and nimesulide have been included in nanoemulsions. The use of these nanocarriers to deliver analgesics, corticosteroids, anticancer agents, etc, is very important, as these drugs are able to act immediately because they do not need to cross extra barriers.^{93,118–123}

Conclusion

The greatest challenge with transdermal drug delivery is the barrier nature of skin, which restricts the entry of most of the drugs. Currently, nanocarriers have been tried and tested to overcome the barrier of SC to achieve higher transdermal permeability, and they have been designed to avoid immune system rejection and to reach target sites. Moreover, the routes these nanocarriers follow are very different. The main advantages of using nanocarriers arise from their peculiar features, such as their tiny size, high surface energy, composition, architecture, and attached molecules. Thus, nanocarriers can penetrate biological membranes to deliver drugs for specific diseases. Advances with regard to materials, fabrication methods, and techniques facilitate the development of new and better nanocarriers. Nonetheless, future research must ensure the benefit and evaluate the risk ratio for many drugs included in nanocarriers.

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Disclosure

The authors report no conflicts of interest.

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