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Review Article

AN OVERVIEW: RECENT DEVELOPMENT IN TRANSDERMAL DRUG DELIVERY

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ABSTRACT

The transdermal drug delivery system is an alternative method of administration of drugs. Most of the drugs are delivered by conventional oral, topical, intravenous, and intramuscular methods and are is of limited efficiency. However, now the clinical use of transdermal delivery is limited because of stratum cornea of the skin act as an effective barrier that limits the permeation of drugs through the skin. To overcome this disadvantage, there are Recent developments in transdermal drug delivery, such as the usage of nanoparticles i.e., liposomes, niosomes, transferosomes, ethosomes, nanoemulsion, virosomes, phytosomes, dendrimers, proniosomes, microneedles, and separable microneedles. This nanoparticulate transdermal drug delivery exhibits great potential to ensure drug permeation through the skin. They are very tiny carriers to detect by the immune system and further, they can be delivering the drug to the targeted site and also have the ability to deliver both hydrophilic and hydrophobic drugs by reducing the complexity. Nanoparticles are made of different materials and they're very different in structure and chemical properties are discussed in this review article.

Keywords: Topical, Stratum cornea, Nanoparticles, Drug permeation, IM, Skin

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INTRODUCTION

The most common form of drug delivery is the oral route; this route of administration has fewer advantages and also has significant drawbacks such as first-pass metabolism and drug degradation due to enzyme and pH to accomplish. Some of the disadvantages of transdermal drug delivery can also be overcome by advanced drug delivery methodologies such as nanoparticular transdermal drug delivery systems.

Transdermal drug delivery system (TDDS), medicated adhesive patches are prepared, which deliver the therapeutically effective amount of drug through the skin. Patches contain one or more ingredients to be applied on the unbroken skin only; they deliver the active ingredients into the systemic circulation, passing via skin barriers. Since the skin is having a complex structure like the stratum corneum, which makes it difficult for the drug to enter into the systemic circulation, different methodologies have been introduced. Physical technology includes sonophoresis iontophoresis, electroporation, ultrasound, microneedles, separable microneedles to open up the skin, and more recently usage of transdermal nanocarrier systems has attracted attention as drug carriers for transdermal delivery. Nowadays, skin patches have widened more commercial success as compared with ointment, creams, and lotions [1].

The skin

The skin is the widened organ of the body, accounting for more than 10% of body mass it enables the body to interact more intimately with the environment; essentially, the skin consists of four main layers.

The stratum corneum (SC), which is the outer layer of the skin, forms the rate-controlling barrier for diffusion for almost all compounds. The skin consists of dead flat and keratin-rich cells. The keratinocytes, these dense cells are surrounded by a complex mixture of intercellular lipids, free fatty acids, ceramides, and cholesterol. Their most important feature is that they are structured as ordered by layer arrays. The most important diffusional path of molecule crossing the stratum corner is intercellular. The remaining layers of the epidermis are visible epidermis. The dermis Subcutaneous tissue (lipid tissue) [2].

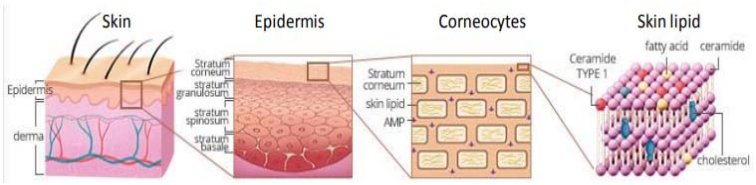

Fig. 1: Anatomy of skin

Three main permeation routes are recognized

The intercellular lipid route

Interlaminar legions in stratum corners, including linker regions, contain less order lipid and more flexible hydrophobic chains. This is the reason for the nonpolar space between crystalline lipid lamellae and their adjacent cells outer membrane fluid lipid in the skin barrier or crucially important for trans epidermal diffusion of lipidic and amphiphilic molecules, occupying this space for the insertion and migration through intercellular lipid layers of such molecules [2]. The hydrophilic molecules diffuse mainly along the surface of the less abundant water-filled interlaminar spaces or through such volumes. Polar molecules can also use the free space between a lamella and a keratinocyte outer membrane to the same end [3].

The transcellular route

The intracellular macromolecular matrix within the subcutaneous abounds in carotene, which does not contribute directly to the skin

diffusive barrier but supports mechanical stability and, thus intactness of the stratum cornea. Diffusion at transcellular is practically unimportant for transdermal drug transport [2]. The narrow aqueous transepidermal pathways have been observed using confocal laser scanning microscopy. Here regions of poor cellular and intercellular lipid packing coincide with wrinkles of the skin surface and are simultaneously the sites of lower skin resistance to the transport of hydrophilic entities. This low resistance pathway leads between clusters of corneocytes are the locations where such cellular groups show no lateral overlap. The contribution of epidermal drug transport can increase with pathway widening or multiplication; for example, that which is caused by exposing the stratum corneum to a strong electrical (electrofusion or iontophoresis), mechanical (sonoporation or sonophoresis), or thermal stimulus are suitable skin piercing (penetrants) [3].

Follicular penetration

Nowadays, follicular penetration has become a major focus of interest. Because drugs targeting the hair follicle is a great interest in the treatment of skin diseases. However, follicular modifies occupy only 0.1% of the total skin surface area. For this reason, it was assumed to be a non-important route of drug penetration. But a variety of studies have been that hair follicles could be an interesting option for drug penetration through the skin [3].

So, the follicular pathways have also been proposed for topical administration

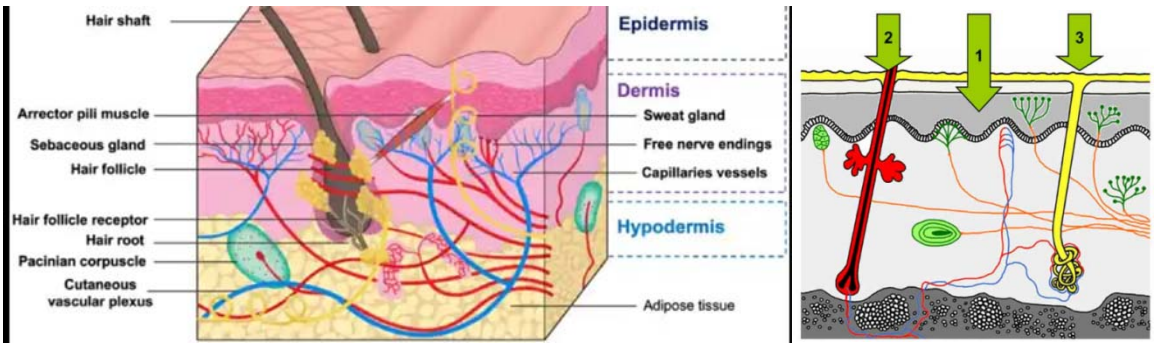

Fig. 2: Routes of drug penetration through the skin

Novel technologies for transdermal application

Transdermal nanocarriers

The types of nanocarriers that are used today have significantly increased in the past 10 y. Nanoparticulated systems can be administered to Organisms by almost all routes including transdermal, which offer several advantages over other delivery systems but with their limitation. The most used and investigated nanocarriers for transdermal drug delivery in the pharmaceutical field are liposomes, transferosomes, ethosomes, proniosomes, niosomes, nanoparticles, and Nanoemulsion. In general, the advantages and limitation of using nanocarriers for transdermal drug delivery are their smaller size, their high surface energy, their composition, their architecture, and their attached molecules [2, 3].

Nanoemulsions

Nanoemulsion single optically isotropic and thermodynamically stable liquid solution. The dispersed phase typically comprises small particles or droplets with a size of 5 to 200 nm, and has very low oil/water interfacial tension. Because the droplet size is less than 25% of the wavelength of visible light, nanoemulsion, or transparent.

Nanoemulsions have many advantages as vehicle systems including low preparation cost, low viscosity with Newtonian behavior, high storage stability, high solubilization capacity for both lipophilic and hydrophilic drugs, and absence of organic solvents, and very small droplet size [8].

Nanoemulsions are non-toxic and non-irritant systems, and they can use for skin or mucous membrane, parental and nonparental administration in general, and they have been utilized in the cosmetic field.

They are stoichiometrically unstable systems in comparison to microemulsions because some nanoemulsion requires high energy to produce them. They are susceptible to Ostwald ripening and as a consequence susceptible to creaming, flocculation, and other physical instability problems associated with emulsions.

Steps to overcome these disadvantages, modifying the composition of oil by adding medium-chain triglycerides or long-chain triglycerides, and surfactants with high surface repulsion.

Nanoemulsions have been a still active substance to the target organ at therapeutically relevant levels, with negligible discomfort and side effects. Recently interest in the development of transdermal drug delivery systems containing novel vehicles such as microemulsions and nanoemulsions, rather than conventional vehicles. It is an effective approach to enhancing the solubilization of certain drugs, particularly poorly soluble class II and IV drugs [10]. The use of these nanocarriers to deliver analgesics, corticosteroids, anti-cancer agents, etc., is very important as the drugs can act immediately because they do not need to cross extra barriers.

Presently, transdermal emulsion formulations are not developed as much as nanoparticles or liposomes due to the stability problems inherent to these dosage forms [20].

Vesicular system

Liposomes

Liposomes have become pharmaceutical nanocarriers for the choice of many applications. The liposomes are microscopic structures of one or more concentric spheres of lipid bilayers enclosing an aqueous compartment. It can be used as a strike carrier for the TDDS system. Liposomes are also proposed as a drug carrier that reduces toxicity and increases efficacy. The nature of liposomes makes them one of the best alternatives for drug delivery because they are non-toxic and remain inside the body for a long period. They have been successfully used in cancer therapy and Skin Melanoma.

Liposomes can encapsulate both lipophilic and hydrophilic drugs stably. As well as many liposome-based drugs have been approved for use in the clinic. Currently, positively charged liposomes have been used in gene therapy for DNA delivery. Also are being used for many antifungal and anti-cancer applications [11].

Transferosomes

Transferosomes are vesicular carrier systems that are specially designed to have at least one inner aqueous compartment that is enclosed by a liquid bilayer, together with an edge activator. This aqueous core surrounded by a liquid bilayer makes ultra-deformable vesicles having both self-optimizing and self-regulating capabilities. By that, transferosomes are elastic and can thereby deform and squeeze themselves as intact vesicles without a

measurable loss through narrow pores or constrictions of the skin that are significantly smaller than the vesical size.

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 the therapeutical number of drugs with efficiency compared to subcutaneous administration [15].

Ethosomes

Ethosomes, soft and malleable vesicle carriers embodying ethanol in relatively high concentrations up to 20-45%, were developed to enhance skin permeation of drugs inside the deep tissue by fluidization of the lipid bilayer of the stratum corneum. They can encapsulate both hydrophilic and lipophilic components. Ability to target organs for drug delivery. Extremely high flexibility of their membrane [16].

Niosomes

Niosomes are Biodegradable and low toxicity versatile carrier systems that can be administered through various routes, including transdermal delivery. Particular efforts have been aimed at using niosomes as effective dermal and transdermal drug-delivery systems. 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 improving penetration of the trapped substances across the skin. In addition, these systems have been reported to lower side effects and to give a considerable drug release.

Niosomal preparations have greater capability for drug cutaneous targeting and could be used as a feasible carrier for the topical delivery of minoxidil in skin diseases such as alopecia. In addition, topical application of niosomes can increase the residence time of drugs in the stratum corneum and epidermis while decreasing the systemic absorption of the drug [17].

Dendrimers

Dendrimers are nonpeptidic fractal 3-D structures made of numerous small molecules. The structure of these molecules shows uniform shapes, sizes, and molecular weights. They are the best alternative for drug-delivery systems; dendrimers can be used in antiviral al, anticancer pharmaceutical therapies, also in vaccine delivery. They increase the stability of therapeutic agents, easily prepared and functionalized. Also, rise in the bioavailability of drugs. They covalently connect drugs. Dendrimers also act as solubility enhancers, increasing the permeation of lipophilic drugs.

Dendrimers have been used for transdermal drug delivery. The main problems with this kind of transdermal carrier are its poor biodegradation and inherent cytotoxicity. The advantage of dendrimers is that they have multivalency, and it is possible to precisely control the functional groups on the surface. Due to their firm size and size, these molecules can carry drugs, imaging agents, etc. Dendrimers interconnect 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. They are usually not good carriers for hydrophilic drugs and the mechanisms underlying permeation enhancement and the interaction of dendrimers with skin [2, 6, 7].

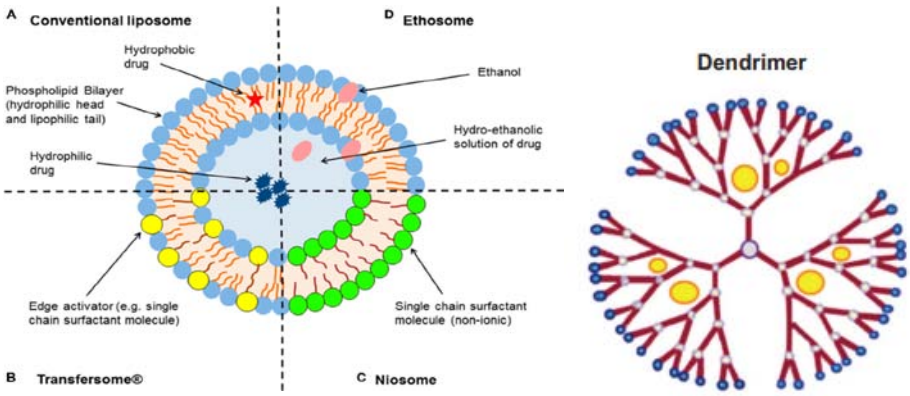

Fig. 3: Internal structure of liposomes, trasferosomes, niosomes, ethosomes, and dendrimer

Proniosomes

Proniosomes are the dry formulation of water-soluble carrier particles that are covered with surfactant and can be apportioned as required and dried out to frame niosomal scattering promptly before use on brief disturbance in hot fluid media inside of minutes. They have promising applications in the conveyance of hydrophobic and hydrophilic medications. Proniosomes offer an adaptable vesicle drug conveyance idea with the potential for the conveyance of medications through a transdermal course. The transdermal course of medication conveyance has numerous focal points as it dodges the first-pass gut and hepatic digestion system and diminished symptoms and relative simplicity of the medication info end in hazardous cases. The vesicular medication conveyance is gainful as vesicles tend to the circuit and stick to the cell surface. This is accepted to expand the thermodynamic movement angle of the medication at the vesicle-stratum corneum interface hence prompting an improved saturation rate [20, 21].

Phytosomes

Phytosomes are a complex of phospholipids and natural active ingredients. Phytosomes increase the absorption of herbal extract when applied transdermally. Phytosomes or herbosomes are lipid-compatible phospholipids complex containing herbal extract bounded with phospholipids. It is a vesicular drug delivery system containing phytoconstituents surrounds by lipid. Phytosomes increase the absorption of phytoconstituents through skin hence improving the bioavailability of phytoconstituents.

Phytosomes differ from liposomes, in phytosomes phytoconstituents and phospholipids are present in a 1:1 or 1:2 ratio, whereas liposomes' water-soluble constituents are surrounded by several phosphatidylcholine units. Phytosomes are lipophilic vesicular drug delivery systems with a definite melting point; these are freely soluble in nonpolar solvents and moderately soluble in fats [21].

Virosomes

Virosomes are drug or vaccine delivery mechanisms consisting of a unilamellar phospholipid membrane, which is either a mono or bi-layer vesicle incorporating virus-derived proteins to allow the virosomes to fuse with target cells.

These are unilamellar spherical vesicles having a mean diameter of 150 nm. They are empty influenza virus envelopes containing

the genetic material of the source virus but devoid of the nucleocapsid. Virosomes cannot replicate but are considered pure fusion active vesicles. Unlike other lipid vesicles, they contain a phospholipid bilayer membrane that can interpolate with functional viral envelope glycoproteins, influenza virus hemagglutinin, and neuraminidase. Characteristics of virosomes essentially depend on bilayer components chosen for the preparation of virosomes. Modifying the content or type of lipids membrane could optimize virosomes to achieve maximum incorporation of the drug or the best physiological effect. A lot of ligands such as cytokines, peptides, and monoclonal antibodies, can be adopted on the virosomal surface. In addition, tumor-specific monoclonal antibody fragments (Fab) could be linked to virosomes to achieve targeting for selected tumor cells.

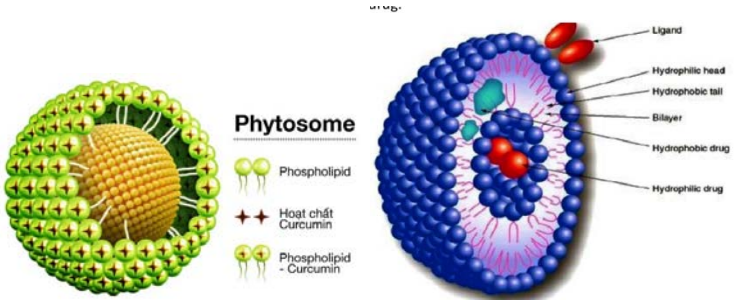

Fig. 4: Structure of phytosomes and proniosomes [20, 21]

Sphingosomes

Sphingosomes are concentric bilayer vesicles in which an aqueous volume is entirely enclosed by a membrane lipid bilayer mainly composed of synthetic or natural sphingolipid. Sphingosomes crack the main drawback of the vesicle system (liposomes, niosomes) such as less stability, less *in vivo* circulation time, and low tumor loading efficacy in the case of cancer therapy. Sphingosomes are clinically used delivery systems for chemotherapeutic agents, biological macromolecules, and diagnostics. Because of flexibility in size and composition, different types of sphingosomes have been developed [21, 22].

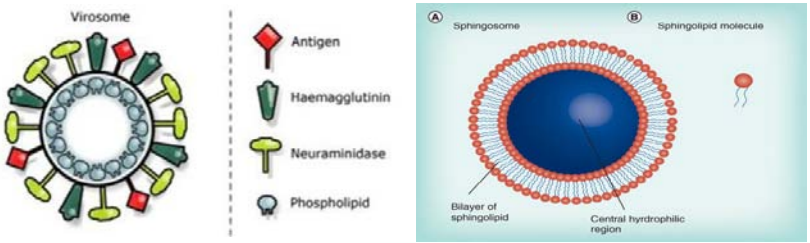

Fig. 5: Structure of virosomes and sphingosomes [21, 22]

Ultrasound-based approaches to improve permeability across stratum corneum

Sonophoresis

Ultrasound is utilized to resemble medical imaging; it is not very effective at increasing skin penetration. However, ultrasound administered in the context of heating tissue can be used to increase drug penetration into the skin. The low-frequency ultrasound used for the transdermal delivery of drugs, referred to as low-frequency sonophoresis has been shown to increase skin penetration to a wide range of therapeutic agents. The first ultrasounds device for transdermal application was approved in 2004 by the FDA for the delivery of lidocaine, local anesthesia. Although, high-intensity ultrasound causes second-degree burns limiting the delivery of macromolecules. With frequencies<1MHz, ultrasound can be used to generate bubbles that can mechanically impact the skin, creating submicroscopic defects in SC. Cavitational ultrasound of the skin has been approved as a pretreatment before the application of lidocaine as a means of accelerating local anesthesia.

Iontophoresis

Iontophoretic skin patches use low physiological acceptable electrical currents (0.1-1 mA cm^{-2}) applied for minutes to hours from an externally placed electrode to drive the drugs across the SC, primarily via the effect of electrophoresis. The success of iontophoretic technologies requires choosing the right disease area and the right molecule, one that is difficult to deliver by other methods, has poor absorption in the gut and can benefit from the use of an electric current to increase the speed or rate of delivery. Drugs that require delivery daily over an extended period (e. g., 24 h per day) may not be ideal for iontophoretic technologies. Unlike other approaches, several iontophoretic-based skin patches are on the market for delivery of drugs such as lidocaine/epinephrine, fentanyl, or most lately a drug against migraine, sumatriptan, known under the commercial name of Zecuity. Zecuity delivers the migraine drug over four hours and at a specified rate with low patient-to-patient variability. The microprocessors continuously monitor skin resistance and can adjust the current delivery of predefined doses.

The transport rate in the transdermal route is proportional to the applied constant current enabling enhancement of transdermal dose and a controlling route ls kinetics of drug. The amount of drug delivered is determined by the maximal current applicable before the pain level is reached. This approach is yet not adapted to the delivery of larger molecules.

Electroporation

In contrast to iontophoretic approaches, electroporation utilizes very short and high voltage (50-500 V) pulses to induce pores in the lipid bilayer of the SC, allowing the diffusion of the drug across the skin. Properly designed systems can minimize sensation from the pulses and facilitates drug delivery, especially hydrophilic and charged molecules into the skin. Also, small and higher molecular weight drugs can be delivered into the skin; the main drawbacks are the lack of quantitative delivery, death of cells with damage of proteins, and thus their bioactivity. This approach is currently at the research stage concerning transdermal delivery. Electroporation is

currently used to deliver chemotherapeutic agents into superficial skin tumors by applying surface or penetrating electrodes [5].

Microneedles

Microneedles (MN) array, consisting of a plurality of micro-sized tips ranging in length from 25-2000 μm offers a highly promising solution for overcoming the barrier of the skin, creates to deliver small molecular as well as macromolecular therapeutics such as vaccines, proteins, and peptides. The first concept of MN array for transdermal drug delivery was filed in 1971 in the US. Patent and is based on the formation of micro-holes of about 1 μm into the skin through which the drug can pass passively without causing pain. However, in 1998 Henry *et al.* established the first proof-of-concept of such a device for enhanced drug delivery into the skin. To quantitatively assess the ability of the MN array to increase transdermal transports, the calcein penetration on the human epidermis with and without inserted MN array was explored. Insertion of MNs into the skin was capable of dramatically increasing permeability to calcein. Insertion of needles for 10s followed by their removal yielded a nearly 10000-fold increase. Placing MN arrays for a longer period increases skin permeability.

Classification of microneedles

Microneedle, drug delivery technology, may include either of the five design types of microneedles such as solid, coated, hollow, dissolving, and hydrogel/swellable microneedles.

Solid microneedles

The Solid microneedles are typically in the range of 150-300 μm in length, tapered at a tip angle of 15-20°. Their time-worn ranges from 30 seconds to 10 min. it is made up of silicon, glass, and metal. Metal and glass are relatively non-biodegradable and safe in their use in situations where they break under the skin.

Coated microneedles

Coated microneedles are first coated with the drug before administration of the latter. This type is an attempt to propel the previous approach forward to single application systems. As a result of this, a particular amount of drug can be delivered upon insertion of microneedles into the skin.

Dissolving microneedles

The dissolving microneedles are intended to release the incorporated drug after dissolving itself in the skin within minutes without generating destruction. These are made up of sugars such as dextrin, galactose, trehalose, and maltose which release the encapsulated drug within a minute. When water-soluble polymers such as methylcellulose, PVP, polyvinyl alcohol, sodium alginate, HPMC, or co-polymer and for controlled release using Poly D, L-lactic-co-glycolic acid over hrs to months are used to develop microneedles is generally termed as dissolving polymeric microneedles. Dissolving microneedles are designed to create channels for drugs, break in the skin, and thereby dissolve and release other compounds to pass into the skin.

Hollow microneedles

Hollow microneedles consist of a drug reservoir (typically allowing up to 200 ml of drug formulation or drug alone) with a hollow dig in the center of the needle and principally indented to administer a large dose of drug solution to avoid the limitation of coated microneedles. When inserted into the skin, the hollow bore can bypass the Stratum corneum layer of skin and produces a direct channel into the other lower layers of the epidermis.

Swellable/Hydrogel forming microneedles

These are composed of a hydrophilic hydrogel framework that absorbs surrounding tissue fluid and swelling occurs to generate microchannels or pathways within the needle through which therapeutic agents can diffuse into the microcirculation. These microneedles can be elaborated as an integrated system that consists of cross-linked needles protruding from a solid base plate to which an adhesive drug reservoir is attached. These are typically fabricated from aqueous blends of poly (methyl vinyl ether/maleic acid) and poly (ethylene glycol) through a micro-molding process using silicone molds or by using laser engineering technology. When a microneedle array is applied to the skin, diffusion of the drug from the patch occurs through the swollen micro-projections [27].

Separable microneedle patch (SMN)

The successful control of COVID-19 is not only relying on the evaluation of vaccines but also depending on the storage, transportation, and administration of the vaccines. Recent approved SARS-CoV-2 vaccines are treated through intramuscular injection, which needs health care professionals for operation and may cause blood-related side effects. Ideally, for effective vaccination, the vaccine should be delivered directly to immune cells or proper tissue (such as lymph nodes). Anyhow, immune cells do not normally reside in the muscle tissue. Compared with muscle tissue, the skin is an ideal site for immunization as it has plenty of APCs and immune accessory cells for inducing potent and durable adaptive immune response; though studies have explained the benefit of intradermal injection of vaccines, difficulty in achieving a reproducible and precise delivery to the intradermal layer using traditional types. To address those limitations, and SMN patch was developed to deliver DNA vaccine-laden nanoparticles to the intradermal layer for effective vaccination. Different plans have been demonstrated to prepare the separable microneedles. For example, sodium bicarbonate and citric acid have been enclosed in the separating layers to form carbon dioxide bubbles, which could detach the backing layer from microneedles. In another method, the sharp microneedles were mounted on blunt metal shafts. After being incorporated into the skin, the blunt metal shafts can be separated from the microneedles and left in the skin [23].

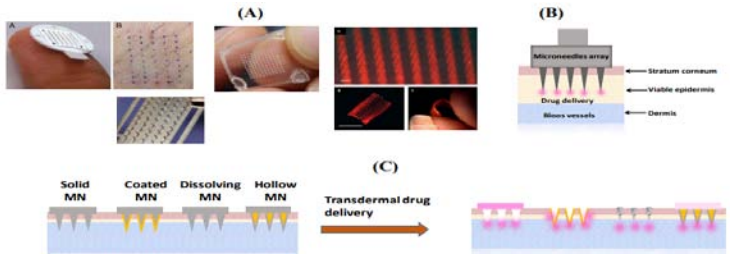

Fig. 6: Structure of microneedles [27]

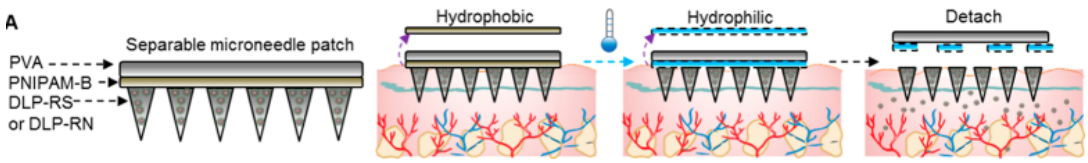

Fig. 7: The structure of separable microneedles [23]

Recent patents

Table 1: Transdermal patchs

S. No.	Patent number	Key of invention
1	US5858394	Agent for transdermal administration that contains Gestodene esters
2	US4911707	The monolithic user-activated transdermal therapeutic system
3	US4704282	A transdermal therapeutic system has improved delivery
4	US20030099695	Stabilized oversaturated transdermal therapeutical matrix systems
5	US6013276	Transdermal matrix system
6	US5066494	Transdermal therapeutic system
7	US20030044453	Transdermal therapeutic system
8	RE34692	Transdermal therapeutic system
9	US6277400	The extendible transdermal therapeutic system
10	US20070243240	Transdermal therapeutic system
11	US6143319	A transdermal therapeutic system containing estradiol
12	US5665378	Transdermal therapeutic formulation
13	US6461636	A transdermal therapeutic system containing pergolide
14	US4559222	The Matrix composition for transdermal therapeutic system
15	US20040166148	Transdermal therapeutic delivery systems with a butanolide
16	US6555131	Therapeutical system for transdermal delivery of levonorgestrel
17	US6555129	Transdermal therapeutic system [TTS] containing oxybutynin
18	US20010033859	Transdermal therapeutic system for delivery of dofetilide
19	US7344733	Matrix-transdermal therapeutic system for the use of pramipexole and ropinirole
20	US20060216336	Transdermal therapeutic system for Parkinson's Disease
21	US20040101551	Transdermal therapeutic system for releasing venlafaxine
22	US5980932	Solid matrix system for transdermal drug delivery [22].

Table 2: Microneedles

S. No.	Patent number	Key of invention
1	US 2010042050	Applicator for microneedles.
2	WO 2013066262	The invention relates to plastic microneedle strips used in TDD to increase the DD rate through the skin.
3	CA 2696810, JP 2011078618, WO 2011043086, AU 2010201434, KR 2011067009, EP 2343102 A1	Microneedle sheets are produced by injecting a needle of raw material into a stamper formed with a concavity in a base material
4	WO 2011084951, US 20110172645	Microneedle is configured to facilitate the delivery of the drug to the subject. The microneedle includes a tip portion and is movable from an inactive position to an activated position [24]

Table 3: A list of drugs can be formulated as a transdermal patch

S. No.	Particles	Drugs
1	Nanoparticles	Minoxidil [52], Triptolide [53], DNA [54], Triamcinolone acetonide acetate [55], Dexamethasone phosphate [56], Cyclosporin A [57], Flufenamic acid [58], Testosterone [19], Caffeine [58], 5-fluorouracil [59], Artemether [60], Chlorhexidine [61], Econazole nitrate [62], Insulin [63], Celecoxib [64], Triclosan [66] and Co-enzyme Q_{10} [65]
2	Liposomes	Melatonin [25], Indinavir [26], Methotrexate [27], Amphotericin B [28], Ketoprofen [29], Estradiol [30] Clindamycin hydrochloride [31] and Lignocaine [32]
3	Transfersomes	Insulin, Diclofenac, Tetanus toxoid, Superoxide dismutase, Corticosteroids, DNA, Ketotifen fumarate, Triamcinolone-acetonide, Interleukin-2, and Ketoprofen [33]
4	Ethosomes	Tacrolimus [34], Clotrimazole [36], Trihexyphenidyl HCl, Ketoprofen [35] and Testosterone [37]
5	Niosomes	Minoxidil and ellagic acid [38]
6	Dendrimers	Tamsulosin [46], Indomethacin [47], Ketoprofen, Diflunisal [48], 5-fluorouracil [49] and Peptides [50]
7	Microneedle	Nicardipine HCl [66], Amantadine HCl [67], Pramipexole dihydrochloride, Propylparaben [68], Tiagabine HCl, Carbamazepine, VLP vaccine [70], Minoxidil [71], Riboflavin [72], Insulin [75], Hyaluronidase, Biomolecules [77], Meloxicam [73], Piroxicam, Ibuprofen sodium [76], Amylopectin [79], Metformin HCl [78], Methotrexate, Bovine serum albumin [80]

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The author have has declared no conflict of interest regarding this review.

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