IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
September 2021 Vol.:22, Issue:2

Microneedle: A Revolution in Transdermal Drug Delivery System

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Yogeshwari Rajendra Deshmukh*, Akshay Popat Jagadale, Bharatee Pandurang Chaudhari, Vivekkumar K. Redasani

Department of Pharmaceutics,
YSPM's Yashoda Technical Campus, Faculty of pharmacy,
Wadhe, Satara, India.

Submitted: 19 August 2021
Accepted: 25 August 2021
Published: 30 September 2021

Keywords: Fabrication, Microneedles, Evaluation, Transdermal, Regulatory Aspects, Biotherapeutics

ABSTRACT

Hypodermic needles, topical lotions, and transdermal patches are the most often used modalities for transdermal medication delivery. Because the stratum corneum layer of the skin acts as a barrier for molecules, only a few molecules are able to reach the site of action. Many decades ago, a new type of delivery device known as microneedles was originally envisaged, addressing shortages and keeping the advantages of hypodermic needle and traditional transdermal drug-delivery methods to some extent. The basic concept is to disturb the skin layer, resulting in micron-sized channels that lead the medicine straight to the epidermis or higher dermis, from whence the treatment can reach the systemic circulation without passing through the barrier. This review discusses the numerous possibilities and uses of microneedles. Microneedles of many sorts can be manufactured, including solid, dissolving, hydrogel, coated, and hollow microneedles. The fabrication process chosen is determined on the kind and material of the microneedle. In addition, they outline the assessment test for the same. This technique is now being used in a variety of sectors, including oligonucleotide distribution, vaccine distribution, insulin distribution, and even cosmetics. Many microneedle devices have entered the market in recent years. Although further study is required to tackle the different hurdles before the microneedles may effectively enter the market.

INTRODUCTION-:

Hypodermic needles and topical creams are most commonly used when it comes to delivery of the drug through the skin. Needles are less accepted by patients due to pain associated with them and topical creams show less bioavailability. Skin serves as the major barrier for delivering drug through the topical route. Skin is made up of three main layers-the outermost stratum corneum, middle epidermis and the thickest of all, dermis. The stratum corneum layer behaves like a major barrier as it allows only certain molecules like lipophilic and low molecular weight drugs to pass through it. The relatively less permeability of the layer presents many problems in designing topical formulation [5,6]. Various topical or transdermal delivery systems have been investigated for improving drug permeation through the skin like nanocarrier loaded topical creams, transdermal patches, and microneedles[7,8]. These structures are used to pierce the skin's upper layer in order to improve transdermal drug distribution by allowing the transport of a variety of molecules that cannot be delivered through the skin through passive diffusion alone[10]. Since the size of these microchannels is in microns and the maximum dimension of standard macromolecules delivered into the body is in nanometers [11]. Microneedles may be used to transport macromolecules such as insulin, growth hormones, immunobiologicals, proteins, and peptides. Microneedle innovations are classified into four types: solid microneedles for skin pretreatment to improve skin permeability, drug-coated microneedles, polymer microneedles that encapsulate drugs and completely or partially dissolve in the skin, and hollow microneedles for drug injection into the skin[13,14]. Microneedles are most widely used for the transdermal delivery of drugs and vaccines that require prolonged exposure, with dissolving and biodegradable microneedle technologies being the most popular.

Skin microanatomy

The biggest human organ and the body's first natural barrier is the skin (cutis). It has a surface area of around 2 m^2 and is 102–104 times less permeable than a blood capillary wall, accounting for about 15% of an adult's overall body weight [15]. The epidermis, dermis, and subcutaneous layers are the three histological layers of the skin that are usually shown in contrast to tissue layers [15]. In humans, the outer epidermis, a 5-layered assembly of keratinocytes (95 percent of cells), is usually 0.02–0.2 mm thick and 50–150 m thin. The dead skin layer, also known as the stratum corneum (SC), is the epidermis' outermost layer and is primarily responsible for the skin's physical properties due to its "brick and mortar"

construction [16]. The hydrated keratin corneocytes are the "bricks" trapped in a "mortar" with several lipid bilayers of ceramides, fatty acids, cholesterol, and cholesterol esters [17]. The dermis is a layer underneath the epidermis and it is much thicker than the epidermis (normally 2–4 mm dense) and includes collagen (70 wt %), certain immunologically active cells, connective tissues, blood and lymph vessels, glands, hair follicles, and nerve endings [18]. The hypodermis, or subcutaneous membrane, is the innermost layer of the skin that lies under the dermis and is mostly made up of adipose tissue (fat). The dynamic capillary network in the dermis and hypodermis is important for transdermal systemic transmission. Despite the fact that it is easy, overcoming these obstructions is quite complex, especially peptides and proteins these are bigger molecules. Many drugs diffuse slowly across the skin, with lead times measured in hours before reaching steady-state fluxes. As a result, reaching therapeutically successful drug levels without increasing skin permeation is difficult. The techniques to penetrate the SC's permeability layer have recently been the subject of extensive study in a controlled and reversible manner. This would potentially increase the number of drugs that can be administered through the skin [19]. In recent years, some physio-chemical approaches to undermine the epidermis and thereby improve transdermal transmission have been developed. Chemical enhancers to MN technology, electrophoresis, iontophoresis, sonophoresis, laser therapy, and synergistic combinations of two or more pathways are one of the methods. MN arrays made from different metallic and polymeric materials have recently been the primary subject and are being extensively researched by the science community. By only reaching the top layer of skin and delivering molecules through the skin membrane, these micron-sized instruments aim to reduce the discomfort associated with hypodermic needle injections.

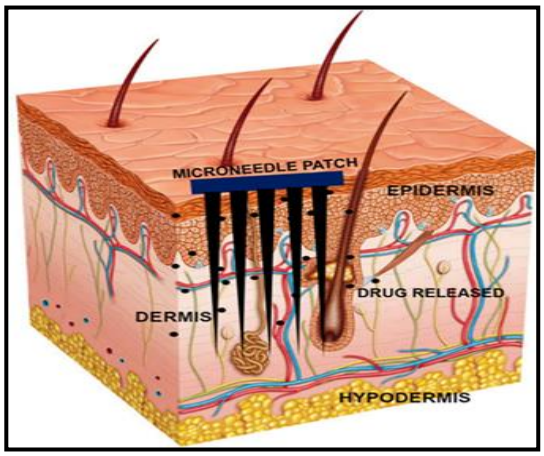

Fig. no 1 Anatomy of skin anatomy

1. Benefits and limitations

Benefits

- Reduction in dosing frequency leads to better patient compliance
- Non-invasive delivery
- Avoidance of first pass metabolism
- Avoid gastrointestinal incompatibility
- No side effects
- Maintain plasma drug level
- Improved bioavailability
- Easy administration of large size molecules
- Suitable for drug with short biological half life and narrow therapeutic index

Limitations

- The dose accuracy is less as compared to hypodermic needle
- The thickness of the SC varies from person to person, so skin penetration varies.
- Variation of delivery due to environmental factors such as weather and skin condition
- The risk of veins collapsing as a result of repeated injections
- In the case of hollow and solid MNs, the tips can break and stay inside the skin.

2. Mechanism of Microneedle

The diffusion mechanism is used to administer the drug through the topical pathway. The skin is briefly damaged during the microneedle drug delivery system. A microneedle implant is created by arranging hundreds of microneedles in clusters on a tiny patch (similar to a standard transdermal patch present in the market) in order to provide a sufficient amount of drug to provide the desired therapeutic reaction. It pierces the stratum corneum, allowing it to bypass the boundary layer. The drug is injected directly into the epidermis or upper dermis layer, where it enters the systemic circulation and produces a therapeutic reaction until it reaches the site of action [6, 7]. Figure 2 illustrates the mechanism of drug delivery through microneedles.

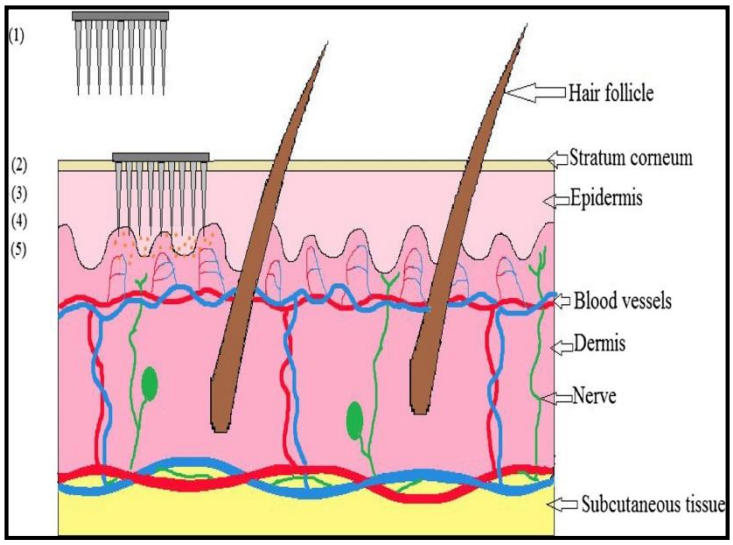

Fig.no 2 Mechanism of drug delivery by microneedle device: (1) Microneedle device with drug (2) Device implanted; (3) Temporary mechanical destruction of the skin; (4) Drug release in the epidermis; (5) Transport of the drug to the sites of action

3. Fabrication material

Microneedls may be made out of a wide range of materials, including metals and polymers. The materials used in the manufacture of microneedls should have properties including such durability, economy, user friendliness, accessibility, high tensile strength, corrosion resistance, mechanical stability, and so on. Microneedls would be more acceptable and useful as a result of this [20].

3.1 Silicon

In the 1990s, silicon was used to build the first microneedle [21]. Silicon has a crystalline structure and is anisotropic in nature. Its properties are determined by the crystal lattice's orientation, which has various elastic moduli (50 to 180 GPa) [22, 23]. Its adaptability allows it to produce needles in various sizes and shapes. It is a flexible substance due to its appealing physical properties.

Silicon-based microneedles have a high mechanical force, allowing them to penetrate the flesh [24]. The needle material and geometry play a role in the silicon microneedle fabrication process. A silicon dry-etching process based on reactive ion etching with a chromium mask was used to create short silicon microneedles. Furthermore, it was the first

material chosen for the manufacture of microneedles. Silicon has played an important part in the construction of microstructures and micro-electro mechanical systems (MEMS).

3.2 Metals

Stainless steel and titanium are the most common metals used. Often used are palladium, copper, and palladium-cobalt alloys. They have excellent mechanical and biocompatibility properties. Metals are more ideal for microneedle processing than silicon because they are solid enough to prevent cracking. Stainless steel was the first metal used in the manufacture of microneedles. Titanium is a suitable stainless steel substitute [25].

3.3 Ceramics

Chemical resistance is the primary reason for the use of alumina (Al2O3). Because of the strongly energetic ionic and covalent bonds within Al and O atoms, it forms a solid oxide. Calcium sulphate dihydrate [Gypsum (CaSO4 0.2H2O)] and calcium phosphate dihydrate [Brushite (CaHPO4.2H2O)] are two other varieties of ceramics used. Ormocer®, a synthetic polymer ceramic, has been used in recent years. It is a cross-linked copolymer in three dimensions [26]. Using various organic units throughout polymerization can result in a polymer with various properties. They are often made using a micromolding technique. A micro-mold is filled with ceramic slurry. Micro-moulding methods are less expensive and have the ability for scale-up [8].

3.4 Glass

Glass is used to make geometrically variable microneedles on a small scale. Despite its brittle appearance, silica glass is commonly used for microneedle preparation. Furthermore, since borosilicate glass is now more elastic, it can be made by hand. As a result, the use of glass as an industrial fabricating medium for microneedles is limited [25].

3.5 Carbohydrates

Carbohydrates such as maltose are also used in the manufacture of microneedles. Microneedles are prepared using heated slurries or softens of carbs. Carbohydrates are the most cost-effective, compatible, and stable material for the production of microneedles. These properties made carbohydrate a viable alternative to silicon, plastics, polymers, and other building materials [27]. Other sugars that can be used to make microneedles include galactose, mannitol, sucrose, trehalose, and xylitol [28]. Temperature-based MN fabrication

may also not be appropriate for thermo labile drugs or materials. As a result, it could have an effect on their storage state, potentially causing reliability problems.

3.6 Polymer

For microneedle preparation, a wide range of polymers have been identified, including polymethyl methacrylate (PMMA), polylactic acid (PLA), polylactic-co-glycolic acid (PLGA), polyglycolic acid (PGA), polycarbonate, cyclic-olefin copolymer, polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), polystyrene (PS), polymethyl vinyl ether-comaleic anhydride, SU-8 photoresist. These polymers are used to make dissolving, biodegradable, and hydrogel-forming microneedle clusters. These polymers produce microneedles that are less strong than other materials but stronger than glass and ceramics [25].

4. Types of microneedles

Strong, polished, dissolving, hollow, and hydrogel microneedles are among the various forms of microneedles that have been fabricated and studied for use in drug distribution. In Figure no. 3, different types of microneedles are seen, each with their own set of characteristics. The drug is delivered into the epidermis in a different manner with each kind of microneedle. Some are used solely to build pores in the stratum corneum, while others are precoated with the drug solution, dissolvable, or prefilled with the drug solution [29–32].

4.1 Solid microneedle

These microneedles employ a "poke and patch" technique. It is first applied to the skin to stimulate pore creation, and then it is removed. Following that, a medication formulation is applied to the skin, which serves as an external reservoir and aids drug absorption. The ‘poke and patch' tactic is used by these microneedles. It is first applied to the skin in order to stimulate pore creation, after which it is removed. Following that, a drug formulation is applied to the skin, which serves as an external reservoir for the medication and aids in its penetration [29-30]. Li et al. investigated polylactic acid microneedles and discovered that biodegradable polymer solid microneedles may puncture the stratum corneum and improve medication absorption. Microneedles with a depth of 800 m and a density of 256 MNs/ cm^2 were shown to improve drug penetration [31].

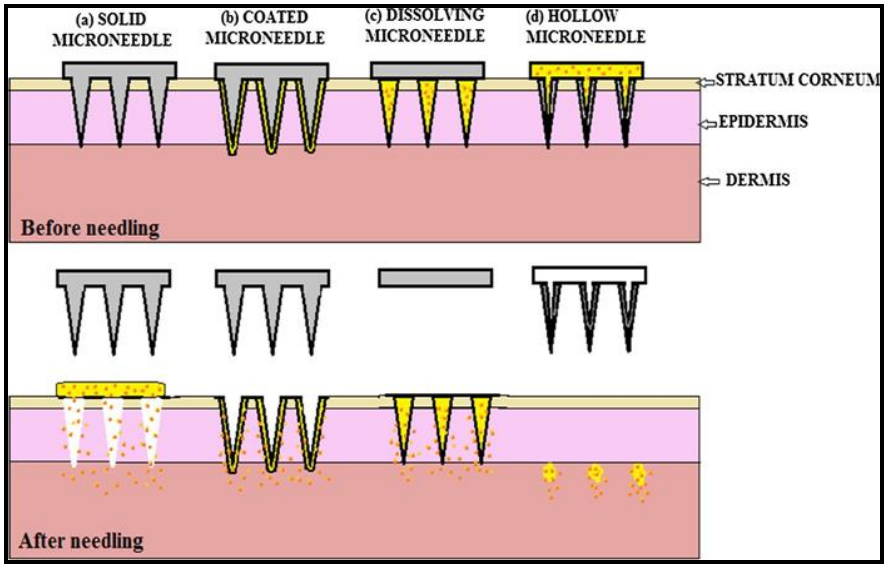

Fig no. 3 Types of microneedles (a) Solid microneedle (b) Coated microneedle (c) Dissolving microneedle (d) Hollow microneedle[25]

4.2 Coated Microneedle

The drug solution or dispersion layer is encapsulated in this type of microneedle, causing drug dissolution and fast delivery. The overall amount of drug loaded is determined by the thickness of the coating layer and the needle size. Coated microneedles have been extensively studied, particularly in the areas of medication delivery, vaccines, DNA, and biomolecules. Coated microneedles may now be used in a wide range of scientific applications because to recent developments in coating composition [32-33]. Li et al. coated each microneedle with distinct formulations and drugs, allowing numerous therapeutics with varying characteristics to be delivered simultaneously. These dyes were given in both water soluble and water insoluble forms [34]. Chen and colleagues coated PLA microneedles with sulforhodamine B and discovered that the drug delivery effectiveness was around 90%. The continuous drug delivery was validated in mice in vitro tests.

4.3 Hollow MN

Traditionally, hollow microneedles, which are similar to micron syringes, are used to inject liquid formulations into the subcutaneous layer of the skin. When compared to solid microneedles, these microneedles can deliver higher medication dosages. A empty area inside these microneedles is filled with the medication solution or dispersion. A particular medicine can be administered into the skin by injecting a liquid formulation through implanted hollow

microneddles. Various strategies including as diffusion, pressure, and electrical aid can be used to distribute medicinal molecules continuously via these hollow microneedles.

Hollow microneedles have been made using a variety of techniques. Large batches of hollow microneedles were made using microelectromechanical systems (MEMS) technology. Yu et al. used MEMS methods to create a cylindrical hollow microneedle that went through three basic procedures: photolithography, Bosch deep reactive ion etching, and micromachining [37]. A wide range of materials, including silicon, metal, glass, ceramics, and polymers, can be used to make hollow microneedles. High molecular weight compounds like as antigens, proteins, and oligonucleotides are widely used. The likelihood of needle apertures clogging during skin piercing and resistance to flow are two key drawbacks of this approach [35-36].

4.4 Dissolving/ biodegradable Microneedle

These microneedles are typically made of a biodegradable polymer in which the medication is enclosed. When they are placed into the skin, the drug dissolves and the medication is released [38]. In comparison to other varieties, it is a one-step application technique, therefore there is no physical removal necessary. Because it is biodegradable, it is one of the most generally approved microneedles and a superior alternative for continuing therapy. Patient compliance improves as a result of bio-acceptability. The drug release time from dissolving microneedles spans from hours to days, and it is dependent on the nature of the dissolution and the kind of polymers [39-40]. Luzuriaga et al. proposed a novel micromachining approach that uses fused deposition modelling (FDM) 3DP to swiftly design and print microneedle density, length, and form. Moreover, to increase feature size resolution, a post-fabrication chemical etching process including 3DP has been devised, with access to microneedle tip sizes as tiny as 1 mm [41].

4.5 Hydrogel forming Microneedle

It's a newer sort of microneedle that makes use of super-swelling polymers. The polymers employed in the fabrication have a higher water absorption capacity. The three-dimensional polymeric network structure absorbs the water. Because of the presence of bodily fluid, when these microneedles are put into the skin, the polymers swell. This results in the formation of conduits, which allow the drug release to reach the microcirculation from the pool. Polymer's swelling properties act as a rate-controlling membrane [20].

5. Fabrication of Microneedle

Microfabrication flourished in the mid-1990s and evolved into a variety of tiny devices, eventually leading to the invention of microneedles. The ALZA collaboration first established the notion of an microneedle, but it wasn't until 1988 that microneedles were explored in scientific studies for TDDS owing to the growth in new developing materials and development in engineering technologies. The needle geometry (size, shape, and breadth) is optimised for insertion into the skin throughout the manufacture process. The materials utilised and their application will be discussed in detail in the next section, as will the details of each methodology for the fabrication of various microneedles.

5.1 Micromolding

Micromolding procedures are the most widely documented methodology for the manufacture of microneedles. Photolithography and moulding techniques are often used to create the PDMS micromold (which is typically manufactured in one step by drilling on the surfaces of 2-mm thick PDMS sheets with a laser beam and then filling with the material such as ceramics and polymeric formulations (sugars, natural and synthetic polymers)). Although this technology enables for upscaling production, it has limits since it often entails many time-consuming procedures such as master preparation, mould creation, and plasticisation of thermoplastic polymers above their glass transition temperature, preventing the use of thermo-liable pharmaceuticals [42].

5.2 Lithography

Etching (both wet and dry) the subtractive procedure has also been described for the manufacture of microneedles (carving a 2D substrate from a 3D structure). Lithography and wet etching are two typical methods for producing silicon and glass microneedles.

The disadvantages of such approaches include the requirement for specialised equipment in clean rooms and the generation of hazardous waste, which is costly, difficult, inconvenient, and harmful to the environment. The benefits of adopting additive technologies for microneedle production, such as drawing lithography, include the ability to manipulate the size and form of microneedles to increase mechanical stability, release kinetics and release profile. However, utilising photocurable polymers can be problematic since UV light has the potential to inactivate the drug and leave harmful photo-initiator residue in the final microneedle. This process has been improved by employing an in situ lens-based lithographic

method to transform the tapered cone generated into bevelled, chisel tip microneedles using microelectromechanical masking and etching [43]. 3D polymer microneedle structures may be created from 2D surfaces or droplets using additive methods like as 3D printing, droplet born air blowing, electro-drawing, and thermal drawing [44].

5.3 3D Printing

3D printing, which first appeared in the 1980s, is a family of technologies that uses computer-aided design (CAD) models to construct a real thing through the fabrication of layers. It has subsequently revolutionized the pharmaceutical industry. This is a one-step procedure that enables for the quick manufacture of microneedles with a wide range of geometries while maintaining a high degree of consistency and complexity.

Stereolithography is one of the technologies that makes up 3D printing (for anticancer therapy, insulin skin delivery as well as delivery of model dye) [45]. Digital light processing (DLP) photopolymerisation-based techniques that allow the production of structures by layer wise polymerisation of UV sensitive polymers via a heating process (photopolymerisation) and Two-Photon Polymerisation (transdermal delivery of polymer-ceramic hybrid materials) [46].

Stereolithography has been widely used as a method of manufacturing MNs in recent years. Fatouros et al. developed successful in vitro TDD utilising stereolithography-printed 3D MNs. Mechanical strength, insertion force, and visualisation investigations were performed on these polymer-based MNs. This study found that these 3D printed MN arrays had good penetration in human skin and significantly increased dye transport across human skin [45]. This demonstrates the enormous potential for 3D printed MN systems in transdermal medication administration.

5.4 Electro-drawing

The electro-drawing approach is a non-contact, low-temperature, UV-free way of producing PLGA microneedles. This method yielded MN arrays with optimized form and size. This approach employs a pyroelectric field and micrometric elements to regulate temperature on a microscale, as well as a pyroelectric crystal to regulate electrohydrodynamic activity once a voltage is introduced to the circuit [47]. 3D printing is a versatile technology that allows for personalization and customization; however, the resolution is restricted, hence the length of the resulting microneedles is measured in millimetres with tip diameters of 100 m. Droplet-

born air blowing offers improved fabrication conditions without the use of heat or UV irradiation, as well as high productivity and has been commercialized [48].

5.5 Thermal Drawing

Thermal drawing includes heating a polymer that is vertically pulled at a regulated pace by a metal pillar arrangement. After cooling, the neck is shattered by quick drawing, generating the microneedle structure. However, there are concerns with the fracture stage, which results in a flat or extended apex, restricting insertion capabilities as well as the tip. Despite the fact that it is a very basic procedure, optimization has proven difficult, therefore other fabrications have been examined in recent years [49].

5.6 Magnetorheological Drawing Lithography

Recently, magnetorheological drawing lithography has been examined as a unique approach for the efficient production of microneedles, bio-inspired microneedles, and microneedle arrays. This additive process swiftly forms a 3D microneedle structure from a droplet of curable magnetorheological fluid extracted straight from any substrate to build a 3D microneedle under a magnetic field. This approach combines the benefits of thermal drawing (without the requirement for a mask or UV irradiation) with the benefit of not requiring temperature modifications throughout the drawing process. These microneedles demonstrated the versatility and viability of the magnetorheological drawing lithography (MRDL) technology [50].

5.7 Droplet Air Born Blowing

Kim et al. investigated the droplet air born (DAB) blowing process and discovered that it provides gentle (4–25 degrees) and rapid (less than 10 minutes) microneedle fabrication while minimising drug loss. The drug content can also be regulated by the droplet dispenser's pressure and time, and also the air blowing shapes the droplet to the microneedle with enough force to penetrate the skin. Insulin DMNs based on DAB have shown promise in providing complete drug delivery with no waste [51]. To make DMNs and test the activity of encapsulated drugs, this method was combined with centrifugal lithography (two droplet DAB). It was reported that the centrifugal lithography manufacturing process for DMNs put less stress on the drug-loaded DMNs, reducing action loss over time, proving centrifugal lithography's efficacy in DMN fabrication [52]. Kim et al. studies of allergen (Dermatophagoides farinae (D. farinae) extract (DfE)) loaded MNs (fabricated using DAB)

for allergen specific immunotherapy (SIT) and atopic dermatitis revealed stable allergenicity at 10 g of DfE sufficient to elicit immunogenic responses all without side effects when compared to 100 g of subcutaneous injection. Each droplet was air blown and strengthened to form an microneedle, so DAB was used. The conditions are also less harsh, removing the need for heat/UV irradiation. It was also feasible to load each microneedle without loss by design, and manufacture was completed in 10 minutes [53].

6. Evaluation of microneedles

6.1 Characterization methods

The medicine can be placed onto or into the microneedles in two forms: suspension/dispersion or encapsulated (liposomes, nanoparticles, nanoliposomes). The polymer solution can be applied to the medication as a coating or as a patch. Depending on the kind of formulation utilized in the microneedles, several physicochemical characterizations such as particle size, polydispersity index, viscosity, and zeta potential can be examined for loaded drug [55]. For a patch that is applied following pre-treatment, drug release, adhesion, and penetration tests are done. Dynamic light scattering, X-ray scattering, and transmission electron microscopy can be used to determine the size, internal structure, and crystallinity of liposomes or nanocarriers. Drug dispersion and microneedle stability may be examined at various temperatures, pH levels, and simulate in-vivo physiological settings (cell line or tissues). Other testing, including as solubility studies, drug content, in-vitro release testing, and biocompatibility studies, are also carried out on microneedle designs [26,54].

6.2 Dimensional evaluation

To analyze the needle geometry and quantify the tip radius, length, and height of the microneedle, many approaches are utilized. Optical or electrical microscopy is the most often used approaches. The analysis of a 3D image provides a more accurate view of needle shape and aids in quality control. This was accomplished using a scanning electron microscope (SEM) and a confocal laser microscope. SEM creates a picture of a sample by scanning it with a focused stream of electrons that interact with the atoms in the sample and produce different signals that provide information about the sample's surface topography and composition. High-resolution pictures are produced using confocal laser microscopes [55,56].

6.3 Mechanical properties or insertion forces

A microneedle must be sharp and slim enough to easily penetrate the skin while also being strong enough not to break once inside the skin. Table 3 lists the mechanical tests performed on microneedles. The force at which the microneedle ends up losing structural integrity and the insertion depth are two critical factors in the safe and efficient design of microneedles. The safety factor' is the ratio of these two forces. The ratio should be as high as feasible [57].

Table no.1 Mechanical characterization studies

Parameter	Test
Insertion force	Dye making, force displacement test or electrical measurement
Insertion depth	Histological cryosectioning and staining, confocal microscopy and optical microscopy
Failure force	Pressing a device on a rigid surface, displacement force tests

6.4 *In-vitro* skin permeation studies

The diffusion cell apparatus is used to determine drug permeation through the skin. The experiment primarily employs pig ear skin, which is mounted between the receptor and donor compartments. The cumulative permeation profiles of microneedle treated and untreated skin are compared [58].

6.5 *In-vivo* animal model studies

The study can make use of hairless rats. To anaesthetize the animal, a suitable technique must be used. Trans-epidermal water loss (TEWL), which is measured before and after microneedling, is one of the parameters considered. This parameter is measured using a Delfin Vapometer [59].

7. Commercialization of Microneedle product

7.1 FDA regulatory requirements for commercialization

Because microneedle technology is a comparatively unique and modern field, no completely separate regulatory requirements for microneedle-based products have been established to date. Traditional transdermal patches are only applied to the skin's surface, whereas microneedles penetrate the stratum corneum barrier and, in some cases, invade into the viable

epidermis and dermis. Interrupting the skin's defensive layer is a completely different mechanism of action, which prompts the emergence of new scientific/regulatory demands. As a result, in addition to the well-defined requirements for the pre-existing transdermal patch systems, new regulatory specifications for microneedle systems should be defined. Some of the major regulatory issues that must be addressed when planning for the commercialization of microneedle devices are as follows [22]:

1. Needle characteristics such as materials, length, adjustability, sharpness, and geometry must be carefully designed.

2. Microneedle devices should maintain adequate microbiological standards.

3. The content of the Microneedle systems should be consistent.

4. High-quality manufacturing techniques, as well as safe and secure packaging, should be used.

5. To avoid the possibility of re-use by patients or others, Microneedle systems made of non-biodegradable materials may require a self-disabling mechanism to ensure a single-use only. Furthermore, safe and non-hazardous disposal procedures for these Microneeedle systems should be defined.

6. If the Microneedle device is reusable, cleaning or disinfection instructions should be included.

7. The issue of safe Microneedle material deposition in the skin without causing adverse skin reactions should be addressed, particularly for microneedle products intended for long-term use.

8. The proposed labelling for the microneedle device, including package labelling and usage instructions, should be provided.

9. Microneedle systems should be simple to use and produce repeatable results without complications. They should also be used in conjunction with the appropriate application device to ensure proper insertion and pain-free delivery.

10. Immunological safety assurance for the microneedle systems may be required.

11. For microneedles requiring intermittent and repeated applications, the long-term safety profile of microneedle application should be discussed.

7.2 Approved products

Derma roller was the first microneedle product. Many microneedle products are now available on the market that have been cleared for medical and cosmetic use. Table 4 contains a list of some of them. Many companies in Germany, the United States, Europe, and Japan sell microneedle products [59,60, 61].

Table no. 2 Approved microneeedle products

Product name	Company name	Product description	Use
Dermaroller®	Dermaroller® Germany,White Lotus	A cylindrical roller with solid or metal microneedles ranging in length from 0.2 to 2.5 mm.	Enhance skin texture, heal scars, and cure hyperpigmentation.
C-8 (Cosmetic type)	The Dermaroller Series by Anastassakis K.	A needle length of only 0.13 mm (130 m) is used.	Used to improve the penetration of topical agents.
MicroHyala®	CosMed transdermal drug delivery	Dissolving microneedle patch with hyaluronic acid	Wrinkle treatment
Macroflux®	Alza/Johnson and Johnson	Coated titanium microprojections	Biopharmaceutical delivery has improved.
Soluvia®	Sanofi Pasteur Europe	A syringe is attached to a hollow microneedle.	Influenza vaccination
h-patch	Valeritas	A small adhesive machine, similar to a patch, is used.	Drug delivery in subcutaneous tissue (insulin)
Microstructured transdermal system	3M	Hollow microneedle	Biologics and other small molecules will be delivered.
MicronJet®	NanoPass Technologies	4 hollow silicon needles with a length of less than 500µm	Used to deliver influenza vaccine.

8. Status of US patents[20]

Patents encourage the use of microneedles as a general-purpose application tool while also integrating research in their respective fields. The authors outlined patents from the previous 12 years (2005–2017) in this review. So far, many researchers have concentrated on approaches that have been developed as novel processes in the fabrication of microneedles. The importance of collecting patent data is to provide an update and overview of current trends and future aspects of microneedles. As a result, the United States (U.S.) has the world's largest pharmaceutical market and the greatest number of patents in terms of microneedles [62]. As a result, the authors retrieved relevant patents granted in the United States that were related to microneedles. This information was gathered and summarized in Table 3 [63, 64].

Table no. 3 US Patent Status in US

Sr.no.	Title of patent	Date	Patent no	Name of inventor
1	Metallic microneedles	13 June 2017	US9675790	Stoeber et al.
2.	Surface micro machined microneedles	23 may 2006	US7048723	Frazier et al.
3.	Method for fabricating microneedles	29 August 2006	US7097776	Govinda Raju
4.	Microneedles and microneedles fabrication	3 March 2009	US7497980	Xu et al.
5.	System and method for drug delivery and microfluidic application using microneedles	14 July 2009	US7560036	Golubovie-Liakopoulos et al.
6.	Molecular sieve and zeolite microneedles and preparation	20 April 2010	US7699819	Yeung et al.
7.	Apparatus and method for manufacturing microneedles	04 May 2010	US7708544	Pricone

8.	Method and/or apparatus for puncturing a surface for extraction, in situ analysis, and/or substance delivery using microneedles	13 July 2010	US7753888	Mukerje et al.
9.	Microneedles and methods of fabricating	31 August 2010	US1185459	Raju et al.
10.	Mechanically robust fast-dissolving microneedles for transdermal drug and vaccine delivery	27 December 2016	US9526884	Yan et al.
11.	Use of cannabidiol prodrugs in topical and transdermal administration with microneedles	03 January 2017	US9533942	Stinchcomb et al.

9. Applications:

Microneedles are a relatively new biomedical advancement with non-invasiveness, high selectivity, and flexibility in use as a therapeutic and diagnostic tool. Furthermore, existing research on microneedles has expanded the range of its formulation with a variety of applications. Microneedles are a relatively new bioengineering innovation with non-invasiveness, high selectivity, and flexibility in use as a therapeutic and diagnostic tool. Furthermore, existing research on microneedles has expanded the range of its formulation with a variety of applications [65, 66]. The most common applications of microneedles are allergy diagnosis, animal identification, blood extraction, cancer therapy, cell surgery, dentistry, drug delivery, fluid sampling, gene delivery, ink-jet printing, micro-dialysis, sensing electrodes, skin treatment, vaccination, and so on.

Therapeutic Applications

Antiglaucoma

Kim et al. introduced drugs into the supraciliary space using hollow microneedles. They demonstrate significant dose sparing of antiglaucoma agents when compared to eye drops.

This method of targeted delivery improves safety, reduces side effects, and allows for a single injection with enough drug for long-term sustained delivery [67]. Ocular drug delivery with microneedles is safe, simple, and effective. However, the limited drug carrying capacity of devices demonstrated thus far may limit clinical interpretation potential. Omid et al. created microneedles that act as aquifers for passive delivery; the capacity of the microneedles can be up to five times that of solid microneedles [68].

Diagnostics

It is impossible to create an effective therapy without a proper diagnosis. This is fundamental and necessary for the success of therapy; thereby, the use of microneedles has aided in this field. Sun et al. invented microneedles that can be used to withdraw protein antigens and therapeutic proteins in the skin for allergen physical examination or immunotherapy [69]. Skoog et al., on the other hand, developed in vivo biosensors that provides the control real-time detection of biomolecules for patient surveillance. They created nitrogen ultra-nanocrystalline diamond coated titanium alloy microneedle arrays that can predict dopamine and uric acid electrochemically [70].

Cancer diagnosis

Keum et al. developed a dual-diagnostic system that combines high-resolution imaging with electrical real-time detection of nitric oxide released from cancer tissues using an endo-microscope and microneedle sensor. This system can be used in biomedical applications to detect cancer in a simple, quick, and accurate manner [71]. In opposed to previous endomicroscopy, which can only identify microscopic pathological characteristics and frequently necessitates biopsy sampling of suspicious lesions for additional histopathological examination of cancers.

Biomarkers

Li et al. demonstrated that surface-modified microneedle arrays could quantify biomarkers in the upper dermis after laser treatment in a reliable and timely manner. It could be done safely by briefly irradiating the microneedle array application site with a laser. As IgG can be measured using this noninvasive procedure, the assay was not affected by the length of the microneedles or molecular mass [72-73].

Other applications are being monitored, such as electrocardiography (ECG), electromyography (EMG), and electroencephalography (EEG), all of which are critical for understanding pathological and physiological conditions in humans. The electrodes are currently utilised, although they have drawbacks that can lead to incorrect results if not correctly placed and necessitate the use of gel. Renxin et al. enhanced the microneedles for EEG monitoring. Parylene-based microneedle electrode arrays (MNEAs) were used as dry electrodes capable of EEG monitoring without skin corrosion and gel. In the study, they create a flexible MNEA that can be adapted to the skin, providing not only conformal but also robust contact in comparison to conventional devices [74].

Vaccine therapy

A vaccination is a biological product. It offers active acquired immunity to a specific illness. Vaccine is a destroyed or weakened version of a disease-causing microorganism, one of its toxins, or one of its surface proteins. Vaccine treatment boosts the body's immune system and protects against future microorganism encounters. The microneedle technique has been shown to be efficient in vaccination treatment [60, 75]. A microneedle was used to administer the DNA vaccination. Immune responses seen were far superior to those obtained with standard doses [76]. An effort was also made to construct a microneedle patch for delivering influenza vaccination [77]. When the medicine is delivered by hollow microneedles rather than intramuscular injection, a lower dosage is required. The use of hollow microneedles to administer anthrax and rabies vaccines was also investigated [22]. Ogai and colleagues created hollow microneedles out of poly-glycolic acid to improve intradermal vaccination effectiveness. The precise administration of the medication in the upper dermis boosts immunity. On the 15th day after immunisation, intradermal immunisation with microneedles resulted in considerably greater antibody titers than subcutaneous injection [78]. The use of dissolving microneedles for intradermal immunisation was also examined [79]. The continued use of MNs may have a positive impact on vaccination programmes across the world. The following are some relevant examples [20]:

Table no. 4 MNs influence on immunization

Animal	Virus	Bacteria
Mouse	Chikungunya, hepatitis B, Hepatitis C	Plague, Tetanus.
Rat	Measles	-
Guinea pig	Influenza	Tuberculosis
Rabbit	-	Anthrax
Pig	Hepatitis B	-
Macaque	Japanese encephalitis, Measles	-
Human	Influenza, Rabies, Polio	-

Ocular delivery

Targeted medication delivery can be used to treat a wide range of posterior segment conditions. Nanoparticles were delivered through the suprachoroidal space via iontophoresis. The particles were observed to localize at the injection site in the absence of iontophoresis. And over 30% of nanoparticles were transported to the posterior portion of the eye when coupled with microneedles [80].

Pain therapy

Polydimethylsiloxane moulds were used to create meloxicam-loaded polymeric microneedles. In-vitro penetration investigations revealed that about 100 percent of the medication was released in 60 minutes. The drug deposition rate was determined to be 63.37 percent, with an enhanced transdermal flux of 1.60 g/cm2 /hr. When compared to a free drug solution, penetration increased 2.58 times [81]. Neuropathic pain is notoriously difficult to manage. The present therapies do not give adequate pain relief and have a number of negative effects. Dissolvable microneedles were investigated for the treatment of neuropathic pain. These supplied a calcitonin gene-related peptide (CGRP) antagonist peptide that was highly specific for the receptors. There was no skin irritation or negative effects with the analgesic microneedle patch. Within 20 minutes of treatment, almost 75% of the microneedle was dissolved [82]. The successful administration of medications by microneedle has created enormous prospects for the pain management businesses.

Cosmetological applications

In today's world, an individual's entire look is a highly crucial criterion. Many individuals regard cosmetics as a basic necessity. Microneedles are establishing their own existence in such a cosmo-techno environment. Microneedles are the most popular type of cosmetic procedure. MNs have been on the cosmetic industry for almost ten years. Typically, a device is used to pierce the skin, followed by the application of a substance to the skin's surface to enhance it. As a result, microneedles are utilized to promote collagen penetration deeper into the skin in order to protect it from micro damage. Microneedles also improves the look of the skin. Pre-treatment of microneedle with eflornithine cream improved its efficiency in preventing hair development in mice [83]. This can be really effective in the treatment of hirsutism. However, microneedles combining finasteride and minoxidil have been shown to promote hair growth in the treatment of alopecia, particularly androgenic alopecia [84]. The microneedles are said to be very good for acne, ageing, burn injury scars, skin lesions, vulgaris, and wrinkles. It is reasonable to believe that microneedle is an example of a successful and safe new therapy [83]. As a result, traditional cosmetics and topical formulations will be microneedled to improve present practice. Furthermore, hyaluronic acid microneedles are gaining favour in the treatment of fine lines and wrinkles. Hyaluronic acid injections are frequently utilized as fillers in the same [85]. Microneedles have also been used successfully to treat acne and acne scars, particularly when combined with other methods like as fractional radiofrequency, microdermabrasion, subcision, laser therapy, CO_2 fractional-laser, and chemical treatments such as acid peels or botulinum toxin an injection etc. [86].

10. Conclusion & future perspective

According to the current review, MNs can be created to distribute drugs in a smart and optimal manner. This approach may provide the necessary medication penetration and therapeutic effectiveness while causing minimal adverse effects. MN consideration in several scientific aspects gives improved direction and a revolution in the field of TDDS. Many researchers tinkered with traditional MNs in order to get the most out of them. MNs are a type of new technology that is very adaptable and may be used for both local and systemic treatments. Microneedles have been discovered to be fabricatable utilising a variety of materials and processes, as mentioned in their respective parts of the publication. These fabrication materials and processes produce MNs that are very effective, safe, and stable. Furthermore, several patents have been submitted in their respective domains, just a handful

of which are described in the article from 2010 to 2017. This shows that MNs are a large and potentially lucrative area of intellectual property rights concern. MNs have a wide range of uses, including aesthetic, diagnostic, and medicinal purposes. The primary goal of microneedle development is to create cost-effective, user-friendly technology that will improve its application. As a result, it has the potential to be a valuable monitoring tool for both developed and developing countries. Lastly, several authorities and regulatory agencies have approved the newly designed microneedles for clinical studies. It will increase the use of microneedles in the near future. Microneedles should be optimised for safety and health concerns in order to become an option of therapy in illnesses and disorders for the benefit of humanity. Microneedles are the cutting-edge introduction of new technologies that will have a substantial influence on TDDS and medication therapy. However, because Microneedles are under clinical trials, the future seems bright for Microneedle-based delivery methods. Microneedles also have a bright future in paediatric medication delivery. Overall, the use of microneedles is a must for the existing world's horizon. This publication attempts to cover microneedle manufacturing procedures, challenges, applications, patents, clinical studies, and future prospects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES:

1. Langer R. Drugs on target, Science 2001;293:58-59
2. Gill HS, Coated microneedles for transdermal delivery, j. control release 2007;117:227-237.
3. Xie Y. et al. controlled transdermal delivery of model drug componds by MEMS microneedle array, nanomedicine 2005;1:184-190
4. Avis KE et al. pharmaceutical Dosage Forms, parentral modifications, 2nd edn. New york; marcel dekkar inc.1992.
5. K. Ita, Transdermal delivery of drug with microneedles- potential and challenges, pharmaceutics, 2015;3:90-105.
6. P.Bora et al. microneedle Technology for Advanced Drug Delivery
7. M. R. Prausnitz, Transdermal Drug Delivery, Nat.Biotechnol. 2018;26:1261-1268.
8. M. Gupta, et al. Nanocarrier-based topical drug delivery for the treatment of skin disease
9. Donnelly R. F. et al. Optical Coherence Tomography on Skin Penetration Characterization and in-skin Dissolution, J.Control Release, 2010;147(3):333-341.
10. Ghosh P. et al. Development of Co-drug approach for sustained drug delivery across microneedle treated skin, J. PharmaSci, 2013;102(5):1458-1467.
11. Felton LA et al. Transdermal and intradermal delivery of therapeutic agents application of physical technologies, Drug Dev.Ind. Pharma, 2012;38(34)513
12. Bariya SH et al. Microneedle: an emerging transdermal drug delivery system, J. Pharma Pharmacol, 2012;64(1):11-29.

13. Gupta J. et al. Infusion pressure and pain during microneedle injection into skin of human subjects, Biomaterials, 2011;32(28):6823-6831.
14. Hirobe S. et al. Transcutaneous Vaccine-Currentand emerging strategies, Expert opin. Drug Delivery 2013;10(4):485-498.
15. J.E. Lai et al. Structure and function of skin, hair and nails, Medicine 2009;37:223-226.
16. E. Candi et al. The cornfield envelope: a model of cell death in the skin, Nat. Rev. Mol. Cell boil,2005(6):328-340
17. M. R. Prausnitz et al. Skin Barrier And Transdermal Drug Delivery, Dermatology, 2012(3);2065-2073.
18. T. Igarashi et al. The appearance of human skin:A survey, Foundation and Trends in computer Graphics and Vision, Vol.3,2007; pp195.
19. Sanjukta Duarah et al. Recent advances in microneedle-based drug delivery; Special emphasis on its use in paediatric population, European Journal of Pharmaceutics and Biopharmaceutics 2019(136) 48-69.
20. Sanjay Sharma et al. Recent advances in microneedle composites for biomedical applications: Advanced drug delivery technologies, Materials Science & Engineering C, 2019(103) 109717.
21. D. Sharma et al. Microneedle: An approach in Transdermal drug delivery-A review, 2017.
22. E. Larraneta et al. Microneedle array as transdermal and intradermal drug delivery system: materials, science, manufacturing & commercial development, Master.Sci.Eng. R Rep. 2016(104)1-32.
23. X. Hong et al. Dissolving and biodegradable microneedle technologiesfor transdermal delivery of drug and vaccine, Drug Des. Devel. Ther. 2013(7) 945-952.
24. G. Yan et al. Evaluation needle length and density of microneddle technologies for transdermal arrays in the pre-treatment of skin for transdermal drug delivery, Int. J. Pharm, 2010(391) 7-12.
25. Tejashree Waghule et al. Microneddle: A smart approach and increasing potential for transdermal drug delivery system, Biomedicine and Pharmacotherapy, 2019(109)1249-1258.
26. S. D. Gittard et al. Pulsed laser deposition of antimicrobial silver coating on Ormocer® microneddles, Biofabrication, 2009;1(4) 41001.
27. R. F. Donnelly et al. Processing difficulties and instability of carbohydrate microneedle array, Drug Dev. Ind. Pharma. 2009(35)1242-1254.
28. T. Miyano et al. Sugar microneedles as transdermic drug delivery system, Biomed Microdevices, 2005(7) 185-188.
29. W. Z. Li et al. Super-short silicon microneddle for transdermal drug delivery applications, Int. J. Pharma. 2010(389) 122-129.
30. S. Pradeep Narayanan et al. Solid silicon microneedle for drug delivery applications, Int. J. Adv. Manuf. Technol, 2017(93) 407-422.
31. Q. Y. Li et al. A solid polymer microneedle patch pre-treatment enhances the permeation of drug molecule into the skin, RSC Adv, 2017;7:15408-15415.
32. Y. Ma et al. Coating solid dispersions on microneedles via a molten dip-coating method: development and in-vitro evaluation for transdermal delivery of a water insoluble drug, J. Pharm. Sci, 2014(103) 3621-3630.
33. Y. Chen et al. Fabrication of coated polymer microneedle for transdermal drug delivery, J. Control Release, 2017(265) 14-21.
34. S. Li et al. Individually coated microneedles for co-delivery of multiple compounds with different properties, Drug Delivery. Transl. Res, 2018;8(5) 1043-1052.
35. H. A. E. Benson et al. Proteins and peptides: strategies for delivery to and across the skin, J. Pharma. Sci. 2008 (97) 35-3610.
36. L. Niu et al. Intradermal delivery of vaccine nanoparticle using hollow microneedle array generates enhanced and balanced immune response, J. Control Release, 2019(294) 268-278.
37. Yu LM et al. A microfabricated electrode with hollow microneedles for ECG measurement, Sensor Actuat A Phys. 2009;151: 17-22.
38. K. Ita et al. Dissolving microneedle for transdermal drug delivery: advances and challenges, Biomed. Pharmacother, 2017(93) 1116-1127.
39. H. L. Quinin et al. Design of a dissolving of a fixed dose combination of cardiovascular drugs, J. Pharma. Sci. 2015(104)3490-3500.

40. J. Chen et al. Fabrication of tip-dissolving microneedles for transdermal drug delivery of meloxicam, AAPS PharmSciTech, 2018(19)1141-1151.
41. Luzuriaga MA et al. Biodegradable 3D printed polymer microneedle for transdermal drug delivery, Lab chip, 2018(18) 12223-30.
42. Wang Q. L. et al. A fabrication method of microneedle molds with controlled microstructures, Mater Sci. Eng. C. 2016;65:135-42.
43. Chen Z. et al. Rapid farbrification of microneedles using magnetorheological drawing lithography, Acta Biomer, 2018:65: 283-91.
44. Indurman S. et al. Current advances in the fabrication of microneedle for transdermal delivery, J. Control release, 2014; 185:130-8.
45. Xenikakis I. et al. Fabrication and finite element analysis of stereolithographic 3D printed microneedles for transdermal delivery of model dyes across human skin in vitro. Eur J Pharm Sci. 2019;137:104976.
46. Ovsianikov A. et al. Two photon polymerization of polymer-ceramic hybrid materials for transdermal drug delivery. Int J Appl Ceram Technol. 2007;4(1):22
47. Ruggiero F et al. Electro-drawn polymer microneedle arrays with controlled shape and dimension. Sensors Actuators B Chem. 2018;255:1553–60.
48. Chen Z et al. Rapid fabrication of microneedles using magnetorheological drawing lithography. Acta Biomater. 2018;65:283–91.
49. Choi CK et al. Spatially discrete thermal drawing of biodegradable microneedles for vascular drug delivery. Eur J Pharm Biopharm. 2013;83(2):224–33.
50. Hegarty C et al. Design of composite microneedle sensor systems for the measurement of transdermal pH. Mater Chem Phys. 2019;227:340 – 6 .
51. Kim JD et al. Droplet-born air blowing: novel dissolving microneedle fabrication. J Control Release. 2013;170(3):430–6.
52. Huh I. et al. Effects of two droplet-based dissolving microneedle manufacturing methods on the activity of encapsulated epidermal growth factor and ascorbic acid. Eur J Pharm Sci. 2018;114:285–92.
53. Kim J. H. et al. Successful transdermal allergen delivery and allergen- specific immunotherapy using biodegradable microneedle patches, Biomaterials, 2018; 150: 38-48.
54. A. C. Williams et al. Penetration enhancers, Adv.Drug Delivery Rev. 2004;56(5) 603-618.
55. K. Cheung et al. Microneedles for drug delivery: trends and progress, Drug Delivery, 2016 (23);7 2338-2354.
56. B. Chen et al. Silicon Microneedle array with biodegradable tips for transdermal drug delivery, Microsyst. Technol. 2008;14(7) 1015-1019.
57. C. O'Mohony et al. Structural characterization and in-vivo reliability evaluation of silicon microneedles, Biomed. Microdevice, 2004;16(3) 333-343.
58. C. Uppulari et al. Effect of microneedle type on transdermal permeation of rizatriptan, AASP Pharm. Sci. Tech. 2017;18(5) 1459-1506.
59. P. Bora et al. Microneedle technology for advanced drug delivery; Evolving Vistas, 2008.
60. J. Li et al. Microneedle patches as drug and vaccine delivery platform, Curr. Med. Chem. 2017(22);24:2413-2422.
61. A. Singh et al. Microneedle: advances and coidening horizons, Indian Dermatol online J. 2016(4)7;244-254.
62. J. Qu et al. Research and development of anti-parkinson's drug: an analysis from the perspective of technology flows measured by patent citation, Expert Opin. Ther.Pat. 2019(29) 127-135.
63. Patft page lofl(n.d.)
64. United states patent and trademark office (n.d.)
65. K. Ita et al. Transdermal delivery of drugs with microneedle potential and challenges, Pharmaceutics, 2015;7: 90-105.
66. M. Gupta et al. Nanocarrier based topical drug delivery for the treatment of skin disease, Expert Opinion Drug delivery, 2012(9) 783-804.
67. Kim Y et al. Targeted delivery of antiglaucoma drugs to the supraciliary space using microneedle, 2014; 55(11): 7387-97.

68. Omid K et al. Fenestrated microneedles for ocular drug delivery. Sensors and Actuators B: Chemical, 2016; 223: 15-23.
69. Sun W, Araci Z, Inayathullah M, Manickam S, Zhang X, Bruce M, Marinkovich M, Lane A, Milla C, Rajadas J, Butte M. Polyvinylpyrrolidone microneedles enable delivery of intact proteins for diagnostic and therapeutic applications. Acta Biomater, 2013; 9(8): 7767-7774.
70. Skoog S, Miller P, Boehm R, Sumant A, Polsky R, Narayan R. Nitrogen-incorporated ultrananocrystalline diamond microneedle arrays for electrochemical biosensing. Diam Relat Mater, 2015; 54: 39-46.
71. Keum D, Jung H, Wang T, Shin M, Kim Y, Kim K, Ahn G, Hahn S. Microneedle Biosensor for RealTime Electrical Detection of Nitric Oxide for In Situ Cancer Diagnosis During Endomicroscopy. Adv Healthc Mater, 2015; 4(8): 1153-8.
72. Strimbu K, Tavel J. What are Biomarkers? Curr Opin HIV AIDS. 2010; 5(6):463-466.
73. Li B, Wang J, Yang S, Zhou C, Wu M. Sample-free quantification of blood biomarkers via laser-treated skin. Biomaterials, 2015; 59: 30-38.
74. Renxin W, Xiaoming J, WeiWang Z. A microneedle electrode array on flexible substrate for long-term EEG monitoring. Sensors and Actuators B. 2017; 244: 750-758.
75. M. R. Prausnitz, engineering microneedle patches for vaccination and drug delivery to skin, Annu.Rev. Chem. Biomol Eng. 2017(8)177-200.
76. J. A. Mikszta et al. Improved genetic immunization via micromechanical disruption of skin barrier function and targeted epidermal delivery, Nat.Med. 2002(4) 415-419.
77. M. J. Mistilis et al. Development of a thermostable microneedle patch for influenza vaccination, J. Pharm. Sci. 2015(2)104; 740-749.
78. N. Ogai, I. Nonaka, Y. Toda, T. Ono, S. Minegishi, A. Inou, M. Hachiya, H. Fukamizu, Enhanced immunity in intradermal vaccination by novel hollow microneedles, Ski. Res. Technol. 24 (2018) 630–635
79. A. M. Rodgers et al. Dissolving microneedles for intradermal vaccination: manufacture, formulation, stakeholder consideration, Expert Opin. Drug Deli. 2018; 1-5.
80. J. H. Jung et al. Ocular drug delivery targeted by iontophoresis in the suprachoroidal space using a microneedle, J. Control Release, 2018(227) 14-22.
81. S. Amodwala et al. Satestically optimized fast dissolving microneedle transdermal patch of meloxicam: a patient friendly approach to manage arthritis, Eur. J. Pharm Sci. 2017(104) 114-123.
82. X. Xie et al. Analgesic microneedle patch for neuropathic pain therapy, ACS Nano, 2017(1)111; 395-406.
83. M. T. C. McCrudden et al. Microneedle applications in improving skin appearance, Expt. Dermatol, 2015(25) 561-566.
84. R. Dhurat et al. Response to microneedling treatment in men with adrogenetic alopecia who failed to respond to conventional therapy, Indian J. Dermatol 60 (n.d.), 260-3.
85. S. Dogra et al. Microneedling for acne scar in Asian skin type: an effective low cost treatment modality, J. Cosmet. Dermatol, 2014(13) 180-187.
86. M.T. Hoang et al. solid microneedles for transdermal delivery of amantadine hydrochloride and Pramipexole Dihydrochloride, Pharmaceutics, 2015(7) 379-396.