WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 14, 227-257. Review Article ISSN 2277–7105

MICROARRAY PATCH TECHNOLOGY: A NEW FRONTIER IN DRUG DELIVERY

Prema R.*, Meenakshi M., Prabhakaran M. and Dr. Sankar C.

*Department of Pharmaceutics, KMCH College of Pharmacy, Kalappatti Road, Coimbatore, India.

Article Received on
22 May 2025,

Revised on 11 June 2025,
Accepted on 01 July 2025,

DOI: 10.20959/wjpr202514-37517

***Corresponding Author**
Prema R.
Department of Pharmaceutics, KMCH College of Pharmacy, Kalappatti Road, Coimbatore, India.

ABSTRACT

Transdermal drug delivery provides a different approach to oral and injectable methods, effectively overcoming challenges like low bioavailability and patient discomfort. However, passive skin permeation remains a challenge, particularly for poorly soluble drugs. Microarray patches (MAPs) have emerged as an advanced transdermal delivery system that enhances drug absorption using micron-scale needles, significantly improving therapeutic efficacy compared to conventional patches. MAPs provide a minimally invasive, self-administered alternative, reducing the burden on healthcare personnel while eliminating sharps waste and minimizing needle-stick injury risks. Their versatility extends to various drug delivery applications, including vaccines, insulin, contraceptives, and cosmetic treatments. Different microneedle types solid, dissolving, hydrogel-based, coated, and hollow are designed to optimize drug delivery based on specific therapeutic needs. Despite their growing commercial interest, challenges remain in optimizing fabrication, characterization, and large-scale production for widespread clinical adoption. This review explores the current advancements in microneedle technology, detailing fabrication techniques, evaluation methods, and clinical applications, particularly in contraceptive and antiretroviral drug delivery. By highlighting the main challenges and potential opportunities, this review seeks to lay the groundwork for future research and encourage the wider integration of MAPs in clinical practice.

KEYWORDS: Microneedle patch, Drug delivery, Fabrication techniques, 3D Printing

technology, Characterization, Patent search.

INTRODUCTION

Transdermal drug delivery is a promising and promptly evolving area in modern medication, commonly serving as another approach in place of conventional oral medications and hypodermic needle injections. Although significant progress in the evolution of transdermal therapeutic systems, several challenges persist. A major limitation is posed by the stratum corneum, the skin's irregular, protective outer layer.[1,2,3] creating substantial obstacles for the transdermal transport of macromolecules, particularly those larger than 500 Daltons, into the deeper skin layers.[4]

Various strategies have been explored to surmount the protective barrier of the skin's outermost layer, including passive or chemical approaches such as formulation optimization and the application of chemical agents that enhance skin permeability. In addition, active or device-assisted methods have been developed, including thermal fractional laser micro ablation, electrical techniques, and mechanical interventions for example, laser-based jet injectors and techniques such as tape stripping and cyanoacrylate stripping, employed to facilitate drug passage through the skin.[5]

Transdermal drug delivery systems are referred as patches, the frequently investigated approaches for transdermal drug delivery. Compared to parenteral drug delivery, they offer a significant advantage by delivering drugs systemically without GI absorption and hepatic processing. As a result, these systems help reduce drug loss and minimize side effects linked to liver metabolism. They also enable more precise dosing, targeted delivery, and improved treatment effectiveness.[6,7]

Microneedle array patches have come into existence as an effective strategy for delivering drugs through the skin, mitigating the challenges posed by conventional approaches such as injections and topical applications. While hypodermic needles are often associated with pain and reduced patient compliance, topical creams suffer from low bioavailability due to the skin's natural barrier properties. Drug permeability is primarily regulated by the skin's structure, especially the stratum corneum, which blocks most drugs except those with low molecular weight and lipophilic nature. This limited permeability presents challenges in designing effective topical formulations. Microneedle array patches offer a minimally invasive approach to bypass the stratum corneum, enhancing drug penetration and improving

therapeutic outcomes.[8]

Microarray patches (MAPs), composed of microscale needles, are utilized in biomedicine for a wide range of diagnostic and therapeutic applications. The first microarray patch (MAP) utilized silicone microneedles to puncture the skin, facilitating enhanced drug permeation.[9]

This review aims to deepen the understanding of microarray patches (MAPs) among clinicians, formulation scientists, and researchers, emphasizing their crucial role in enhancing treatment outcomes for various medical conditions. Additionally, the review advocates for the broader clinical adoption of MAPs, recognizing their potential to reshape drug delivery systems and elevate standards of patient care globally.

1.1. History of microneedles in drug delivery

Dr. Ernst Kromayer provided the first documented evidence of the implementation of microneedles in 1905, proposing the application of motorized dental burs to cure hyperpigmentation and scarring. Rather, in the 1960s, a notable growth was seen in the deployment of microneedles platforms for drug administration.[10] MN started out in the 1970s by Virgil A. and Martin S. Gerstel. The mechanical transdermal method referred to as MNs was initially developed in 1976 to deliver drugs through the skin's natural barrier.[11] In order to enable drug effects at the site of application as well as within the bloodstream, the drug was administered percutaneously to the dermis layer using this drug delivery device, according to a report documented in the late 1990s. It is employed to enhance the absorption of protein-based drugs such as insulin, vaccines, monoclonal antibodies and peptide therapeutics along with its pain-free characteristic.[12]

Microneedles have been used experimentally in the context of targeted and localized medication delivery, mostly in the transdermal drug delivery field. This may be because they can be made to better penetrate the skin outer most layer and increase the permeability of molecules across the skin.[13]

Even though delivery applications accounted for 73.4% of papers on microneedles as of 2021,[13] the usage of microneedles is not just restricted to medication administration methods. Furthermore, these platforms have been used for cosmetic and diagnostic purposes.[14]

1.2. Basic Principles of Microneedle Technology

When compared to conventional drug/vaccine administration methods including intramuscular, subcutaneous, and oral injections, MNs have the benefits of reducing pain for patients and increasing the medication's stability.[15] The third generation of transdermal drug delivery systems is represented by MN technology, which disrupts the stratum corneum to directly target the deeper layers of the skin. The first generation primarily consists of transdermal patches, while the second generation uses chemicals and techniques to increase skin permeability by reducing the stratum corneum's barrier function.

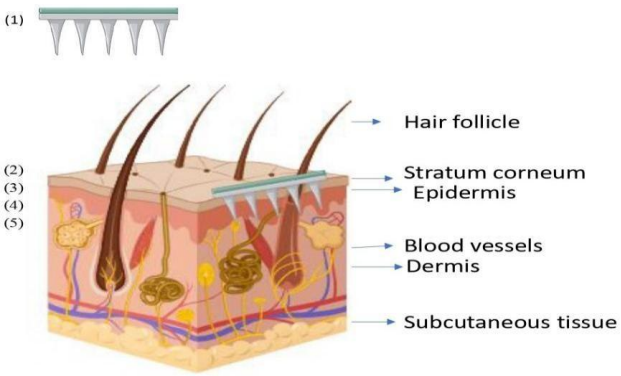

Figure 1: Drug Delivery Mechanism via Microneedle Device: (1) The microneedle device containing the drug solution; (2) Insertion of the device into the skin; (3) Temporary disruption of the skin's surface; (4) Release of the drug into the epidermis; (5) Delivery of the drug to the target site for action.

1.3. Microarray patches measurement

Microneedles can be designed in different sizes based on the type and material used. Given that the epidermis can be as thick as 1500 μm, a needle length of up to 1500 μm is adequate for drug delivery within the epidermis. Longer or thicker needles, however, can penetrate deeper into the dermis, potentially damaging nerves and causing pain.[16]

MNs generally vary in size, with lengths ranging from 150 to 1500 microns, widths between 50 and 250 microns, and tip thicknesses of 1 to 25 microns. To create micron-sized transport pathways, the needle diameter is typically kept in the micron range. The tips of microneedles can take on various shapes, such as cylindrical, triangular, pointed, pentagonal, octagonal, and others.[1]

2. MICRO ARRAY PATCHES

2.1. Fabrication materials and its properties

2.1.1. Silicon

In the 1990s, The first microneedle was made from silicon.[18] Silicon has an anisotropic nature with a crystalline structure, meaning its properties vary based on the alignment within the crystal lattice. This results in different elastic moduli ranging from 50 to 180 GPa.[19]

Silicon's flexibility enables the fabrication of microneedles in various sizes and shapes, making it a versatile material due to its favorable physical properties. Its substrates can be precisely engineered and support large-scale production. However, the high expense of silicon and its complex, time- consuming production method limit its widespread integration in microneedle-based technology. Additionally, biocompatibility concerns arise due to silicon's brittleness, as fractured fragments may remain in the skin, potentially leading to health risks.[20]

2.1.2. Metal

Stainless steel and titanium are the primary metals utilized for microneedle fabrication, with palladium, nickel, and palladium-cobalt alloys also being employed. These metals exhibit excellent mechanical strength and biocompatibility, making them well-suited for biomedical applications. Their high structural integrity minimizes the risk of breakage, offering a significant advantage over silicon in microneedle production. Stainless steel was the first metal introduced for manufacturing microneedles.[21,22]

2.1.3. Ceramic

Alumina (Al_2O_3) is primarily utilized for its exceptional chemical resistance. Its stability arises from the strong ionic and covalent bonding between aluminium and oxygen atoms, which enables the formation of a robust and durable oxide layer.[23] Additional ceramic materials used include calcium sulphate dihydrate, commonly known as gypsum.[24]

Recently, Ormocer®, an organically modified ceramic, has been introduced. This material features a three-dimensional cross-linked copolymer network, providing enhanced stability and versatility for various applications.[25]

2.1.4. Silica glass

Glass can be utilized to create microneedles with diverse geometries on a small scale. Silica glass is physiologically inert but exhibits brittleness,[26] while borosilicate glass, composed of silica and boron trioxide, offers greater elasticity. Due to the predominantly manual fabrication process, glass microneedles are less time-efficient.[27] As a result, they are no longer commercially utilized and are currently limited to experimental research.[20]

2.1.5. Carbohydrate

Carbohydrates serve as a key material in microneedle fabrication, with maltose being among the most commonly used, alongside mannitol, trehalose, sucrose, xylitol, and galactose.[28] These sugars, as well as polysaccharides, can be processed into microneedles through molding techniques that utilize silicon or metal templates. During fabrication, a drug-loaded carbohydrate solution is cast into the molds, allowing for the formation of microneedles that dissolve at a controlled rate, facilitating drug release within the skin. While carbohydrates are cost-effective and biocompatible, their thermal instability presents challenges in large-scale production.[20,29]

2.1.6. Polymer

Various polymers have been explored for microneedle fabrication, including synthetic materials such as PMMA, PLA, PLGA, PGA, polycarbonate, and cyclic-olefin copolymer, as well as water-soluble and biodegradable options like PVP, PVA, and hydrogel-forming polymers. Additionally, polystyrene, SU-8 photoresist, and poly (methyl vinyl ether-co-maleic anhydride) have been investigated for specialized applications. These polymers are commonly used to create dissolving and biodegradable microneedle arrays. Although they generally possess lower mechanical strength than metals and silicon, they offer greater toughness compared to glass and ceramics, making them suitable for various biomedical applications.[30]

2.2. Fabrication of Different Types of Microneedles

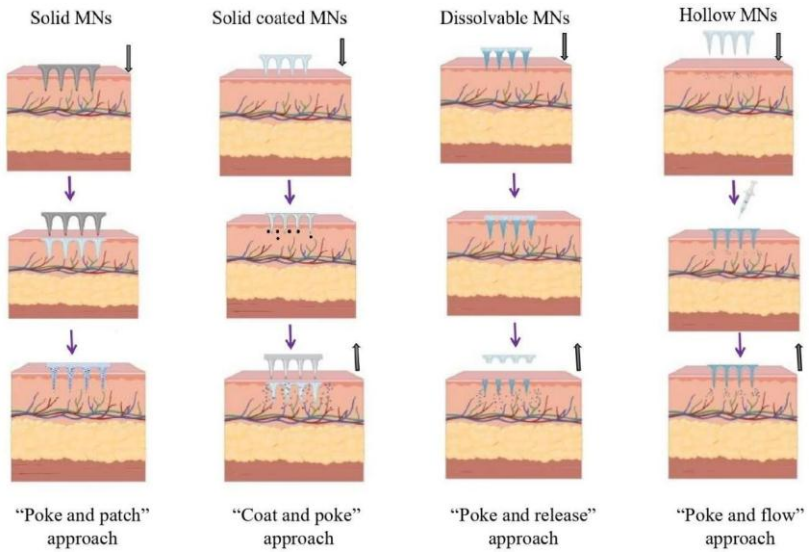

Fig. 2: Schematic diagram represents different fabrication techniques of MNs.

2.2.1. Solid microneedles

Solid microneedles, first mentioned in 1971, serve as a skin pre-treatment method. Solid NDMNs were among the first micro needle types developed. Instead, they pierce the skin's outer layer, forming microchannels.[31] Specifically, they penetrate the skin to create microchannels through which drugs can be administered. A key advantage of solid microneedles is their ability to facilitate drug delivery in a safe manner.[32] The first solid microneedle (SMN) was manufactured from silicon using a reactive ion etching microfabrication technique. Additionally, it was the first published study to utilize fabricated microneedles for enhancing transdermal drug delivery.[33]

Solid silicon microneedles with a long, tapered structure were fabricated using the tetramethylammonium hydroxide (TMAH) etching process. The resulting microneedles had an average height of 158 µm and a base width of 110.5 µm.[34] Later, he also developed gold-coated solid silicon microneedles with a height of 250 µm, a base width of 52.8 µm, an aspect ratio of 4.73, a tip angle of 24.5°, and a tip diameter of 45 µm. The results indicated enhanced bioavailability and mechanical strength.[35] Various researchers have also studied stainless steel microneedles. The application of stainless-steel microneedle arrays has been investigated for enhanced delivery of captopril and metoprolol tartrate.[8]

When solid microneedles (SMNs) are made from degradable polymers or water-soluble materials like maltose, galactose, polyvinyl alcohol (PVA), or hyaluronic acid, they are

classified as dissolving or polymeric microneedles.[36,37,38] Solid silicon microneedle arrays, each 150 μm in length, to deliver the hydrophilic peptide acetyl hexapeptide-3.The results demonstrated that the microneedle patch effectively facilitated peptide delivery into the skin.[39] PLA microneedle with a height of 600 μm was designed to enhance the transdermal delivery of small-molecule drugs. This study laid the foundation for clinical applications and potential use in the cosmetic industry. Overall, solid microneedles show great promise as an effective tool for improving drug delivery in transdermal drug delivery systems.[40]

2.2.2. Coated microneedles

While solid microneedles are widely used to enhance transdermal drug delivery by creating channels in the skin, they come with the drawback of a complex administration process, typically requiring two steps: insertion of the microneedles followed by drug application. The introduction of coated microneedles has resolved this issue.[41] These microneedles, which are coated with drugs at their tips using methods like dipping, gas-jet drying, ink-jet printing, or spraying, allow for a simpler, single-step delivery, streamlining the process and improving efficiency.[42] The drug delivery mechanism of coated microneedles is known as the "coat and poke" approach. In this process, the microneedle patch is first inserted into the skin, and then the drug, which is coated on the tips of the microneedles, is released directly into the skin.[43] Lidocaine-coated microneedles offer local analgesic effects, and when compared to the commercial lidocaine/prilocaine EMLA cream, the lidocaine-coated microneedle patch delivers a much faster onset of local analgesia, achieving relief within just one minute.[44]

The coating method and materials must also be fine-tuned to ensure strong adhesion, preventing the coating from being wiped off during needle insertion into the skin.[45] Various coating techniques have been widely reported and integrated in the development of microneedle systems.[46] Of these, dip coating is the most widely used due to its simplicity and cost-effectiveness.[47] Coated microneedles, crafted from a range of biodegradable and biocompatible materials, offer a rapid bolus delivery system for large sized compounds delivered into the dermal layer . Additionally, investigations have revealed that drugs applied in a rigid state on microneedles maintain the stability over extended periods.[48]

2.2.3. Dissolving microneedles

Dissolving microneedles were initially introduced in 2005.[49] Dissolving microneedles offer several advantages over solid or coated microneedles, including ease of production, convenience, and a high drug-loading capacity.[50] Dissolving microneedles typically operate

based on a "poke and release" mechanism: as the microneedle patch penetrates the skin, the drug stored in the tips of the microneedles is released.[51]

Micromoulding, casting, hot embossing, injection moulding, photopolymerization, and drawing lithography are some of the most common techniques used to manufacture dissolving microneedles, which are gaining popularity across various fields.[52]

The dissolving microneedles, composed of polyvinyl alcohol (PVA), completely dissolved within four minutes of being inserted into the skin. The microneedle patch not only triggered a stronger immune response but also enhanced the stability of the vaccine.[53] It offers the benefits of directly loading the drug into the array, removing the need for a two-step administration. However, it requires the drug's physicochemical properties to be compatible with fabrication conditions, avoiding heat or light exposure for sensitive compounds.[54]

Doxorubicin was loaded into various sections of the microneedle arrays, including the base and needle shafts, with different amounts of the drug in each location, leading to varying drug delivery outcomes. For instance, loading the drug onto both the base surface and the needle shafts resulted in up to a three- fold increase in drug delivery. The research demonstrated that both microneedle size and the drug's placement in the array affect delivery efficiency.[55]

The atomized spray process, used for the first time in microneedle fabrication, offers a simple, scalable method that avoids extreme conditions, enabling incorporation of sensitive substances. Despite its advantages, only 17% of ketoprofen was delivered across the skin, indicating that geometric factors play a larger role in drug delivery.[56] In brief dissolving microneedle patches offer an effective, convenient, and well-tolerated approach for transdermal drug delivery.

2.2.4. Hollow Microneedles

Hollow MAPs utilize a "poke and flow" method, where a liquid bio cargo formulation (such as a vaccine) is delivered through microchannels formed by microarrays across the skin layers.[57] Hollow microneedles mark a major engineering advancement, utilizing various materials like polymers, metals, and silicon. Their hollow design serves as a channel for delivering drugs, cells, and other biomedical substances.[58] Hollow microneedles have demonstrated their effectiveness in clinical trials, particularly for vaccine administration.[59]

The fabrication of hollow microneedles requires precise techniques like 3D printing, drawing

lithography, and etching, ensuring high accuracy for both human safety and product efficacy.[60,61] Hollow MAPs are used either to directly inject liquid cargo into the skin or to create channels that allow cargo from a reservoir to passively diffuse into the skin.[62] The hollow design of these microneedles allows for precise vaccine delivery into the skin, providing an alternative to conventional injections. This approach reduces injection-related discomfort while improving delivery efficiency. Additionally, hollow microneedles offer a reliable and effective method for extracting interstitial fluid (ISF) for biomarker monitoring.[63,64]

Unlike solid MAPs, which temporarily enhance skin permeability, hollow MAPs provide continuous bio cargo delivery through their openings and can administer larger doses than other MAP types. A key advantage of hollow MAPs is their ability to deliver liquid cargo solutions without requiring dry formulations. However, optimizing formulations remains crucial to ensure effective skin concentrations, given the limited volume that can be delivered to the cutaneous microenvironment. Hollow MAPs have been designed using a variety of materials, including metals, polymers, silicon, and glass, allowing for diverse structural adaptations to enhance performance.[65,66,67]

2.2.5 Hydrogel Microneedles

This can be regarded are considered a subclass of polymer-based microneedles, characterized by polymers that exhibit the physicochemical properties of hydrogels.[68] This recently developed type of microneedle is made from super-swelling polymers, which feature a hydrophilic structure capable of absorbing significant amounts of water into their three-dimensional network. Upon insertion into the skin, these polymers swell in response to interstitial fluid, creating channels that connect the capillary circulation with the drug patch. Initially, these microneedles serve to disrupt the skin barrier, but once swollen, they function as a rate-controlling membrane. They offer flexibility in size and shape, can be easily sterilized, and can be removed from the skin intact key advantages that enhance their practicality and effectiveness.[69] Due to the similarities among these polymers, their fabrication methods remain largely the same, regardless of whether they possess hydrogel properties.[70]

Hydrogel-forming MAPs are a rapidly advancing type of MAP designed for skin-targeted biomolecule delivery, utilizing a "poke and release" mechanism without leaving microarray material in the skin.[71] Hydrogel-forming microneedles offer the advantage of resisting pore

closure during use, ensuring their effectiveness while in place. Additionally, they help prevent the deposition of microneedle tips after insertion, a common issue with dissolving microneedles and solid microneedles (SMNs), which might break during implantation.[72] As a result, hydrogel-forming MAPs can deliver higher doses of bio cargo compared to other dry MAP dosage forms while theoretically leaving no polymer residue in the skin microenvironment.[73]

2.2.6 Porous Microneedles

Porous MAPs, characterized by varying pore sizes and densities, represent another explored type of MAP.[74,75] Porous MAPs are infused with a bio cargo solution, which dries within the microarray pores. When applied, these microarrays penetrate the stratum corneum, allowing the bio cargo to diffuse from the pores into the skin.[76,77] Various materials, including stainless steel, titanium have been used to fabricate porous MAPs for targeted skin delivery of diverse bio cargos.[78] Furthermore, due to their porous structure, these microarrays are generally weaker than solid ones, increasing the risk of accidental breakage in the skin. This necessitates the use of biodegradable materials for porous MAPs. Moving forward, comprehensive studies on their design, biomaterials, fabrication, and application particularly skin insertion capability and delivery efficiency will be crucial to fully explore their potential for skin- targeted vaccination.[79]

It is crucial to optimize porous MNs to ensure they possess adequate mechanical strength for maintaining their structure and effectively penetrating the patient's skin. Additionally, further research and development are needed to establish scalable fabrication methods for mass production.[80]

2.2.7 Hybrid Microneedles

Hybrid MAP systems have been less explored due to challenges in scalable fabrication and ensuring reliable, user-friendly application without mechanical failure, leakage, or clogging. Therefore, future research should focus on developing hybrid MAPs that are scalable, patient-friendly, easy to use, and cost-effective for skin vaccination.[79] For example in recent years, multiple studies have explored the antibacterial properties of these hybrid MNs for use in treating infections and wounds.[81]

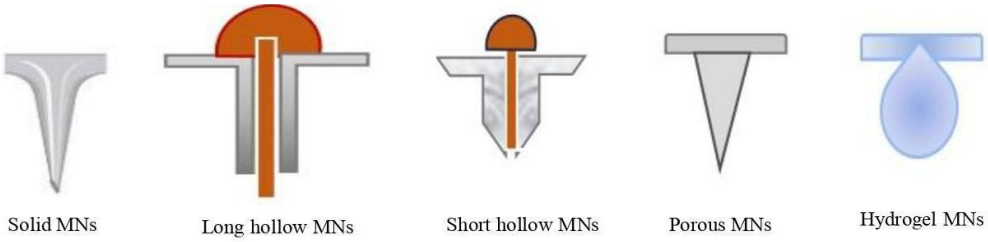

Fig 3: Schematic diagram represents different types of microneedles.

Table 1: Fabrication techniques for different types of microneedles.

Type of microneedle	Fabrication techniques
Solid microneedle ➢ Silicon microneedle ➢ Metal microneedles ➢ Polymer icroneedles ➢ Ceramic icroneedles	Silicon dry-etching process, Isotropic etching, Anisotropic wet etching, Dicing a silicon substrate and then acid etching. Three- dimensional laser ablation ➢ Laser cutting, Wet etching, Metal electroplating methods. ➢ Photolithography. ➢ Ceramic micro moulding and sintering lithography
Coated microneedles	Dipping or spraying the microneedles with an aqueous solution of increased viscosity to retain more formulation during drying and which contains a surfactant, the active agent and a stabilizing agent. Microneedles can be dipped one time or more than one time into a coating solution, each individual microneedle can be dipped into a microwell containing drug solution or a film of drug solution previously formed on the roller can be applied. Layer-by-layer coating techniques.
Dissolving microneedles	Micro moulding.
Hollow microneedles	Micro-electromechanical systems (MEMS) techniques-laser micromachining, deep reactive ion etching of silicon, an integrated lithographic moulding technique, deep X-ray photolithography, wet chemical etching and micro-fabrication.
Hydrogel Microneedles	➢ Micro-moulding ➢ Drawing lithography ➢ Injection moulding
Porous Microneedles	➢ Electrochemical anodization, ➢ Wet etching, ➢ Mild micro‑moulding, ➢ Sintering process, ➢ Pyrogen leaching, ➢ Hot embossing, ➢ Phase separation, ➢ Emulsion and bonding

2.3. Characterization and Evaluation

2.3.1. Physical characterization

2.3.1.1.Microneedle geometry assessment through visual examination and microscopic analysis: Microneedle geometry is commonly assessed using observational examination, stereo-optical microscopy and electron microscopy.[82] These techniques enable the

examination of micro-needle size measurement, topography, and the dispersion pattern of needles across the array.[83] The geometry of the microneedle tip is crucial to its performance. Early designs primarily featured conical and pyramidal shapes. Experimental measurements, combined with analytical and finite element modelling, revealed that reducing the microneedle tip radius from 80 to 30 μm significantly improved insertion efficiency. This was evidenced by a decrease in insertion force required to penetrate the stratum corneum from 3.04 N to 0.08 N per needle.[84]

2.3.1.2.Fracture strength assessment

For effectively permeate the dermal layer and enhance therapeutic diffusion, they must exhibit adequate mechanical strength. However, the skin's inherent viscoelastic properties can hinder the piercing ability of microneedles.[85] The force required for microneedles to penetrate the stratum corneum is typically around 0.098 N per needle.[86] However, penetration may be achievable with an insertion force as low as 0.03 N per needle. The most commonly used method to assess microneedle structural integrity is the longitudinal compression test, also known as the needle mechanical failure test. In this test, a microneedle array is attached to a probe and pressed at a controlled speed onto a flat aluminium block until a peak force is recorded on the force-distance curve, representing the microneedle's fracture force.[87] Additionally, brittleness can be determined from the gradient of the force-displacement curve, where a steeper gradient indicates higher brittleness.[88] The structural integrity of microneedles is often reported as force applied to each needle. Obtained by dividing the peak force by the number of needles. On the other hand, this calculation assumes that all the needles will fail at the same time under the maximum force. This assumption may not be accurate, as some needles in the array could buckle or break prematurely during the compression test, potentially leading to an overestimation of the microneedle's tensile strength.[89]

2.3.2. Performance Evaluation

2.3.2.1.Insertion studies

Microneedle insertion is limited by the skin’s viscoelasticity, with depth classified as true or estimated. True depth measurement methods include confocal microscopy, X-ray computed tomography, and optical coherence tomography (OCT), while histological cross-sectioning and staining provide approximate extent. Each technique has advantages and limitations, which are explored in this segment.[90]

Microneedle insertion studies have been conducted using excised animal or human skin, placed on a flat surface to mimic underlying tissue. The skin is gently stretched before manually applying the microneedles. After insertion and removal, dyes such as gentian violet, methylene blue, or trypan blue are applied to stain microneedle channels. These dyes penetrate hydrophilic channels or selectively bind to nucleated epidermal and dermal cells, allowing visualization and calculation of the microneedle penetration success ratio.[91,92]

Ex-vivo microneedle insertion studies use histological sectioning and fluorescence or confocal microscopy to assess pore depth and penetration.[93] The Z-stack function enhances depth evaluation.[94] While histology provides valuable insights, careful sample preparation is essential, as freezing and sectioning may alter skin structure, leading to inaccurate penetration estimates.[95]

2.3.2.2 Skin Permeation Test Using Franz Cells

Diffusion cells are the primary *in vitro* method for studying microneedle-enhanced dermal permeation. They consist of donor and receptor compartments separated by a membrane, such as *Ex vivo* skin or a polymer. Permeants diffuse from the donor to the receptor compartment and are analysed using HPLC. Diffusion cells are categorized into two types: static (Franz-type) and flow-through (Bronaugh-type). Static diffusion cells maintain a thermostatically controlled receptor compartment with continuous mixing. Samples are manually collected at intervals and replaced with fresh media to track permeation over time. Alternatively, a final sample at the experiment's end determines the total permeated substance.[96]

Franz-type diffusion cells are classified as side-by-side or upright. Side-by-side cells, once common, are now rarely used due to skin damage risk and overestimated permeation. In 1975, Thomas Franz introduced upright diffusion cells, which better mimic natural skin conditions by exposing the stratum corneum to ambient environments.[97,98] Flow-through diffusion cells, introduced by Bronaugh and Stewart in 1984, use a peristaltic pump to maintain sink conditions, mimicking dermal blood flow. They allow automated sampling for continuous absorption monitoring. Despite these advantages, Franz-type static diffusion cells remain more common due to the complexity and cost of flow-through systems.[97,99] In microneedle-mediated Franz cell studies, microneedles are applied before assembling the diffusion cell. Unlike conventional methods, dermatome the skin may be unnecessary, as it alters skin tension and elasticity, leading to over-penetration. To preserve biomechanical

properties, some researchers conduct permeation studies using full-thickness skin.[100,101]

2.3.2.3.*In vivo* models

The skin has metabolic activity; *in vivo* models are essential for assessing microneedle performance beyond permeation. Swine skin closely resembles human skin in thickness, structure, and elasticity, making it the preferred preclinical model for studying transdermal drug delivery.[102,103]

Rodent models, especially rats, are widely used for microneedle studies due to cost efficiency and handling ease. While rat skin resembles human skin, its higher permeability may underestimate delivery efficiency. Factors like skin thickness, tissue rigidity, and lymphatic absorption at different injection sites also impact microneedle performance.[104,105,106]

Meticulous characterization of microneedles is crucial to assess their ability to penetrate the skin and deliver therapeutics safely and effectively. While no standardized evaluation methods currently exist, summarizing existing approaches may guide future protocol development. Standardization will be essential to ensure reproducibility, efficacy, and patient safety in commercialized microneedle systems.

2.3.2.4.Skin Irritation and Recovery Studies

Microneedle insertion may cause mild, transient erythema, with occasional oedema during fluid infusions via hollow microneedles. These effects are dependent on the condition such as microneedle size, material, and the delivered formulation or therapy.[107]

Microneedle-induced irritation can be assessed using Dermatoscopic observation, stereo microscopy, or visual and touch assessments. *In vivo* studies on guinea pig and swine skin noted whitish rings, blotches, and recovery time.[108] The Draize method quantitatively evaluates erythema and oedema, though its subjective nature may lead to variability between observers.[109] Trans epidermal Water Loss (TEWL) measurement assesses skin barrier integrity before and after microneedle application. Intact skin shows low TEWL (20-30 $g/m^2/h$), while successful microneedle insertion raises TEWL, which decreases as pores reseal. Factors like skin type, experimental setup, needle length, and equilibration time influence the resealing rate, with animal skin healing faster than human skin.[110]

2.4. 3D Printed Microneedles

Microneedle (MN) innovation has considered as an effective approach in transdermal drug

delivery (TDD) due to its minimally invasive nature, reduced systemic toxicity, and improved patient compliance. Over the past two decades, the integration of 3D printing has significantly enhanced MN design, fabrication, and functionality, enabling precise control over microneedle shape, size, and drug loading capabilities.

2.4.1. Advancements in 3D Printing for MN Development

3D printing technologies have revolutionized MN fabrication by offering versatile manufacturing processes with high precision. These methods allow the production of MN arrays with customized geometries, controlled drug release profiles, and improved mechanical strength to ensure effective skin penetration.

2.4.2. Key Challenges and Solutions

Despite advancements, 3D printed MNs face several challenges

Material Limitations: Developing biocompatible materials with appropriate mechanical strength, flexibility, and stability is crucial. Innovations in polymer blends and composite materials have improved MN durability and performance.

Drug Stability: Certain drugs may degrade under high temperatures or UV radiation during the 3D printing process. Optimizing printing conditions and exploring alternative curing methods are essential.

Controlled Drug Release: Achieving sustained or adjustable drug release remains a challenge. Layered MN designs and advanced material combinations are being explored to enhance drug release profiles.

2.4.3. Clinical and Commercial Potential

3D printed MNs have demonstrated promising outcomes in preclinical and clinical studies, particularly for vaccines, insulin, and pain management therapies. Products like Derma roller and Derma pen have paved the way, but further efforts are needed to commercialize biodegradable MNs. Regulatory considerations, enhanced patient safety trials, and scalable manufacturing processes are key to accelerating market adoption.3D printed MNs have revolutionized TDD by enabling precise, customizable designs with improved efficacy and patient compliance. Ongoing advancements in materials, fabrication techniques, and clinical research are expected to address current challenges and unlock their full potential in healthcare applications.[111]

3. Applications

3.1. Drug delivery

The first use of microneedles (MN) for drug delivery was demonstrated in 1998 with the application of solid silicon microneedles.[33] A dissolvable microneedle (MN) patch was utilized for percutaneous administration of somatotropin targeted to the exposed skin surface of nude rats, enabling targeted and efficient drug administration.[112] A dissolvable microneedle patch loaded with caffeine successfully managed the weight of obese mice, serving as an effective anti-obesity treatment. Additionally, a coated microneedle patch was utilized to deliver salmon calcitonin.[113]

A solid microneedle was used to administer the protein antigen ovalbumin into the skin of hairless guinea pigs. Solid silicon and metal microneedles were also applied for delivering calcein, BSA, and insulin.[27] Additionally, microneedles have been utilized for the transdermal delivery of various drugs, including ibuprofen, ketoprofen, and paracetamol. Other medications administered through microneedles include L-ascorbic acid, riboflavin, aspirin, docetaxel, pilocarpine, lidocaine hydrochloride, ketoprofen, and glycerol.[114] Although most studies have focused on using microneedle arrays for drug delivery into the skin of mice, pigs, and humans, there have been other studies that successfully demonstrated microneedle injection into chicken thigh tissue and brain tissue.

3.2 Vaccine delivery

Dissolvable microneedles are commonly employed for vaccine delivery, offering an alternative to traditional hypodermic needles. These microneedles are biocompatible, durable, scalable, and environmentally friendly, as they do not generate biohazardous waste. Due to these advantages, dissolvable microneedles have been successfully used to administer vaccines for a range of diseases, including malaria, diphtheria, influenza, Hepatitis B, HIV, and polio.[115] Although dissolvable microneedles are predominantly used for vaccine delivery, coated microneedle arrays have also been effectively utilized for vaccination. One study highlighted a simple, safe, and compliant approach to enhance immune responses in pigs by administering the Bacillus Calmette–Guérin (BCG) vaccine via a coated microneedle. Additionally, another study successfully delivered a DNA vaccine encoding the hepatitis C virus protein using a coated microneedle.[116] The microneedle was successfully used to prime specific cytotoxic T lymphocytes (CTLs) in mice. Additionally, a coated microneedle was employed to deliver influenza virus antigens for vaccination purposes in mice.[117] Hollow

microneedles have been used to administer the anthrax recombinant protective antigen vaccine to rabbits as an alternative to traditional injections. Additionally, a hollow microneedle was tested for vaccination against plague in a mouse model. A clinical trial in humans using hollow microneedles for influenza vaccination demonstrated immune system responses comparable to those seen with intramuscular injections.[118,119]

3.3 Disease Diagnosis

Disease diagnosis and the assessment of therapeutic efficacy are traditionally carried out through bioassays that analysed body fluids to monitor health conditions. These methods, however, often involve pain, complex procedures, specialized equipment, and require trained medical professionals. In comparison, micro needle technology offers a more accessible solution for bioassays, providing a painless experience and enabling straightforward implementation.[120]

Chiappini *et al.*, used a 5 µm tall porous silicon nanoneedle to detect local cytosolic enzymatic activity, aiming for early cancer diagnosis. The study focused on cathepsin B (CTSB), a cysteine protease commonly found in solid tumors, as a biomarker. The nanoneedle biosensor effectively mapped CTSB activity both in cell culture and over large areas of biopsy tissue, offering a promising tool for early cancer detection.[121]

3.4 Cosmetic Application

Microneedles (MNs) are extensively used in cosmetic applications, including skin treatments and promoting hair growth. For example, Kim et al. created a dissolvable MN patch made of hyaluronic acid for the intradermal delivery of ascorbic acid and retinyl retinoate.[122]

3.5 Dermatological Disorders

Microneedles (MNs) have emerged as innovative strategies for managing dermatological conditions, as evidenced by the healing response following needle insertion. The use of blank MNs promotes wound healing without altering skin morphology. These therapeutic techniques highlight the unique role of MNs in dermatological interventions. MNs have shown promise in treating atrophic scars, actinic keratoses, alopecia, and pigmentation disorders like melasma. Offering a cost-effective and minimally invasive treatment option, MNs are gaining recognition for their ability to stimulate stem cells in the dermal papilla, enhance blood flow near hair follicles, promote growth factors, and trigger signaling pathways for hair restoration, making them a key tool in addressing baldness.[123,124,125]

3.6 Oligonucleotide delivery

This delivery face challenges in reaching their intracellular targets. To address this, various methods have been developed to enhance their delivery. One such method involved using microneedles to deliver a 20-merphosphorothioated oligodeoxynucleotide. The microneedles, made of materials like stainless steel or titanium, were employed in a "poke with patch" technique. This approach resulted in a greater amount of the drug reaching the target site compared to when applied to intact skin. Additionally, combining iontophoresis with the microneedle technique yielded better outcomes than iontophoresis alone.[126,127]

4. PATENTS

The following patent numbers are obtained through European Patent Office

TOPICS	TYPES OF MICRONEEDLES USED	PATENT NO
Viscous microneedle patch for tracheal fistula plugging and preparation method thereof	Viscous (adhesive) microneedle with expandable mechanical fixation properties	CN119185171A
Microneedle loaded with polyvinylpyrrolidone modified iridium nanoparticles and basic fibroblast growth factors and application	Dissolvable microneedle	CN119015209A
Preparation and application of soluble oligo deoxyribonucleotide microneedle for whitening and removing freckles	Soluble slow-release microneedle	CN118948650A
pH-Responsive Super-Long Dual-Network Hydrogel Composite Microneedle and Preparation Method Thereof	pH responsive super-long dual-network hydrogel microneedle	CN119185168A
Closed-Loop Insulin controlled Release System Based on Microneedle Array Patch	Electrically controlled insulin-releasing microneedle	CN119075164A
CFS Nano-Enzyme and Application Thereof in Preparation Of CFS-Ion-MN Wound Repair Microneedle Patch	CFS-ion-loaded dissolving microneedle	CN119240801A
Microneedle and treatment method thereof	Sensor-integrated energy-stimulating microneedle	CN119139128A
Microneedle patch	Moisture-balanced dissolving microneedle	WO2016157985A1
Aptamer-coated microneedle-based diagnostic skin patch	Aptamer-coated diagnostic microneedle	WO2017007271A1
Microneedle patch system for transdermal drug delivery	High drug-loading microneedle	US2025018162A1
Microneedle module and bio patch comprising same	Hollow microneedles	WO2024225529A1
Microneedle patch case	Microchannel microneedle	US11484695B2
Microstructure for non-patch type	Non-patch-type microneedles	

microneedle device and non-patch type microneedle device		WO2020204274A1
Preparation method and application of lappaconitine analgesic hydrogel microneedle	Hydrogel microneedle.	CN119139211A

LIST OF ABBREVIATIONS		
S.NO	**ACRONYMN**	**ABBREVIATIONS**
1	MAPs	Microarray patches
2	MN	Microneedles
3	GPa	Gigapascal.
4	Al_2O_3	Alumina
5	$CaSO_4 \cdot 0.2H_2O$	Calcium sulphate dihydrate
6	PMMA	Poly (methyl methacrylate)
7	PLA	Poly (lactic acid)
8	PLGA	Poly (lactic-co-glycolic acid)
9	PGA	Poly (glycolic acid)
10	SU-8 photoresist	An epoxy-based negative photoresist
11	SMN	Solid Microneedle
12	TMAH	Tetramethylammonium Hydroxide
13	PVA	Polyvinyl Alcohol
14	EMLA	Eutectic Mixture of Local Anesthetics
15	3D printing	Three-dimensional printing
16	PMVE/MA	Poly (Methyl Vinyl Ether-Co-Maleic Acid)
17	PEG	Polyethylene Glycol
18	MEMS	Micro-Electromechanical Systems
19	SEM	Scanning Electron Microscopy
20	OCT	Optical Coherence Tomography
21	HPLC.	High-Performance Liquid Chromatography.
22	TEWL	Trans Epidermal Water Loss
23	TEER	Trans Endothelial Electrical Resistance.
24	TDD	Transdermal Drug Delivery
25	SLA	Stereolithography
26	FDM	Fused Deposition Modelling
27	DLP	Digital Light Processing
28	FDA	Food And Drug Administration
29	CMC	Carboxymethyl Cellulose
30	API	Active Pharmaceutical Ingredient

REFERENCES

1. Choe C, Lademann J, Darvin ME. A depth-dependent profile of the lipid conformation and lateral packing order of the stratum corneum in vivo measured using Raman microscopy. Analyst, 2016; 141(6): 1981-7.
2. Prausnitz MR, Langer R. Transdermal drug delivery. Nature biotechnology, 2008 Nov; 26(11): 1261-8.
3. Proksch E, Brandner JM, Jensen JM. The skin: an indispensable barrier. Experimental

dermatology, 2008; 17(12): 1063-72.

4. Bos JD, Meinardi MM. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. Experimental Dermatology: Viewpoint. 2000; 9(3): 165-9.
5. Limcharoen B, Wanichwecharungruang S, Banlunara W, Darvin ME. Seeing through the skin: Optical methods for visualizing transdermal drug delivery with microneedles. Advanced Drug Delivery Reviews. 2024; 115478.
6. Paudel KS, Milewski M, Swadley CL, Brogden NK, Ghosh P, Stinchcomb AL. Challenges and opportunities in dermal/transdermal delivery. Therapeutic delivery, 2010; 1(1): 109-31.
7. Bird D, Ravindra NM. Transdermal drug delivery and patches—An overview. Medical Devices & Sensors, 2020; 3(6): e10069.
8. Ita K. Transdermal delivery of drugs with microneedles potential and challenges. Pharmaceutics, 2015; 7(3): 90-105.
9. Blicharz TM, Gong P, Bunner BM, Chu LL, Leonard KM, Wakefield JA, Williams RE, Dadgar M, Tagliabue CA, El Khaja R, Marlin SL. Microneedle-based device for the one-step painless collection of capillary blood samples. Nature biomedical engineering, 2018; 2(3): 151-7.
10. Aldawood FK, Andar A, Desai S. A comprehensive review of microneedles: Types, materials, processes, characterizations and applications. Polymers. 2021; 13(16): 2815.
11. Gerstel MS, Place VA. Drug delivery device. US patent, 1976; 22: 3(964,482).
12. Halder J, Gupta S, Kumari R, Gupta GD, Rai VK. Microneedle array: applications, recent advances, and clinical pertinence in transdermal drug delivery. Journal of Pharmaceutical Innovation, 2021; 16: 558-65.
13. Ingrole RS, Azizoglu E, Dul M, Birchall JC, Gill HS, Prausnitz MR. Trends of microneedle technology in the scientific literature, patents, clinical trials and internet activity. Biomaterials, 2021; 267: 120491.
14. Iriarte C, Awosika O, Rengifo-Pardo M, Ehrlich A. Review of applications of microneedling in dermatology. Clinical, cosmetic and investigational dermatology, 2017; 289-98.
15. Ai X, Yang J, Liu Z, Guo T, Feng N. Recent progress of microneedles in transdermal immunotherapy: a review. International Journal of Pharmaceutics, 2024; 662: 124481.

16. Barry B, Williams A. Penetration enhancers. Adv Drug Deliv Rev. 2003; 56: 603-18.
17. Akhtar N. Microneedles: An innovative approach to transdermal delivery A review. Int. J. Pharm. Pharm. Sci, 2014; 6(4): 18-25.
18. Sharma D. Microneedles: an approach in transdermal drug delivery: a Review. PharmaTutor, 2018; 6(1): 7- 15.
19. Hong X, Wei L, Wu F, Wu Z, Chen L, Liu Z, Yuan W. Dissolving and biodegradable microneedle technologies for transdermal sustained delivery of drug and vaccine. Drug design, development and therapy, 2013; 945-52.
20. Larraneta E, Lutton RE, Woolfson AD, Donnelly RF. Microneedle arrays as transdermal and intradermal drug delivery systems: Materials science, manufacture and commercial development. Materials Science and Engineering: R: Reports, 2016; 104: 1-32.
21. Donnelly RF, Singh TR, Woolfson AD. Microneedle-based drug delivery systems: microfabrication, drug delivery, and safety. Drug delivery, 2010; 17(4): 187-207.
22. Verbaan FJ, Bal SM, Van den Berg DJ, Groenink WH, Verpoorten H, Lüttge R, Bouwstra JA. Assembled microneedle arrays enhance the transport of compounds varying over a large range of molecular weight across human dermatomed skin. Journal of controlled release, 2007; 117(2): 238-45.
23. Gorgieva S, Kokol V. Collagen-vs. gelatine-based biomaterials and their biocompatibility: review and perspectives. Biomaterials applications for nanomedicine, 2011; 2(2011): 17-52.
24. Williams AC, Barry BW. Penetration enhancers. Advanced drug delivery reviews, 2012; 64: 128-37.
25. Gittard SD, Narayan RJ, Jin C, Ovsianikov A, Chichkov BN, Monteiro-Riviere NA, Stafslien S, Chisholm B. Pulsed laser deposition of antimicrobial silver coating on Ormocer® microneedles. Bio fabrication, 2009; 1(4): 041001.
26. Gupta J, Felner EI, Prausnitz MR. Minimally invasive insulin delivery in subjects with type 1 diabetes using hollow microneedles. Diabetes technology & therapeutics, 2009; 11(6): 329-37.
27. McAllister DV, Wang PM, Davis SP, Park JH, Canatella PJ, Allen MG, Prausnitz MR. Microfabricated needles for transdermal delivery of macromolecules and nanoparticles: fabrication methods and transport studies. Proceedings of the National Academy of Sciences, 2003; 100(24): 13755-60.
28. Lee K, Lee CY, Jung H. Dissolving microneedles for transdermal drug administration prepared by stepwise controlled drawing of maltose. Biomaterials. 2011; 32(11): 3134-40.

29. Martin CJ, Allender CJ, Brain KR, Morrissey A, Birchall JC. Low temperature fabrication of biodegradable sugar glass microneedles for transdermal drug delivery applications. Journal of controlled Release, 2012; 158(1): 93-101.
30. Waghule T, Singhvi G, Dubey SK, Pandey MM, Gupta G, Singh M, Dua K. Microneedles: A smart approach and increasing potential for transdermal drug delivery system. Biomedicine & pharmacotherapy, 2019; 109: 1249-58.
31. Sabri AH, Kim Y, Marlow M, Scurr DJ, Segal J, Banga AK, Kagan L, Lee JB. Intradermal and transdermal drug delivery using microneedles–Fabrication, performance evaluation and application to lymphatic delivery. Advanced drug delivery reviews, 2020 Jan 1; 153: 195-215.
32. Hoang MT, Ita KB, Bair DA. Solid microneedles for transdermal delivery of amantadine hydrochloride and pramipexole dihydrochloride. Pharmaceutics. 2015; 7(4): 379-96.
33. Henry S, McAllister DV, Allen MG, Prausnitz MR. Microfabricated microneedles: a novel approach to transdermal drug delivery. Journal of pharmaceutical sciences, 1998; 87(8): 922-5.
34. Pradeep Narayanan S, Raghavan S. Solid silicon microneedles for drug delivery applications. The International Journal of Advanced Manufacturing Technology, 2017; 93: 407-22.
35. Pradeep Narayanan S, Raghavan S. Fabrication and characterization of gold-coated solid silicon microneedles with improved biocompatibility. The International Journal of Advanced Manufacturing Technology, 2019; 104(9): 3327-33.
36. Gujjar M, Banga AK. Iontophoretic and microneedle mediated transdermal delivery of glycopyrrolate. Pharmaceutics, 2014; 6(4): 663-71.
37. 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 Jul 7; 97(3): 503-11.
38. Liu S, Jin MN, Quan YS, Kamiyama F, Katsumi H, Sakane T, Yamamoto A. The development and characteristics of novel microneedle arrays fabricated from hyaluronic acid, and their application in the transdermal delivery of insulin. Journal of controlled release, 2012; 161(3): 933-41.
39. Zhang S, Qiu Y, Gao Y. Enhanced delivery of hydrophilic peptides in vitro by transdermal microneedle pretreatment. Acta Pharmaceutica Sinica B, 2014; 4(1): 100-4.
40. Li QY, Zhang JN, Chen BZ, Wang QL, Guo XD. A solid polymer microneedle patch pretreatment enhances the permeation of drug molecules into the skin. Rsc Advances,

2017; 7(25): 15408-15.

41. Chu LY, Prausnitz MR. Separable arrowhead microneedles. Journal of controlled release, 2011; 149(3): 242-9.
42. Haj-Ahmad R, Khan H, Arshad MS, Rasekh M, Hussain A, Walsh S, Li X, Chang MW, Ahmad Z. Microneedle coating techniques for transdermal drug delivery. Pharmaceutics. 2015; 7(4): 486-502.
43. DeMuth PC, Min Y, Huang B, Kramer JA, Miller AD, Barouch DH, Hammond PT, Irvine DJ. Polymer multilayer tattooing for enhanced DNA vaccination. Nature materials, 2013; 12(4): 367-76.
44. Zhang Y, Brown K, Siebenaler K, Determan A, Dohmeier D, Hansen K. Development of lidocaine-coated microneedle product for rapid, safe, and prolonged local analgesic action. Pharmaceutical research, 2012; 29: 170-7.
45. Gill HS, Prausnitz MR. Coated microneedles for transdermal delivery. Journal of controlled release, 2007; 117(2): 227-37.
46. Ma Y, Gill HS. Coating solid dispersions on microneedles via a molten dip-coating method: development and in vitro evaluation for transdermal delivery of a water-insoluble drug. Journal of pharmaceutical sciences, 2014; 103(11): 3621-30.
47. Du G, Woythe L, van der Maaden K, Leone M, Romeijn S, Kros A, Kersten G, Jiskoot W, Bouwstra JA. Coated and hollow microneedle-mediated intradermal immunization in mice with diphtheria toxoid loaded mesoporous silica nanoparticles. Pharmaceutical research, 2018; 35: 1-2.
48. Tuan-Mahmood TM, McCrudden MT, Torrisi BM, McAlister E, Garland MJ, Singh TR, Donnelly RF. Microneedles for intradermal and transdermal drug delivery. European Journal of Pharmaceutical Sciences, 2013; 50(5): 623-37.
49. Miyano T, Tobinaga Y, Kanno T, Matsuzaki Y, Takeda H, Wakui M, Hanada K. Sugar micro needles as transdermic drug delivery system. Biomedical Microdevices, 2005; 7: 185-8.
50. Leone M, Monkare J, Bouwstra JA, Kersten G. Dissolving microneedle patches for dermal vaccination. Pharmaceutical research, 2017; 34: 2223-40.
51. Qiu Y, Li C, Zhang S, Yang G, He M, Gao Y. Systemic delivery of artemether by dissolving microneedles. International Journal of Pharmaceutics, 2016; 508(1-2): 1-9.
52. Ita K. Dissolving microneedles for transdermal drug delivery: Advances and challenges. Biomedicine & Pharmacotherapy, 2017; 93: 1116-27.
53. Yang HW, Ye L, Guo XD, Yang C, Compans RW, Prausnitz MR. Ebola vaccination using

a DNA vaccine coated on PLGA-PLL/γPGA nanoparticles administered using a microneedle patch. Advanced healthcare materials, 2017; 6(1): 1600750.

54. Donnelly RF, Morrow DI, Singh TR, Migalska K, McCarron PA, O'Mahony C, Woolfson AD. Processing difficulties and instability of carbohydrate microneedle arrays. Drug development and industrial pharmacy, 2009; 35(10): 1242-54.
55. Nguyen HX, Bozorg BD, Kim Y, Wieber A, Birk G, Lubda D, Banga AK. Poly (vinyl alcohol) microneedles: Fabrication, characterization, and application for transdermal drug delivery of doxorubicin. European journal of pharmaceutics and biopharmaceutics, 2018; 129: 88-103.
56. Al-Qallaf B, Das DB. Optimizing microneedle arrays to increase skin permeability for transdermal drug delivery. Annals of the New York Academy of Sciences, 2009; 1161(1): 83-94.
57. Paredes AJ, McKenna PE, Ramoller IK, Naser YA, Volpe-Zanutto F, Li M, Abbate MT, Zhao L, Zhang C, Abu-Ershaid JM, Dai X. Microarray patches: poking a hole in the challenges faced when delivering poorly soluble drugs. Advanced Functional Materials, 2021; 31(1): 2005792.
58. Gade S, Glover K, Mishra D, Sharma S, Guy O, Donnelly RF, Vora LK, Thakur RR. Hollow microneedles for ocular drug delivery. Journal of Controlled Release, 2024; 371: 43-66.
59. Sheng T, Luo B, Zhang W, Ge X, Yu J, Zhang Y, Gu Z. Microneedle-mediated vaccination: innovation and translation. Advanced Drug Delivery Reviews, 2021; 179: 113919.
60. Li R, Zhang L, Jiang X, Li L, Wu S, Yuan X, Cheng H, Jiang X, Gou M. 3D-printed microneedle arrays for drug delivery. Journal of Controlled Release, 2022; 350: 933-48.
61. Luo X, Yang L, Cui Y. Microneedles: materials, fabrication, and biomedical applications. Biomedical Microdevices, 2023; 25(3): 20.
62. Van Der Maaden K, Jiskoot W, Bouwstra J. Microneedle technologies for (trans) dermal drug and vaccine delivery. Journal of controlled release, 2012; 161(2): 645-55.
63. Tehrani F, Teymourian H, Wuerstle B, Kavner J, Patel R, Furmidge A, Aghavali R, Hosseini-Toudeshki H, Brown C, Zhang F, Mahato K. An integrated wearable microneedle array for the continuous monitoring of multiple biomarkers in interstitial fluid. Nature Biomedical Engineering, 2022; 6(11): 1214-24.
64. Abbasiasl T, Mirlou F, Mirzajani H, Bathaei MJ, Istif E, Shomalizadeh N, Cebecioglu

RE, Ozkahraman EE, Yener UC, Beker L. A wearable touch-activated device integrated with hollow microneedles for continuous sampling and sensing of dermal interstitial fluid. Advanced Materials, 2024; 36(2): 2304704.

65. Bae WG, Ko H, So JY, Yi H, Lee CH, Lee DH, Ahn Y, Lee SH, Lee K, Jun J, Kim HH. Snake fang– inspired stamping patch for transdermal delivery of liquid formulations. Science translational medicine, 2019; 11(503): eaaw3329.
66. Cárcamo-Martínez Á, Mallon B, Domínguez-Robles J, Vora LK, Anjani QK, Donnelly RF. Hollow microneedles: A perspective in biomedical applications. International journal of pharmaceutics, 2021; 599: 120455.
67. Vinayakumar KB, Kulkarni PG, Nayak MM, Dinesh NS, Hegde GM, Ramachandra SG, Rajanna K. A hollow stainless steel microneedle array to deliver insulin to a diabetic rat. Journal of Micromechanics and Microengineering, 2016; 26(6): 065013.
68. Demir YK, Akan Z, Kerimoglu O. Characterization of polymeric microneedle arrays for transdermal drug delivery, PloS one. 2013; 8(10): e77289.
69. Donnelly RF, Singh TR, Alkilani AZ, McCrudden MT, O'Neill S, O'Mahony C, Armstrong K, McLoone N, Kole P, Woolfson AD. Hydrogel-forming microneedle arrays exhibit antimicrobial properties: Potential for enhanced patient safety. International journal of pharmaceutics, 2013; 451(1-2): 76-91.
70. Donnelly RF, McCrudden MT, Zaid Alkilani A, Larrañeta E, McAlister E, Courtenay AJ, Kearney MC, Singh TR, McCarthy HO, Kett VL, Caffarel-Salvador E. Hydrogel-forming microneedles prepared from "super swelling" polymers combined with lyophilised wafers for transdermal drug delivery. PloS one, 2014; 9(10): e111547.
71. Courtenay AJ, Rodgers AM, McCrudden MT, McCarthy HO, Donnelly RF. Novel hydrogel-forming microneedle array for intradermal vaccination in mice using ovalbumin as a model protein antigen. Molecular pharmaceutics, 2018; 16(1): 118-27.
72. Ita K. Transdermal delivery of drugs with microneedles potential and challenges. Pharmaceutics, 2015 Jun 29; 7(3): 90-105.
73. Al-Kasasbeh R, Brady AJ, Courtenay AJ, Larrañeta E, McCrudden MT, O'Kane D, Liggett S, Donnelly RF. Evaluation of the clinical impact of repeat application of hydrogel-forming microneedle array patches. Drug delivery and translational research, 2020; 10: 690-705.
74. Gholami S, Mohebi MM, Hajizadeh-Saffar E, Ghanian MH, Zarkesh I, Baharvand H. Fabrication of microporous inorganic microneedles by centrifugal casting method for transdermal extraction and delivery. International journal of pharmaceutics, 2019; 558:

299-310.

75. De Groot AM, Platteel AC, Kuijt N, Van Kooten PJ, Vos PJ, Sijts AJ, Van der Maaden K. Nanoporous microneedle arrays effectively induce antibody responses against diphtheria and tetanus toxoid. Frontiers in Immunology, 2017; 8: 1789.
76. He YT, Liang L, Zhao ZQ, Hu LF, Fei WM, Chen BZ, Cui Y, Guo XD. Advances in porous microneedle systems for drug delivery and biomarker detection: A mini review. Journal of Drug Delivery Science and Technology, 2022 Aug 1; 74: 103518.
77. Bao L, Park J, Bonfante G, Kim B. Recent advances in porous microneedles: materials, fabrication, and transdermal applications. Drug delivery and translational research, 2022; 12(2): 395-414.
78. Cahill EM, Keaveney S, Stuettgen V, Eberts P, Ramos-Luna P, Zhang N, Dangol M, O'Cearbhaill ED. Metallic microneedles with interconnected porosity: A scalable platform for biosensing and drug delivery. Acta Biomaterialia, 2018; 80: 401-11.
79. Korkmaz E, Balmert SC, Sumpter TL, Carey CD, Erdos G, Falo Jr LD. Microarray patches enable the development of skin-targeted vaccines against COVID-19. Advanced Drug Delivery Reviews, 2021; 171: 164-86.
80. Bao L, Park J, Bonfante G, Kim B. Recent advances in porous microneedles: materials, fabrication, and transdermal applications. Drug delivery and translational research, 2022; 12(2): 395-414.
81. Ziesmer J, Larsson JV, Sotiriou GA. Hybrid microneedle arrays for antibiotic and near-IR photothermal synergistic antimicrobial effect against Methicillin-Resistant Staphylococcus aureus. Chemical Engineering Journal, 2023; 462: 142127.
82. Chen MC, Huang SF, Lai KY, Ling MH. Fully embeddable chitosan microneedles as a sustained release depot for intradermal vaccination. Biomaterials, 2013; 34(12): 3077-86.
83. Kolli CS, Banga AK. Characterization of solid maltose microneedles and their use for transdermal delivery. Pharmaceutical research, 2008; 25: 104-13.
84. Aoyagi S, Izumi H, Fukuda M. Biodegradable polymer needle with various tip angles and consideration on insertion mechanism of mosquito's proboscis. Sensors and Actuators A: Physical, 2008; 143(1): 20-8.
85. Nguyen HX, Banga AK. Enhanced skin delivery of vismodegib by microneedle treatment. Drug delivery and translational research, 2015; 5: 407-23.
86. Lee J, Park SH, Seo IH, Lee KJ, Ryu W. Rapid and repeatable fabrication of high A/R silk fibroin microneedles using thermally-drawn micromolds. European Journal of Pharmaceutics and Biopharmaceutics, 2015; 94: 11-9.

87. Larraneta E, Lutton RE, Brady AJ, Vicente-Pérez EM, Woolfson AD, Thakur RR, Donnelly RF. Microwave-assisted preparation of hydrogel-forming microneedle arrays for transdermal drug delivery applications. Macromolecular materials and engineering, 2015; 300(6): 586-95.
88. Yu W, Jiang G, Zhang Y, Liu D, Xu B, Zhou J. Polymer microneedles fabricated from alginate and hyaluronate for transdermal delivery of insulin. Materials Science and Engineering: C., 2017 Nov 1; 80: 187- 96.
89. Röomgens AM, Bader DL, Bouwstra JA, Baaijens FP, Oomens CW. Monitoring the penetration process of single microneedles with varying tip diameters. journal of the mechanical behavior of biomedical materials, 2014; 40: 397-405.
90. Kochhar JS, Soon WJ, Choi J, Zou S, Kang L. Effect of microneedle geometry and supporting substrate on microneedle array penetration into skin. Journal of pharmaceutical sciences, 2013; 102(11): 4100-8.
91. Jeong HR, Kim JY, Kim SN, Park JH. Local dermal delivery of cyclosporin A, a hydrophobic and high molecular weight drug, using dissolving microneedles. European Journal of Pharmaceutics and Biopharmaceutics, 2018; 127: 237-43.
92. Verbaan FJ, Bal SM, Van den Berg DJ, Dijksman JA, Van Hecke M, Verpoorten H, Van Den Berg A, Luttge R, Bouwstra JA. Improved piercing of microneedle arrays in dermatomed human skin by an impact insertion method. Journal of controlled release, 2008; 128(1): 80-8.
93. Ling MH, Chen MC. Dissolving polymer microneedle patches for rapid and efficient transdermal delivery of insulin to diabetic rats. Acta biomaterialia, 2013; 9(11): 8952-61.
94. Sturm B, Creytens D, Cook MG, Smits J, van Dijk MC, Eijken E, Kurpershoek E, Kusters-Vandevelde HV, Ooms AH, Wauters C, Blokx WA. Validation of whole-slide digitally imaged melanocytic lesions: Does z-stack scanning improve diagnostic accuracy? Journal of Pathology Informatics, 2019; 10(1): 6.
95. Loizidou EZ, Inoue NT, Ashton-Barnett J, Barrow DA, Allender CJ. Evaluation of geometrical effects of microneedles on skin penetration by CT scan and finite element analysis. European Journal of Pharmaceutics and Biopharmaceutics, 2016; 107: 1-6.
96. Moss GP, Gullick DR, Wilkinson SC. Predictive methods in percutaneous absorption. Springer Berlin Heidelberg, 201.
97. Franz TJ. Percutaneous absorption. On the relevance of in vitro data. Journal of Investigative Dermatology, 1975; 64(3): 190-5.
98. Benson HA, Watkinson AC, editors. Topical and transdermal drug delivery: principles

and practice. John Wiley & Sons, 2012.

99. Bronaugh RL, Stewart RF. Methods for in vitro percutaneous absorption studies IV: The flow-through diffusion cell. Journal of pharmaceutical sciences, 1985; 74(1): 64-7.
100. Ng KW, Pearton M, Coulman S, Anstey A, Gateley C, Morrissey A, Allender C, Birchall J. Development of an ex vivo human skin model for intradermal vaccination: tissue viability and Langerhans cell behaviour. Vaccine, 2009; 27(43): 5948-55.
101. Vora LK, Donnelly RF, Larrañeta E, González-Vázquez P, Thakur RR, Vavia PR. Novel bilayer dissolving microneedle arrays with concentrated PLGA nano-microparticles for targeted intradermal delivery: Proof of concept. Journal of Controlled Release, 2017; 265: 93-101.
102. Van De Sandt JJ, Meuling WJ, Elliott GR, Cnubben NH, Hakkert BC. Comparative in vitro–in vivo percutaneous absorption of the pesticide propoxur. Toxicological sciences, 2000; 58(1): 15-22.
103. Eilstein J, Lereaux G, Budimir N, Hussler G, Wilkinson S, Duche D. Comparison of xenobiotic metabolizing enzyme activities in ex vivo human skin and reconstructed human skin models from SkinEthic. Archives of Toxicology, 2014; 88(9): 1681-94.
104. Oesch F, Fabian E, Oesch-Bartlomowicz B, Werner C, Landsiedel R. Drug-metabolizing enzymes in the skin of man, rat, and pig. Drug metabolism reviews, 2007; 39(4): 659-98.
105. Kagan L, Gershkovich P, Mendelman A, Amsili S, Ezov N, Hoffman A. The role of the lymphatic system in subcutaneous absorption of macromolecules in the rat model. European Journal of Pharmaceutics and Biopharmaceutics, 2007; 67(3): 759-65.
106. Lotte C, Rougier A, Wilson DR, Maibach HI. In vivo relationship between transepidermal water loss and percutaneous penetration of some organic compounds in man: effect of anatomic site. Archives of dermatological research. 1987; 279: 351-6.
107. Zhu DD, Wang QL, Liu XB, Guo XD. Rapidly separating microneedles for transdermal drug delivery. Acta biomaterialia, 2016; 41: 312-9.
108. Burton SA, Ng CY, Simmers R, Moeckly C, Brandwein D, Gilbert T, Johnson N, Brown K, Alston T, Prochnow G, Siebenaler K. Rapid intradermal delivery of liquid formulations using a hollow microstructured array. Pharmaceutical research, 2011; 28: 31-40.
109. Kusamori K, Katsumi H, Abe M, Ueda A, Sakai R, Hayashi R, Hirai Y, Quan YS, Kamiyama F, Sakane T, Yamamoto A. Development of a novel transdermal patch of alendronate, a nitrogen-containing bisphosphonate, for the treatment of osteoporosis. Journal of Bone and Mineral Research, 2010; 25(12): 2582-91.

110. Gomaa YA, El-Khordagui LK, Garland MJ, Donnelly RF, McInnes F, Meidan VM. Effect of microneedle treatment on the skin permeation of a nanoencapsulated dye. Journal of Pharmacy and Pharmacology, 2012; 64(11): 1592-602.
111. Elahpour N, Pahlevanzadeh F, Kharaziha M, Bakhsheshi-Rad HR, Ramakrishna S, Berto F. 3D printed microneedles for transdermal drug delivery: A brief review of two decades. International Journal of Pharmaceutics, 2021; 597: 120301.
112. Lee JW, Choi SO, Felner EI, Prausnitz MR. Dissolving microneedle patch for transdermal delivery of human growth hormone. Small, 2011; 7(4): 531-9.
113. Tas C, Mansoor S, Kalluri H, Zarnitsyn VG, Choi SO, Banga AK, Prausnitz MR. Delivery of salmon calcitonin using a microneedle patch. International journal of pharmaceutics, 2012; 423(2): 257-63.
114. Smita N, Sanidhya S, Bhaskar V. Microneedle technology for transdermal drug delivery: applications and combination with other enhancing techniques. Journal of Drug Delivery & Therapeutics, 2016; 6(5): 65-83.
115. Marshall S, Sahm LJ, Moore AC. The success of microneedle-mediated vaccine delivery into skin. Human vaccines&immunotherapeutics, 2016; 12(11): 2975-83.
116. Hiraishi Y, Nandakumar S, Choi SO, Lee JW, Kim YC, Posey JE, Sable SB, Prausnitz MR. Bacillus Calmette-Guerin vaccination using a microneedle patch. Vaccine, 2011; 29(14): 2626-36.
117. Zhu Q, Zarnitsyn VG, Ye L, Wen Z, Gao Y, Pan L, Skountzou I, Gill HS, Prausnitz MR, Yang C, Compans RW. Immunization by vaccine-coated microneedle arrays protects against lethal influenza virus challenge. Proceedings of the National Academy of Sciences, 2009; 106(19): 7968-73.
118. Mikszta JA, Dekker III JP, Harvey NG, Dean CH, Brittingham JM, Huang J, Sullivan VJ, Dyas B, Roy CJ, Ulrich RG. Microneedle-based intradermal delivery of the anthrax recombinant protective antigen vaccine. Infection and immunity, 2006; 74(12): 6806-10.
119. Van Damme P, Oosterhuis-Kafeja F, Van der Wielen M, Almagor Y, Sharon O, Levin Y. Safety and efficacy of a novel microneedle device for dose sparing intradermal influenza vaccination in healthy adults. Vaccine, 2009; 27(3): 454-9.
120. Zhu J, Zhou X, Libanori A, Sun W. Micro needle-based bioassays. Nanoscale Advances, 2020; 2(10): 4295- 304.
121. Chiappini C, Campagnolo P, Almeida CS, Abbassi-Ghadi N, Chow LW, Hanna GB, Stevens MM. Mapping local cytosolic enzymatic activity in human esophageal mucosa with porous silicon nanoneedles. Advanced Materials (Deerfield Beach, Fla.), 2015;

27(35): 5147.

122. Park YH, Ha SK, Choi I, Kim KS, Park J, Choi N, Kim B, Sung JH. Fabrication of degradable carboxymethyl cellulose (CMC) microneedle with laser writing and replica molding process for enhancement of transdermal drug delivery. Biotechnology and bioprocess engineering, 2016: 110-8.
123. Alster TS, Graham PM. Microneedling: a review and practical guide. Dermatologic Surgery, 2018; 44(3): 397-404.
124. Choi SY, Kwon HJ, Ahn GR, Ko EJ, Yoo KH, Kim BJ, Lee C, Kim D. Hyaluronic acid microneedle patch for the improvement of crow's feet wrinkles. Dermatologic Therapy, 2017; 30(6): e12546.
125. Hong JY, Ko EJ, Choi SY, Li K, Kim AR, Park JO, Kim BJ. Efficacy and safety of a novel, soluble microneedle patch for the improvement of facial wrinkle. Journal of cosmetic dermatology, 2018; (2): 235- 41.
126. Bora P, Kumar L, Bansal AK. Microneedle technology for advanced drug delivery: Evolving vistas. Curr Res Inf Pharm Sci., 2008; 9(1): 7-10.
127. Lin W, Cormier M, Samiee A, Griffin A. Transdermal delivery of antisense oligonucleotides with microprojection patch (Macroflux (R)) technology. Pharmaceutical research, 2001; 18(12): 1789.