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MICRONEEDLE-BASED DRUG DELIVERY SYSTEMS

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ABSTRACT

Drug delivery via the skin has several benefits over oral or parenteral routes, including safety, compliance, avoidance of hepatic first-pass metabolism. Topical creams, transdermal patches, and hypodermic needles are the most popular techniques for administering medications transdermally. The ability of transdermal drug delivery systems (TDDS), which are used to administer drugs or therapeutically active substances topically, mostly thru the skin, is limited.Transdermal drug delivery methods are now employed in a number of therapeutic domains, including the treatment of heart disease, motion sickness, hormone replacement, pain management, and quitting smoking, among others. TDDS reduces the relative adverse effects of medications while increasing their potency. The primary obstacle to transdermal medication administration is the stratum corneum. Here, we primarily concentrated on the transdermal medication delivery method based on microneedles (MNs). The main idea is to break the skin layer in order to create micron-sized routes that carry the medication straight to the upper dermis or epidermis, where it can enter the systemic circulation without encountering any barriers. Microneedles can be made in a variety of ways, including solid, hollow, coated, dissolving, hydrogen-forming, and swellable. Drug delivery, vaccine delivery, oligonucleotide delivery, peptide delivery, hormone delivery, cosmetic application, lidocaine distribution, pain therapy, ophthalmic therapy, and cancer therapy are just a few of the several domains in which this method has expanded its use. The market has seen the introduction of numerous microneedle products in recent years. However, before the microneedles can effectively enter the market, a great deal of study must be done to address the numerous obstacles.

KEYWORDS: Microneedle, Transdermal Drug Delivery System, Trans-epidermal Water Loss, Stratum Corneum.

INTRODUCTION

❖ The function and structure of the skin

The largest and most accessible organ in the human body, the skin preserves homeostasis and offers defense from the outside world.[1] The epidermis, dermis, and hypodermis are its three primary layers (Fig. 1). Keratinocytes are the main component cells of the epidermis, which is between 50 and 150 µm thick. The movement of substances from the epidermal/dermal layer to the hypodermis circulation is facilitated by the diffusion process since the epidermis lacks blood microcirculation.[2] The epidermis has two sub-layers: the stratum corneum (SC) and the viable epidermis. Since water makes up 70% of the viable epidermis, it is regarded as a hydrophilic layer. The SC, on the other hand, has only 13% water and is hydrophobic. The SC, which is 10–20 µm thick, is the outermost layer of the epidermis.[3]

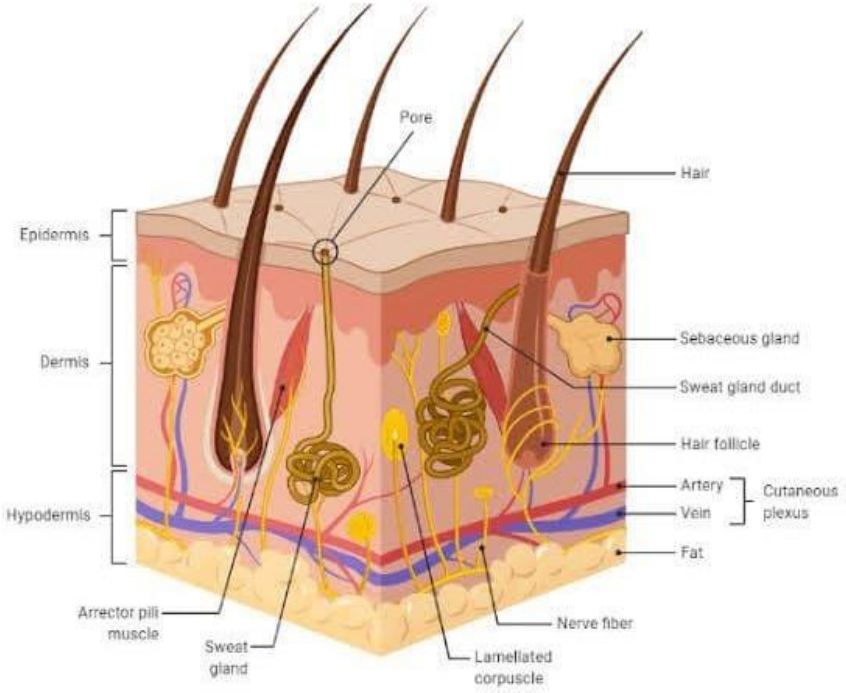

Figure No. 1: Structure of skin.

The dermis has blood vessels and nerves, and it is hydrophilic in nature. This layer, which gives the skin its mechanical strength, is composed of connective tissue and is 600–3000 μm thick.[3] The dermis, which includes skin appendages like hair, sebaceous, and sweat glands, is shown as a gel-like matrix of fibrous proteins, including collagen. This layer of skin contains cells such mast cells, fibroblasts, melanocytes, and macrophages. Adipocytes make up the hypodermis, also known as the subcutaneous layer, which is innervated and supplied with blood vessels. Protection and heat insulation are this layer's main purposes.[2]

❖ Drug delivery systems

Drugs have been administered in a number of methods to enhance health and prolong life. From chewing medicinal leaves to capsules, tablets, injectables, and implantable devices, drug delivery techniques have undergone significant advancements.[4] Targeting the specific area of a disease while lessening its harmful effects on healthy cells has improved a drug's therapeutic efficacy over time.[5] Patients' upsetting symptoms can be alleviated by increasing the drug's absorption and transport. The human body can get drugs thru a variety of methods, such as oral, parenteral, inhalation, transdermal, etc. The oldest method that is practical for patients and rather simple to administer is the oral route. The oral route has adverse effects for long-term drugs since it affects important organs including the kidneys and liver. The parenteral route uses intramuscular, subcutaneous, and intravenous routes to deliver hydrophobic medications to the human body.[6]

❖ Transdermal drug delivery systems

The most popular methods for delivering medication thru the skin are topical lotions and hypodermic needles. Patients are less likely to accept needles because of the pain they cause, and topical treatments have lower bioavailability. The main obstacle to topical medication delivery is the skin. Only specific compounds, such as lipophilic and low molecular weight medications, can pass thru the stratum corneum layer, which functions as a primary barrier. When creating topical formulations, the layer's comparatively low permeability causes numerous issues.[7] Applying the medication directly to the skin is the first step in transdermal drug delivery. The medication passes throughout the dermis and epidermis before penetrating the stratum corneum. When the medication reaches the dermal layer, it might be absorbed. The first generation used patch-based technologies leveraging natural diffusion with the goal of delivering a minimal drug dose. The second generation concentrated on activating drug delivery with the use of chemical precursors. Thermal ablation, electroporation, and microneedles are examples of third-generation technologies that can precisely target the medicine upon penetration into the stratum corneum.

Lastly, the fourth generation uses drug delivery microneedles in conjunction with sensing modalities to precisely regulate the release of medicinal substances. Compared to alternative drug delivery techniques, transdermal drug delivery (TDD) offers a number of benefits. TDD has the capacity to sustainably and carefully administer the medication to the blood at the appropriate dosage.[8] By keeping medications from getting to vital organs like the liver and kidneys, the transdermal method also reduces adverse drug reactions.[9]

MICRONEEDLE HISTORY

Microneedle conceptions have changed over time,

starting with the usage of big needles and ending with the current design. Different sizes of motor-powered dental burs were used in 1905 by German dermatologist Dr. Ernst Kromayer to treat skin conditions such as hyperpigmentation and scarring. In 1921, Chambers used a microneedle to insert the needle into the nucleus of an egg, which is the first documented use of a microneedle.[10] The 1970s saw the introduction of the microneedle concept, but it wasn't until the 1990s that this idea was proven experimentally.[11] In order to alleviate motion sickness, the first transdermal method of delivering scopo-Lamine was authorized in 1979. This method involved placing a three-day patch.The application of microfabricated microneedles to improve drug administration thru the skin was discussed in the study. Extensive study in the microneedle realm was prompted by this paper. To create microneedles, several materials were used, including glass, ceramic, metal, and polymers. A number of fabrication techniques and materials were investigated for the goal of transdermal drug delivery (TDD) after a microneedle array was utilized in 2004 to puncture holes in the skin.[12] MNs can be classified as solid, coated, hollow, dissolvable, or hydrogel-forming. Additionally, a variety of manufacturing techniques, including photolithography, laser ablation, micro-injection molding, etc. The first reports of a dissolvable microneedle being used for TDD were made in 2005 as a result of these discoveries.[13]

MECHANISMS OF DRUGS DELIVERY

The diffusion mechanism is followed while administering the medication topically. The skin is momentarily disturbed in the microneedle drug delivery device. To administer enough medication to provide the necessary therapeutic response, a microneedle device is created by arranging hundreds of microneedles in arrays on a tiny patch, similar to a typical transdermal patch on the market. It avoids the barrier layer by penetrating the stratum corneum. The medication is applied directly to the epidermis or higher dermis layer, where it enters the systemic circulation and, once it reaches the site of action, exhibits a therapeutic reaction. Figure no.2, shows the mechanism of medication delivery via microneedles.

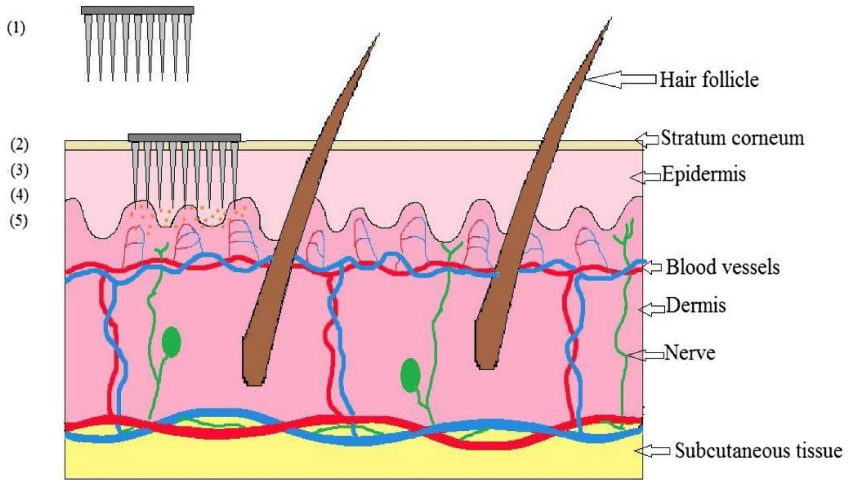

Figure No. 2: Mechanisms of Drug Delivery system.

DIMENSIONS OF MICRONEEDLE

Depending on the type and substance, microneedles can be made in different sizes. A needle length of up to 1500 µm is adequate to distribute the medication into the epidermis because the epidermis can be as thick as 1500 µm. Longer and thicker needles have the potential to penetrate deeply into the dermis, harm nerves, and produce pain.[14] They are typically 50–250 microns wide, 150–1500 microns long, and have tips that are 1–25 microns thick. As was previously said, the purpose of the microneedle device is to establish a transport pathway that is micron-sized; the diameter of the needles is kept within a few microns. Microneedle tips come in a variety of forms, including cylindrical, triangular, pointed, pentagonal, and octagonal.

TYPES OF MICRONEEDLE

Solid, coated, dissolving, hollow, and hydrogel microneedles are among the various kinds of microneedles that have been created and studied for use in drug administration. Table No.1. shows many microneedle kinds and their distinctive characteristics.

A) Solid

The primary purpose of solid microneedles is to create pores in the skin for pre-treatment. When a medicine patch is applied, the needles' pointed tips pierce the skin and form micron-sized channels that allow the medication to enter the skin's layers directly, improving penetration. For the medication to have a systemic effect, the capillaries absorb it. A local impact can also be achieved with it.[15] The medication is delivered to skin layers by solid microneedles thru passive diffusion.[7] Narayanan et al. used the etching process of tetramethylammonium hydroxide to create long, tapered solid silicon microneedles. Microneedles were successfully created with an average height of 158 µm and a base width of 110.5 µm.[16] Subsequently, he created gold-coated solid silicon microneedles that measured 250 µm in height, 52.8 µm in base width, 4.73

in aspect ratio, and 24.5° in tip angle and 45 μm in diameter. The outcomes showed increased mechanical strength and bioavailability.[77] Numerous researchers are also investigating stainless steel microneedles. Following the use of stainless steel MN arrays, improved distribution of captopril and metoprolol tartrate was investigated.[7]

B) Hollow

Drug fluid is injected or kept in the hollow microneedle's hollow or empty core or chamber. The hollow microneedle can handle a higher dose/amount of medication solution than the solid microneedle.[18] Additionally, a hollow microneedle can transport the medication into the dermis or viable epidermis. It is appropriate for molecules with large molecular weights. Hollow microneedles are an active drug delivery method that creates a channel for drug diffusion, in contrast to solid microneedles, which mainly elute pharmaceuticals based on the osmotic gradient.

Into the dermis using a drug reservoir that is not under pressure. Similar to hypodermic needles, hollow microneedles can be designed to allow modulation of flow rate and pressure. Process parameters like Microneedle aspect ratio (height to base diameter ratio) can be controlled for rapid release, slow infusion, or time-varying delivery rate. Both material formulation and fabrication parameters of hollow microneedles can be leveraged to enable tunable release kinetics. Higher concentration drugs can result in burst release drug profiles, whereas matrix-loaded drugs can enable a steady-state drug release that lasts, depending on the intended use.[19] Hollow microneedles are comparable to hypodermic needles. Can be made to allow for pressure and flow rate regulation.

For quick release, slow infusion, or time-varying delivery rate, process variables such the microneedle aspect ratio (height to base diameter ratio) can be adjusted.[20] The hollow microneedle has been effectively used in numerous vaccines and inoculations throughout the years.[13] However, compared to the solid microneedle, this kind of microneedle attracted less attention since the hollow microneedle is comparatively weaker and necessitates careful needle design and insertion technique.[21] Additionally, technical issues with the hollow microneedle include blockage and leaking during injection.[13]

C) Coated

The drug payload is delivered into the skin when coated MNs pierce the SC.

The coated area is quite small and can only give a bolus of a very small amount of medication (less than 1 mg), making accurate coating rather difficult.[22] Particular attention has been drawn to coated MN arrays for the administration of vaccinations and powerful chemicals. Coated MN arrays were used to distribute several substances, including DNA, fluorescein sodium, desmopressin, salmon calcitonin, and parathyroid hormone (PTH).[23]

D) Dissolving

A "poke and release" delivery method is used by Dissolvable MN. The medication is either dissolved or suspended in the MN formulation of these polymer-based MN arrays. The polymers are inexpensive and do not leave the skin with any sharp or biohazardous waste. The self-disabling nature of these MN arrays ensures their safe disposal and prevents their reuse.[24] Some have employed aqueous mixtures of amylopectin and carboxymethylcellulose.

Others have used hydrophilic polymers with different molecular weights to create dissolving MN arrays. Low molecular weight hydrophilic polymers dissolve in a matter of minutes, resulting in a one-step bolus medication administration that minimizes the time required for skin application.[25] The distribution of a variety of medications, including small compounds like caffeine and lidocaine and macromolecules like insulin and human growth hormone, as well as a number of vaccine antigens and diagnostic materials, was successfully improved by dissolving MN arrays.[26]

Table No. 1: Types of Microneedle.

MN Type	Characteristics	Advantages	Disadvantages	Application	Material	Reference
Solid	Solid makes channels in the skin that let medications get to the epidermis. sufficient mechanical power. sharper tip.	Makes it possible for more medications to enter the skin. simple to produce.	To prevent infections, skin damage and microincisions must be sealed	Drug Delivery Cosmetic	Silicon Metal Polymer	[7,15-17]
Hollow	A blank form to be filled with medication. the capacity to regulate the release of drugs over time.	Manages a high dosage or volume of medication solution.	Weak needles. requires careful consideration of the needle's design and insertion technique. may result in clogging and leaks.	Disease Diagnosis	Silicon	[13,18-21]
Coated	Because of its design, it contains less medication.	Deliver the medication to the	Easily infected.	Drug Delivery	Silicon	[22,23]

	the capacity to deliver DNA and proteins in a minimally invasive way.	skin rapidly.		Vaccine Delivery		
Dissolving	Promotes the quick release of macromolecules.	One-step application makes administrati on simple for patients.	Manufacturing calls for technical know-how. dissolves slowly.	Drug Delivery Cosmetic Vaccine Delivery	Polymer	[24-26]

MICRONEEDLE MATERIALS

A) Silicon

The first microneedle was created from silicon in the 1990s. Silicon has a crystalline structure and is anisotropic by nature. The alignment in the crystal lattice, which exhibits varying elastic moduli (50 to 180 GPa), determines its characteristics. Its flexible nature permits creating needles of varying sizes and shapes. It is a versatile material because of its appealing physical characteristics. Silicon substrates can be produced in large quantities and with accuracy. The use of silicon in microneedles is restricted by its high cost and labor-intensive, complicated fabrication method. Furthermore, because silicon is fragile, some of it may break and stay in the skin, which could lead to health problems.[27]

B) Metal

Titanium and stainless steel are the primary metals utilized. Additionally, alloys of palladium, nickel, and palladium-cobalt are utilized. They are biocompatible and have good mechanical qualities. Metals are more suitable than silicon for the manufacturing of microneedles because they are robust enough to not break. Stainless steel was the first metal utilized to make microneedles.[28] An excellent substitute for stainless steel is titanium.[27]

C) Ceramic

The primary application of alumina (Al2O3) is due to its chemical resistance. The extremely strong ionic and covalent interactions between the Al and O atoms lead it to form a stable oxide.[29] Calcium phosphate dihydrate [Brushite (CaHPO4.2H2O)] and calcium sulfate dihydrate [Gypsum (CaSO4 0.2H2O)] are two more kinds of ceramics that are utilized. Ormocer®, an organically modified ceramic, has been utilized in recent years. It is a copolymer that is cross-linked in three dimensions. Diverse organic units can be used during polymerization to create a polymer with diverse characteristics. They are mostly made by a process called micro-molding. A micro-mold is filled with ceramic slurry. Micro-molding methods can be scaled up and are less expensive.[27]

D) Polymer

These polymers are typically used to create hydrogel-forming, dissolving, or biodegradable microneedle arrays. These polymers are more durable than glass and ceramics, but they are not as strong as other materials when used to make microneedles.[27] For the preparation of microneedles, a wide range of polymers have been reported, including poly (methyl methacrylate) (PMMA)[30], polyglycolic acid (PGA)[31], cyclic-olefin copolymer, poly (vinylpyrrolidone) (PVP)[32], poly (vinyl alcohol) (PVA)[33], polystyrene (PS)[34], and poly (methyl vinyl ether-co-maleic anhydride).[55]

E) Carbohydrates

One of the most widely utilized sugars is maltose. Metal or silicon templates are used to mold carbohydrate slurries. To create the microneedles, the drug-loaded carbohydrate mixture is cast into the molds.[36] The medication release inside the skin is controlled by the time-based disintegration of carbohydrates. Although carbohydrates are inexpensive and safe for human health, their breakdown at high temperatures complicates the manufacturing process.[27]

METHODS OF MANUFACTURING MICRONEEDLES

The MN arrays can be made using a variety of techniques. Laser ablation, micro-molding, additive manufacturing, injection molding, chemical isotropic etching, surface/bulk micromachining, and lithography-electroforming-replication are the most widely used techniques.

Table No. 2: Microneedle Manufacturing Method.

Manufacturing Method	Description	Advantages	Disadvantages	Reference
Laser ablation	Creates an MN array on a substrate using a concentrated optical light beam.	Take less time	The substrate (MN array) may develop fatigue resistance or a crack. expensive. Unsuitable for mass production.	[37]
Lithography	Applies the geometric shapes' master pattern to a substrate's	Creates MN from a range of materials. Exceptionally accurate geometries vertical	Time consuming.	[37]

	surface.	sidewall that is smooth.		
Micro -moulding	Makes a duplicate of a master mold and casts it using a solution.	For large-scale manufacturing. Economical.	Manages the penetration depth. capacity for drug loading. mechanical actions.	[38]
Injection Moulding	Filling a mold with molten plastic materials.	Production in large quantities.	Expensive initial outlay (cost of machine equipment). intricate procedures.	[39,40]
Additive manufacturing	Printing the MNs in layers.	Modifiable style.	Needs a top-notch 3D printer. Provide a limited level of accuracy.	[41]

A) Laser Ablation

In order to construct MN arrays, laser ablation uses a concentrated optical light beam to remove material from a substrate. For the production of MN arrays, several types of lasers have been investigated. These include femtosecond laser machines, CO2, and UV excimer. The laser ablation technique is thot to be a quick and efficient way to fabricate MNs. It takes ten to one hundred nanoseconds for the laser beam to get close to the material sheet's burn point. Any metal could also be shaped with a laser. This technique is linked to heat processes at the cutting surface that change the mechanical characteristics and structure of the MN. This could have in unfavorable consequences for MNs, like fatigue resistance or cracking. Low heat loads are applied to the substrate during the non-contact laser ablation process.Nevertheless, the laser is more expensive than other kinds of equipment.[37] Large-scale production is not a good fit for the laser ablation technique.

B) Lithography

The master pattern of the geometric shapes is transferred onto a substrate's surface using lithography technique.

Because photolithography has so many applications in the realm of microelectronics, it is mostly employed for pattern transfer. Lithography is the initial step in the fabrication of an MN in other methods like microelectronics and micromachining. Precise photoresist processing is necessary for lithography. This method accounts for between 30 and 35 percent of integrated circuit manufacturing expenses. Glass, metal, ceramics, polymers, and other materials can all be used to build goods using lithography. It also creates clean vertical sidewalls and accurate geometry.[37]

C) Micro-molding

Replicating the master mold is the process of micro-molding. A solution containing active medicinal ingredients and a polymer is poured into the mold. Micro-moulding is a mass production technique that is thought to be economical. For MN creation, micro-molding is frequently utilized with polymer material. In micro-molding processes, the PDMS offers a number of benefits, including low cost, convenience of usage, low surface energy, and thermal stability. The technique's drawbacks include challenges in regulating the polymer's mechanical behavior, drug load capacity, and depth of penetration.[38]

D) Injection Moulding

Another MN fabrication technique is injection molding. The method of creating MNs utilizing hot embossing and injection molding. Lhernould et al. created a 4 × 4 hollow polymer MN array using poly carbonate (PC) material. The MNs were utilized for several insertions without blunting the needle and were demonstrated to be able to sustain high force. Another study created a solid MN using a micro-injection molding technique. High molecular weight, hydrophilic compounds could be delivered using these needles. Sammoura et al. used plastic molding to create a polymeric MN.[39] A fresh chicken leg and beef liver were successfully penetrated by the needles, and around 0.04 μL of liquid was extracted from these tissues. The suggested technique makes it possible to produce MNs in large quantities at a minimal cost.When plasticization and polymer melt injection are separated, micro-injection molding also provides high injection flow rates, precise dosing, and great repeatability. Due to the common screw size of 15–150 mm and the greater initial equipment cost, the injection molding technique is limited in its ability to manage small shot sizes.[40]

E) Manufacturing

Additive manufacturing, or 3D printing, has drawn a lot of interest lately as a way to create MN arrays. Layer by layer, the desired material is deposited by a 3D printer to create an object. In recent years, 3D printing technologies for tissue engineering implants have become increasingly popular in the biomedical device sector.[41] The flexibility of design parameters and shortened processing lead times are two benefits of manufacturing an MN array with 3D printers.

APPROACHES TO ENHANCE PENETRATION

Penetration enhancers are used to increase drug and drug molecule penetration thru various skin layers. Since the stratum corneum is the primary obstacle to transdermal medication administration, methods for getting around

the stratum corneum-specific obstacles can also be major groups.

A) Prodrugs

The prodrug method is highly suitable for increasing transdermal drug delivery. The addition of the promoiety to the prodrug design raises both the drug's solubility and the inappropriate partition coefficient. Additionally, it is crucial for the movement of drugs thru the stratum corneum. Anti-inflammatory and non-steroidal medications can be made more permeable with this method.

B) Eutectic system

Eutectic systems are composed of a mixture of elements or compounds that, when held at low temperatures, change into solid states. According to a theory of solution, a material's solubility in a given solution is inversely proportional to its melting point. The melting points of DDS are lowered using eutectic mixtures. EMLA Cream, for instance.[42]

C) Liposomes and vehicles

Liposomes are spherical vesicles that can encapsulate drugs and include lipid bilayers. These kinds of formulations and encapsulations are also found in cosmetics, such as in enzymes and humectants. Cholesterol is added to the makeup of liposomes to strengthen their rigidity and solidify their structure. The method by which liposomes improve drug penetration throughout the stratum corneum is unclear. Following their penetration of the stratum corneum, liposomes may interact slightly with the lipids and release drugs.[43]

D) Nanoparticles

Solid lipid nanoparticles are employed as carriers to improve penetration in various cosmetic formulations, such as sunscreen, and to deliver glucocorticoids and vitamins A and E. The main cause of these formulations' improved penetration is the occlusive layer that forms on the skin's surface, which is in charge of making the skin more hydrated.[53]

E) Electroporation

This technique creates transient pores by applying high voltage pulses to the skin. This technology primarily uses a voltage of about 100V for milliseconds. This system makes skin more permeable to molecules of various sizes and lipophilicity, such as proteins and peptides. Additionally, it applies to molecules weighing less than 7 Kda.[44]

Nerve excitation can occur when a high-voltage electric field is applied directly to the skin. This method may result in intraepidermal vacuolization and temporary erythema.

F) Ultrasound

This technique increases skin permeability by using low-frequency ultrasonic waves, roughly 55 kHz, for 15 seconds. Sonophoresis and phonophoresis are two techniques in this system that use ultrasonic energy. The Stratum corneum is disturbed and gaseous cavities are created in skin lipids using ultrasonic energy. Frequencies between 20 kHz and 16 MHz are typically used to improve skin penetration. The utilization of frequencies below 100 kHz in transdermal medication delivery systems is highly significant.[45]

G) Laser radiation

Acne and other dermatological problems are frequently treated with laser radiation. This technique exposes the skin to laser radiation either directly or under controlled conditions. The Stratum corneum is removed by this laser exposure to the skin without harming the underlying epidermis.Clinical therapy have long made extensive use of lasers. They are also used in cosmetic rejuvenation treatments, where radiation quickly destroys the target cells. This method's ablation of the stratum corneum shows improved drug penetration, both hydrophilic and lipophilic.[46]

H) Magnetophoresis

This device contains a diamagnetic solute, and an external force in the form of a magnetic field is applied to allow the solute to diffuse across the skin's membrane. When a magnetic field is applied to the skin, it may trigger structural changes that enhance the skin's permeability. This method's primary drawback is the requirement for diamagnetic materials.[47]

I) Skin abrasion

Dermatologists utilize this technique extensively to treat skin conditions like acne and skin imperfections. The top layers of skin are either directly removed or disturbed in order to improve the permeability of the substances applied topically. The potential for drug distribution in this system is not adversely affected by the physiochemical characteristics of the medication. Vitamin C and medications with hydrophilic properties are delivered using this technique.[48] A portion of the stratum corneum will be removed by the device without affecting the other layers. This approach has the following benefits:

1. Reducing patient discomfort
2. Improving patient adherence
3. It's simple to use
4. There is little chance of infection.
5. Painless
6. More practical than cannulas and hypodermic needles.

J) Needle less injection

The fundamental idea behind transdermal medication delivery is the drug's extraordinarily rapid penetration of the skin's outer layer utilizing a suitable energy source. In this approach, the device is filled with compressed helium gas. The compressed gas contains the drug. The gas is expelled via a nozzle to create a jet flow that travels at a sufficient speed to pierce the skin.[49] This is

a painless way to apply the medication to the skin. This technique should not be used on a regular basis for drug delivery since the rapid bombardment of drug particles on the skin could cause issues.

K) Skin puncture and perforation

This system's gadgets are comparable to those in the microneedle system. Thru their needle-like projections, they create tiny holes in the skin to disturb the skin's barrier. Projections should be the appropriate length to prevent them from penetrating layers beyond the epidermis. Different medication delivery techniques, such as active and passive approaches, are available. The needle-like projections pierce the skin, allowing the medication inside the device to enter. Via the system's micro-holes.[50]

L) Stretching

One of these technologies is the ability to retain skin under stress in a unidirectional or multidirectional manner. A stress or strain of roughly 0.01–10 mPa is necessary for the creation of micro pathways. Bidirectional skin stretching facilitates the opening of channels with delayed closure, which improves medication penetration. The channels open and the microneedle can readily pierce the skin when the skin has been stretched. Certain techniques, such as pressure, electro transport, passive mechanism, and osmotic mechanism, use devices for transdermal drug delivery in conjunction with skin stretching.[51]

EVALUATION OF MICRONEEDLE

A) Characterization Method

The medication can be encapsulated (liposomes, nanoparticles, or nanoliposomes) or put onto or into the microneedles in suspension or dispersion form.[52] The medication can be applied as a patch or coated with the polymer solution. Depending on the type of formulation employed in the microneedles, a variety of physicochemical characteristics, such as particle size, polydispersity index, viscosity, and zeta potential, can be assessed for loaded medication. Tests for drug release, adhesion, and penetration are conducted for a patch that is applied following pre-treatment. Dynamic light scattering, X-ray scattering, and transmission electron microscopy can be used to determine the liposomes' or nanocarriers' size, internal structure, and crystallinity. Drug dispersion and microneedle stability studies can be conducted at various pH levels, temperatures, and simulated in-vivo physiological settings (tissues or cell lines). The proposed microneedle is further subjected to other testing such as drug content, solubility, in vitro release, and biocompatibility.

B) Dimensional Evaluation

The microneedle's tip radius, length, and height are measured using a variety of techniques to assess the needle geometry. Electrical or optical microscopy are the most widely used techniques. A 3D image analysis improves the needle geometry and aids in quality assurance. For this, confocal laser microscopes and scanning electron microscopes (SEM) have been employed. SEM creates an image of a sample by using a concentrated electron beam that interacts with the sample's atoms during scanning, producing a variety of signals that reveal details about the composition and topography of the sample's surface. High-resolution images are produced with a confocal laser microscope.[53]

C) Mechanical characterization

To maximize the effectiveness of MN devices, a basic understanding of the mechanics of needle insertion into the skin is crucial. Sharp-tipped needles may pierce the skin with the least amount of force. Nevertheless, the latter would weaken the area at the needle tip, and bending of the needle tips might occur, particularly for needle prototypes with extremely thin tips (less than 20°). Needle prototypes with a small tip diameter and a thick wall are preferred for insertion because it has been shown that the fracture force increases with needle wall thickness. The penetrating force may also be impacted by the needle density of a baseplate in a particular region. The bed of nails effect would be caused by the excessive needle density. Fracture and buckling are the two main types of failure modes associated with needle insertion into the skin.[54] The primary mechanical tests for MN arrays are described in Table. 1and include axial force, transverse force, and insertion force.

Table No. 3: Mechanical Test.[55]

Mechanical Test	Description
Axial force	The needle tip is subjected to a vertical force.
Transverse force	The MN base is subjected to parallel force application
Insertion force	A skin or simulated membrane is treated with the MN array.

D) In- vitro Skin Permeation Studies

One crucial factor in getting a specific dosage form approved by regulatory agencies is in-vitro research. Cells, microorganisms, or other biological molecules outside of their biological entity are used in in vitro investigations.

Solid, hollow, or dissolvable microneedles can be studied in vitro using a variety of techniques, such as Franz diffusion cells, in vitro skin penetration studies, in vitro drug release studies in saline conditions, etc. Drug penetration throughout the skin is measured using diffusion cell equipment. For this permeation investigation, pig ear skin and saline fluid were used as receptor fluids. During the experiment, the receptor fluid was kept at 600 RPM, and caution should be used to avoid trapping air bubbles in the pig ear skin and receptor solution. 500 µL of receptor solutions with too much rizatriptan applied topically. Samples were analyzed using HPLC after being submerged at regular intervals of six hours to forty-eight hours. The same procedure was done using a microneedle containing

rizatriptan, and the results were compared to ascertain the drug's penetration rate in the microneedle.[56]

E) In-vivo Animal Model Studies

Trans-epidermal water loss (TEWL), which is measured before and after microneedling using a Delfin Vapometer, is one of the parameters taken into consideration. Hairless rats may be used for the study; an appropriate method of anesthesia must be used.[56]

Table No. 4: In-vivo Success of MNs Based Formulations.

Types of MNs	Drug Incorporated	In-vivo model	Reference
Dissolving Bilayer MNs Array	Vitamin B	Rat	[57]
Dissolving MNs	Levonorgestrel	Female Rat	[58]
Dissolving MNs	Insulin	Rat	[59]
Two layered dissolving MNs	Doxycycline Monohydrate	Rat	[60]
	Albandazole Salfone		
	Diethyl - Carbamazine		
Dissolving MNs	Bevacizumab	Female spargue	[61]
		Dawley Rat	
Dissolving MN Array	Naltrexol	Guinea pig	[62]
Dissolving MNs	Rhodamine B	Mice	[63]
Dissolving MNs	Nicotine	Rat	[64]

APPLICATION

A) Drug Delivery

In 1998, a solid silicon MN patch was used to deliver human growth hormone transdermally to the skin of hairless rats; a dissolvable MN patch loaded with caffeine was used to control the weight of obese mice and function as an anti-obesity treatment plan; a coated MN patch was used to deliver salmon calcitonin[65]; a solid microneedle was used to deliver a protein antigen (ovalbumin) into the skin of hairless guinea pigs; and solid silicon and metal MNs were used to deliver insulin, BSA, and calcein. Additionally, MNs have been utilized for transdermal penetration of a number of medications, including paracetamol, ketoprofen, and ibuprofen. L-ascorbic acid, riboflavin, aspirin, docetaxel, pilocarpine, lidocaine, hydrochloride, ketoprofen, and glycerol are additional medications administered via microneedles. Some studies successfully demonstrated microneedle injection into brain tissue, even tho the majority of studies used microneedle arrays for drug delivery into mice, pigs, and human skin.[66]

B) Vaccine Delivery

A biological preparation is called a vaccine. It offers active acquired immunity against a specific illness. A vaccine is made up of a disease-causing microorganism, its toxins, or one of its surface proteins that has been killed or weakened. Vaccine therapy boosts the body's immune system and offers defense against microorganisms in the future. It was discovered that the microneedle method worked well for vaccination treatment.[15] A microneedle was used to administer the DNA vaccine. Compared to the standard injections, the observed immune responses were significantly better. Additionally, an effort was made to create a microneedle patch that could be used to administer the influenza vaccine. When using hollow microneedles instead of intramuscular injection, a lower dosage is needed. Additionally, the use of hollow microneedles to administer the rabies and anthrax vaccines was investigated.[27]

Ogai and associates created hollow microneedles from poly-glycolic acid to improve intradermal vaccination effectiveness. Immunity is boosted by the drug's precise administration in the upper dermis. Following the vaccination, intradermal vaccination using microneedles resulted in significantly higher antibody titers than subcutaneous injection on the 15th day.

C) Oligonucleotide delivery

Short DNA or RNA molecules are known as oligonucleotides. It is challenging to deliver oligonucleotides to their intracellular site of action. As a result, several methods to improve the delivery were found. The microneedle method was used in an attempt to deliver 20-merphosphorothioated oligodeoxynucleotide. The poke with patch method of delivering oligonucleotides was tested using solid microneedles composed of titanium or stainless steel. Compared to intact skin, a greater quantity of medication was discovered to reach the site of action. Results were better when iontophoresis was combined with the microneedle technique than when iontophoresis was used alone.[68]

D) Peptide Delivery

When peptides are taken orally, they are broken down by enzymes. This is avoided by transdermal delivery, although less peptide can pass thru the skin. Microneedle delivery of peptides can help overcome the peptides' poor skin penetration. A synthetic version of the powerful peptide hormone vasopressin is called desmopressin. Low levels of vasopressin are replaced with it. This drug is used to treat hemophilia A, diabetes insipidus, and bedwetting in young children. Research on

the use of microneedles to administer desmopressin revealed that this method was safer and more effective than other methods.[68] Cyclosporin A is a high molecular weight, water-insoluble cyclic peptide used to treat a variety of skin conditions. Cyclosporine A-containing dissolving microneedles measuring 600 μm in length and 250 μm in width were created by molding. After 60 minutes of pressing manufactured microneedles containing 10% cyclosporine A into the porcine skin, approximately 65% of the microneedles with 34 ± 6.5 μg of drug were dissolved.[69]

E) Hormone Delivery

A peptide hormone is insulin. The drug is used to reduce elevated blood sugar levels. Microneedle delivery of insulin has been shown to more effectively lower blood glucose levels. Li et al. created solid microneedles and investigated how insulin delivery affected the blood glucose levels in diabetic mice. The improved permeability of insulin to the skin using microneedles was confirmed by the results, which showed a drop in blood glucose to 29% of the starting level at 5 hours. Ye and colleagues studied microneedles combined with pancreatic β-cell capsules that detect blood glucose levels and release insulin. However, it was discovered that the patch did not work well.[70]

F) Cosmetic Application

The use of microneedles in cosmetics is becoming more and more popular, particularly for treating scars and imperfections on the skin. The microneedle method was used in an effort to deliver some cosmetic active ingredients, such as ascorbic acid, eflornithine, and retinyl retinoate.[17] Melanin was added to phosphatidylcholine liposomes (nanoliposomes), which demonstrated improved lipid solubility. It was discovered that using an e-roller increased the amount of pigment that penetrated deeply close to the hair structures.

G) Lidocaine Delivery

For local anesthesia, lidocaine is utilized. Patient compliance is higher when lidocaine is administered via microneedle because it is less painful than hypodermic injection.It applied lidocaine to the tips of the microneedles. These microneedles demonstrated improved drug delivery in two minutes and consistent in vitro skin penetration. Microneedles can therefore be used for quick and painless local anesthesia. When compared to the topical formulation, microneedles coated with PEG-lidocaine dispersions demonstrated better drug delivery within three minutes in one study.[7]

H) Pain therapy

Polydimethylsiloxane molds were used to create polymeric microneedles loaded with meloxicam. About 100% of the drug was released in 60 minutes, according to the in-vitro permeation studies. Improved transdermal flux of 1.60 μg/cm2/hr was noted, and the drug deposition was found to be 63.37%. In comparison to the free drug solution, the penetration rose 2.58 times.[71] Treatment for neuropathic pain is typically challenging. The current therapies have certain adverse effects and are unable to adequately relieve pain. The use of dissolvable microneedles to treat neuropathic pain was investigated. These demonstrated high specificity against the receptors and delivered a specific calcitonin gene-related peptide (CGRP) antagonist peptide. No adverse effects or skin irritation were observed with the analgesic microneedle patch. After 20 minutes of application, about 75% of the microneedle dissolved.[72] Microneedle delivery of therapeutics has created enormous opportunities for the pain management industry.

I) Ocular therapy

Drug delivery targeting can be used to treat a number of posterior segment indications. Nanoparticles were delivered thru the suprachoroidal space using iontophoresis. The particles were observed to localize at the injection site in the absence of iontophoresis. The posterior segment of the eye received over 30% of the nanoparticles when combined with microneedles.[73]

J) Cancer therapy

Every year, a large number of people worldwide are affected by cancer, and there are many obstacles in the way of cancer treatment. Microneedles have been studied for the delivery of several anticancer medications. Anti-PD-1 (aPD1) was delivered in a sustained manner using self-degradable microneedles for the treatment of melanoma. Microneedles were used to administer pH-sensitive dextran nanoparticles loaded with glucose oxidase and anti-PD-1.[74] Basal cell carcinoma is treated with a topical cream that contains 5-fluorouracil. Applying the cream to skin treated with solid microneedles increased the permeability of 5-fluorouracil by up to 4.5 times. Improved efficacy with microneedles was further confirmed by significant inhibition of tumor growth.[75]

REFERENCE

1. Ghasemiyeh P, Mohammadi-Samani S. Potential of nanoparticles as permeation enhancers and targeted delivery options for skin: Advantages and disadvantages. Drug Design, Development and Therapy, 2020; 12: 3271–3289. https://doi.org/10.2147/DDDT.S264648.
2. Benson HA, Watkinson AC (2012) Transdermal and Topical Drug Delivery. John Wiley & Sons, Hoboken, New Jersey. https://doi.org/10.1002/9781118140505.ch18.
3. Mendelsohn R, Flach CR, Moore DJ Determination of molecular conformation and permeation in skin via IR spectroscopy, microscopy, and imaging. Biochimica et Biophysica Acta (BBA)-Biomembranes, 2006; 1758: 923–933. https://doi.org/10.1016/j.bbamem.2006.04.009.
4. Ranade V.V., Hollinger M.A., Cannon J.B. Drug Delivery Systems. CRC Press; Boca Raton, FL, USA: 2003. [Google Scholar].

5. Tiwari G., Tiwari R., Bannerjee S., Bhati L., Pandey S., Pandey P., Sriwastawa B. Drug delivery systems: An updated review. Int. J. Pharm. Investig, 2012; 2: 2–11. Doi: 10.4103/2230-973X.96920. [DOI] [PMC free article] [PubMed] [Google Scholar]
6. Robbie G., Wu T., Chiou W.L. Poor and unusually prolonged oral absorption of amphotericin B in rats. Pharm. Res., 1999; 16: 455–458. Doi: 10.1023/A:1011961322883. [DOI] [PubMed] [Google Scholar]
7. K. Ita, Transdermal delivery of drugs with microneedles-potential and challenges Pharmaceutics, 2015; 7(3): 90-105.
8. Verma, N.K.; Panda, P.; Mishra, J.N.; Vishwakarma, D.K.; Singh, A.P.; Alam, G. Advances and development in transdermal drug Delivery system—A Review. Int. J. Adv. Pharm. Int. J. Adv. Pharm., 2017; 6: 49–62.
9. Goodman, M.P. Are all estrogens created equal? A review of oral vs. transdermal therapy. J. Women's Health, 2012; 21: 161–169.[CrossRef]
10. Chambers, R. Microdissection studies, III. Some problems in the maturation and fertilization of the echinoderm egg. Biol. Bull., 1921; 41: 318–350. [CrossRef]
11. Reed, M.; Lye, W.-K. Microsystems for Drug and Gene Delivery. Proc. IEEE, 2004; 92: 56–75. [CrossRef]
12. Prausnitz, M.R. Microneedles for transdermal drug delivery. Adv. Drug Deliv. Rev. 2004; 56: 581–587.
13. Dang, N.; Liu, T.Y.; Prow, T.W. Nano-and Microtechnology in Skin Delivery of Vaccines. In Micro and Nanotechnology in Vaccine Development; William Andrew Publishing: Norwich, NY, USA, 2017.
14. N. Akhtar, Microneedles: an Innovative Approach to Transdermal Delivery- a Review, 2014.
15. J. Li, M. Zeng, H. Shan, C. Tong Microneedle patches as drug and vaccine delivery platformC Med. Chem., 2017; 24(22): 2413-2422.
16. S.P. Narayanan, S. Raghavan, Solid silicon microneedles for drug delivery applications Int. J. Adv. Manuf. Technol., 93(1-4) October), 2017; 407-422.
17. S.P. Narayanan, S. Raghavan, Fabrication and characterization of gold-coated solid silicon microneedles with improved biocompatibility Int. J. Adv. Manuf. Technol, 2018; 1-7.
18. Cheung, K.; Das, D.B. Microneedles for drug delivery: Trends and progress. Drug Deliv, 2014, 23, 2338–2354.
19. Donnelly, R.F.; Morrow, D.I.J.; McCrudden, M.T.C.; Alkilani, A.Z.; Vicente-Pérez, E.M.; O'Mahony, C.; González-Vázquez, P.;McCarron, P.; Woolfson, A.D. Hydrogel-Forming and Dissolving Microneedles for Enhanced Delivery of Photosensitizers and Precursors. Photochem. Photobiol, 2014; 90: 641–647. [CrossRef]
20. Mishra, R.; Bhattacharyya, T. MEMS-based hollow microneedles for transdermal drug delivery. Drug Deliv. Devices Ther. Syst., 2020; 325–344. [CrossRef]
21. Zhang, P.; Dalton, C.; Jullien, G.A. Design and fabrication of MEMS-based microneedle arrays for medical applications. Microsyst. Technol, 2009; 15: 1073–1082. [CrossRef]
22. Donnelly RF, Singh TR, Woolfson AD Microneedle-based drug delivery systems: microfabrication, drug delivery, and safety. Drug Delivery, 2010a; 17: 187–207. https://doi.org/10.3109/10717541003667798.
23. Cormier M, Johnson B, Ameri M, Nyam K, Libiran L, Zhang DD, Daddona P Transdermal delivery of desmopressin using a coated microneedle array patch system. Journal of Controlled Release, 2004; 97: 503–511. https://doi.org/10.1016/S0168-3659(04)00171-3.
24. Park JH, Allen MG, Prausnitz MR Biodegradable polymer microneedles: fabrication, mechanics and transdermal drug delivery. Journal of Controlled Release, 2005; 104: 51–66. https://doi.org/10.1016/j.jconrel.2005.02.002
25. McCrudden MT, Alkilani AZ, McCrudden CM, McAlister E, McCarthy HO, Woolfson AD, Donnelly RF Design and physicochemical characterisation of novel dissolving polymeric microneedle arrays for transdermal delivery of high dose, low molecular weight drugs. Journal of Controlled Release, 2014; 180: 71–80. https://doi.org/10.1016/j.jconrel.2014.02.007
26. Rodgers AM, Courtenay AJ, Donnelly RF. Dissolving microneedles for intradermal vaccination: manufacture, formulation, and stakeholder considerations. Expert Opinion on Drug Delivery, 2018; 15: 1039–1043. https://doi.org/10.1080/17425247.2018.1522301
27. E. Larrañeta, R.E.M. Lutton, A.D. Woolfson, R.F. Donnelly, Microneedle arrays as transdermal and intradermal drug delivery systems: materials science, manufacture and commercial development Mater. Sci. Eng. R Rep., 2016; 104: 1-32.
28. F.J. Verbaan, S.M. Bal, D.J. van den Berg, W.H. Groenink, H. Verpoorten, R. Luttge, J.A. Bouwstra, Assembled microneedle arrays enhance the transport of compounds varying over a large range of molecular weight across human dermatomed skin J. Control. Release, 2007; 117(2): 238-245.
29. S. Gorgieva, V. Kokol, Biomaterials Applications for Nanomedicine Chapter, 2011; 2.
30. F. Pérennès, B. Marmiroli, M. Matteucci, M. Tormen, L. Vaccari, E. Di Fabrizio, Sharp Beveled Tip Hollow Microneedle Arrays Fabricated by LIGA and 3D Soft Lithography With Polyvinyl Alcohol, 2006.
31. S. Aoyagi, H. Izumi, Y. Isono, M. Fukuda, H. Ogawa, Laser fabrication of high aspect ratio thin holes on biodegradable polymer and its application to a microneedle, Sens. Actuators A Phys., 2007; 139(1): 293-302.
32. M. Han, D.H. Hyun, H.H. Park, S.S. Lee, C.H. Kim, C. Kim, A novel fabrication process for out-of-plane

microneedle sheets of biocompatible polymer J. Micromech. Microeng., 2007; 17(6): 1184-1191.
33. L.Y. Chu, S.O. Choi, M.R. Prausnitz, Fabrication of dissolving polymer microneedles for controlled drug encapsulation and delivery: bubble and pedestal microneedle designs J. Pharm. Sci., 2010; 99(10): 4228-4238.
34. Y.-C. Kim, F.-S. Quan, R.W. Compans, S.-M. Kang, M.R. Prausnitz, Formulation of microneedles coated with influenza virus-like particle vaccine AAPS PharmSciTech, 2010; 11(3): 1193-1201.
35. R.F. Donnelly, R. Majithiya, T.R. Singh, D.I. Morrow, M.J. Garland, Y.K. Demir, K. Migalska, E. Ryan, D. Gillen, C.J. Scott, A.D. Woolfson, Design, optimization and characterisation of polymeric microneedle arrays prepared by a novel laser-based micromoulding technique Pharm. Res., 2011; 28(1): 41-57.
36. T. Miyano, Y. Tobinaga, T. Kanno, Y. Matsuzaki, H. Takeda, M. Wakui, K. Hanada, Sugar micro needles as transdermic drug delivery system Biomed. Microdevices, 2005; 7(3): 185-188.
37. Jeggy C. Micro-Injection Moulding: From Process to Modelling. Presses Univ. de Louvain; Louvain-la-Neuve, Belgium, 2004.
38. Kim M.J., Park S.C., Rizal B., Guanes G., Baek S.-K., Park J.-H., Betz A.R., Choi S.-O. Fabrication of Circular Obelisk-Type Multilayer Microneedles Using Micro-Milling and Spray Deposition. Front. Bioeng. Biotechnol, 2018; 6: 54. Doi: 10.3389/fbioe.2018.00054.
39. Sammoura F., Kang J., Heo Y.-M., Jung T., Lin L. Polymeric microneedle fabrication using a microinjection molding technique. Microsyst. Technol, 2006; 13: 517–522. Doi: 10.1007/s00542-006-0204-1.
40. Juster H., van der Aar B., de Brouwer H. A review on microfabrication of thermoplastic polymer-based microneedle arrays. Polym. Eng. Sci., 2019; 59: 877–890. Doi: 10.1002/pen.25078.
41. Bidanda B., Desai S. Strategic planning models for prototyping and product development centres. Int. J. Prod. Dev., 2004; 1: 133. Doi: 10.1504/IJPD.2004.005701.
42. E. Touitou, H.E. Junginger, N.D. Weiner, T. Nagai, M. Mezei, Liposomes as carriers for topical and transdermal delivery, J. Pharm. Sci., 1994; 83: 1189–1203.
43. S.A. Wissing, R.H. Müller, The influence of solid lipid nanoparticles on skin hydration and viscoelasticity–in vivo study, Eur. J. Pharm. Biopharm, 2003; 56: 67–72.
44. R.H. Guy, Y.N. Kalia, M.B. Delgado-Charro, V. Merino, A. López, D. Marro, Iontophoresis: electrorepulsion and electroosmosis, J. Control. Release, 2000; 64: 129–132.
45. J.E. Riviere, N.A. Monteiro-Riviere, R.A. Rogers, D. Bommannan, J.A. Tamada, R.O. Potts, Pulsatile transdermal delivery of LHRH using electroporation: drug delivery and skin toxicology, J. Control. Release, 1995; 36: 229–233.
46. W.-R. Lee, S.-C. Shen, H.-H. Lai, C.-H. Hu, J.-Y. Fang, Transdermal drug delivery enhanced and controlled by erbium: YAG laser: a comparative study of lipophilic and hydrophilic drugs, J. Control. Release, 2001; 75: 155–166.
47. P. Treffel, F. Panisset, P. Humbert, O. Remoussenard, Y. Bechtel, P. Agache, Effect of pressure on in vitro percutaneous absorption of caffeine., Acta Derm. Venereol, 1993; 73: 200–202.
48. W.-R. Lee, S.-C. Shen, K.-H. Wang, C.-H. Hu, J.-Y. Fang, Lasers and microdermabrasion enhance and control topical delivery of vitamin C, J. Invest. Dermatol, 2003; 121: 1118–1125.
49. M.B. Brown, M.J. Traynor, G.P. Martin, F.K. Akomeah, Transdermal drug delivery systems: skin perturbation devices, in: Drug Deliv. Syst., Springer, 2008; 119–139.
50. N.A. Godshall, R.R. Anderson, Method and apparatus for disruption of the epidermis, 1999.
51. A.P. Neukermans, A.I. Poutiatine, S. Sendelbeck, J. Trautman, L.L. Wai, B.P. Edwards, K.P. Eng, J.R. Gyory, K.L. Hyunok, W.Q. Lin, Device and method for enhancing microprotrusion skin piercing, Pat. WO., 2001; 141863.
52. S. Li, W. Li, M. Prausnitz, Individually coated microneedles for co-delivery of multiple compounds with different properties Drug Deliv. Transl. Res., 2018; 8(5): 1043-1052.
53. K. Cheung, D.B. Das, Microneedles for drug delivery: trends and progress Drug Deliv., 2016; 23(7): 2338-2354.
54. Zhang P, Dalton C, Jullien GA. Design and fabrication of MEMS-based microneedle arrays for medical applications. Microsystem technologies, 2009; 15: 1073–1082. https://doi.org/10.1007/s00542-009-0883-5
55. Aldawood FK, Andar A, Desai S.A comprehensive review of microneedles: Types, materials, processes, characterizations and applications. Polymers, 2021; 13: e2815. https://doi.org/10.3390/polym13162815.
56. C. Uppuluri, A.S. Shaik, T. Han, A. Nayak, K.J. Nair, B.R. Whiteside, B.N. Nalluri, D.B. Das, Effect of microneedle type on transdermal permeation of rizatriptan, AAPS PharmSciTech., 2017; 18: 1495–1506.
57. I.K. Ramöller, I.A. Tekko, H.O. McCarthy, R.F. Donnelly, Rapidly dissolving bilayer microneedle arrays–A minimally invasive transdermal drug delivery system for vitamin B12, Int. J. Pharm., 2019; 566: 299–306.
58. G. Yao, G. Quan, S. Lin, T. Peng, Q. Wang, H. Ran, H. Chen, Q. Zhang, L. Wang, X. Pan, Novel dissolving microneedles for enhanced transdermal delivery of levonorgestrel: In vitro and in vivo characterization, Int. J. Pharm., 2017; 534: 378–386.
59. S. Liu, M. Jin, Y. Quan, F. Kamiyama, H. Katsumi, T. Sakane, A. Yamamoto, The development and characteristics of novel microneedle arrays fabricated from hyaluronic

acid, and their application in the transdermal delivery of insulin, J. Control. Release, 2012; 161: 933–941.
60. A.D. Permana, I.A. Tekko, M.T.C. McCrudden, Q.K. Anjani, D. Ramadon, H.O. McCarthy, R.F. Donnelly, Solid lipid nanoparticle-based dissolving microneedles: A promising intradermal lymph targeting drug delivery system with potential for enhanced treatment of lymphatic filariasis, J. Control. Release, 2019; 316: 34–52.
61. A.J. Courtenay, M.T.C. McCrudden, K.J. McAvoy, H.O. McCarthy, R.F. Donnelly, Microneedle-mediated transdermal delivery of bevacizumab, Mol. Pharm., 2018; 15: 3545–3556.
62. S.L. Banks, R.R. Pinninti, H.S. Gill, K.S. Paudel, P.A. Crooks, N.K. Brogden, M.R. Prausnitz, A.L. Stinchcomb, Transdermal delivery of naltrexol and skin permeability lifetime after microneedle treatment in hairless guinea pigs, J. Pharm. Sci., 2010; 99: 3072–308.
63. J. Kennedy, E. Larrañeta, M.T.C. McCrudden, C.M. McCrudden, A.J. Brady, S.J. Fallows, H.O. McCarthy, A. Kissenpfennig, R.F. Donnelly, In vivo studies investigating biodistribution of nanoparticle-encapsulated rhodamine B delivered via dissolving microneedles, J. Control. Release, 2017; 265: 57–65.
64. A. Panda, P.K. Sharma, H.N. Shivakumar, M.A. Repka, S.N. Murthy, Nicotine loaded Dissolving Microneedles for Nicotine Replacement therapy, J. Drug Deliv. Sci. Technol, 2020; 102300.
65. Tas C., Mansoor S., Kalluri H., Zarnitsyn V.G., Choi S.-O., Banga A.K., Prausnitz M.R. Delivery of salmon calcitonin using a microneedle patch. Int. J. Pharm., 2012; 423: 257–263. Doi: 10.1016/j.ijpharm.2011.11.046.
66. Chen J., Wise K.D., Hetke J.F., Bledsoe S.C. A multichannel neural probe for selective chemical delivery at the cellular level. IEEE Trans. Biomed. Eng., 1997; 44: 760–769. Doi: 10.1109/10.605435.
67. A.M. Rodgers, A.J. Courtenay, R.F. Donnelly, Dissolving microneedles for intradermal vaccination: manufacture, formulation, and stakeholder considerations Expert Opin. Drug Deliv, 2018; 1-5.
68. P. Bora, L. Kumar, A. Bansal, Microneedle Technology for Advanced Drug Delivery: Evolving Vistas, 2008.
69. H.R. Jeong, J.Y. Kim, S.N. Kim, J.H. Park, Local dermal delivery of cyclosporin A, a hydrophobic and high molecular weight drug, using dissolving microneedles Eur. J. Pharm. Biopharm., 2018; 127: 237-243.
70. Y. Ye, J. Yu, C. Wang, N.Y. Nguyen, G.M. Walker, J.B. Buse, Z. Gu, Microneedles integrated with pancreatic cells and synthetic glucose-signal amplifiers for smart insulin delivery Adv. Mater. Weinheim, 2016; 28(16): 3115-3121.
71. S. Amodwala, P. Kumar, H.P. Thakkar, Statistically optimized fast dissolving microneedle transdermal patch of meloxicam: a patient friendly approach to manage arthritis Eur. J. Pharm. Sci., 2017; 104: 114-123.
72. X. Xie, C. Pascual, C. Lieu, S. Oh, J. Wang, B. Zou, J. Xie, Z. Li, J. Xie, D.C. Yeomans, M.X. Wu, X.S. Xie, Analgesic microneedle patch for neuropathic pain therapy ACS Nano, 2017; 11(1): 395-406
73. J.H. Jung, B. Chiang, H.E. Grossniklaus, M.R. Prausnitz, Ocular drug delivery targeted by iontophoresis in the suprachoroidal space using a microneedle J. Control. Release, 2018; 277: 14-22.
74. C. Wang, Y. Ye, G.M. Hochu, H. Sadeghifar, Z. Gu, Enhanced Cancer immunotherapy by microneedle patch-assisted delivery of Anti-PD1 antibody Nano Lett., 2016; 16(4): 2334-2340.
75. Y.W. Naguib, A. Kumar, Z. Cui, The effect of microneedles on the skin permeability and antitumor activity of topical 5-fluorouracil Acta Pharm. Sin. B., 2014; 4(1): 94-99.