Microneedle patches: revolutionizing transdermal drug delivery – a comprehensive review

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ABSTRACT

Transdermal drug delivery offers a non-invasive method for administering medications, bypassing issues associated with oral delivery. However, challenges such as molecular size and Hydrophilicity limit its efficacy. Microneedles have garnered significant attention in recent years as a minimally invasive drug delivery system with potential applications in various fields such as medicine, cosmetics, and vaccinations. This review provides an overview of microneedle and its types, methodology, applications, challenges like compatibility, safety, cost- effectiveness and recent advances of microneedles are discussed. Moreover, the potential of microneedles in enhancing drug delivery efficiency, improving patient compliance, and enabling pain-free administration is highlighted. Microneedles can be fabricated by blending polyvinyl alcohol (PVA), Hydroxyethyl cellulose (HEC), and glycerol to create a biocompatible matrix suitable for drug delivery through the skin. The combination offers mechanical strength, flexibility, and enhanced skin penetration.

Keyword: Microneedle patches, Transdermal drug delivery, Hollow microneedles, Fabrication techniques, Micromolding, Recent advancements in microneedle technology, SDG 3: Good Health and Well-Being

1. Introduction

A medicated adhesive patch called a transdermal patch is applied to the skin in order to transfer a certain dosage of medication through the skin and into the bloodstream. Because the patch enables a regulated flow of the medication into the patient, transdermal drug delivery has a benefit beyond other forms of administration techniques (which include oral, cutaneous, intravenous, or subcutaneous). This is usually achieved by either using body heat to melt thin layers of medication incorporated in the adhesives or by covering a medication reservoir with a porous membrane [1]. The primary drawback of transdermal administration methods is that only drugs whose molecules are tiny enough to pass through the skin can be administered using this technique because the epidermis is an extremely effective barrier.

To overcome skin restriction, researchers have developed microneedle transdermal patches (MNPs), which are composed of a variety of microneedles. This makes it possible for a greater range of compounds or molecules to penetrate the epidermis without first micronising the drug. MNPs offer the advantages of controlled medication release and simple application without requiring the assistance of a medical professional. Advanced MNPs technology allows for the customisation of medication administration for local applications, such as skin whitening. MNPs applied to the face. Many MNP types have been developed in order to enter tissue apart from skin, which includes within tissues of the oral cavity and the gastrointestinal tract. These facilitate the molecule's quicker and more direct distribution to the intended location [2]. These attributes of microneedle-based transdermal systems support Sustainable Development Goal 3 (Good Health and Well-Being) by promoting safer, more effective, and patient-friendly drug delivery approaches.

The main components to a transdermal patch are

Liner - keeps the patch intact during storage. The liner is removed before use.
Drug - The medication solution near the release liner
Adhesive - Required to hold the patch's parts together and adhere it to the skin.
Membrane - Controls the drug's release from numerous layer patches and reservoirs.
Backing - This shields the patch from the outside world.
Penetration enhancers - are drug permeation promoters that improve drug delivery.
Matrix Filler - Gives the matrix bulk; some also serve as agents that stiffen the matrix.

2. Microneedle patch

Microneedle patches (MNPs) are an advanced transdermal drug delivery system that retain the benefits of conventional patches while overcoming their major limitations. They penetrate the stratum corneum (~20 μm thick), enabling the delivery of macromolecules that cannot pass through the skin by passive diffusion. A typical microneedle patch contains approximately 10^2–10^4 microneedles per square centimetre, which are either coated with or loaded with therapeutic agents. Unlike traditional transdermal systems that are limited to small, lipophilic drugs such as nicotine and hormonal contraceptives, microneedles (100–1000 μm in length) bypass the skin barrier without stimulating pain receptors, ensuring a minimally invasive and painless application [3].

Microneedles are generally classified as water-soluble needles made from biodegradable polymers or saccharides, and non-water-soluble needles fabricated from metals, ceramics, or polymers. In addition to transdermal delivery, microneedle technology is being investigated for drug administration across various external and internal tissues, including the eyes, scalp, oral cavity, gastrointestinal tract, and vascular walls. This approach allows localized and precise drug delivery, reducing dependence on systemic diffusion and improving therapeutic efficiency compared to conventional transdermal patches [4].

2.1 MNPs drug delivery

MNPs provide more effective delivery than topical or oral consumption, as was previously indicated. Researchers aim to achieve quicker peak concentrations (C max) in MNPs as opposed to alternative approaches in drug delivery studies. According to the study, oral consumption achieves highest concentration in an hour, whereas MNPs reach maximal concentration as quickly as twenty minutes (t max). Additionally, compared to oral ingestion, the C max from MNPs is up to 6 times higher. ensuring that the appropriate medications are delivered quickly and that the body receives the highest concentration of them. Only direct injection can equal this value; however, MNPs could be a substitute to attain roughly the same time and concentration in cases of skin injuries and needle anxiety [3][6].

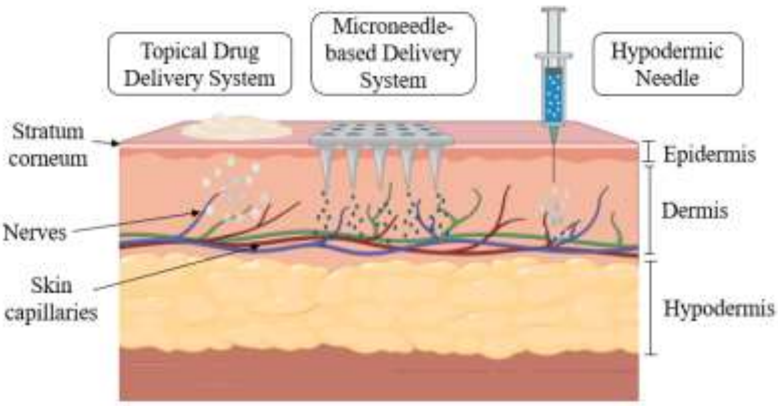


Figure 1. Schematic representation of different type of delivery system

Table 1. MNPs can be applied to tissues other than the skin.

INTERNAL SURFACE	EXTERNAL SURFACE
Mouth	Skin
Vagina	Eye
Gastrointestinal tract	Finger
Vascular wall	Scalp

2.2. Classification of microneedles

Different MNs may be chosen depending upon various situations and several advances have been made in terms of microneedles that can be fabricated [5].

2.2.1. Biodegradable MNs

Water-dissolving needles, typically composed of dissolving polymers or saccharides, face challenges in efficiently delivering drugs to the dermal layer due to premature dissolution. However, researchers have addressed this issue by creating a water-insoluble backing layer. This innovation extends the lifespan of the needles within the body environment, enabling more effective drug delivery. With this design, over 90% of the drug can be efficiently delivered within just 5 minutes of applying these microneedle patches to the skin [6].

2.2.2. Solid MNs

Solid microneedle patches (MNs) made of materials like metal or ceramic offer consistent drug delivery without dissolution in the body. While they provide better performance, they're considered the older version of MNPs. However, they pose waste management challenges. Recycling these materials is difficult due to the small quantities used in each patch, making the process cost-prohibitive [7]. To address this, researchers are working on developing dissolvable MNPs with similar performance characteristics. These innovations aim to achieve effective drug delivery while mitigating waste issues associated with non-soluble MNs [8].

2.2.3. Hollow MNs

Hollow microneedles are a significant advancement in drug delivery and monitoring applications. These microneedles have the capability to penetrate the skin, enabling the extraction of bodily fluids and the administration of medications into living skin layers [8]. Unlike other types of microneedles, hollow microneedles have made their way into the pharmaceutical market as medical devices. They offer advantages such as controlled drug release over time, the ability to handle large doses of drug solutions, and the potential for quick drug delivery to the skin. However, they require careful design and insertion methods to prevent issues like leakage, clogging, and infection. Hollow microneedles are particularly valuable for applications in drug delivery, vaccine delivery, and disease diagnosis [9].

2.2.4. Coated MNs

Coated microneedles can retrieve bodily fluids or administer medications into the layers of skin that are still alive. They are therefore useful for applications including the delivery of medications, vaccinations, and disease diagnosis. In order to increase medication delivery efficiency and decrease drug waste, coating techniques have been developed to specifically coat only the microneedle shafts without contaminating the base substrate. A vast array of materials, including as proteins, DNA, viruses, and microparticles, can be used to apply coatings. Coatings can be designed to swiftly melt into the skin [8].

2.2.5. Hydrogel forming MNs

Hydrogel-forming microneedles (HFMs) are a promising transdermal drug delivery system with several advantages over traditional microneedles. According to the search results:

HFMs are composed of cross-linked polymers that, upon insertion into the skin, can quickly absorb interstitial fluid, forming continuous conduits between the drug reservoirs attached to them and the dermal microcirculation. Drug release can continue in this way. varied levels of polymerization in the hydrogel matrix can lead to varied profiles of drug release and swelling rates.

Flowing hydrogel state of the microneedle matrix is put into a mold and allowed to dry, a process known as micro molding that can be used to create HFMs. Drug release characteristics, including burst and sustained release, differ due to the variable degrees of polymerization of the cross-linked polymers employed in HFMs, which provide different swelling and water absorption capabilities and structures. Using "super-swelling" polymers like PMVE/MAPEG, HFMs can release medications in a sustainable manner by rapidly absorbing interstitial fluid after insertion into the skin, creating continuous conduits between the dermal microcirculation and the drug reservoir [10].

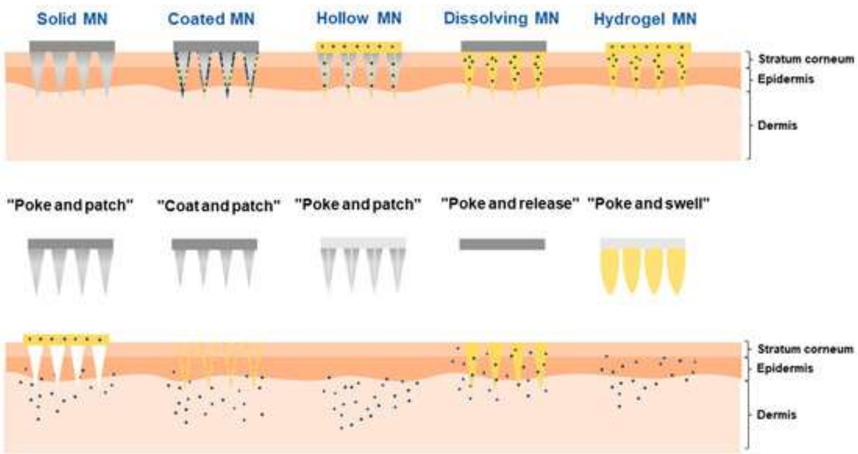


Figure 2. Different types of Microneedles

3. Methodology

Silicon was initially used to make microneedles because the microelectronics sector offered instruments for producing integrated circuits that could be modified for microneedle production. Silicon is currently the most widely used material for microneedles. Despite the fact that this technology has generated a lot of interest and has the potential to be produced in large quantities, the manufacturing process involves a number of intricate steps and costly equipment that is housed in cleanroom facilities specifically designed for planar integrated circuit designs but modified for microelectromechanical systems. Two-photon polymerization (TPP) and 3D printing are two promising new revolutionary technologies that have emerged in recent years for alternative manufacturing. Using layer-by-layer processing, these additive manufacturing techniques produce three-dimensional structures. Rapid prototyping techniques, in contrast to previous microfabrication methods created for microneedles, do not necessitate costly cleanroom facilities and enable the realization of complex geometries with less technical competence and in a shorter amount of time. This is a significant benefit for the creation of microneedle patch arrays that need microfluidic elements integrated for drug delivery or point-of-care diagnostics. The recent commercialization of TPP microtechnology by German companies like Nanoscribe GmbH has made submicron resolution production precise, versatile, and possible [11].

3.1. Fabrication without mould

3.1.1. Photolithography with etching

Metal deposition, selective etching, and photolithography were used to make the microneedles. Photolithography is used in the manufacturing process to create a microsized pattern, and then metals, like chromium, are deposited as a layer of mask material. The patterned wafer is etched using either a wet or dry etching technique, this may create a series of spiky silicon peaks brought on by vertical etching of the exposed silicon layer and a small lateral under-etch masked zone [12].

3.1.2. Laser engraving

In applications involving micro drilling and cutting, laser ablation has been a commonly used top-down material processing method. A 3D microneedle structure with the required height and pitch can be directly created using laser processing. Since PDMS has a low melting point, laser processing would result in uneven depth and issues with burning and resolidification. However, the laser approach can be used to manufacture an array of microneedles from a range of materials, including metals, PMMA, and PDMS. Instead, a CO_2 direct writing laser was used to manufacture the PMMA microneedle mould structure, enabling the secondary casting PDMS approach to create the PLGA microneedles with a 700 µm–1100 µm range. The surface roughness of the produced PMMA microneedles was one of its drawbacks. produced the metal solid microneedles using an optical vortex process with circular polarisation. The laser-generated plasma rotated along the light intensity curve during the ablation process, creating a smoother microneedle surface. They produced a variety of metal microneedles having uniform needle height and shape using this method [13].

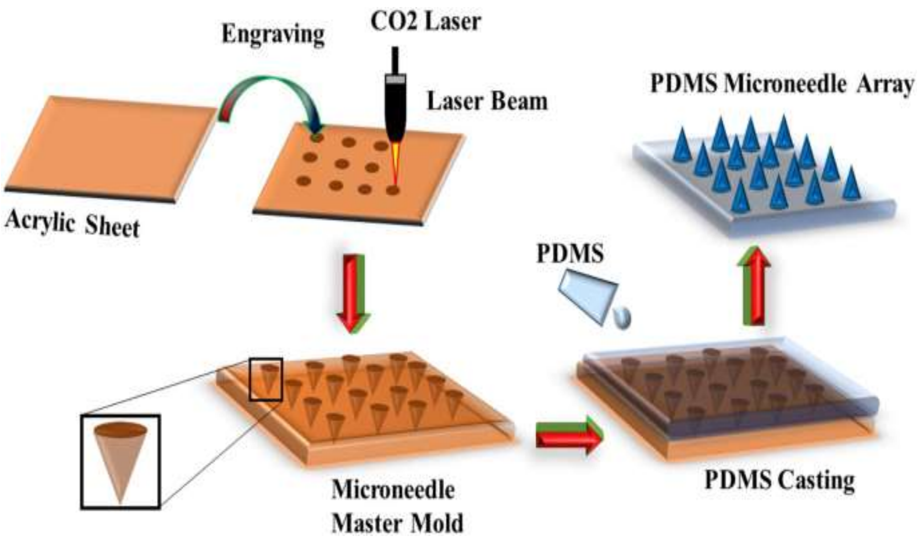


Figure 3. Laser Engraving

3.1.3. Micro-milling

Another technique for producing microneedles was micro-milling. An array of ball-end micro-end milling cutters for creating conical-shaped stainless-steel needles was produced. However, the technology is economically inappropriate because to its extremely long production time, and it is difficult to adapt repeated batch processes to high-throughput manufacturing scalability. Additionally, this procedure would wear out or even ruin the tool [14].

3.1.4. 3D printing

Making microneedles quickly is possible with 3D printing. It is possible to construct the microneedle structure instantly from computer graphics data without the use of molds or machining. This greatly speeds up the process of developing new products, lowers wasteful material usage, boosts productivity, and lowers production costs. The microneedle 3D printing process often consists of multiple phases. Initially, a few parameters are needed to build the microneedle structure using tools like SolidWorks. The right materials and characteristics for a 3D printer to process are then developed and determined using a simulation study, which takes stress, pressure, and force into account. Stereolithography (SLA), fused deposition modelling (FDM), and digital light processing (DLP) are the three main 3D printing methods that have been researched. For these two methods, a feature size as small as 100 µm can be used. The precision of FDM printing technology is influenced by two factors: temperature and release nozzle size [15].

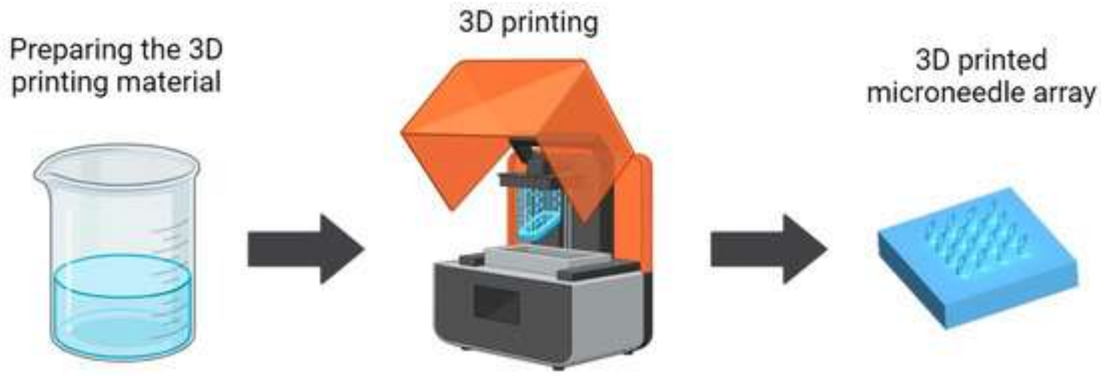


Figure 4. A schematic illustrating the 3D printing (resin-based) process for fabricating MNAs

3.2. Fabrication with mould

3.2.1. Soft Lithography

An approach that is frequently utilized for pattern transfer is soft lithography. Typically, the transfer process involves pouring polymeric materials into a mold, from which the desired material's microneedles are extracted once they have dried and been demolded. Microfabrication, traditional machining, or 3D printing were used to create the initial architectures of microneedles or cavities. Microneedles or their adverse pattern, the voids, could have been the original mould. A two-step transfer method was employed for the microneedle structure-based mould: the microneedles were first placed into the cavities, and then they were transferred into the required material using the cavities. The microneedles for the structure-based cavity mould are obtained immediately through a one-step transfer process. The microneedles that are produced can be made of PMMA, SU-8, Si, or PDMS [16].

3.2.2. Vapor deposition

Vapor deposition by itself is not sufficient to complete the fabrication process and must be combined with additional steps such as photolithography and etching. Its primary function is to deposit a metal layer onto the silicon substrate, after which the deposited films are patterned using suitable photolithographic and etching techniques [16]. The raw materials are heated in physical vapor deposition-based processes, which cause vapors to be released from the source (the substance to be coated) and deposit on the substrate surface. Chemical reactions between the heated substrate and inert carrier gases inside the deposition chamber create thin coatings in chemical vapour deposition.

3.2.3. Micro-injection molding

The microneedles in the required material are made using a similar pattern transfer method called hot embossing and micro-injection moulding. For the micro-injection, a micro-injector and compression technique were used to inject the solution into the mold's cavities. The quality of microneedles during the injection process is significantly impacted by the injection rate, melt temperature, and secondary gripping pressure [17].

3.2.4. Hot Embossing

Hot embossing involves heating the material to the moulding temperature, applying and maintaining pressure during cooling, controlling displacement and mechanical strength under isothermal conditions, and finally demoulding the patterned structure. The quality of the resulting microneedles is governed by embossing parameters such as temperature, pressure, and processing time, with the process dependent on the interaction between the thermal gradient and the applied pressure field.

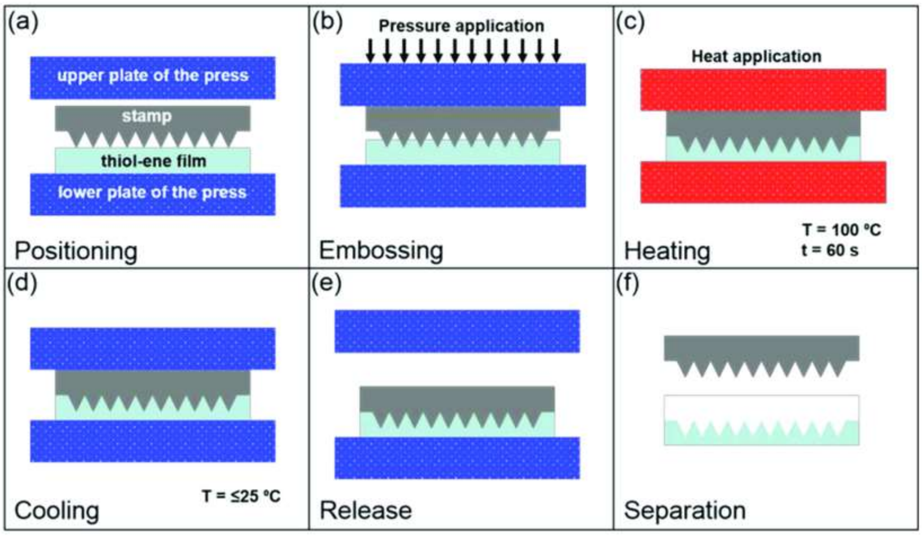


Fig-5. Hot Embossing

3.2.5. Fabrication of carbohydrate and polymeric microneedles

Numerous mould-based approaches have been used to make polymeric MNs. Among these processes include casting, hot embossing, injection moulding, investment moulding, drawing lithography, and X-ray based methods. Conversely, however, lithographic sketching is a unique additive process for producing MNs. This method directly expands 2D viscous polymeric materials to form 3D polymeric structures. The polymer is cooled to the point at which it becomes a viscous, thick liquid. The transverse upward movement of the drawing pillars leads 3D objects to be selectively stretched from the 2D glassy liquid-plate once they interact with a covered glassy liquid surface through plate movement. The polymer is then isolated and cured [18].

4. Applications of microneedle array technique in transdermal drug delivery

Microneedles indeed offer a range of advantages in medical applications. In drug delivery, they provide targeted and controlled release, while in biosensors, they enable precise and minimally invasive monitoring. Their versatility makes them valuable tools in advancing healthcare technology. Application of transdermal microneedles: medication delivery, identification, and bodily fluid extraction

- **Biosensing**

A potential method for the painless and ongoing identification of biomarkers, improving illness monitoring and management, is provided by microneedle-based biosensors. The range of biosensors built with microneedles, including those for alcohol, glucose, lactate, beta-lactam, and lactate, demonstrate their promise in a number of different medical applications.

- **Lactate biosensor**

In the beginning, lactate buildup may result in pain and exhaustion; but, if treatment is not received, it may induce body acidification and major health problems. Using dynamic light micro-stereo lithography, Miller created a hollow microneedle sensor.
Electrodeposited Au multiwalled carbon nanotubes and electro-polymerized mediators, such as methylene blue, functionalized the microneedles, improving the sensor's stability in interstitial fluid and anti-interference ability. In both human serum and artificial interstitial fluid, the sensor performed admirably [19].

- **Alcohol biosensor**

Drinking alcohol can lead to a number of illnesses that impact the heart, pancreas, liver, brain, and even raise the chance of cancer. Vinu Mohan and associates created a subcutaneous alcohol sensor that makes use of microneedles. This gadget used silver and platinum wires as electrodes and was made up of three hollow microneedles. Alcohol content could be measured in mice isolated skin models and artificial interstitial fluid using alcohol oxidase mounted on a platinum wire

- **Beta-lactam biosensor**

Strong bactericidal properties, little toxicity, a wide range of applications, and superior clinical efficacy are all displayed by beta-lactam antibiotics. By electro positing iridium oxide on platinum microneedle surfaces and immobilizing β-lactamase with a hydrogel, Timothy and associates created a beta-lactam microneedle sensor. To find the beta-lactam concentrations, they used data analysis and the logarithmic plot for the potential of open circuits and the Hill's potential equation [20].

4.1. Clinical applications of microneedle sensing

Recently, UCSD started research to create a minimally invasive microneedle detector that would track levodopa levels in real time, with a focus on Parkinson's disease patients. Beginning in November 2022, the project assessed the device's safety, accuracy, and tolerability.

Gowers et al. presented a unique microneedle-based biosensor that uses a pH-sensitive iridium oxide layer to detect local pH changes brought on by β-lactamase hydrolysis. The biosensors' real-time tracking of penicillin concentrations was shown through trials involving participants in good health.

An integrated glucose sensor was created by Ribet et al. It consists of a tiny sensing probe with a 3-electrode electrochemical battery inside a hollow silicon microneedle. This technology uses capillaries to draw tissue fluid; the transdermal component is a lot smaller than those seen in currently available commercial goods.

Human forearm amperometric studies produced results with adequate sensitivity and measurement latency in line with physiological predictions.

A completely integrated wearable microneedle technique was presented by Tehrani et al. for the wireless, continuous, real-time detection of glucose and alcohol levels in volunteer tissue fluids. This creative method tackles the usefulness of wearable technology for measuring epidermal sweat [21].

- **Soluble microneedles:**

Soluble microneedles dissolve after delivery, releasing drugs like metformin and lidocaine quickly. Challenges include maintaining drug stability during preparation. Thermal activation accelerates drug release, and they’re versatile, delivering drugs like insulin and growth hormone to various body regions rapidly [8].

- **Hollow microneedles:**

Hollow microneedles enable precise drug delivery, yielding faster absorption, but their preparation is complex and tissue resistance can be challenging. However, they offer advantages like increased serum insulin levels and reduced patient discomfort with techniques like side opening with beveled tips. They’re also explored for ocular medication to enhance drug bioavailability [9].

4.2. Other applications

- **Blood extraction:**

Researchers are developing innovative methods for blood collection using microneedles, like Blicharz et al.’s device with a vacuum system for pain reduction and Li et al.’s invention with an elastic actuator for dynamic blood collection without external power.

- **Interstitial fluid extraction:**

Interstitial fluid serves as a valuable sample containing various biomarkers relevant to health and disease, making it pivotal for health monitoring. Several methods for extracting interstitial fluids include using solid microneedles followed by vacuum extraction, among others.

5. Prospective advancements in microneedle technology

Dependable and effective microneedle infiltration is vital for effective applications. Skin thickness variations and needle-tissue interlocking can affect monitoring reliability. Material selection, parameter optimization, skin preparation, and controlled insertion techniques are key factors for improving microneedle performance.

Long-term microneedle use is complicated by foreign body reactions and biological contamination. Surface modifications and coatings can mitigate these issues, while advancements like personalized drug release rates and intelligent systems enhance precision. Integrated architectures coupling drug delivery and detection enable efficient disease management.

6. Challenges

In the near future, authorising the exchange of MNs from research laboratories to pertinent businesses will be an exciting but challenging process. As soon as feasible, some significant issues and challenges should be taken into account in order to move this ground-breaking technology from the lab bench to commercially viable goods. The main challenges and issues that we think could have an impact on the future development of a microneedle-based delivery system are listed below [22].

Figure 6. Microneedle delivery system Consideration

6.1. Parameters influencing MN insertion

The successful penetration of microneedle (MN) patches into the skin is crucial for their effectiveness, considering the variability in skin characteristics among individuals and across different body regions. Several parameters influence MN insertion and penetration behavior:

6.1.1. Geometry: Triangular and square-based microneedles have better insertion depths and skin penetration compared to hexagonal ones. Cone-shaped MNs are ideal for efficient delivery and rapid dismantling, enhancing immune response.

6.1.2. Tip Diameter and Sharpness: Smaller tip diameters (<15 µm) and sharper tips facilitate smoother skin penetration and controlled delivery of therapeutics. However, increasing tip sharpness may reduce puncture force while compromising structural strength, increasing the chance of breakage.

6.1.3. Application Velocity and Force: Penetration depth increases application velocity and force. Controlled application approaches or devices may be necessary to ensure consistent penetration, with insertion forces ranging from 10 mN to 30 mN per microneedle.

6.1.4. Length: MN length affects insertion depth and drug delivery efficiency. Shorter microneedles may suffice for surface pore creation, while longer microneedle is used for enhanced permeability, especially for insulin delivery.

6.1.5. Interspace (Centre-to-Centre Spacing): The skin's topographic diversity and deformation capacity influence the number of punctures needed for high-density MN arrays. Higher density and number of microneedles require more energy for skin puncture, potentially causing discomfort and necessitating larger or stronger devices. However, denser arrays may allow for enhanced drug diffusion, albeit with the risk of the "bed-of-nails" effect.

6.2. Compatability

Biocompatibility, Biodegradability, and Stability

Microneedle systems undergo rigorous biocompatibility assessments, including cytotoxicity, sensitization, irritation, and intracutaneous reactivity tests, with a focus on prolonged contact periods. Biodegradable polymeric materials are preferred for construction, enabling controlled drug release and safe elimination. Manufacturing at room temperature from aqueous polymeric mixtures maintains medication stability. Stability of cargo, especially proteins, is ensured through temperature-dependent storage and stabilizer addition. Water content is crucial for cargo stability and MN mechanical properties. Dissolvable MNs require dry, cool storage for extended shelf-life. Overall, meticulous attention to material properties, manufacturing, and storage conditions is vital for clinical efficacy and safety.

6.3. Limited range of drug dose

Only a certain quantity of medication can be delivered using microneedles due to their tiny size. As a result, applying them is challenging when a high dosage or continuous medication release is needed. The immediate constraints can be addressed by applying many patches simultaneously or by regularly replacing the microneedle patch in order to get around this restriction. However, more study is required to increase the drug dose that can be put into the microneedles in order to broaden their application in medicine.

6.4. Sustained drug-releasing technology

The focus of research on drug delivery using microneedles has shifted from fast dissolution for single administrations to continuous drug release. In order to facilitate extended medication distribution, separable microneedles were created, which quickly separate the formulation from the microneedle. Various studies have explored minimizing patch-wearing time and introducing technology with continuous release for long-term medication delivery. For instance, Li developed separable microneedles for contraceptive hormone release, maintaining therapeutic levels for around a month. This research opens avenues for applying different drugs to microneedle patches and developing modified formulations for effective, long-term drug delivery. Additionally, there's a need to develop adhesive patches that are non-toxic for extended wear.

6.5. Loading capacity and dosage accuracy

6.5.1. Loading Capacity: Microneedles provide precise drug delivery; coated microneedles offer a bolus dosage of about 1 mg, while hollow microneedles allow continuous administration or instant dosing.

Passive diffusion into the skin poses challenges for administering large dosages, impacting the success of microneedle delivery. Difficulties in monitoring dose delivery and potential loss on the skin's surface have raised concerns, particularly in clinical applications like vaccine distribution. Achieving the threshold dosage for vaccine-induced immunity may be challenging through passive diffusion alone.

6.5.2. Dosage accuracy: Dosage accuracy in continuous drug delivery via microneedles is critical, with separable microneedles proposed to minimize patch-wearing time and facilitate quick removal. Storing and delivering protein drugs require careful consideration due to their quick degradation; stabilizers and precise manufacturing parameters are necessary. Solid microneedles pose challenges for accurate delivery, while coated microneedles have limited loading capacity. Dissolvable microneedles made from suitable materials enable efficient drug delivery without debris. Additionally, they enhance the penetration of nanoparticles through the epidermal barrier by stabilizing and preserving compositions that are nanoscale. For the purpose of tracking nanomaterials and their payloads in both in vitro and in vivo investigations, numerous analytical methods have been developed.

6.6. MN fabrication

6.6.1. Cost of Microneedle Fabrication: Microneedle (MN) technology shows promise for therapy, but its large-scale production and economic viability need improvement. Costs are high due to complex processes, with limited economic evaluations. MN-based vaccine delivery may save costs, particularly for large-scale programs. Economic models suggest MN vaccination can be cost-effective. Studying MN-related costs is crucial given healthcare pressures. Success depends on fabrication techniques and material choice, with scalability requiring strategic planning. Material selection is key for performance without compromising stability, and an ideal production method should allow for easy modifications.

6.6.2. Sterilization of microneedle: Sterilization of microneedle (MN) patches is crucial for commercial products, but traditional methods may adversely affect sensitive cargoes like biomolecules and vaccines. While the risk of bio burden introduction is lower than with hypodermic needles, regulatory bodies may mandate complete sterilization for safety. Choice of method depends on MN material. Solid MNs can use dry heat, moist heat, or gamma radiation. Coated MNs need careful evaluation to maintain stability. Carbohydrate and polymer MNs, like dissolving MNs, pose challenges in sterilization affecting both cargoes and MN properties. Gamma irradiation at SAL 10^-6 can sterilize hydrogel-forming MNs, but may affect drug stability. Alternative methods like ethylene oxide and electron beam require further investigation [22].

6.7. Regulation of the Microneedle

Concerns over the calibre of combination medication applications have been voiced by the USFDA - based on microneedles, pointing to problems with manufacturing, risk assessment, stability testing, content uniformity, and sterility validation. Despite promising therapeutic applications, the regulatory approval process for microneedles is complex, requiring extensive clinical studies and trials to demonstrate safety, efficacy, and repeatability. Clear guidelines are needed to classify microneedle devices accurately, potentially as medical devices or combination products for drug delivery. The approval of Qtrypta in 2020 signifies progress in bringing microneedle-based products to market, but addressing regulatory concerns is crucial for successful adoption in transdermal drug delivery [23].

7. Recent advancements in microneedle-mediated drug delivery

7.1. Transdermal Drug Delivery with Microneedle Arrays

In recent years, there has been a lot of interest in microneedles (MNs) as a novel medication delivery technology. By piercing the skin’s corneum layer, these tiny needles create microchannels that allow drugs to be delivered directly into the epidermis. Because of their small size, which doesn't activate nerves, MNs are painless. They can also administer a variety of medications, such as proteins, vaccinations, and small compounds [24]. The need for a more effective and user-friendly drug delivery method has driven the creation of MNs. MNs offer a non-invasive, self-administered alternative to conventional techniques like syringes and hypodermic needles, which can be uncomfortable and require specific training for administration. This is especially helpful for patients who require regular medicine doses. The four primary different types of MNs are coated, hollow, solid, and dissolving. Drug formulations are released upon skin application by coated MNs, liquid pharmaceuticals are delivered straight into the skin by hollow MNs, and solid MNs form Microchannels for drug delivery [25].

7.2. Design and Fabrication Innovations

Microneedle (MN) technology has become a ground-breaking breakthrough in Biomedical Science on a global scale. MN-based drug delivery has the potential to solve the current constraints of drug delivery, including as poor biodistribution, low bioavailability, insufficient skin penetration, and poor absorption. The application of nanotechnology has had a profound effect on the processes used in the manufacturing of microneedles (MNs), resulting in a change from conventional to creative designs that make use of a range of natural and synthetic materials and their combinations. Because of its many diverse and wide-ranging applications, MNs technology is now widely recognized in medication delivery and scientific research globally. An extensive summary of MNs is given in this review, together with information on their many forms, production processes, composition, characterization, applications, latest developments, and worldwide intellectual circumstances [25].

7.3. Microneedle Technology for Multifaceted Biomedical Applications

Global biomedical science has recently witnessed a breakthrough with the development of microneedle (MN) technology. The current issues with drug delivery, including as poor skin penetration, low bioavailability, restricted absorption, and insufficient biodistribution, can be resolved by utilizing MN-based drug delivery. Microneedles (MNs) have undergone significant breakthroughs in fabrication techniques due to the integration of nanotechnology, which has resulted in a shift from conventional procedures to new ones. This change entails improving the form and performance of microneedles by using a wide variety of natural and synthetic materials, either separately or in combination.

7.4. Microneedles for biomedical applications

Over the years, the microneedle (MN) has attracted a great deal of attention from the scientific community and the industrial sector because of its unique qualities, which include safe, high therapeutic efficacy, low cost, and painless skin penetration. The promise of microneedles in transdermal drug administration is highlighted in this paper, along with their capacity to produce complex devices for biomedical applications. The article goes into great detail about the developments in microneedle technology, covering new materials and advanced fabrication techniques like 3DP. In addition, it explores the various biomedical uses of microneedles, from illness management to aesthetic improvements, giving a thorough picture of their adaptability. In order to showcase advanced microneedles' prospective position as a cutting-edge tool for a variety of biomedical applications, the review finishes by talking about the implications and future possibilities of these tools in the field of biomedicine [26].

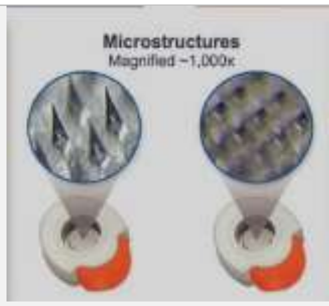
7.5. Cosmetic Applications

Percutaneous collagen induction, also known as microneedling, has become very popular in cosmetic applications. This method has been widely used to treat acne scars, skin care, hair loss, melasma, skin rejuvenation, and even skin cancer. It makes use of manufactured microneedle patches and microneedling equipment. By creating micro-channels in the stratum corneum, microneedling keeps the skin smooth and youthful-looking by facilitating the delivery of cosmetic chemicals and stimulating the creation of collagen and elastin through the wound-healing cascade. Using microneedling, a range of cosmetic chemicals, including peptides, hyaluronic acid, retinoid, niacinamide, and ascorbic acid, have been effectively administered. The purpose of this review is to draw attention to the ways in which manufactured microneedle patches and microneedling devices can be used to administer cosmetic chemicals through the layers of the skin. The research also examines the variations among the different types of microneedling devices, which are frequently used either alone or in conjunction with topical treatments. Furthermore, included are the possible side effects of microneedling, such as skin irritation, pain perception, systemic or skin infections, and the safety of the biological and chemical components utilized to make the needles. In conclusion, microneedles are making it possible for medications to be delivered more effectively and for patients to receive cosmetic procedures that are less intrusive and painful.

8. Marketed products

Table 2. Marketed products

S.NO	MANUFACTURING COMPANY	DEVICE NAME	FIGURE	DESCRIPTION
1.	**BECTON-DICKINSON TECHNOLOGIES**	SOLUVIA		Very short, hollow needle,that allows successful ID injection from a conventional syringe barrel
2.	**NANOPASS TECHNOLOGY**	MICROJET 600		The plastic gadget is attached to four hollow silicon needles. utilized for the intradermal delivery of lidocaine, insulin,

				and influenza vaccination.
3.	**3M COMPANY**	MICROSTRUCTURED TRANSDERMAL SYSTEM		Coated microneedle that enables the effective delivery of polar, ionic, and water-soluble molecules through the skin in a matter of seconds.
4.	**ZOSANO PHARMA COOPERATION**	QTRYPTA		It is applied in the acute management of migraines.
5.	**CLEARSIDE BIOMEDICAL**	SCS MICROINJECTOR		It consists of a syringe and two hollow MN needles with a gauge of 30 and is used to inject a range of medications into the suprachoroidal space.
6.	**BECTON DICKINSON TECHNOLOGIES**	MICROINFUSOR		It distributes a variety of drugs to the subcutaneous tissue over time.
7.	**CORIUM INTERNATIONAL**	MICROCOR		It is the dissolving MN for transdermal medicine and vaccination delivery without the need for needles.

8.	**MERCATOR MEDSYSTEMS**	BULLFROG MICRO-INFUSION DEVICE		Therapeutic compounds are injected into adventitial tissues via blood vessel walls using this technique

9. Conclusion

The Recent advances in microneedle patch technology underscore their growing significance as a transformative platform in transdermal drug delivery and personalized medicine. By effectively overcoming the stratum corneum barrier, microneedle systems enable painless, minimally invasive, and targeted delivery of a wide range of therapeutic agents, including macromolecules, vaccines, and biologics. Their versatility in design, material selection, and fabrication techniques has expanded their application beyond conventional drug delivery to include diagnostics, biosensing, and cosmetic and dermatological treatments.

Despite the promising progress, several challenges remain in terms of large-scale manufacturing, long-term safety, regulatory approval, and clinical translation. Issues such as material biocompatibility, mechanical strength, dose accuracy, and patient-to-patient variability must be carefully addressed to ensure consistent therapeutic outcomes. Continued advancements in fabrication technologies, surface modifications, and smart microneedle systems—such as stimuli-responsive and integrated sensing-delivery platforms—are expected to further enhance precision, efficacy, and patient compliance.

Overall, microneedle patches represent a powerful and evolving drug delivery strategy with the potential to reshape future healthcare practices. Ongoing interdisciplinary research, coupled with regulatory support and industrial collaboration, will be crucial for translating laboratory innovations into clinically viable and commercially successful microneedle-based products.

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