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NANOCARRIER FOR TRANSDERMAL DRUG DELIVERY SYSTEMS

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ABSTRACT

Transdermal drug delivery offers an attractive alternative to the conventional drug-delivery methods of oral administration and injection. 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, liposomes, nanoemulsions, Polymer Matrix.

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. 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. (Brower *et al.*, 2006)

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. Over time, the skin has become an important route for drug delivery when topical, regional, or systemic effects are desired. 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. 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. (Escobar-Chávez *et al.*, 2012)
Delivery a therapeutically effective amount of drug across the patient's skin. Provides controlled and constant administration of the drug. Allows continuous input of drug with short biological half lives. Eliminates pulsated entry of drug into systemic circulation.

Advantages

- Avoidance of first pass metabolism of drug.
- Reduces plasma concentration levels of drug with decreased side effects.
- Utilization of drug candidates with short half-life and low therapeutic index.
- Easy elimination of drug delivery in case of toxicity.
- Reduction of dosing frequency.
- Patient compliance

Disadvantages

- Possibility of local irritation at the site of application
- Skin irritation or contact dermatitis due to drug or excipients

THE SKIN

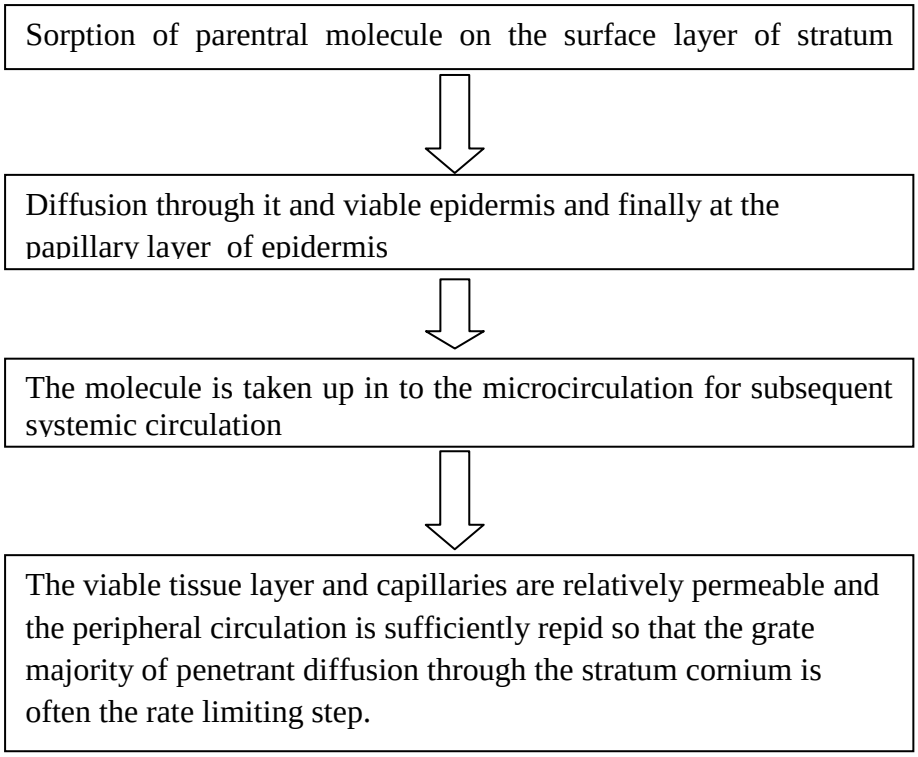
The skin is the largest organ of the body, accounting for more than 10% of body mass; it enables the body to interact more intimately with its environment. Essentially, the skin consists of four layers. (Díaz-Torres *et al.*, 2010)

1. The SC, which is the outer layer of the skin. It forms the rate-controlling barrier for diffusion for almost 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. The predominant diffusional path for a molecule crossing the SC appears to be intercellular.
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.

Mechanism of skin

It consist of series of stem in sequences



Transdermal Drug Delivery

Transdermal drug delivery system (TDDS) is the dosage forms which deliver a therapeutically effective amount of drug across a patient's skin . Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood-level profile resulting in reduced systemic side effects and sometimes, painless and offer multi-day dosing. Since the first transdermal patch was approved in 1981 to prevent the nausea and vomiting associated with motion sickness, the FDA has approved, throughout the past 22 years, more than 35 transdermal patch products, spanning 13 molecules.

Advantages

Transdermal drug delivery enables the avoidance of gastrointestinal absorption, with its associated pitfalls of enzymatic and pH associated deactivation

- This method also allows for reduced pharmacological dosaging due to the shortened metabolization pathway of the transdermal route versus the gastrointestinal pathway.
- The simplified medication regimen leads to improved patient compliance and reduced inter & intra – patient variability.
- Self administration is possible with these systems.
- The drug input can be terminated at any point of time by removing transdermal patch.

Disadvantages

- The drug that requires high blood levels cannot be administered and may even cause irritation or sensitization of the skin
- Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin's impermeability.
- High cost of the product is also a major drawback for the wide acceptance of this product
- Contact dermatitis is another drawback reported in TDDS
- Barrier function of skin varies from site to site during application in same person

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. (Hadgraft *et al.*, 2005)

It is hard to say what is the ideal nanocarrier, because every day new advantages and disadvantages of each are discovered. We can mention as general advantages improvements

in drug solubility, permeability, half-life, bioavailability, and stability, among other properties, and the main disadvantages are low load capacity in many cases and lack of stability of the system per se.

An important point highlighted (Panariti *et al.*, 2005) 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. (Barry *et al.*, 2001)

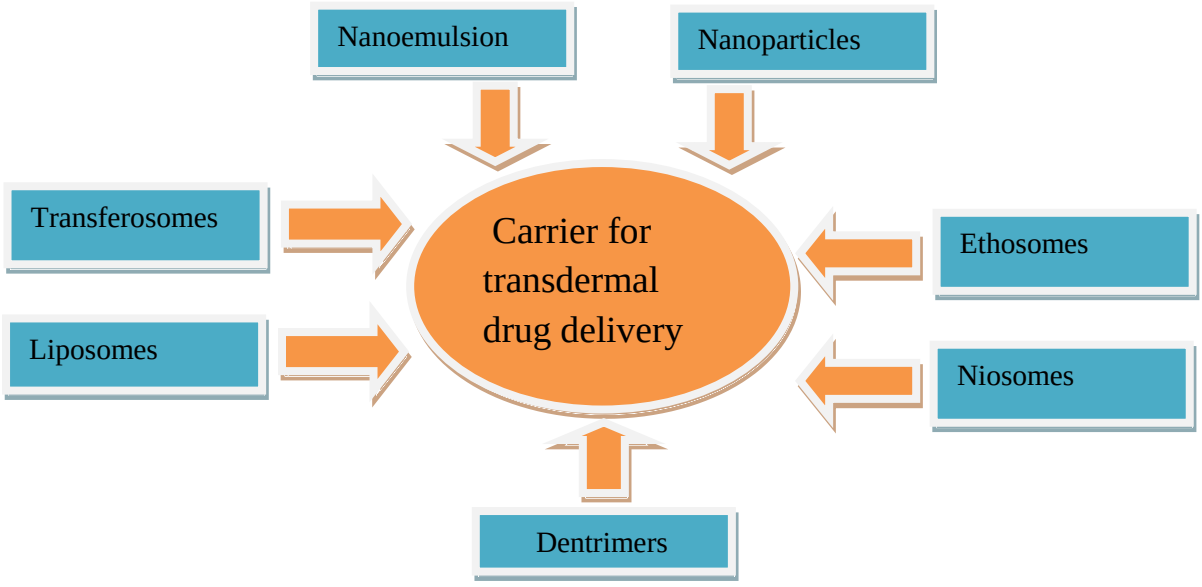
Novel technologies for transdermal delivery system

Nanoparticle for transdermal application such as liposome,ethosomes as well as other type of nanosized drug carrier havr been developed. Different carrier system have been proposed in an attempt to favour the transport of drug through the skin, facultative drug retention and in some cases permitting a sustained release. skin penetration is crucial variety of current consideration.

Physiochemical properties of nanovascular system confirm the nitration with biological system and nanocarrier cell acquisition. The main physiochemical properties have an effect on cellular uptake are size, shape, rigidity, and change in the surface of properties. The foremost used and investigated nanocarries for transdermal drug delivery in the pharmaceutical field include liposome, transferosome, ethosomes, noisome, dentrimers, nanoparticle- lipid and polymer nanoparticle and nanoemulsion.

TYPE OF NANOCARRIER FOR TRANSDERMAL DRUG DELIVERY

The most important carriers for transdermal drug delivery



LIPOSOMES

Liposomes are lipid bilayer systems that can carry hydrophilic drugs inside the core and lipophilic drugs between the bilayer. 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. (Rizwan *et al.*, 2001)

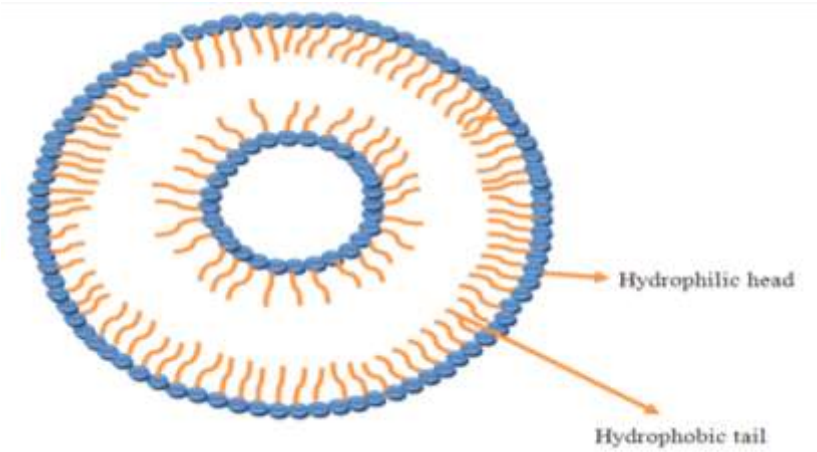


Figure 1: Structure of liposomes.

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. (Zaborova et al., 2011)

Liposomes preparation techniques follow three basic steps with particular features depending on safety, potential scale up and simplicity:

1) Lipid must be hydrated,

2) Liposomes have to be sized

3) Nonencapsulated drug has to be removed.

Advantages

- Control release based on natural lipids.
- High biocompatibility.
- Simple manufacture.

- Protein carriers increase their stability.
- High drug loads.

Disadvantages

- 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

Application

- Liposomes can encapsulate both lipophilic and hydrophilic drugs in a stable manner.
- 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.
- liposomes are being used for many antifungal and anticancer applications.

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. (Gandhi *et al.*, 2011)

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. (Patel *et al.*, 2009)

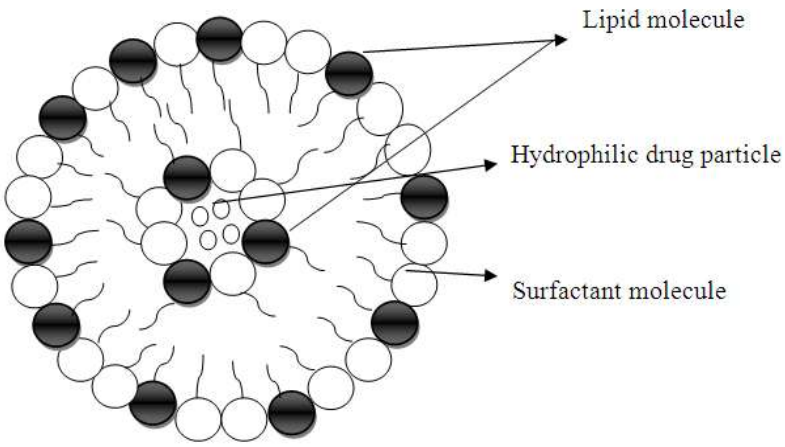


Figure 2: Structure of transferosomes.

Advantages

- Used as non invasive drug delivery.
- Improve large molecular weight drug delivery across the skin.
- Improve transdermal bioavailability.
- Reduction in toxicity of the encapsulated agent.
- Improve pharmacokinetic effects
- Less stability
- Aggregation
- Discomfort in storage

Application

Several studies have reported that deformable liposomes were able to improve in vitro skin delivery of various drugs, and to penetrate intact skin in vivo, transferring therapeutic amounts of drugs, with efficiency comparable to subcutaneous administration

ETHOSOMES

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. (Chourasia *et al*., 2001) 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.

Advantages

- Softness, malleability.
- They can encapsulate both hydrophilic and lipophilic moieties.
- Ability to target organs for drug delivery.
- Extremely high flexibility of their membrane

Disadvantages

- Formulations are expensive.

Application

- Ethosomes could be used in the treatment of atopic dermatitis.
- Ethosomes can be used for Parkinsonian syndrome and for dystonia therapy.

NIOSOMES

Niosomes are made of lipids 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. (Keservani *et al.*, 2010) 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. 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.

Advantages

- Biodegradable and low toxicity.
- Batter patient compliance.
- Drug targeting to various organs.
- Enhance the skin permeation of drug.

Disadvantages

- Predisposition to oxidative degradation.

App1lication

- 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.

DENDRIMERS

Dendrimers are nano-sized, radially symmetric molecules with well-defined, homogeneous, and monodisperse structure that has a typically symmetric core, an inner shell, and an outer shell. (Gopalan *et al*.,2007).

Dendrimers are nearly monodisperse macromolecules that contain symmetric branching units built around a small molecule or a linear polymer core(Bryszewska et al.,2001).In the context of controlled chemical delivery, dendrimers have been explored for drug delivery, gene therapy, and delivery of contrast agents. (Uchegbu *et al., 2008*)

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. These nanocarriers have been used to transport photosensitizers for photochemical therapy and antifungal molecules.

Advantages

- 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.

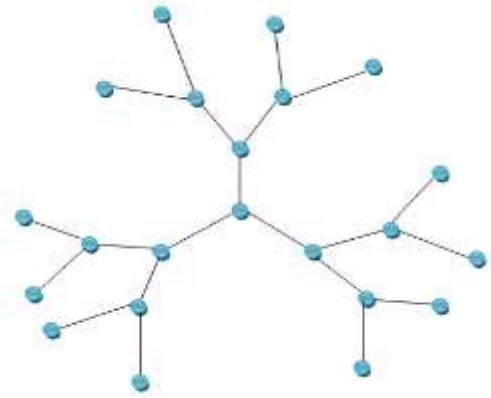


Figure 3: Structure of dertrimers

Disadvantages

- 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.
- They are not good carriers for hydrophilic drugs.

Application

- Dendrimers have been used in numerous applications such as gene therapy, delivery of contrast agents, controlled drug delivery, light-harvesting agents, catalysts, chemical sensors, and cross-linking agents.
- .Dendrimers also act like solubility enhancers, increasing the permeation of lipophilic drugs.
- Dendrimers have been studied to assess biocompatibility and toxicity

NANOPARTICLES

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained.Nanoparticles can be composed of polymers, lipids, polysaccharides and proteins. (Astruc *et al.*, 2010) Nanoparticles preparation techniques are based on their physicochemical properties. They are made by emulsification-diffusion by solvent displacement, emulsificationpolymerization, in situ-polymerization, gelation,

nanoprecipitation, solvent evaporation/extraction, inverse salting out, dispersion polymerization and other derived from these one.(Lee *et al*.,2005)

Advantages

- They can be made of a lot of biodegradable materials.
- They can include antibodies in their surface to reach target organs.
- Both hydrophilic and hydrophobic drugs can be loaded in ananoparticle.
- They are able to avoid the immune system due to their size.

Disadvantages

- 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.

Application

- Nanoparticles have been used successfully in the treatment of diseases such as cancer and diabetes.
- Polymeric nanoparticles are used to deliver therapeutic agents for various types of tumors, bone healing, and vaccination.

NANOEMULSIONS

Nanoemulsions/Sub-micron emulsions (SMEs)/Mini-emulsions/Ultrafine emulsions are thermodynamically stable transparent (translucent) dispersions of oil and water stabilized by an interfacial film of surfactant and cosurfactant molecules having a droplet size of less than 100 nm. The dispersed phase typically comprises small particles or droplets, with a size range of 5 nm-200 nm, and has very low oil/water interfacial tension. Because the droplet size is less than 25% of the wavelength of visible light, Nanoemulsions are transparent. (Mishra *et al* .,2008) .Nanoemulsions can be prepared by three methods mainly.

1. High-pressure homogenization,
2. Microfluidization,
3. 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.

Advantages

- They can be formulated as foams, liquids, creams, and sprays.
- They are nontoxic and nonirritant.
- Easily applied to skin and mucous membranes.

Disadvantages

- Surface charge has a marked effect on stability.
- Variable kinetics of distribution processes and clearance.

PATENT RELATED TO TRANSDERMAL DRUG DELIVERY SYSTEMS

A few patents granted for transdermal drug delivery are mentioned below in table 1.

Patent no.	Title	Year	Patentee/ assignee	References
US 8,980,309	Transdermal testosterone formulation for minimizing skin residues	March 17, 2015	Antares Pharma IPL AG (Zug, CH)	Norberto et al.
US 9,005,653	Transdermal delivery of hormones with low concentration of penetration enhancers	April 14, 2015	Bayer Intellectual Property GmbH (Monheim, DE)	Thomas et al.
US 9,056,061	Transdermal nicotine salt delivery system	June 16, 2015	Gale; Robert, M. Audett; Jay Padmanabhan; Rama V., Cormier; Michel J. N. Luciano; Allison	Robert et al.
US 9,066,886	Transdermal drug delivery system containing granisetron	June 30, 2015	Choi; Hoo-Kyun	Hoo-kyun et al.
US 9,078,810	Transdermal delivery system	July 14, 2015	Setiawan; Kerrie Watkinson; Adam (Melbourne, AU)	Kerrie Watkinson et al.
US 9,144,552	Rapidly dissolving film for delivery of an active agent	September 29, 2015	Singh; Parminder,Mudumba; Sri Bayramov; Danir F. Kulichikhin; Valery G. Feldstein; Mikhail M. Cleary; Gary W.	Paeminder et al.
US 9,155,711	Transdermal drug delivery system containing donepezil	October 13, 2015	Choi; Hoo-Kyun Chun; Myung-Kwan,Mo; Y. Joseph .	Hoo- kyun chun.
US9,155,712	Transdermal drug delivery device including an occlusive backing		Kanios; David (Miami, FL), Mantelle; Juan A. (Miami, FL), Nguyen; Viet (Miami, FL)	David et al.

Marketed formulation of nanocarriers in transdermal drug delivery.

Type of transdermal nanocarriers	Marketed formulation
Liposomes	Indinavir, methotrexate, amphotericin B, ketoprofen, estradiol,clindamicyn hydrochloride, and lignocaine.
Transfersomes	diclofenac, insulin, tetanus toxoid, corticosteroids, superoxide dismutase, DNA, triamcinolone-acetonide, ketoprofen, interleukin-2, and ketotifen fumarate.
Ethosomes	tacrolimus, clotrimazole, trihexyphenidyl HCl,ketoprofen,and testosterone.
Niosomes	minoxidil
Dendrimers	vaccines
Nanoparticles	triamcinolone acetonide acetate, dexamethasone phosphate, cyclosporin A, flufenamic acid,testosterone,caffeine, 5-fluorouracil,arthemeter,chlorhexidine,econazole nitrate, insulin, celecoxib,coenzyme $Q_{10}$and triclosan.

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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