REVIEW ARTICLE

Nanocarriers: A Novel Approach for Enhanced Drug Delivery through Skin

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Abstract

In pharmaceuticals, about 90% of all medicines, active pharmaceutical ingredients are in the form of solid particles. With the development of nanotechnology, nanotechnology is a new approach within promising applications in the area of medicine, especially pharmaceutical for safe, controlled, and targeted drug delivery system. Nanotechnology is frequently applied in fiber textile, agriculture, electronics, forensic science, space, and medical therapeutics, namely, in disease detection, controlled drug delivery, as biosensors in tissue engineering. A nanocarrier drug delivery system formulation reduces the patient expenses and gives patient compliance. The major challenges in the development of nanoparticles as a drug delivery system are the control of particle size, surface properties and release of the active moiety to get the site-specific action at the desired rate and dose. Nanocarriers are being used as a transport moiety for another molecule. Nanocarriers are micelles, polymers, carbon-based materials, and liposome, and other substances are used for the delivery of drugs in the control or sustain release. Nanocarriers have recently been studied for their use in drug delivery for their unique characteristic use of chemotherapy. The colloidal system used in drug delivery with size ranging from 10 to 100 nm, use for sustained drug delivery system. In the present scenario nanotechnology has improved the diagnosis and treatment of dermatological conditions. The challenges associated with nanocarriers through the skin permeation are one of the hurdles, and it will soon overcome.

Key words: Liposome, nanocarriers, nanotechnology, promises challenges

INTRODUCTION

Transdermal drug delivery of a therapeutic agent is one of the catchiest ways of delivery and also an alternative option for conventional drug delivery, but there are some limitations to Transdermal drug delivery system (TDDS) like not all drug molecules are able to penetrate and can reach to the site of action. This is happening because stratum corneum of skin can act as an effective barrier to these molecules.[1] To know about these barriers, we should know all about skin structure, skin functions and which the different approaches to permeation enhancement are, all these parameters are discussed further in the respective article.[2] Skin is one of the biggest and the largest organ of the human body which gives protection to the human body from various conditions. Skin combines with an internal mucosal lining of the respiratory tract, digestive system, urinary tract to separate internal body structure from external it forms capsule.[3] The skin is very versatile organ it has its capacity to change the cells or regeneration of new cells over the dead cells. Skin act as a physical barrier to the environment and for various microorganisms.[4]

Structure of skin

For an average 70 kg human with skin surface area of 1.8 m whose sq.cm covers 10 hair follicles, 12 nerves, 15 sebaceous glands, and 3 blood vessels with 92 cm total length. The diagrammatic representation of skin is shown in Figure 1.

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Received: 08-11-2017
Revised: 27-11-2017
Accepted: 09-12-2017

Anatomy and physiology of skin

This is the simple structure of skin, which consist of three layers:

- Epidermis
- Dermis
- Subcutaneous.

Epidermis

Epidermis is the outermost part of the skin. Whose thickness varies from due to cell size and a number of cell layers are present. Like the thickness of epidermis at eyelid is 0.05 mm while 0.8–1.5 mm for the sole of feet and palm.[3] Epidermis consist of cells such as keratinocytes, melanocytes, and merkel cells

epidermis consist of:

- Stratum corneum
- Stratum basale
- Stratum granulosum.

Dermis

Dermis is the second most layer of the skin, which consist of a matrix of connective tissue, which contains blood vessels and nerve. The thickness of dermis is 3–5 mm. It provides nutrients and oxygen to the skin and the removal of toxins through the body.

Subcutaneous

It is the fatty tissue, which supports the dermis and epidermis. This layer is also known for the storage of fat. This layer helps to regulate temperature, provide nutrition. For delivery of the drug, the drug has to permeate through these three layers.

Functions of skin

- Gives protection to various internal organs
- Regulate the body temperature
- Reflex actions due to sensory neurons
- Formation of Vitamin D
- Absorption through skin or penetration through skin for drug delivery
- Excretion through the skin.

Mechanism of skin permeation

The stratum corneum is act as a skin permeation barrier. Skin is a fantastic organ for the delivery of nanoparticles drugs and can extend or sustained they are released.[5] In brief, how the permeation is happening through the skin is given by following Figure 2.

Percutaneous absorption of the substance through the skin involves passive diffusion. A molecule may use two divisional routes to penetrate the normal intact skin.[4]

Factors influencing transdermal drug delivery system

Although transdermal drug delivery is one of the advantages over conventional drug delivery that may have some lacuna. There are some barriers or factors that affect the TDDS those are as follows:

- Skin condition
- Skin age
- Blood supply
- Regional skin site
- Skin metabolism
- Species differences
- Area of application
- Contact time.

METHODS OF PENETRATION ENHANCEMENT[2]

For better physiological action drug has to penetrate through the skin for that need there are several methods used for the penetration enhancement of skin those methods are given in Figure 3.

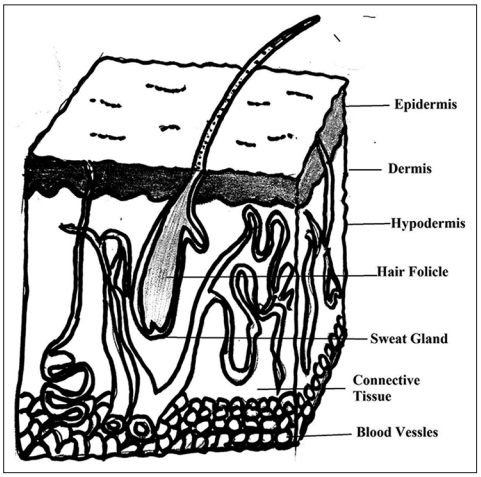

Figure 1: Structure of skin

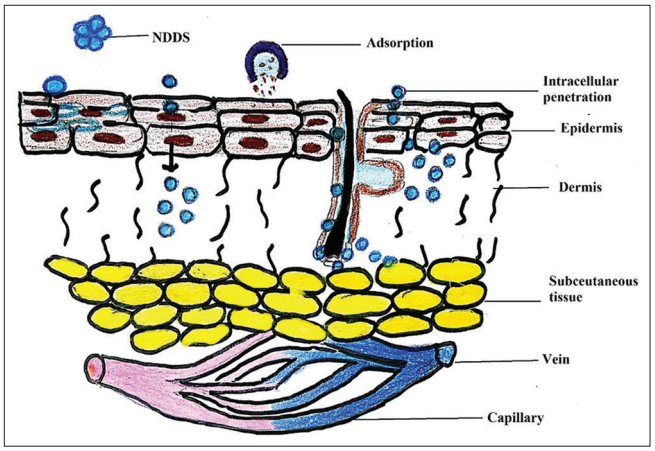

Figure 2: Mechanism of skin penetration

APPROACHES FOR PENETRATION ENHANCEMENT

Penetration enhancers having a broad potential and if we would use it properly then it can be an effective mode of drug delivery. It facilitates the drug delivery through the skin; it also called as accelerated or sorption enhancers.[3] There are four major approaches for the enhancement of penetration are shown in Figure 4.

NANOTECHNOLOGIES FOR TRANSDERMAL DRUG DELIVERY SYSTEM

In pharmaceuticals 90% of all medicines, the active pharmaceutical ingredients is in the form of a solid particle with the development of nanotechnology. Nanotechnology is frequently applied in fiber textiles, agriculture, electronics, forensics science, space, and medical therapeutics, namely, in disease detection and controlled drug delivery.[2] The nanoparticle drug formulation reduces the patient expenses and risk of toxicity it increases drug efficacy, specificity, tolerability, and therapeutic index of corresponding drugs. Nanocarriers are the emerging trend in the pharmaceutical industry which has, moreover, advantages on the conventional dosage form, and also they are used in the transdermal dosage form. Nanocarriers are generally divided into two types Figure 5.

VARIOUS NANOCARRIERS USED FOR TOPICAL DELIVERY[15]

Liposomes

Liposome is the bilayer vesicle of phospholipids. Phospholipids and cholesterol are basic components of the liposome. Liposome is one of the leading nanocarriers in transdermal drug delivery systems for the systemic (intravenous) administration of drugs as well as topical drug delivery. There are various advantages of liposomes over the conventional drug delivery of the drug. Liposome is, generally, used for the sustained or controlled drug delivery of a system. There are two types of phospholipids, phosphoglycerides, and sphingolipids. Colloidal size is the

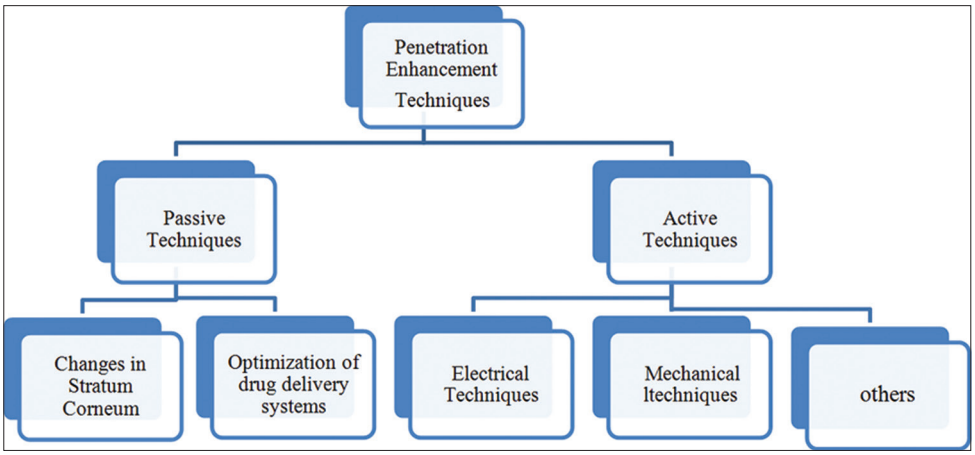

Figure 3: Methods of penetration enhancement

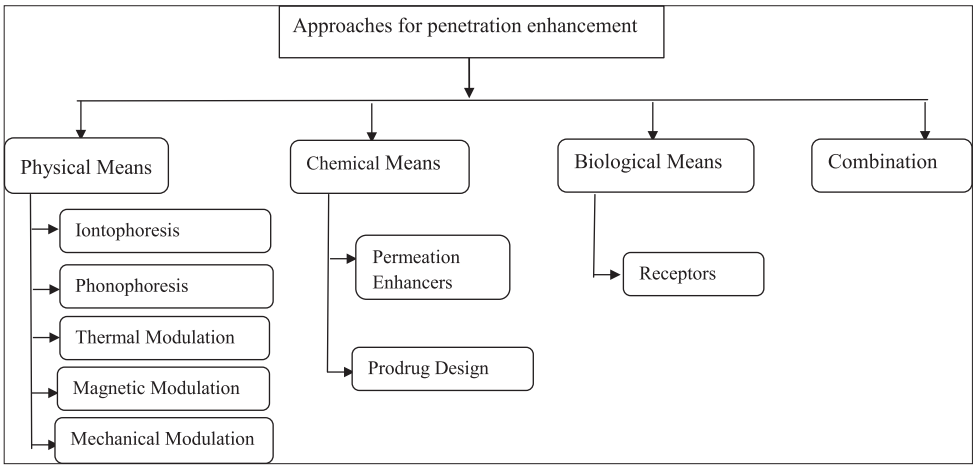

Figure 4: Approaches to penetration enhancement

most important property uniform distribution of particle size in the range of 20 nm to 10nm and surface characteristics. [5] Main components of liposome are cholesterol and phospholipids. Phospholipids are a major component of biological membrane. In general, for preparation of liposome, the phospholipids are used from the natural and synthetic origin. It consists of a polar head and nonpolar tail. These are the bilayer vesicle of phospholipids, which imparts the more efficacy in TDDS.[6-8] Liposome is also used in the case of a targeting drug delivery system. Liposomes having several advantages such as increased efficacy and therapeutic index, increased stability of encapsulated drug, reduction in the toxicity, flexibility with site-specific ligands, and selective passive targeting.[9] Liposome is often distinguished according to their number, of lamellae and size: Small unilamellar vesicles (UV), large UV, large multilamellar vesicle, and multivesicular vesicle.[10,11] Liposome is used in parasitic and infection used in bioengineering also used in cosmetics liposome also imparts in agro food industry also used in anticancer therapy.[12]

Niosomes

Niosome is another novel drug delivery system, in which the drug can be encapsulated into a vesicle.[13,14] Niosomes are a potential tool used for the delivery of the drug in microscopic size. Niosome is the microscopic lamellar structures formed on the admixture of a non-ionic surfactant, cholesterol, and diethyl ether with subsequent hydration in aqueous media.[15] There are several advantages over liposome such as niosome is osmotically active and stable, used in the cosmetics, niosome is biodegradable, biocompatible and non-immunogenic, act as a depot and release the drug in controlled manner, muscle relaxant. Table 1 shows the examples of the drug.

Ethosomes

Ethosomes are the modified form of liposome, which has a quite high content of alcohol. This is lipid vesicle contain phospholipid ethanol and molecule in the size range of microns or in nanometers this size of ethosome, generally, depends on the how they prepared or by which method they are prepared.[20] Ethosomes are mainly emphasized on drug delivery through topical or transdermal route. In comparison with liposome ethosome having higher penetration rate through the skin, i.e., stratum corneum barrier, which gives the path of penetration to various drugs and used as an excellent nanocarrier.[17,18] There might be reason of high penetration of drug through the ethosome system that the presence of a high concentration of ethanol content in it and phospholipids as we know biological membrane is made up of lipid bilayer so that penetration can happen easily. [19] Ethosome having several advantages such as it gives patient compliance. Ethosome is widely used in cosmetics, pharmaceuticals, and veterinary medicines.[20] Ethosome can be characterized on the basis of vesicle shape, size, zeta potential, stability, etc.[21] We can entrap and deliver the wide category of drugs through the ethosome such as lipophilic, hydrophilic, or amphiphilic. Opportunity for non-invasive, drug delivery of small to large size drug molecules through ethosome.[22] Ethosomes are mainly used as a replacement of a liposome, delivery of various drugs through it like, HIV, antifungal, nonsteroidal anti-inflammatory drug (NSAID), etc. Ethosome used in transdermal drug delivery system, there are several applications of ethosome.[23]

Transfersomes

Transfersomes are the phospholipids vesicles prepared similarly to transdermal drug delivery. It has a capacity of reproducibility of drug delivery, depending on the skin and site of administration. The term transfersome was introduced in 1991 by Gregor Cevc.

Transfersomes are lipid vesicles, elastic in nature, which much smaller in size as compared to another nanocarrier. The name transfersome is known as "carrying body," and it was derived from the Latin word "transferre," meaning of this is "to carry across," and the Greek word "soma," for a "body."[15] Transfersome having ultradeformable vesicle contains an aqueous layer surrounded by the lipid bilayer.[24] Delivery of drug through topical route there are some problems associated with other nanocarriers such as permeation through the skin, breaking of vesicle, and leakage of drug.[25] Transfersomes

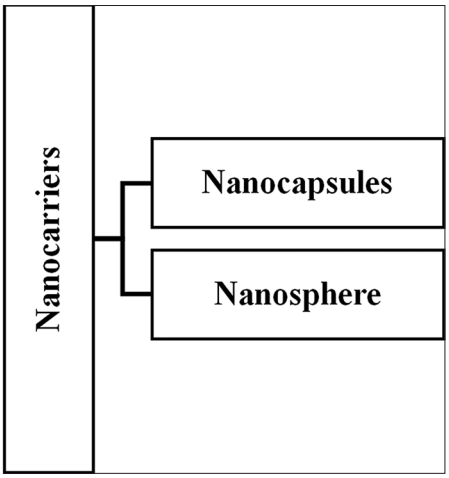

Figure 5: Classification of nanocarriers

Table 1: Examples of drugs incorporated in Niosome

Drug	Composition	Reference
Erythromycin	Crbapol934 - span 20,60,80	[16]
Aceclofenac	Gel - carbapol980 span 60	[17]
Ibuprofen	Carbopol tween 40,60,80	[18]
Ellagic acid	Span 60 tween 80	[19]

are having the capacity to deliver the drugs whose molecular weight is high.[26] These are artificial vesicles, and they are more alterable than liposomes.[27] When drug is delivered through this nanocarrier which increased the penetration of drugs through the skin.[28] Transfersome usually composed lipid bilayer in which inner layer is aqueous layer. Span 80, tween 80, sodium cholate, sodium deoxycholate, are some surfactants that have been used as edge activators. Transfersome is usually apply in the form of semi-diluted suspension. Transfersomes having several advantages such as biocompatible, biodegradable, possess high entrapment efficiency, and act as depot system released their contents slowly. Transfersomes have the potential for controlled release of the drugs and having the higher stability of labile substances, used for peripheral drug targeting; vaccines can be given topically although high molecular weight used as a carrier for interferon these are application in the pharmaceutical field.

Polymeric micelle

Micelles have size usually within a range of 5–100 nm. Micelles consist of amphiphilies or surfactants, which exist two different regions: Mostly a hydrophilic head and a hydrophobic tail. Amphiphilic molecules exist separately in an aqueous medium in lower concentration if the concentration is increased agglomeration increased.[28,29] The concentration at which micelles forms are called the critical micelle concentration. Due the removal of hydrophobic groups and introduction of hydrogen bonds in water leads to the formation of micelle.[30,31] Due to the formation of an Van Der Waals bonds between hydrophobic groups energy is generated which forms micelles. The use of certain special amphiphilic molecules as micelle building blocks can also extend the blood half-life on intravenous administration. Due to their small size (5–100 nm), so that, the penetration through the skin can be easy.[32,33] Polymeric micelles having broad area of application such as delivery of anticancer agents to treat tumors, drug delivery to the brain to treat neurodegenerative diseases, delivery of antifungal agents, stimuli-responsive nanocarriers for drug and gene delivery, ocular drug delivery, and used in cosmetics and topical drug delivery. Table 2 shows the composition of various vesicular system.

COMPOSITION OF VARIOUS VESICULAR SYSTEM[34]

Various nanocarriers are composed of various lipids, so the general composition of nanocarriers is given in Table 2.

APPLICATION OF NANOCARRIERS IN TOPICAL DRUG DELIVERY

Nanocarriers are the emerging areas of a pharmaceutical sciences having several uses such as delivery of anticancer agents to treat tumors, drug delivery to the brain to treat neurodegenerative diseases, delivery of antifungal agents, stimuli-responsive nanocarriers for drug and gene delivery, ocular drug delivery, and used in cosmetics and topical drug delivery.[35-37] Transfersomes have the potential for controlled release of the drugs and having higher stability of labile substances, used for peripheral drug targeting, vaccines can be given topically although high molecular weight, used as an carrier for interferon, mainly used as an replacement of an liposome, delivery of various drugs through it such as HIV, antifungal, and NSAID[38-40] used in transdermal drug delivery system, nanocarriers are osmotically active and stable, used in the cosmetics, nanocarriers are biodegradable, biocompatible and non-immunogenic, act as a depot and release the drug in a controlled manner, and also used as a muscle relaxant.[41,42]

DISADVANTAGES OF TOPICAL DELIVERY SYSTEMS[43]

Even though topical delivery systems have a lot of advantages over conventional topical formulation, it still suffers from a lot of limitations.

- Not all drugs are given by topical route.
- Drugs that require high blood levels cannot be administered.
- The adhesive used may not adhere well to all types of skin.
- Drugs or drug formulation may cause irritation.
- The patches are uncomfortable to wear, but its elegance is a concern.
- The manufacturer requires specialized equipment's, expensive.

Table 2: Composition of various vesicular system[34]

Vesicular system	Composition
Liposome	Phospholipids
Ethosome	Phospholipids+ethanol
Transfersomes	Phospholipids+mono chain surfactant
Niosome	Non-ionic surfactant+lipids
Polymeric micelle	Polar head+lipid monolayer

Table 3: Examples of marketed drugs

Drugs	Nanocarriers	Reference
Porphyrins, amphotericin B	Liposome	[45]
Methotrexate, doxorubicin	Neosome	[46]
Ethinylestradiol, corticosteroids	Transfersome	[44,47,48]
Zovirax, diclofenac potassium, fluconazole	Ethosome	[49,50]
Genexol-PM	Polymeric micelle	[51]

Table 4: List of approved drugs by FDA

Drug	Brand name	Name of company	Targeted disease	Month and year of approval
Bavencio	Avelumb	Pfizer	Merkel cell carcinoma	March 2017
Dupixent	Dupilumab	Regeneron pharmaceuticals	Atopic dermatitis	March 2017
Siliq	Brodalumab	Valeant pharmaceuticals	Plaque psoriasis	February 2017
Eucrisa	Crisaborole ointment	Pfizer	Atopic dermatitis	December 2016
Taltz	Ixekizumab	Eli Lilly	Plaque psoriasis	March 2016
Cosentyx	Secukinumab	Novartis	Plaque psoriasis	January 2015
Catellic	Cobimetinib	Genentech	Melanoma	November 2015
Enstilar	Betamethasone dipropionate	LEO pharmaceuticals	Psoriasis	October 2015
Dalvance	Dalbavancin	Durata therapeutics	Acute bacterial skin infection	May 2014
Kerydin	Tavaborole	Anacor	Onychomycosis of the toenails	July 2014
Luzu	Luliconazole	Valeant pharmaceuticals	Tinea corporis	November 2013
Mekinist	Trametinib	GSK	Unresectable or metastatic melanoma	May 2013

FDA: Food and drug administration

- There is a requirement for low dose and high permeable drug through the skin.

CHALLENGES IN NANOCARRIERS USED TOPICALLY

While formulation and development of transdermal delivery we came across various challenges such as:

- Dose equivalence: There should be equal, and even distribution of the drug in particular system is one of the major challenges.[44]
- Penetration through skin: As stratum corneum is one of the barriers for penetration of the drug through the skin so it is challenge for formulator how the drug can be penetrated and shows its action.
- Potent drugs: Potent drugs are those drugs which show more action in less required amount or concentration it can be one of the challenges in front of scientist.[44]
- Stability parameters and bioavailability: Stability of any formulation and its bioavailability is challenge in front of every formulator the drugs which are used that should be stable and shows specific bioavailability, but due to some barriers this can be hamper so it is one more challenges along with safety toward patients, and their immunological system responds toward it.

EXAMPLES OF MARKETED DRUGS

Table 3 shows the marketed nanocarriers for topical use.

LIST OF APPROVED DRUG BY FOOD AND DRUG ADMINISTRATION (FDA) FOR DERMATOLOGY[52]

FDA gives approval to the various new moieties every year some of these drug lists along with approval year is given in Table 4.

CONCLUSION

The conclusion from this article can be after large emphasized on the nanocarriers used in various topical preparation having the effectiveness in various tropical diseases, it is a novel approach, and there will be more challenges in future for delivery of drugs. Furthermore, nanocarriers having very promising novel approach for the drug delivery not only by the topical route but also through the various route of administration. These system shows less side effect, less toxic effects, more patient compliance, ease of administration, and in some cases prolong released of drug.

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Source of Support: Nil. **Conflict of Interest:** None declared.