IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

REVIEW ARTICLE ON ADVANCEMENTS IN MICRONEEDLE TECHNOLOGY

Wankhede Tanuja[1], Deore Neha[2], Gosavi Siddhi[3],

Assistant professor[1], UG student[2], UG student[3]

DEPARTMENT OF PHARMACEUTICAL ASSURANCE,

MAHATMA GANDHI VIDYAMANDIR’S PHARMACY COLLEGE, PANCHAVATI, NASHIK.

Abstract

Transdermal drug delivery (TDD) presents a promising avenue for drug administration, circumventing the limitations of oral intake and hypodermic injections. However, the stratum corneum, the outermost layer of the skin, poses a formidable barrier to efficient TDD. Microneedles, a technology evolving since the 1970s and refined with modern microfabrication techniques, offer a solution to this challenge. This review delves into the evolution, mechanisms, and applications of microneedle technology in enhancing transdermal drug delivery.

Microneedles, ranging from solid to hollow, coated, and dissolvable, are engineered to penetrate the skin barrier effectively, facilitating drug delivery into the epidermis or dermis. Their minimally invasive nature, coupled with precise fabrication methods, ensures painless application and minimal tissue damage. Solid microneedles, fabricated from materials like silicon, metals, or polymers, create microchannels in the skin, enabling drug diffusion without the need for a hollow core. Hollow microneedles, on the other hand, offer continuous drug delivery through a bore at the needle's centre. Coated microneedles provide rapid drug delivery into the skin, while dissolvable microneedles gradually release drugs upon insertion, offering controlled dosing and enhanced patient compliance. Advancements in microneedle technology have led to their application in various fields, including drug delivery, vaccination, diagnostics, and cosmetic procedures. Coated and dissolvable microneedles show promise in rapid drug delivery and combination therapy, while solid microneedles are revolutionizing drug administration, diagnostics, and cosmetic treatments. Moreover, ongoing research aims to optimize microneedle fabrication methods, materials, and integration with wearable devices, paving the way for their widespread adoption in medical practice. microneedles represent a transformative approach to transdermal drug delivery, offering a versatile, minimally invasive platform for precise and efficient drug administration. With continued innovation, microneedles hold immense potential to enhance therapeutic outcomes, patient comfort, and healthcare delivery.(31)

Keywords

Microneedles, Transdermal drug delivery, minimally invasive, Fabrication techniques, Solid microneedles, Hollow microneedles, Coated microneedles, Dissolvable microneedle, Drug delivery applications, Biomedical advancements.

Introduction

Oral drug administration is convenient, but it may not be feasible for some drugs due to poor absorption or enzymatic degradation in the gastrointestinal tract or liver. As an alternative, hypodermic needle injections have been in use for over a century, despite causing pain, invasiveness, and generating bio-hazardous waste[1].Notably, in vaccine delivery, hypodermic needles penetrate muscle, where immunological reactions are weaker than in the skin. Transdermal drug delivery (TDD) emerges as a promising option, avoiding hepatic first-pass metabolism and enabling non-invasive, self-administration without pain. However, the outer layer of the skin, the stratum corneum, poses a significant barrier for TDD, limiting its efficiency and the types of drugs that can be transported. Microneedles, introduced in 1976 and further developed with contemporary microfabrication techniques since the 1990s, provide a novel solution to the limitations of conventional TDD, offering a diverse range of successfully fabricated microneedles (MNs).[1-5]

Microneedles, when engineered with precision and optimal physical attributes, can effectively penetrate the skin barrier. It's vital to apply just the right amount of force during insertion to prevent the microneedles from bending or snapping prematurely. The safety margin is determined by comparing the forces needed for insertion and fracture, with a value above 1 indicating safe penetration without damage. To maximize safety, microneedles should have a fine tip for smooth insertion and sturdy walls to withstand the forces involved. In drug delivery applications, these microneedles create tiny channels in the skin, allowing drugs to penetrate into the epidermis or upper dermis. Because of their small size, microneedles are minimally invasive, causing no pain or bleeding during application and sparing the surrounding nerves and blood vessels.[6-9]

The transdermal route of drug delivery stands as an enticing prospect in modern pharmacotherapy, offering a non-invasive means of administering medications with enhanced bioavailability compared to traditional oral routes. By bypassing the gastrointestinal tract and first-pass metabolism, transdermal delivery holds promise for improving therapeutic outcomes and patient compliance. However, this approach is not without its challenges, particularly regarding the physicochemical properties of the drugs suitable for transdermal administration. To effectively traverse the skin barrier, molecules intended for transdermal delivery ideally exhibit a molecular weight below 500 Da and a log P within the range of 2–3. [10-12]

Central to the efficacy of transdermal drug delivery is the stratum corneum, the outermost layer of the skin, which presents a formidable barrier to the penetration of therapeutic agents[13]. Numerous technologies have been developed to disrupt the stratum corneum and enhance skin permeability[14], including iontophoresis[15], sonophoresis[16], and electroporation[17]. While these methods show promise, their widespread applicability is hindered by practical and economic constraints. Consequently, researchers have sought alternative approaches to improve transdermal drug delivery, leading to the exploration of microneedle technology as a novel solution to overcome the limitations of conventional methods.

Microneedle drug delivery represents a cutting-edge advancement in transdermal drug delivery, offering a minimally invasive means of delivering a wide range of therapeutic agents directly into the skin. These micron-sized needles are designed to create microchannels in the skin, allowing for the efficient diffusion of drugs into the dermal layer, which is richly vascularized. Unlike traditional hypodermic needles, microneedles penetrate the skin without causing pain, bleeding, or infection. Moreover, the fabrication of microneedles enables precise control over their dimensions, materials, and geometries, facilitating customization for various drug delivery applications [18].

Research into microneedle technology has demonstrated its versatility in delivering not only small molecules but also macromolecules, cosmeceuticals, and even micro/nano-particles. Recent advancements have seen the application of coated and dissolving microneedles for non-invasive transdermal vaccination, patient monitoring, and diagnostic purposes. Furthermore, the development of microneedle manufacturing processes has progressed to the stage of large-scale production and commercialization, paving the way for their widespread adoption in medical practice [19,20].

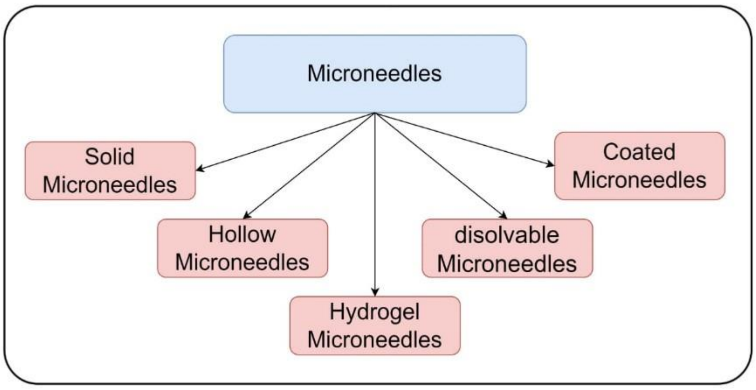
In summary, the limitations of traditional transdermal drug delivery methods have prompted the development of innovative approaches such as microneedle technology. Microneedles offer a promising solution to the challenges posed by the stratum corneum, providing a versatile and minimally invasive platform for drug delivery. With ongoing advancements in fabrication techniques and increasing evidence of their efficacy and safety, microneedles are poised to revolutionize transdermal drug delivery, offering new opportunities for improved therapeutic outcomes and patient care [18-20].

Classification:

Microneedles can be classified based on several criteria, including their fabrication method, material composition. Here's a brief overview:

A. Based on fabrication methods

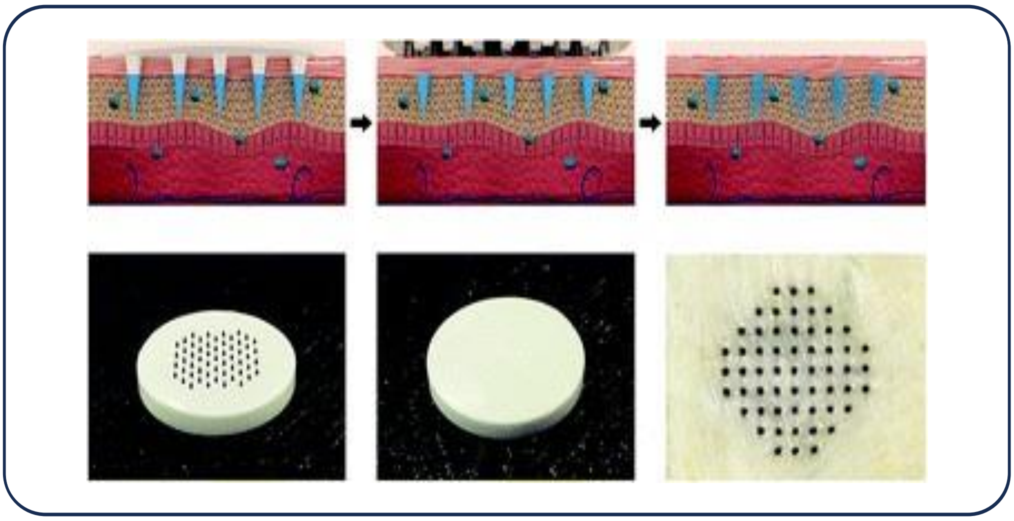
Microneedles are categorized by fabrication methods into solid, hollow, dissolving, coated, and hydrogel-forming types[22] Solid microneedles, fabricated through techniques like micro-moulding, offer robustness. Hollow microneedles, created through processes such as glass drawing, enable fluid delivery. Dissolving microneedles, made by casting dissolvable materials, release drugs upon insertion. Coated microneedles, involving deposition methods like dip coating, apply drug coatings onto needle surfaces. Hydrogel-forming microneedles, produced by methods like photopolymerization, sustain drug release via swellable matrices.



A: Classification of Microneedles based on fabrication method

a. Solid microneedles

Made entirely of a single material, such as silicon [27], metal, or polymer. Used for skin pretreatment before administering active pharmaceutical ingredients (APIs) from an external reservoir [23]. Solid microneedles are marvels of modern engineering, meticulously crafted through sophisticated fabrication techniques like photolithography, etching, or laser ablation [62]. These methods allow for precise control over their size, shape, and composition. They can be made from various materials such as silicon, metals like stainless steel or titanium, and biocompatible polymers like PLA or PGA, each chosen for its specific properties [24,25].

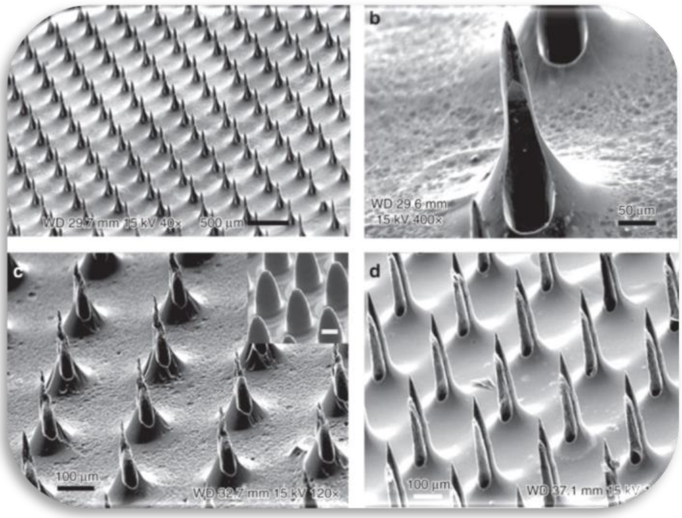


A.a: Solid Microneedles

These tiny needles come in different shapes, including cones, pyramids, cylinders, and blades, each designed for specific applications and skin types. When inserted into the skin, they create tiny channels without the need for a hollow core, allowing for precise drug delivery or fluid extraction [26]. Unlike traditional needles, they penetrate only the top layers of the skin, making them minimally invasive and reducing pain and discomfort. In healthcare, solid microneedles are revolutionizing drug delivery, diagnostics, and cosmetic procedures. They offer a non-invasive way to deliver medication directly into the skin, bypassing the digestive system or injections [28,29]. They can also be used for diagnostic purposes, such as monitoring glucose levels or collecting interstitial fluid for analysis [30]. In cosmetic treatments, they're used for collagen induction therapy [31], scar reduction [32], and other aesthetic procedures. Overall, solid microneedles represent a groundbreaking approach to medical treatment, offering precision, efficiency, and minimal discomfort. With their versatility and potential for customization, they hold promise for a wide range of applications in improving patient care and enhancing medicinal treatments [33].

b. Hollow microneedles

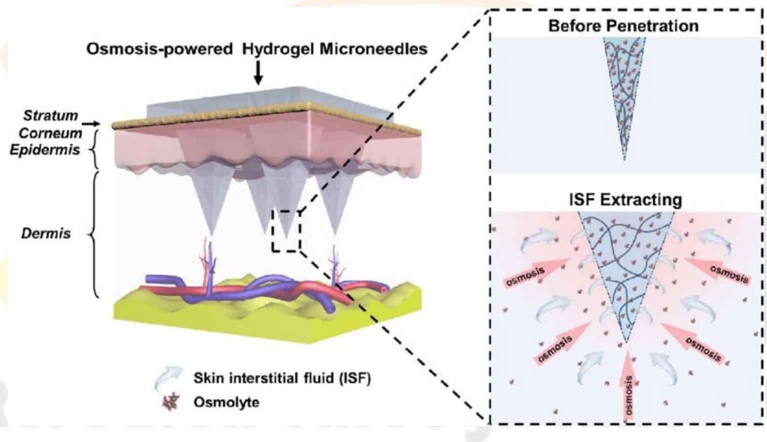
Have a hollow core that allows for the delivery or extraction of fluids enhancing medical treatments. Hollow microneedles are employed for continuous administration of drugs. It is having a hollow bore at the centre of needle and upon insertion into skin it directly delivers drug solution into the lower layer of epidermis. It shows an enhanced drug infusion rate as pressure can be applied across the length of the hollow microneedles during administration. The pressure as well as rate of flow of liquid formulation can be modulated for the rapid bolus injection, slow rate infusion or for variable administration rate over time. Additionally, it has been employed to work as a conduit for drug diffusion into skin from a non-pressurized drug reservoir [34,35].



A.b: Hollow Microneedles

c. Hydrogel microneedles

Hydrogel microneedles are an innovative approach to drug delivery, incorporating hydrogel materials into microneedle design. Hydrogels, composed of hydrophilic polymer chains, offer biocompatibility and the ability to retain large amounts of water or biological fluids. Fabrication typically involves crosslinking hydrogel precursors within microneedle Moulds, forming solid yet swellable structures. These microneedles can be solid or hollow, depending on application requirements. With their ability to penetrate the skin painlessly, hydrogel microneedles enable minimally invasive drug delivery directly into the dermal tissue, offering advantages over traditional needles. Controlled release kinetics can be achieved by engineering the hydrogel matrix, allowing tailored drug delivery profiles. Hydrogel microneedles are versatile, accommodating various drug types and formulations, including

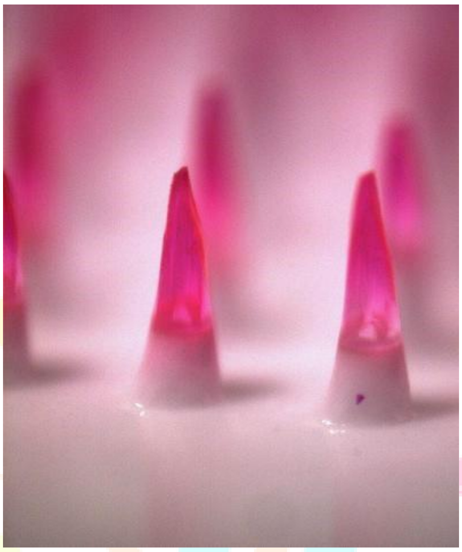


A.c: Hydrogel Microneedles

proteins and nucleic acids. They also hold promise for site-specific delivery and biomedical sensing applications, with potential for targeted therapy and real-time monitoring of biomarkers. Continued research and development are expected to advance hydrogel microneedle technology, enhancing its clinical translation and expanding its applications in healthcare and biotechnology [36].

d. Dissolvable microneedles

Dissolvable microneedles represent a cutting-edge innovation in drug delivery, offering a novel and minimally invasive method of introducing therapeutic substances into the body. These microneedles are intricately crafted from biocompatible materials like polymers or sugars, carefully selected for their ability to dissolve or degrade within the skin after insertion. This dissolution process allows for the gradual release of the encapsulated drug payload, ensuring a controlled and sustained delivery over time. One of the primary benefits of dissolvable microneedles is their ability to minimize discomfort and pain during administration, compared to traditional injections. Additionally, their precise dosing capabilities and predictable release kinetics enhance the therapeutic efficacy of the delivered drugs.



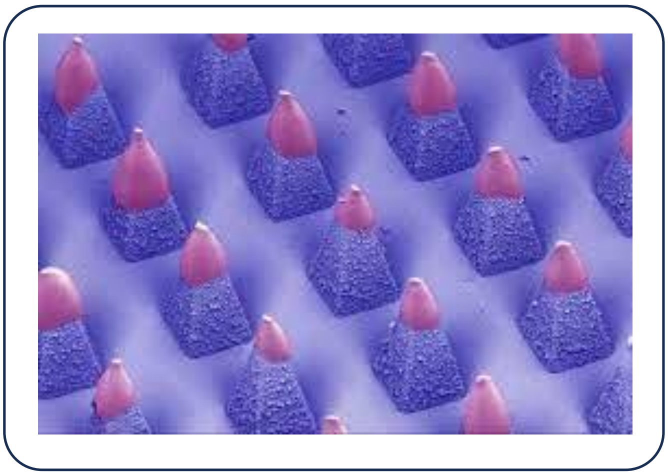
A.d: Dissolvable microneedles

Beyond their therapeutic advantages, dissolvable microneedles offer logistical benefits as well. They can improve patient compliance by offering a convenient and user-friendly alternative to conventional drug delivery methods. Furthermore, the biodegradable nature of these microneedles eliminates the need for needle disposal, reducing medical waste and environmental impact. In terms of applications, dissolvable microneedles have garnered interest across various fields including vaccination, drug delivery, and cosmetic procedures. They hold promise for delivering a wide range of therapeutics, from vaccines and hormones to pain relievers and anti-inflammatory agents. In cosmetic treatments, dissolvable microneedles are used for applications such as skin rejuvenation, scar reduction, and targeted drug delivery for dermatological conditions.

Overall, dissolvable microneedles represent a significant advancement in healthcare technology, offering a safe, efficient, and patient-friendly approach to drug delivery. Their versatility, precision, and convenience make them a promising tool for improving the efficacy and accessibility of medical treatments across diverse patient populations [37,38].

e. Coated microneedles

Coated microneedles represent a cutting-edge technology in drug delivery, leveraging solid arrays composed of materials like metal and silicon to deliver drugs rapidly into the skin, often within seconds. This rapid delivery capability makes them particularly suitable for instant bolus delivery of molecules, catering to scenarios where quick therapeutic action is crucial.

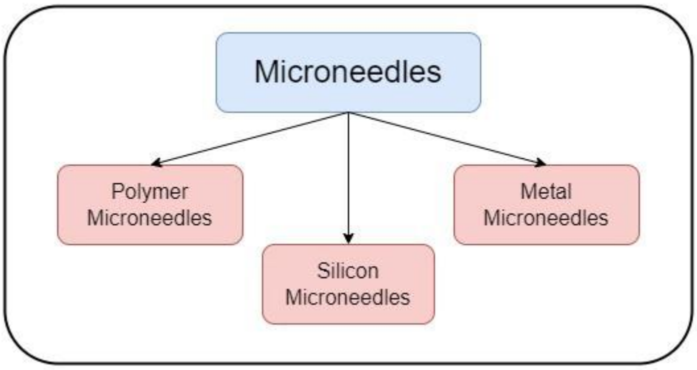


A.e: Coated microneedles

Moreover, coated microneedles offer a versatile platform for the co-delivery of multiple drugs with different properties using a single formulation. This capability opens up new avenues for combination therapy, allowing for more effective treatment of complex medical conditions. Recent advancements in coated microneedle technology have focused on enhancing biocompatibility, stability, and integration with wearable devices. Researchers are exploring new materials and coatings to improve the compatibility of microneedles with the skin, reducing the risk of adverse reactions. Additionally, efforts are underway to optimize drug coatings for enhanced stability, ensuring consistent and reliable drug delivery over time. Furthermore, there is growing interest in integrating coated microneedle patches with wearable devices for continuous monitoring and on-demand drug delivery. This integration could revolutionize personalized healthcare by providing real-time feedback and tailored treatment regimens. Beyond drug delivery, coated microneedles are being investigated for a range of applications, including diagnostics, vaccination, and cosmetic treatments. Their minimally invasive nature and precise delivery capabilities make them promising candidates for various biomedical interventions. Overall, the ongoing research and development efforts in coated microneedle technology highlight its potential to transform healthcare delivery by offering efficient, targeted, and patient-friendly solutions for drug administration and beyond.

B. Based on Material composition

Microneedles are classified by material composition into silicon, metal, and polymer types. Silicon microneedles offer precision and compatibility with microengineering, while metal microneedles provide mechanical strength for biomedical implants. Polymer microneedles offer versatility and biodegradability, ideal for controlled drug release in various applications.



B: Classification of Microneedles based on Material Composition.

a. Polymer Microneedles

Constructed from biocompatible polymers such as polylactic acid (PLA), polyglycolic acid (PGA), or poly (lactic-co-glycolic acid) (PLGA). Polymer microneedles offer flexibility and versatility in design and fabrication. They are widely used in applications requiring biodegradability, controlled drug release, and patient comfort, such as dissolvable microneedles for transdermal drug delivery and cosmetic treatments. Each type of microneedle material has its unique properties and advantages, allowing for tailored solutions to various biomedical and healthcare challenges [39].

b. Silicon Microneedles

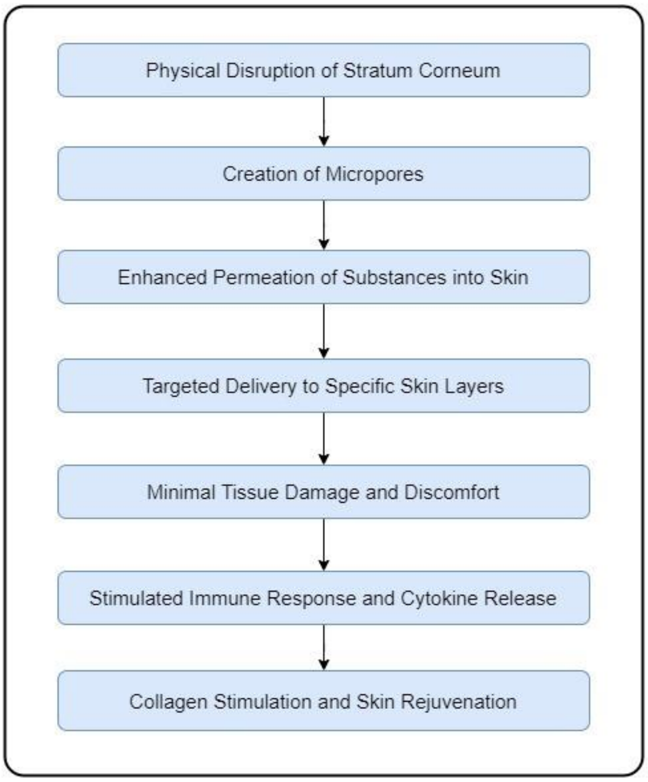
Fabricated from silicon using microfabrication techniques. Silicon microneedles are known for their precision and compatibility with microengineering processes. They are commonly used in applications where precise control over needle geometry and dimensions is essential, such as transdermal drug delivery and biosensing [40].

c. Metal Microneedles

Made from metals like stainless steel, titanium, or nickel. Metal microneedles are valued for their mechanical strength and durability. They are often used in applications where robustness and reliability are critical, such as biomedical implants and solid microneedles for drug delivery [41].

Mechanism of Action of Microneedles:

Microneedles operate through a sophisticated mechanism that involves the precise physical disruption of the skin's outermost layer, the stratum corneum. These tiny needles, typically ranging from 25 to 2000 micrometres in length, create minuscule channels or micropores upon penetration [42]. This action enhances the permeability of the skin, allowing for the facilitated delivery of therapeutic agents, vaccines, or cosmetic compounds into the deeper layers of the skin, such as the epidermis and dermis. Importantly, microneedles can be designed to target specific depths within the skin, offering precise delivery of substances to achieve desired therapeutic effects. Unlike conventional needles, microneedles produce minimal discomfort and tissue damage due to their controlled penetration and small size. Additionally, the micro-injuries induced by microneedles can stimulate a localized immune response, amplifying the efficacy of vaccines and promoting collagen synthesis for skin rejuvenation. This dual action of enhanced drug delivery and skin regeneration makes microneedles a promising technology for a wide range of applications in dermatology, drug delivery, and cosmetics [43].



C: Mechanism of Microneedle Assisted Transdermal Delivery

Materials in Microneedle Fabrication

Get ready to explore each material type as we examine their roles and characteristics in microneedle fabrication. From silicon to polymers, ceramics, and metals, each offers unique advantages and considerations for designing microneedle arrays. Understanding these properties is key to improving performance and advancing microneedle technology.

a. Silicon

Initially, solid microneedles were predominantly made from silicon due to its compatibility with high precision microelectronics tools and flexibility. Silicon emerged as the pioneer material for MN fabrication in the 1990s due to its inherent flexibility, enabling the production of MNs in diverse shapes and sizes [44]. Solid, hollow, and coated MNs have been successfully fabricated using silicon. However, drawbacks such as time-consuming fabrication processes, high costs, and the potential for causing skin fractures have been associated with silicon-based MNs. silicon microneedles are prone to breakage due to their brittle nature [45].

b. Stainless-Steel

Stainless steel microneedles offer sufficient mechanical strength for skin penetration. They are durable and can withstand repeated use, making them suitable for various applications. Stainless steel is a widely used material for microneedle fabrication due to its excellent mechanical properties, biocompatibility, and corrosion resistance. It was one of the first metals employed for microneedles and remains popular in the field. Stainless steel microneedles offer high fracture toughness and yield strength, making them durable and less prone to breakage during skin penetration compared to materials like silicon. They are suitable for various applications, including drug delivery, biosensing, and cosmetic procedures. Despite their advantages, stainless steel microneedles may cause discomfort or allergic reactions in some individuals due to the presence of nickel, a common component of stainless-steel alloys. Researchers continue to explore surface modifications and coatings to enhance the performance and biocompatibility of stainless-steel microneedles for diverse applications [46].

c. Titanium

Titanium microneedles possess similar mechanical properties to stainless steel but are lighter in weight. They are biocompatible and corrosion-resistant, making them suitable for biomedical applications. Titanium stands as a prominent material in the realm of microneedle technology, prized for its exceptional biocompatibility, robustness, and lightweight properties. It offers mechanical strength comparable to stainless steel but with the added advantage of being lighter, rendering it ideal for applications where weight is a critical factor. Its corrosion resistance and compatibility with the human body make it a favoured choice in medical and biomedical fields. Titanium microneedles find extensive use in various applications, including drug delivery systems, biomedical sensing devices, and cosmetic procedures. Fabrication techniques such as laser cutting, micro-milling, and electrochemical machining are employed to create titanium microneedles with precision. While titanium microneedles generally exhibit good biocompatibility, ongoing research aims to optimize their performance further through surface modifications and coatings to minimize potential adverse reactions and enhance their utility in diverse applications [46].

d. Nickel-Iron Alloy

Nickel-iron alloys, such as nitinol, are known for their elasticity, shape-memory capability, and biocompatibility. Nitinol microneedles are used in various medical devices, including those for vascular surgery. Nickel-iron (NiFe) alloys have emerged as promising materials for microneedle production, leveraging their unique combination of mechanical strength, corrosion resistance, and biocompatibility. With excellent mechanical properties, including high strength and hardness, NiFe alloys are well-suited for fabricating durable microneedles capable of penetrating the skin without risk of fracture or deformation. Moreover, their good corrosion resistance makes them suitable for prolonged use in environments prone to oxidation or moisture exposure, ensuring the long-term stability and functionality of microneedles, especially in biomedical applications requiring contact with bodily fluids. NiFe alloys are generally considered biocompatible, minimizing the risk of adverse reactions or tissue irritation when in direct contact with biological tissues, which is crucial for applications like transdermal drug delivery. Fabrication techniques such as micro-machining and laser cutting allow for precise shaping and customization of NiFe alloy microneedles to meet specific design requirements and application needs. These microneedles find potential applications in drug delivery, biosensing, and cosmetic procedures, where their mechanical strength and biocompatibility are advantageous. However, considerations such as cost, material availability, and further research to optimize performance and biocompatibility remain important for advancing the use of NiFe alloy microneedles in diverse healthcare solutions [47].

e. Ceramics

Ceramic materials, notably alumina, have been utilized for MN fabrication due to their superior chemical properties and compression resistance. However, ceramics generally exhibit lower tensile strength compared to other materials. Techniques such as micro-moulding enable cost-effective scaled-up production of ceramic MNs. Despite their potential, studies have reported instances of ceramic MNs fracturing upon manual application to the skin. Surface modifications and coatings are being developed to enhance the performance and biocompatibility of ceramic microneedles. These modifications may involve the application of biocompatible coatings or functionalization with biomolecules to improve tissue interaction and reduce the risk of fracture upon skin insertion. Advancements in manufacturing techniques, such as additive manufacturing (3D printing) and laser-based machining, are enabling the precise fabrication of ceramic microneedles with complex geometries and tailored properties. These techniques offer scalability and customization, allowing for the production of ceramic microneedles tailored to specific applications and requirements [48,49].

f. Polymeric Materials

Various polymers, such as poly (glycolic acid) (PGA), polylactic-co-glycolic acid (PLGA), poly (vinyl alcohol) (PVA), and polylactic acid (PLA), are commonly used for microneedle fabrication. Polymers present a promising alternative for MN fabrication, offering excellent biocompatibility, low toxicity, and cost-effectiveness. Although polymers have lower strength compared to silicon and metals, they find extensive use in various types of MN arrays, including dissolvable, hydrogel-forming, solid, coated, and hollow arrays. Biodegradable polymers like poly (methyl methacrylate) (PMMA), polylactic acid (PLA), and SU-8 photoresist have been employed for drug delivery applications using MNs [50,51].

g. Water Soluble Polymers

Water-soluble polymers, including carboxymethyl cellulose (CMC), are used to fabricate dissolving microneedles. These microneedles dissolve upon insertion into the skin, releasing encapsulated drugs or vaccines. Water-soluble polymers are increasingly favoured in microneedle technology due to their exceptional biocompatibility, low toxicity, and ability to dissolve or swell upon contact with water or bodily fluids. These polymers offer numerous advantages for microneedle fabrication and drug delivery applications. Firstly, their biocompatibility ensures minimal risk of adverse reactions or tissue irritation, making them suitable for transdermal drug delivery and other biomedical uses. Secondly, they enable controlled drug release by loading drugs or bioactive compounds into the polymer matrix, facilitating precise delivery over time while minimizing side effects. Additionally, water-soluble polymers are easy to process using techniques like casting, moulding, or 3D printing, allowing for the fabrication of customized microneedles tailored to specific applications. They can also be tailored to exhibit different dissolution rates, mechanical properties, and swelling behaviours, offering versatility in design optimization. Furthermore, many water-soluble polymers are biodegradable, promoting tissue healing and reducing the risk of polymer accumulation. Their compatibility with a wide range of active pharmaceutical ingredients allows for the delivery of diverse therapeutics, expanding their potential applications in healthcare. Overall, water-soluble polymers hold immense promise for advancing microneedle technology and improving patient care [52].

h. Sugars

Sugars such as maltose, dextran, and galactose are utilized to fabricate dissolving microneedles. These sugars are biocompatible and readily dissolve in aqueous environments, facilitating drug release. Solid and hollow microneedles (MNs) and Moulds for dissolving MNs have been fabricated directly from suitable material substrates using Microelectromechanical Systems (MEMS) methods.

Microneedles Production Methods

Get ready to dive into detailed examinations of different microneedle production methods. We'll cover each method thoroughly, with a *special focus on microfluidic-based formulations*, a promising but relatively unexplored area offering ample research opportunities

a. Microelectromechanical systems

Solid and hollow microneedles (MNs) and Molds for dissolving MNs have been fabricated directly from suitable material substrates using Microelectromechanical Systems (MEMS) methods [16]. This production involves a precisely controlled three-step process: deposition, patterning, and etching of materials, leading to the formation of complex three-dimensional (3D) structures due to differences in selectivity to the etchant between different materials [53,54]. In the first step, a film with a thickness ranging from a few nanometres to 100µm is formed on a substrate through chemical (CVD) or physical vapor deposition (PVD) methods [53,55,56]. In PVD, the film is formed by atoms transferred directly from the source to the substrate through the gas phase, while in CVD, chemical reactions on the substrate surface lead to film formation [56]. Subsequently, during the patterning phase, a two-dimensional master pattern of the desired material is transferred from the original photomask to the photosensitive-coated substrate. Typically, a silicon wafer is used as a substrate, and the transfer process is facilitated using a radiation source with photolithography [57], ion beam lithography, or X-ray lithography methods. Photolithography, the most common type, is based on the principle that some materials, like metals, are not transparent when exposed to UV light (λ = 193–236 nm), while others, like glass, are transparent. An opaque mask, created from a quartz plate or flat glass, allows light to pass only through a defined pattern, generating the desired pattern [58]. The silicon substrate is initially exposed to steam or humidified oxygen at around 900 °C to produce an oxide layer. Then, it is rotated and coated with an organic polymer sensitive to UV light, known as photoresist material. Heat treatment followed by UV radiation removes the solvent and forms the desired photoresist pattern. This step can utilize two types of resists: positive and negative, each affecting the solubility of the photoresist polymer differently after exposure to UV light [56].

b. Laser Cutting

Metal microneedles (MNs) are crafted using various methods, such as 3D laser cutting, laser ablation, and electroplating or electroless plating onto positive or negative MN Moulds. Moreover, fabrication techniques extend to hollow MNs and Moulds for dissolving MN patches. These techniques showcase the versatility and potential applications of metal MNs in drug delivery and biomedical fields. Arrays of solid MNs are typically created by shaping stainless steel or titanium sheets with an infrared laser, following predefined designs using computer-aided design (CAD) software. Dissolving MN patches are produced using a CO2 laser on polymethylmethacrylate (PMMA) sheets. Afterward, a drug-containing mixture is poured into PMMA Moulds, resulting in dissolving MNs that release the drug upon skin insertion. Hollow MNs are fashioned by forming holes in polymer sheets with a KrF laser, followed by micro-moulding to achieve the desired structure. These MNs undergo cleaning, bending, and electropolishing to refine their geometry and ensure sharp tips. This approach allows for the production of single or two-dimensional arrays of metallic MNs with diverse geometries. Additionally, ongoing research focuses on enhancing fabrication processes, optimizing drug delivery efficiency, and exploring new materials to further expand the capabilities of metal MNs in healthcare applications [59,60,61].

c. Laser Ablation

Omatsu introduced a novel, time and cost-effective fabrication method of manufacturing metal MNs based on circularly polarized optical vortices that have nonzero total angular momentum. The top-down method for processing materials, including metals, involves using light pulses to create the desired shape on a metal plate, forming solid metal arrays. While effective, the high-intensity laser pulses can lead to the formation of plasma of ions and electrons, which may not be suitable for the fabrication of structured materials. The authors reported on the fabrication of tantalum MNs with a vertical height of over 10 µm and significantly small tip radii. This approach is both time and cost-effective, offering advantages over traditional methods. Additionally, recent advancements in this field have focused on improving the precision and scalability of the fabrication process. Researchers are exploring innovative techniques to enhance the uniformity and quality of metal microneedles, as well as investigating new materials with superior mechanical properties and biocompatibility. Furthermore, there is ongoing research into optimizing the design and performance of metal microneedles for various applications, including drug delivery, biosensing, and cosmetic procedures. These efforts aim to push the boundaries of microneedle technology and unlock new possibilities for healthcare and biomedical engineering [62,63].

d. Micro-moulding method

Dissolving microneedles (MNs) are typically manufactured by filling a pre-prepared MN Mould with a liquid formulation. Typically, the Mould is crafted from a silicon wafer, which undergoes oxidation at 1000°C. Following this, needle geometry is patterned onto the wafer using lithography methods, and reactive ion etching (RIE) is employed to define the shape. Chemical vapor deposition (CVD) is then utilized to coat the wafer. A liquid polymeric solution is poured into the prepared Moulds, with air voids subsequently removed using vacuum or centrifugation. The Moulds are then dried in an oven, and the MNs are extracted after cooling. This method offers several advantages, including relatively simple and cost-effective MN production at ambient temperature. Additionally, it enables the fabrication of biodegradable polymer MNs using both natural and synthetic materials, boasting appropriate geometry and sufficient strength for skin penetration. Intriguingly, micro-moulding techniques have also been leveraged for the production of ceramic MNs [64,65,66,2].

e. Atomized Spraying Method

The atomized spraying method offers a solution to the challenges associated with the limited capacity for mass production of dissolving microneedles (MNs) with desired geometry and physical characteristics. Additionally, it helps minimize issues related to liquid surface tension and viscosity when filling the MN Moulds. This method allows for the production of dissolving MNs from various materials, including sugars such as trehalose, fructose, and raffinose, as well as polymers like PVA, PVP, CMC, HPMC, and sodium alginate. In this process, a nozzle connected to an air source and liquid formulation generates an atomized spray, facilitating uniform deposition onto PDMS Moulds. The filled Moulds are then dried for 2 hours at ambient temperature. Moreover, the atomized spraying method enables the fabrication of laminate-layered and horizontally-layered dissolving MNs, providing versatility in design and application [67,65].

f. Droplet-Born Air Blowing Method (DAB)

The Drawing Lithography-Assisted Bulge (DAB) method, introduced by Kim et al., revolutionizes microneedle (MN) fabrication by offering a gentle yet efficient alternative to traditional manufacturing techniques. Beyond addressing concerns of drug inactivity associated with UV light and heat exposure, the DAB method presents several noteworthy advantages. Firstly, it preserves the integrity of sensitive drug compounds, ensuring their efficacy during fabrication under mild conditions. Additionally, its scalability makes it suitable for mass production, catering to industrial demands for large quantities of MNs. The method's versatility allows for the fabrication of MNs with diverse geometries, sizes, and drug-loading capacities to accommodate various applications requirements. Moreover, its cost-effectiveness, achieved by eliminating the need for specialized equipment, enhances its appeal for widespread adoption. Furthermore, the environmentally friendly nature of the process, characterized by reduced energy consumption and minimized environmental impact, aligns with sustainable manufacturing practices. With precise control over droplet elongation and shaping, the DAB method enables the production of MNs with uniform dimensions and sharp tips, optimizing their performance for effective skin penetration and drug delivery. Overall, the DAB method represents a significant advancement in MN fabrication technology, promising enhanced efficacy and safety in transdermal drug delivery systems. The application of one drop of polymer per microneedle (MN) allows for direct control over the size of drops and the concentration of active pharmaceutical ingredients (API). This efficient process, lasting only 10 minutes, was utilized to produce insulin-loaded dissolving MNs that effectively lowered blood glucose levels in diabetic mice. Additionally, a novel method employing a shadow mask was introduced to achieve uniform MN production, addressing issues associated with low throughput in droplet formation. This innovative approach enabled controlled drug dosage through optimization of hole width and thickness of the shadow mask, further enhancing the precision and efficacy of MN fabrication for drug delivery applications [65,68].

g. Pulling pipettes

The pulling pipettes method, tailored for hollow glass microneedles (MNs), involves pulling fire-polished borosilicate glass pipettes at high temperatures using a micropipette puller and beveler. This technique has been successfully employed by two research teams to produce glass MNs, highlighting its applicability and effectiveness. Hollow MNs fabricated through this method have shown promising results in delivering bolus insulin to patients with type 1 diabetes, emphasizing their therapeutic potential. Moreover, recent advancements in this field have focused on enhancing the fabrication process to achieve greater precision and uniformity in MN production. Additionally, it has been observed that glass MNs possess the capability to infuse millilitres of fluid into the skin, demonstrating their versatility and capacity for drug delivery beyond small-volume applications. Furthermore, MNs produced using this method have been utilized for intraocular drug delivery, delivering 6-aminoquinolone and Rose Bengal to the eye. This innovative approach offers a less invasive and less painful alternative to conventional macroscale hypodermic needles, potentially improving patient comfort and treatment outcomes in ocular drug delivery [69-71].

h. Digital life processing

Digital Light Processing (DLP) is a photopolymerization-based technology that operates by polymerizing photosensitive polymers through projections of light. Unlike Stereolithography (SLA), DLP is known for its speed, as it utilizes a high-definition projector to flash the entire cross-section of an object simultaneously, forming volumetric pixels. Researchers have explored the applications of DLP in microneedle (MN) fabrication with promising results. Gittard et al. demonstrated the feasibility of using DLP to print solid MN array structures using an acrylate-based polymer, particularly for wound healing applications. Similarly, El-Sayed et al. successfully employed a desktop DLP 3D printer to create MN Moulds for nanoparticle delivery. Additionally, Lu et al. utilized a micro stereolithographic DLP apparatus to fabricate drug-loaded MN arrays for transdermal delivery of a chemotherapeutic drug [Reference needed]. These studies highlight the versatility of DLP technology in manufacturing MNs for various biomedical applications [72-74].

i. Two-Photon Polymerisation

Two-Photon Polymerization (2PP) is a method that enables the cost-effective layer-by-layer fabrication of 3D structures at the microscale and nanoscale using solid, liquid, or powder precursors. This technique involves focusing a femtosecond or picosecond laser inside a liquid resin droplet to polymerize it into microneedle (MN) structures. The process relies on the temporal and spatial overlap of photons to achieve photopolymerization. Advantages of 2PP include high flexibility, scalable resolution, precise geometry control, and compatibility with conventional facilities. Gittard et al. suggested that 2PP can create MNs with a wide range of geometries, including in-plane, out-of-plane, rocket shaped, and mosquito fascicle-shaped MNs. Researchers have successfully utilized 2PP for various MN applications. Doraiswamy et al. were among the first to utilize 2PP for producing MNs using Ormoc® (organically modified ceramic) materials. Trautmann et al. demonstrated the fabrication of hollow MNs with internal laser-generated microchannels using 2PP. Another research group successfully printed ultra-sharp polymer MNs via 2PP. Additionally, Cordeiro et al. described a method for creating high-quality MN array master templates using 2PP 3D printing. Recent advancements in 2PP technology have further expanded its capabilities, such as the integration of real-time monitoring systems for enhanced precision and control during fabrication. Moreover, efforts are underway to optimize 2PP processes for scalability and compatibility with a broader range of materials, paving the way for more widespread adoption in MN fabrication and other biomedical applications. These developments highlight the ongoing evolution and potential of 2PP [62,72,73].

j. Stereolithography

Stereolithography (SLA) stands out as a widely utilized technology for printing microneedles (MNs), offering high resolution, accuracy, and a smooth surface finish. Ovsianikov et al. pioneered the use of lithography-based multiphoton polymerization 3D printing to create MN arrays for transdermal drug delivery. This method relies on the photopolymerization of liquid resin with photo-active monomers under UV light, with MNs formed through the solidification of subsequent resin layers exposed to high energy light, typically a UV laser beam guided by scanner mirrors. Following printing, MNs are washed in an alcohol bath to remove unpolymerized resin residues and then cured in a UV chamber. Despite its ability to produce high-quality parts with fine resolution (down to 10 µm), SLA is characterized by its relatively slow speed, high cost, and limited range of printing materials, particularly in terms of biocompatibility. Nonetheless, numerous research groups have leveraged SLA in MN manufacturing, yielding solid MNs, hollow MNs, and MN Moulds. Pere et al. and Economidou et al. utilized SLA to fabricate MN arrays using a Class 1 biocompatible resin with excellent mechanical strength, coated with insulin-sugar films. These advancements underscore SLA's potential in MN fabrication, particularly when combined with biocompatible materials, paving the way for enhanced transdermal drug delivery systems. In addition to its applications in microneedle (MN) fabrication, stereolithography (SLA) has found extensive use in various industries, including automotive, aerospace, and healthcare. In the healthcare sector, SLA is employed for rapid prototyping of medical devices, surgical tools, and anatomical models for preoperative planning and medical education. Its ability to produce highly detailed and accurate models allows surgeons to visualize complex anatomical structures and practice surgical procedures before performing them on patients, thus improving surgical outcomes and reducing surgical time. Moreover, SLA is increasingly being explored for tissue engineering applications, where it is used to fabricate scaffolds with precise microarchitectures to support cell growth and tissue regeneration. By precisely controlling the geometry and porosity of the scaffolds, SLA enables the creation of biomimetic environments that closely resemble native tissues, facilitating more effective tissue regeneration. Furthermore, advancements in SLA technology, such as the development of biocompatible and bioresorbable materials, are opening up new possibilities for personalized medicine and regenerative therapies. Overall, SLA continues to drive innovation across various fields by offering high precision, versatility, and customization capabilities [74,75,76].

k. Additive manufacturing

Additive manufacturing, also known as 3D printing, is a revolutionary method for formulating microneedles in the pharmaceutical industry. The process begins with designing microneedle geometries using computer-aided design (CAD) software. This step allows for precise customization of microneedle shapes, sizes, and arrays to meet specific application requirements. Once the design is finalized, it is converted into a standard tessellation language (STL) file, which defines the 3D shape by dividing it into small triangles. The STL file is then sliced into thin layers corresponding to the desired thickness of the microneedles. Each layer is sequentially deposited or cured using additive manufacturing techniques such as stereolithography (SLA), fused deposition modelling (FDM), or selective laser sintering (SLS). These methods enable the precise deposition of materials layer by layer, resulting in the formation of microneedles with intricate structures and high resolution. One of the key advantages of additive manufacturing in microneedle formulation is its versatility in material selection. Various biocompatible polymers, metals, and ceramics can be used as feedstock materials, allowing for the fabrication of microneedles with tailored properties such as strength, flexibility, and biodegradability. Moreover, additive manufacturing offers rapid prototyping capabilities, allowing for quick iteration and optimization of microneedle designs. This accelerates the development process and reduces time-to-market for new microneedle formulations. Overall, additive manufacturing has revolutionized the formulation industry of microneedles by enabling precise, customizable, and rapid production of microneedle arrays with enhanced performance and functionality [72,75,77,78,79,80,81].

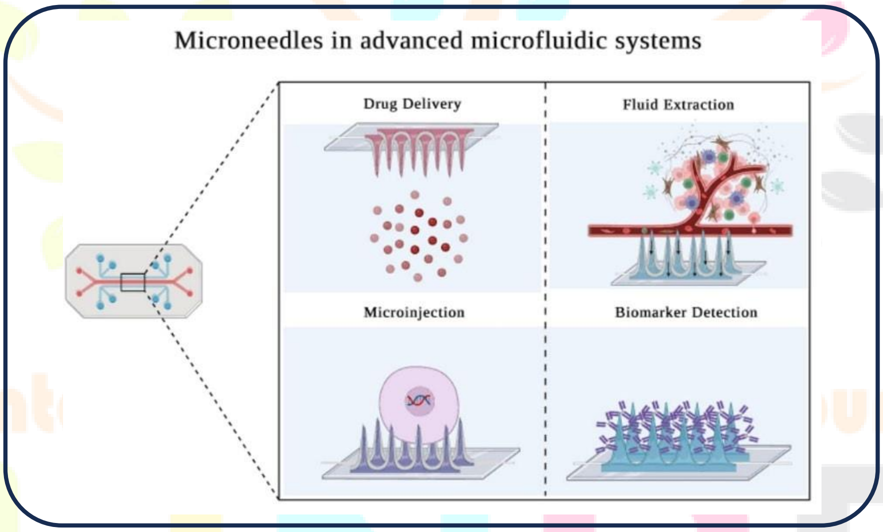
l. Fused Deposition Modelling (FDM)

Fused Deposition Modelling (FDM) stands as a widely adopted additive manufacturing technique in the pharmaceutical realm for crafting intricate microneedles. Within FDM, microneedles take shape through the extrusion of thermoplastic materials via a heated nozzle onto a designated build platform. The process unfolds with meticulous precision as the nozzle navigates, layer by layer, depositing material according to the predefined 3D model. With each layer fused seamlessly with its predecessor, the microneedle structure gradually emerges. One of the paramount advantages of FDM lies in its flexibility regarding material selection, accommodating a spectrum of biocompatible polymers like polylactic acid (PLA) and poly(lactic-co-glycolic acid) (PLGA). This versatility empowers researchers and engineers to tailor microneedle properties such as geometry, size, and array configuration, suiting specific requirements in drug delivery applications. Moreover, FDM boasts rapid prototyping capabilities, significantly expediting the developmental timeline and expediting the introduction of novel microneedle formulations to the market. Despite its myriad benefits, FDM is not without limitations. Notably, its inherent drawback lies in its relatively low printing resolution, which may impact the fidelity of intricate features. However, innovative strategies such as post-fabrication etching hold promise in addressing this challenge. Ultimately, Fused Deposition Modelling remains a cornerstone in the pharmaceutical arsenal, furnishing a cost-effective and efficient avenue for the production of microneedle arrays endowed with heightened performance and functionality, poised to revolutionize drug delivery paradigms [72,75,77,78,80,81].

As mentioned earlier, our exploration will involve a comprehensive analysis of various microneedle production methods. Each method will be examined in detail to provide a thorough understanding. However, amidst these established techniques lies a captivating prospect: microfluidic-based formulations. This intriguing approach, as highlighted previously, remains relatively unexplored but holds immense promise for the future of microneedle fabrication. Now, let's delve deeper into this innovative method and explore the exciting research avenues it offers.

m. Microfluidic based formulations

The microfluidic-based formulation method for microneedles involves the precise manipulation of small volumes of fluids and materials within microfluidic devices to fabricate microneedles with controlled size, shape, and composition. This approach enables the integration of various materials, including polymers, drugs, and bioactive agents, into microneedle structures for applications such as transdermal



drug delivery, biomedical sensing, and tissue engineering. By leveraging microfluidic technology, researchers can achieve high precision, scalability, and versatility in microneedle fabrication, opening up new possibilities for innovative drug delivery and biomedical applications. One novel formulation method for microneedles that has received limited prior attention in the research literature is the integration of microfluidic technology for fabrication. Microfluidic-based fabrication offers precise control over the composition, size, and morphology of microneedles, leading to enhanced efficiency and performance [82,83,84].

Procedure

The procedure for microfluidic-based formulation of microneedles involves several steps, each aimed at precisely manipulating fluids and materials within microfluidic devices to fabricate microneedle structures. Here's a detailed overview of the procedure:

Design and Fabrication of Microfluidic Devices:

- Design microfluidic devices with channels and chambers tailored to the desired microneedle geometry and array configuration.

- Fabricate the microfluidic devices using microfabrication techniques such as photolithography and soft lithography.

Preparation of Microneedle Formulation:

- Prepare a formulation containing the desired materials for microneedle fabrication, such as polymers, drugs, and additives.
- Ensure the formulation is compatible with microfluidic processing and suitable for the intended application.

Loading of Microneedle Formulation:

- Introduce the microneedle formulation into the microfluidic device through inlet ports or channels.
- Control the flow rate and pressure to precisely manipulate the formulation within the microfluidic channels.

Patterning and Solidification of Microneedles:

- Use microfluidic channels and chambers to pattern the microneedle formulation into the desired shape and size.
- Employ mechanisms such as photopolymerization, solvent evaporation, or cooling to solidify the microneedles into a stable structure.

Removal and post-processing:

- Remove the fabricated microneedles from the microfluidic device, ensuring they maintain their integrity and structural integrity.
- Conduct any necessary post-processing steps, such as cleaning, sterilization, or coating, to prepare the microneedles for use in biomedical applications.

Characterization and Evaluation:

- Characterize the fabricated microneedles using techniques such as microscopy, spectroscopy, and mechanical testing to assess their size, morphology, composition, and mechanical properties.
- Evaluate the performance of the microneedles in relevant biomedical applications, such as transdermal drug delivery, tissue engineering, or biomedical sensing.

By following this detailed procedure, researchers can utilize microfluidic technology to fabricate microneedles with precise control over their size, shape, composition, and functionality, enabling a wide range [85,86,87].

Advantages

a. Precise control: Microfluidic devices allow for precise control over the flow rate, composition, and concentration of materials, resulting in uniform and reproducible microneedle structures.

b. High throughput: Microfluidic fabrication enables the simultaneous production of multiple microneedle arrays, increasing fabrication throughput and scalability.

c. Versatility: Microfluidic devices can accommodate a wide range of materials, including polymers, drugs, and biomolecules, making them suitable for diverse applications in drug delivery and biomedical engineering.

d. Integration of functional components: Microfluidic platforms can be designed to incorporate functional components, such as sensors or actuators, enabling the development of "smart" microneedle systems for controlled drug release or feedback-controlled delivery. Reduced Material Waste: Microfluidic devices allow for precise control over fluid volumes, minimizing material waste during the fabrication process. This can lead to cost savings and increased efficiency in microneedle production.

e. Enhanced Uniformity and Consistency: The controlled flow of materials within microfluidic channels enables the fabrication of microneedles with uniform size, shape, and composition. This consistency is essential for ensuring reproducibility and reliability in biomedical applications.

f. Customization and Tailoring: Microfluidic devices can be designed and optimized for specific microneedle formulations and applications. Researchers can tailor the device geometry, channel dimensions, and flow parameters to achieve desired microneedle characteristics, such as drug loading capacity and release kinetics.

g. Integration of Multiple Components: Microfluidic-based fabrication allows for the integration of multiple components within microneedles, such as drugs, nanoparticles, or biomolecules. This integration enables multifunctional microneedle designs with enhanced therapeutic capabilities or diagnostic functionalities.

h. Scalability and Automation: Microfluidic fabrication processes can be easily scaled up to accommodate high-throughput production of microneedle arrays. Furthermore, these processes can be automated, reducing the need for manual intervention and increasing manufacturing efficiency.

i. Compatibility with Lab-On-Chip Systems: Microfluidic-based microneedle fabrication can be seamlessly integrated with lab-on-chip systems for on-site analysis or point-of-care applications. This integration enables the development of miniaturized and portable devices for personalized healthcare and diagnostics [86,87].

Disadvantages

a. Complexity of Device Fabrication: Designing and fabricating microfluidic devices can be technically challenging and require specialized equipment and expertise.

b. Cost of Infrastructure: The initial investment in microfluidic fabrication equipment and infrastructure may be relatively high, limiting accessibility to this technology.

c. Integration Challenges: Integrating functional components, such as sensors or actuators, into microfluidic-based microneedle systems may pose challenges in terms of compatibility and functionality [86,87,88].

Applications

a. Personalized Medicine: Microfluidic-based microneedles have the potential to enable personalized drug delivery regimens tailored to individual patient needs, based on factors such as genetics, metabolism, and disease state.

b. Point-of-Care Diagnostics: Microfluidic-based microneedles could be integrated with diagnostic assays or biosensors for rapid, on-site detection of infectious diseases, biomarkers, or environmental contaminants.

c. Regenerative Therapies: Advances in microfluidic-based microneedle technology may lead to new regenerative therapies for treating degenerative diseases, injuries, and chronic conditions by delivering bioactive molecules or cells directly to damaged tissues.

d. Vaccine Delivery: Microfluidic-based microneedles can be used for the painless and efficient delivery of vaccines, including DNA vaccines, viral vectors, and protein subunit vaccines. These microneedles enable targeted delivery to the skin's immune-rich environment, enhancing vaccine efficacy.

e. Cosmetic and Aesthetic Treatments: Microneedles formulated using microfluidic technology can deliver cosmetic and aesthetic agents, such as hyaluronic acid, vitamins, and peptides, for skin rejuvenation, scar reduction, and wrinkle treatment. This approach offers a minimally invasive alternative to traditional cosmetic procedures.

f. Gene Therapy: Microfluidic-based microneedles have potential applications in gene therapy by delivering nucleic acids, such as plasmid DNA or small interfering RNA (siRNA), to target cells in the skin. This targeted delivery approach may improve the efficiency and safety of gene therapy treatments.

g. Intradermal Drug Delivery: Microfluidic-based microneedles enable precise intradermal delivery of drugs for the treatment of various skin conditions, including psoriasis, acne, and eczema. These microneedles can penetrate the stratum corneum barrier, facilitating drug absorption and therapeutic efficacy.

h. Point-of-Care Diagnostics: Microfluidic-based microneedles integrated with biosensors or diagnostic assays can enable rapid, minimally invasive detection of biomarkers or analytes in the interstitial fluid or blood. This approach has applications in disease diagnosis, monitoring, and management at the point of care.

i. Pain Management: Microneedles formulated using microfluidic technology can deliver analgesic agents, such as lidocaine or fentanyl, directly to nerve endings in the skin, providing localized pain relief for conditions such as chronic pain, neuropathy, or post-operative pain.

j. Dermal Imaging and Monitoring: Microfluidic-based microneedles can be functionalized with optical fibres or sensors to enable real-time imaging and monitoring of physiological parameters, such as hydration levels, pH, or glucose concentrations, in the skin. This non-invasive approach has applications in dermatology, wound healing, and skincare 85,86,87].

Limitations of microneedles

a. Depth of Penetration: Microneedles are designed to penetrate the outermost layer of the skin, known as the stratum corneum. However, they may not reach deeper skin layers where systemic drug delivery or targeting specific tissues is required. This limited depth of penetration can restrict their effectiveness for certain applications.

b. Drug Loading Capacity: The small size of microneedles imposes constraints on the amount of drug that can be loaded into each microneedle. This limited drug loading capacity may not be sufficient for delivering high doses of certain therapeutics, particularly large molecular weight drugs or biologics.

c. Uniformity and Consistency: Fabricating microneedles with consistent size, shape, and mechanical properties across a large array can be challenging. Variations in microneedle dimensions or composition may lead to inconsistent drug delivery or penetration efficacy, affecting treatment outcomes.

d. Skin Variability: The efficacy of microneedles can be influenced by individual variations in skin properties, such as thickness, hydration levels, and elasticity. Skin variability among different anatomical sites or patient populations may impact the performance and reliability of microneedle-based therapies.

e. Biocompatibility and Safety: The materials used in microneedle fabrication must be biocompatible to minimize the risk of skin irritation, allergic reactions, or tissue damage. Ensuring the safety of microneedle formulations, particularly when using novel materials or drug combinations, requires comprehensive biocompatibility testing.

f. Manufacturing Scalability: Scaling up microneedle production to meet large-scale demand for clinical or commercial applications can be challenging. Manufacturing processes must be optimized for high throughput, cost-effectiveness, and reproducibility without compromising microneedle quality or performance.

g. Patient Acceptance and Compliance: Acceptance of microneedle-based therapies by patients may vary due to factors such as fear of needles, discomfort during application, or perceived efficacy compared to traditional delivery methods. Ensuring patient comfort, convenience, and adherence is essential for the success of microneedle-based treatments.

h. Regulatory Approval: Microneedle-based products must undergo rigorous regulatory scrutiny and approval processes to ensure their safety, efficacy, and quality standards. Meeting regulatory requirements for microneedle-based therapies can involve significant time, resources, and clinical validation studies [88,89,90].

Future Scope of Microneedle Technology

a. The future scope of microneedle technology holds immense potential across various fields, including healthcare, biotechnology, and pharmaceuticals. Here's a detailed overview of the future prospects of microneedle technology:

b. Advanced Drug Delivery Systems: Microneedles offer a promising platform for the development of advanced drug delivery systems capable of delivering a wide range of therapeutics, including small molecules, biologics, and nucleic acids. Future research aims to optimize microneedle designs, materials, and formulations to enhance drug delivery efficiency, precision, and therapeutic outcomes.

c. Personalized Medicine: Microneedle technology enables personalized and patient-centric approaches to drug delivery and healthcare. By tailoring microneedle formulations and treatment regimens to individual patient needs and preferences, personalized medicine can be realized, leading to improved treatment efficacy, safety, and patient satisfaction.

d. Combination Therapies: Microneedles facilitate the co-delivery of multiple drugs or therapeutic agents within a single administration, enabling combination therapies for synergistic or complementary effects. Future developments may focus on integrating different classes of therapeutics, such as drugs, vaccines, and immunomodulators, to address complex diseases and medical conditions more effectively.

e. Point-of-Care Diagnostics: Microneedle-based biosensors and diagnostic devices offer rapid, minimally invasive, and cost-effective solutions for point-of-care testing and disease diagnosis. Future advancements may involve the integration of advanced sensing technologies, such as microfluidics, nanoparticles, and biomarkers, to enable real-time monitoring and detection of diseases, infections, and biomarkers.

f. Wearable and Implantable Devices: Microneedles can be incorporated into wearable and implantable devices for continuous drug delivery, monitoring, and treatment. Future innovations may focus on developing smart microneedle patches, implants, and wearables equipped with sensors, actuators, and feedback mechanisms to provide personalized and responsive healthcare solutions.

g. Biomedical Imaging and Monitoring: Microneedles functionalized with imaging agents or biosensors enable non-invasive imaging and monitoring of physiological parameters, biomarkers, and disease progression. Future research may explore the integration of advanced imaging modalities, such as fluorescence, near-infrared (NIR), and photoacoustic imaging, into microneedle-based devices for enhanced biomedical imaging and diagnostics.

h. Regenerative Medicine and Tissue Engineering: Microneedles offer novel approaches for regenerative medicine and tissue engineering applications, including cell delivery, tissue regeneration, and organ-ona-chip systems. Future developments may focus on optimizing microneedle-based scaffolds, growth factors, and cell delivery strategies to promote tissue repair, regeneration, and organ transplantation.

i. Global Health Initiatives: Microneedle technology has the potential to address global health challenges, such as vaccine delivery in resource-limited settings, disease surveillance, and outbreak response. Future efforts may aim to develop cost-effective, scalable, and easy-to-use microneedle-based solutions for immunization campaigns, disease prevention, and healthcare delivery in underserved populations [86,87,88,89,90].

Conclusion

Microneedle technology represents a progressive approach with vast potential in healthcare and biotechnology. Offering minimally invasive drug delivery, diagnostics, and tissue engineering solutions, microneedles are poised to revolutionize patient care. Additionally, the integration of microfluidic-based formulation adds a new dimension to microneedle technology, enabling precise control over drug release kinetics and the development of smart microneedle systems. With ongoing research and innovation, microneedles coupled with microfluidic-based formulation hold immense promise for addressing unmet medical needs and improving healthcare delivery worldwide.

References

[1] Cheung, K.; Das, D.B. Microneedles for drug delivery: Trends and progress. Drug Deliv. 2016, 23, 2338–2354. [CrossRef]

[2] Larrañeta, E., Lutton, R. E. M., Woolfson, A. D., & Donnelly, R. F. (2016). Microneedle arrays as transdermal and intradermal drug delivery systems: Materials science, manufacture and commercial development. Materials Science and Engineering: R: Reports, 104, 1 - 32. https://doi.org/10.1016/j.mser.2016.03.001

[3] S. Wiedersberg et al.Transdermal drug delivery: 30+ years of war and still fightingJ. Contr. Release (2014)

[4] oxhed, N., Gasser, T. C., Griss, P., Holzapfel, G. A. & Stemme, G. Penetration- enhanced ultrasharp microneedles and prediction on skin interaction for efficient transdermal drug delivery. J. Micro. Syst. 16, 1429–1440 (2007).

[5] Mooney, K.; McElnay, J.C.; Donnelly, R.F. Children's views on microneedle use as an alternative to blood sampling for patient monitoring. Int. J. Pharm. Pract. 2014, 22, 335–344. [CrossRef]

[6] 2-G. Li In vitro transdermal delivery of therapeutic antibodies using maltose microneedles (2009)
[7] C.Martin Low temperature fabrication of biodegradable sugar glass microneedles for transdermal drug delivery applications (2012)
[8] N.N Aung Fabrication, characterization and comparison of α-arbutin loaded dissolving and hydrogel forming microneedles (2020)
[9] E.M. Migdadi Hydrogel-forming microneedles enhance transdermal delivery of metformin hydrochloride (2018)
[10] Dugam S, Tade R, Dhole R, Nangare S. Emerging era of microneedle array for pharmaceutical and biomedical applications: recent advances and toxicological perspectives. Future Journal of Pharmaceutical Sciences. 2021 Dec; 7(1):1-26.
[11] Donnelly, R.F.; Singh, T.R.R.; Morrow, D.I.J.; Woolfson, A.D. Microneedle-Mediated and Intradermal Drug Delivery; John Wiley & Sons, Ltd.: Chichester, UK, 2012.
[12] Milewski, M.; Stinchcomb, A.L. Vehicle composition influence on the microneedle-enhanced transdermal flux of naltrexone hydrochloride. Pharm. Res. 2011, 28, 124–134. [CrossRef]
[13] Schoellhammer C.M., Blankschtein D., Langer R. Skin Permeabilization for Transdermal Drug Delivery: Recent Advances and Future Prospects. Expert Opin. Drug Deliv. 2014; 11:393–407. doi: 10.1517/17425247.2014.875528. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
[14] S.N. Murthy et al.Magnetophoresis for enhancing transdermal drug delivery: mechanistic studies and patch design J. Contr. Release(2010)
[15] Y. Li Fabrication of sharp silicon hollow microneedles by deep-reactive ion etching towards minimally invasive diagnostics (2019)
[16] Y.-C. Kim et al. Microneedles for drug and vaccine delivery Adv. Drug Deliv. Rev.2012
[17] X. Chen Dry-coated microprojection array patches for targeted delivery of immunotherapeutics to the skin (2009)
[18] Tuan-Mahmood, T.-M.; McCrudden, M.T.C.; Torrisi, B.M.; McAlister, E.; Garland, M.J.; Singh, T.R.R.; Donnelly, R.F. Microneedles for intradermal and transdermal drug delivery. Eur. J. Pharm. Sci. 2013, 50, 623–637. [Google Scholar] [CrossRef] [PubMed] [Green Version]
[19] L.C. Ng et al.Transdermal drug delivery systems in diabetes management: A review Asian J. Pharm.Sci.(2020)
[20] L.M. Prisant et al. Novel drug-delivery systems for hypertension Am. J. Medicine. (1992)
[21] Y.H. Chen et al. Implantable microneedles with an immune-boosting function for effective intradermal influenza vaccination Acta Biomatter. (2019)
[22] Prausnitz, M.R. Microneedles for transdermal drug delivery. Adv. Drug Deliv. Rev. 2004, 56, 581–587. [CrossRef]
[23] Kim, Y.C.; Park, J.H.; Prausnitz, M.R. Microneedles for drug and vaccine delivery. Drug Deliv. Transl. Res. 2015, 5, 311–312. [Google Scholar] [CrossRef] [Green Version]
[24] Yang J, Liu X, Fu Y, Song Y. Recent advances of microneedles for biomedical applications: drug delivery and beyond. Acta Pharmaceutica Sinica B. 2019 May 1; 9(3):469-83. https://doi.org/10.1016/j.apsb.2019.03.007
[25] Guillot AJ, Cordeiro AS, Donnelly RF, Montesinos MC, Garrigues TM, Melero A. Microneedle-based delivery: An overview of current applications and trends. Pharmaceutics. 2020 Jun; 12(6):569. https://doi.org/10.3390/pharmaceutics12060569
[26] C. Jäger et al.Transmission electron microscopy investigations of the formation of macropores in n- and p-Si(001)/(111) Mater. Sci. Eng. (2000)
[27] Z. Zhao, Y. Chen, Y. Shi, Microneedles: a potential strategy in transdermal delivery and application in the management of psoriasis, RSC Adv. 10 (2020) 14040–14049.
[28] S.L. Banks J. Pharm. Sci. (2010)

[29] G. Roy Int. J. Pharm. (2019)

[30] L. Olansky, et al., Finger-stick glucose monitoring issues of accuracy and specificity, Diabetes Care 33 (2010) 948–949.

[31] Falabella AF, Falanga VFeinkel RK, Woodley DT. Wound healing The Biology of Skin. 2000 New York Parthenon:281–99

[32] Orentreich D, Orentreich N. Acne scar revision update. Dermatol Clin. 1987; 5:359–68. [PubMed] [Google Scholar]

[33] T Pooja, K V T. Gopal, T Narayana Rao, B Gayatri Devi, S Ashwin Kumar. A randomized study to evaluate the efficacy fractional CO2laser, microneedling and platelet rich plasma in post-acne scarring. Indian Dermatology Online Journal. 2020;11(3):349-354. https://pubmed.ncbi.nlm.nih.gov/32695692/

[34] S.R. Patel, A.S.P. Lin, H.F. Edelhauser, M.R. Prausnitz Suprachoroidal drug delivery to the back of the eye using hollow microneedles Pharm. Res., 28 (2011), pp. 166-176, 10.1007/s11095-010-0271-y

[35] R.R. Thakur Singh, I. Tekko, K. McAvoy, H. McMillan, D. Jones, R.F. Donnelly Minimally invasive microneedles for ocular drug delivery Expert Opin. Drug Deliv., 14 (2017), pp. 525-537, 10.1080/17425247.2016.1218460

[36] Hong, X.; Wu, Z.; Chen, L.; Wu, F.; Wei, L.; Yuan, W. Hydrogel Microneedle Arrays for Transdermal Drug Delivery. Nano-Micro Lett. 2014, 6, 191–199. [CrossRef]

[37] Ling, M.H.; Chen, M.C. Dissolving polymer microneedle patches for rapid and efficient transdermal delivery of insulin to diabetic rats. Acta Biomater. 2013, 9, 8952–8961. [CrossRef]

[38] Quinn, H.L.; Bonham, L.; Hughes, C.M.; Donnelly, R.F. Design of a Dissolving Microneedle Platform for Transdermal Delivery of a Fixed-Dose Combination of Cardiovascular Drugs. J. Pharm. Sci. 2015, 104,3490–3500. [CrossRef]

[39] Yuan, W.; Hong, X.; Wu, Z.; Chen, L.; Liu, Z.; Wu, F.; Wei, L.L. Dissolving and biodegradable microneedle technologies for transdermal sustained delivery of drug and vaccine. Drug Des. Dev. Ther. 2013, 7, 945–952. [Google Scholar] [CrossRef] [Green Version]

[40] O'Mahony, C. Structural characterization and in-vivo reliability evaluation of silicon microneedles. Biomed. Microdevices 2014, 16, 333–343. [Google Scholar] [CrossRef] [PubMed]

[41] Donnelly, A.D.W.R.F.; Singh, T.R.R.; Morrow, D.I.J. Microneedle-Mediated Transdermal and Intradermal Drug Delivery; John Wiley & Sons: Hoboken, NJ, USA, 2012. [Google Scholar]

[42] Singh T., Mcmillan H., Mooney K., Alkilani A., Donnelly R. Microneedles for drug delivery and monitoring. Microfluid. Devices Biomed. Appl. 2013:185–230. doi: 10.1533/9780857097040.2.185. [CrossRef] [Google Scholar]

[43] Donnelly R.F., Singh T.R.R., Larrañeta E., McCrudde M.T.C. Microneedles for Drug and Vaccine Delivery and Patient Monitoring. John Wiley and Sons, Incorporated; Hoboken, NJ, USA: 2018. [Google Scholar]

[44] Sharma, D. Microneedles: An Approach in Transdermal Drug Delivery: A Review. PharmaTutor 2018, 6, 7–15. [CrossRef]

[45] Badilescu, S.; Packirisamy, M. BioMEMS: Science and Engineering Perspectives; CRC Press: Boca Raton, FL, USA, 2016.

[46] Verbaan, F.; Bal, S.; Berg, D.-J.V.D.; Groenink, W.; Verpoorten, H.; Lüttge, R.; Bouwstra, J. Assembled microneedle arrays enhance the transport of compounds varying over a large range of molecular weight across human dermatomed skin. J. Control. Release 2007, 117, 238–245. [CrossRef] [PubMed]

[47] J. M. Quemper, S. Nicolas, J. P. Gilles, J. P. Grandchamp, A. Bosseboeuf, T. Bourouina, and E. Dufour-Gergam, Sens. Act. A, 74(1–3), 1 (1999)

[48] Pignatello, R. Biomaterials: Applications for Nanomedicine; BoD–Books on Demand: Norderstedt, Germany, 2011

[49] Indermun, S.; Luttge, R.; Choonara, Y.; Kumar, P.; du Toit, L.; Modi, G.; Pillay, V. Current advances in the fabrication of microneedles for transdermal delivery. J. Control. Release 2014, 185, 130–138. [CrossRef]

[50] Jeggy, C. Micro-Injection Moulding: From Process to Modelling; Presses Univ. de Louvain: Louvain-la-Neuve, Belgium, 2004.

[51] Lee H, et al. porous microneedles on a paper for screening test of prediabetes. Med Devices Sens. 2020;3(4): e10109.

[52] Wang, M.; Hu, L.; Xu, C. Recent Advances in the Design of Polymeric Microneedles for Transdermal Drug Delivery and Biosensing. Lab Chip 2017, 17, 1373–1387. [Google Scholar] [CrossRef]

[53] Bariya S.H., Gohel M.C., Mehta T.A., Sharma O.P. Microneedles: An emerging transdermal drug. J. Pharm. Pharmacol. 2012; 64:11–29. doi: 10.1111/j.2042-7158.2011.01369. x. [PubMed] [CrossRef] [Google Scholar]

[54] Roxhed N. A Fully Integrated Microneedle-Based Transdermal Drug Delivery System. KTH—Royal Institute of Technology; Stockholm, Sweden: 2007. [Google Scholar]

[55] Razali A.R., Qin Y. A review on micro-manufacturing, micro-forming and their key issues. Procedia Eng. 2013; 53:665–672. doi: 10.1016/j.proeng.2013.02.086. [CrossRef] [Google Scholar]

[56] Nuxoll E. BioMEMS in drug delivery. Adv. Drug Deliv. Rev. 2013; 65:1611–1625. doi: 10.1016/j.addr.2013.07.003. [PubMed] [CrossRef] [Google Scholar]

[57] Kathuria H., Kang K., Cai J., Kang L. Rapid microneedle fabrication by heating and photolithography. Int. J. Pharm. 2020; 575:118992. doi: 10.1016/j.ijpharm.2019.118992. [PubMed] [CrossRef] [Google Scholar]

[58] Ita K. Transdermal delivery of drugs with microneedles: Strategies and outcomes. J. Drug Deliv. Sci. Technol. 2015; 29:16–23. doi: 10.1016/j.jddst.2015.05.001. [CrossRef] [Google Scholar]

[59] Gill H.S., Prausnitz M.R. Coated microneedles for transdermal delivery. J. Control. Release. 2007; 117:227–237. doi: 10.1016/j.jconrel.2006.10.017. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[60] Martanto W., Davis S.P., Holiday N.R., Wang J., Gill H.S., Prausnitz M.R. Transdermal delivery of insulin using microneedles in vivo. Pharm. Res. 2004; 21:947–952. doi: 10.1023/B: PHAM.0000029282.44140.2e. [PubMed] [CrossRef] [Google Scholar]

[61] Gill H.S., Prausnitz M.R. Coating formulations for microneedles. Pharm. Res. 2007; 24:1369–1380. doi: 10.1007/s11095-007-9286-4. [PubMed] [CrossRef] [Google Scholar]

[62] Nagarkar R., Singh M., Nguyen H.X., Jonnalagadda S. A review of recent advances in microneedle technology for transdermal drug delivery. J. Drug Deliv. Sci. Technol. 2020; 59:101923. doi: 10.1016/j.jddst.2020.101923. [CrossRef] [Google Scholar]

[63] Omatsu T., Chujo K., Miyamoto K., Okida M., Nakamura K., Aoki N., Morita R. Metal microneedle fabrication using twisted light with spin. Opt. Express. 2010; 18:7616–7622. doi: 10.1364/OE.18.017967. [PubMed] [CrossRef] [Google Scholar]

[64] Norman J.J., Choi S.O., Tong N.T., Aiyar A.R., Patel S.R., Prausnitz M.R., Allen M.G. Hollow microneedles for intradermal injection fabricated by sacrificial micromolding and selective electrodeposition. Biomed. Microdevices. 2013; 15:203–210. doi: 10.1007/s10544-012-9717-9. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[65] Park J.H., Allen M.G., Prausnitz M.R. Biodegradable polymer microneedles: Fabrication, mechanics and transdermal drug delivery. J. Control. Release. 2005; 104:51–66. doi: 10.1016/j.jconrel.2005.02.002. [PubMed] [CrossRef] [Google Scholar]

[66] Indermun S., Luttge R., Choonara Y.E., Kumar P., Du Toit L.C., Modi G., Pillay V. Current advances in the fabrication of microneedles for transdermal delivery. J. Control. Release. 2014; 185:130–138. doi: 10.1016/j.jconrel.2014.04.052. [PubMed] [CrossRef] [Google Scholar]

[67] McGrath M.G., Vucen S., Vrdoljak A., Kelly A., O'Mahony C., Crean A.M., Moore A. Production of dissolvable microneedles using an atomised spray process: Effect of microneedle composition on skin penetration. Eur. J. Pharm. Biopharm. 2014; 86:200–211. doi: 10.1016/j.ejpb.2013.04.023. [PubMed] [CrossRef] [Google Scholar]

[68] Wu L., Takama N., Park J., Kim B., Kim J., Jeong D. Shadow mask assisted droplet-born air-blowing method for fabrication of dissoluble microneedle; Proceedings of the 12th International Conference on Nano/Micro Engineered and Molecular Systems; Los Angeles, CA, USA. 9–12 April 2017; pp. 456–459. [Google Scholar]

[69] Gupta J., Felner E.I., Prausnitz M.R. Minimally invasive insulin delivery in subjects with type 1 diabetes using hollow microneedles. Diabetes Technol. Ther. 2009; 11:329–337. doi: 10.1089/dia.2008.0103. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[70] Martanto W., Moore J.S., Kashlan O., Kamath R., Wang P.M., O'Neal J.M., Prausnitz M.R. Microinfusion using hollow microneedles. Pharm. Res. 2006; 23:104–113. doi: 10.1007/s11095-005-8498-8. [PubMed] [CrossRef] [Google Scholar]

[71] . Mahadevan G., Sheardown H., Selvaganapathy P. PDMS embedded microneedles as a controlled release system for the eye. J. Biomater. Appl. 2013; 28:20–27. doi: 10.1177/0885328211433778. [PubMed] [CrossRef] [Google Scholar]

[72] Economidou S.N., Lamprou D.A., Douroumis D. 3D printing applications for transdermal drug delivery. Int. J. Pharm. 2018; 544:415–424. doi: 10.1016/j.ijpharm.2018.01.031. [PubMed] [CrossRef] [Google Scholar]

[73] Gittard S.D., Miller P.R., Jin C., Martin T.N., Boehm R.D., Chisholm B.J., Stafslien S.J., Daniels J.W., Cilz N., Monteiro-Riviere N.A., et al. Deposition of antimicrobial coatings on microstereolithography-fabricated microneedles. Jom. 2011; 63:59–68. doi: 10.1007/s11837-011-0093-3. [CrossRef] [Google Scholar]

[74] El-Sayed N., Vaut L., Schneider M. Customized fast-separable microneedles prepared with the aid of 3D printing for nanoparticle delivery. Eur. J. Pharm. Biopharm. 2020; 154:166–174. doi: 10.1016/j.ejpb.2020.07.005. [PubMed] [CrossRef] [Google Scholar]

[75] Jamróz W., Szafraniec J., Kurek M., Jachowicz R. 3D Printing in Pharmaceutical and Medical Applications—Recent Achievements and Challenges. Pharm. Res. 2018; 35:176. doi: 10.1007/s11095-018-2454-x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[76] Pere C.P.P., Economidou S.N., Lall G., Ziraud C., Boateng J.S., Alexander B.D., Lamprou D.A., Douroumis D. 3D printed microneedles for insulin skin delivery. Int. J. Pharm. 2018; 544:425–432. doi: 10.1016/j.ijpharm.2018.03.031. [PubMed] [CrossRef] [Google Scholar]

[77] Alhnan M.A., Okwuosa T.C., Sadia M., Wan K.W., Ahmed W., Arafat B. Emergence of 3D Printed Dosage Forms: Opportunities and Challenges. Pharm. Res. 2016; 33:1817–1832. doi: 10.1007/s11095-016-1933-1. [PubMed] [CrossRef] [Google Scholar]

[78] Prasad L.K., Smyth H. 3D Printing technologies for drug delivery: A review. Drug Dev. Ind. Pharm. 2016; 42:1019–1031. doi: 10.3109/03639045.2015.1120743. [PubMed] [CrossRef] [Google Scholar]

[79] Lim S.H., Kathuria H., Tan J.J.Y., Kang L. 3D printed drug delivery and testing systems—A passing fad or the future? Adv. Drug Deliv. Rev. 2018; 132:139–168. doi: 10.1016/j.addr.2018.05.006. [PubMed] [CrossRef] [Google Scholar]

[80] . Goole J., Amighi K. 3D printing in pharmaceutics: A new tool for designing customized drug delivery systems. Int. J. Pharm. 2016; 499:376–394. doi: 10.1016/j.ijpharm.2015.12.071. [PubMed] [CrossRef] [Google Scholar]

[81] Awad A., Trenfield S.J., Gaisford S., Basit A.W. 3D printed medicines: A new branch of digital healthcare. Int. J. Pharm. 2018; 548:586–596. doi: 10.1016/j.ijpharm.2018.07.024. [PubMed] [CrossRef] [Google Scholar]

[82] Chen, C., Mehl, B. T., Munshi, A. S., Townsend, A. D., Spence, D. M., & Martin, R. S. (2016). 3D-printed microfluidic devices: fabrication, advantages and limitations—a mini review. Analytical Methods, 8(31), 6005-6012.

[83] Cheng, Z., Gu, Y., Li, S., Wang, Y., Chen, H., Cheng, J., & Liu, P. (2017). Enclosed casting of epoxy resin for rapid fabrication of rigid microfluidic chips. Sensors and Actuators B: Chemical, 252, 785-793.

[84] Chung, B. G., Lee, K. H., Khademhosseini, A., & Lee, S. H. (2012). Microfluidic fabrication of microengineered hydrogels and their application in tissue engineering. Lab on a Chip, 12(1), 45-59.

[85] Jung W., Han J., Choi J.-W., Ahn C.H. Point-of-care testing (POCT) diagnostic systems using microfluidic lab-on-a-chip technologies. Microelectron. Eng. 2015; 132:46–57. doi: 10.1016/j.mee.2014.09.024. [CrossRef] [Google Scholar]

[86] Patabadige D.E.W., Jia S., Sibbitts J., Sadeghi J., Sellens K., Culbertson C.T. Micro Total Analysis Systems: Fundamental Advances and Applications. Anal. Chem. 2016; 88:320–338. doi: 10.1021/acs.analchem.5b04310. [PubMed] [CrossRef] [Google Scholar]

[87] Samper I.C., Gowers S.A.N., Booth M.A., Wang C., Watts T., Phairatana T., Vallant N., Sandhu B., Papalois V., Boutelle M.G. Portable Microfluidic Biosensing System for Real-Time Analysis of Microdialysate in Transplant Kidneys. Anal. Chem. 2019; 91:14631–14638. doi: 10.1021/acs.analchem.9b03774. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[88] Ita K. Transdermal Delivery of Drugs with Microneedles-Potential and Challenges. Pharmaceutics. 2015; 7:90–105. doi: 10.3390/pharmaceutics7030090. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[89] Alimardani V., Abolmaali S.S., Yousefi G., Rahiminezhad Z., Abedi M., Tamaddon A., Ahadian S. Microneedle Arrays Combined with Nanomedicine Approaches for Transdermal Delivery of Therapeutics. J. Clin. Med. 2021; 10:181. doi: 10.3390/jcm10020181. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[90] Henry S., McAllister D.V., Allen M.G., Prausnitz M.R. Microfabricated microneedles: A novel approach to transdermal drug delivery. J. Pharm. Sci. 1998; 87:922–925. doi: 10.1021/js980042+. [PubMed] [CrossRef] [Google Scholar]

[91] Avcil M., Akman G., Klokkers J., Jeong D., Çelik A. Clinical efficacy of dissolvable microneedles armed with anti-melanogenic compounds to counter hyperpigmentation. J. Cosmet. Dermatol. 2021; 20:605–614. doi: 10.1111/jocd.13571. [PubMed] [CrossRef] [Google Scholar]