

Revisiting the advancement with painless microneedles for the diagnosis and treatment of dermal infections: A review

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Abstract: Dermal infections present a major health risk and challenge in clinical and community settings. Painful procedures are often involved in conventional diagnostic and treatment methods, causing patient discomfort and non-compliance. Pain-free and minimally invasive approaches are offered by microneedles as a promising technology for the diagnosis and mitigation of dermal infections. The focus of this paper is on the advancements and approaches to fabricating painless microneedles for the mitigation and diagnosis of dermal infections. Microneedles provide a painless and minimally invasive option compared to traditional techniques. Additionally, it emphasizes incorporating sensing technologies to diagnose infections. Microneedles that don't cause pain could change dermatology practices by offering patient-friendly and effective solutions for diagnosing and managing dermal infections. The article covers regulatory concerns, scalability, and cost-effectiveness, stressing the necessity for additional research and development for implementing this technology in clinical settings. The significance of painless microneedles in improving patient comfort, adherence, and early detection of dermal infections is emphasized. In conclusion, the invention of pain-free microneedles is notable progress in preventing and diagnosing skin infections. The successful implementation of painless microneedles has the potential to revolutionize dermatology practices, enabling effective and patient-friendly approaches for the management and diagnosis of dermal infections..

Keywords: Dermal Infections; 3D Printing; 4D Printing; Micro-fabrication; Microneedle; Nanofabrication.

HIGHLIGHTS

- Microneedles-based localized delivery of therapeutics in the management of dermal infections.
- Microneedles are a promising device for revolutionizing disease treatment and diagnosis with cosmetic applications.
- The review focuses on additive-manufactured microneedles using biomaterials.
- Regulations and challenges of microneedle delivery system highlighted.
- Discussing the development and future perspectives of microneedles in dermal infections.

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1. INTRODUCTION

Dermal infections are a clinical condition that can ensue anywhere on the body and range in severity from insignificant to life-threatening diseases. These infections are characterized by erythema, inflammation, edema, pus (furuncles), pain, itching, etc. in the skin. Systemic symptoms and indications, such as fever, chills, malaise, and occasionally hemodynamic instability and organ failure, may coexist with local manifestations (Eron *et al.*, 2003). Such infections can be produced by a variety of microorganisms, and poor blood circulation, along with an immune system disease, can be the driving force behind the dermal infection. Additionally, these infections are more likely to affect older adults, diabetics, the malnourished, the obese, and people whose immune systems have been compromised by chemotherapy or other immunosuppressant medications (Falagas & Kompoti, 2006). Although immunocompromised individuals are more vulnerable to these infections because of anomalies in their innate or adaptive immune responses, immunocompetent persons can also serve as hosts (Jamaledin *et al.*, 2020). Infections caused by bacteria (cellulitis, impetigo, staphylococcal (staph) infections, etc.), fungi (athlete's foot, yeast infections, etc.), viruses (shingles, warts, herpes simplex, etc.), and parasites (body lice, scabies, etc.) are among the most common infections worldwide (Peterson *et al.*, 2019). Topical application of drugs is successful in curing superficial infections but is ineffective against deep dermal infections because of the decreased drug permeability through the tough layer, the stratum corneum (Alkrad & Neubert, 2022). Apart from the barriers to treating the skin infection, treatment resistance caused by the infection is potentially fatal (Aslam *et al.*, 2018). Hence, to combat skin infections, it is essential to develop methods that are effective and safe to use and treat these skin conditions.

The conventional formulations cannot overcome the skin barriers and hence can't treat dermal infections efficiently. Hence, researchers are constantly trying to develop novel drug delivery approaches for the fruitful treatment of dermal infections. Liposomes, polymeric nanoparticles, silica nanoparticles, and framework nucleic acid nanostructures have been seen to have great potential in overcoming the skin barrier, boosting the absorption of the medication through the skin, and allowing for a controlled and sustained release of the drug (Cui *et al.*, 2020).

Conversely, these formulations have certain drawbacks, including toxicity, poor knowledge of the process of penetration, and an inability to regulate the depth of penetration precisely (Kumar *et al.*, 2023). Therefore, the production of efficient drug delivery systems that can effectively transfer the drugs to and across the skin must be accompanied by the development of such innovative therapies. To administer the medication at the desired place with a regulated release pattern, physical approaches such as hypodermic needles, iontophoresis, microneedles, sonophoresis, electroporation, phonophoresis, needleless injection, ablation, micro scission, and abrasion can be utilised (Swain *et al.*, 2011) (Fig. 1). However, each of these methods has its limitations; for example, ablation and abrasion involve the painful removal of the upper layer of skin (Brown *et al.*, 2006). Standard hypodermic needles, while effective for drug delivery, are painful and can cause tissue damage (Thakur Singh *et al.*, 2017). Additionally, they compromise the skin's natural barrier function for a longer period, which leaves the body vulnerable to infections. Other methods raise the cost by requiring a device to be linked to a power source or by using an additional energy source. Furthermore, a skilled individual is needed to do the work. Microneedle technology seems to be a promising drug delivery technology that can breach the skin with insignificant aching (Prausnitz, 2004). For the administration of therapies that would otherwise be inappropriate for transdermal or intradermal delivery, they can create transitory microchannels (Tuan-Mahmood *et al.*, 2013). These tiny needle arrays can also be employed as diagnostic tools for infectious cutaneous devices (Rachael V. Dixon *et al.*, 2021). They are self-administrable and can detect biomarkers from dermal interstitial fluid in a minimally invasive manner to detect disease (Amani *et al.*, 2021).

Microneedles, which are structures similar to needles but smaller with diameters and lengths of only 1 mm, can access the dermis layers without touching blood vessels or pain-sensing neurons in the stratum corneum (10-40 μm in thickness) and the process is so easy that it does not require specialised training (Ma & Wu, 2017; Van Der Maaden *et al.*, 2012). Over the past few decades, microneedle technology has advanced significantly. Microneedles have proven to have many benefits over conventional drug delivery methods for treating dermal infections, including the ability to give medication in a painless, non-invasive, and

controlled manner. These tiny, micron-sized devices conveniently transfer molecules across the skin barrier. Hypodermic needle injections are made less uncomfortable by only entering the top layer of the skin. Several studies have revealed that hypodermic needle piercing is significantly more painful than microneedle insertion (Haq *et al.*, 2009; Wermeling *et al.*, 2008). They also decrease the spread of blood-borne infectious diseases and damage from needle sticks.

The inception of microneedle-based drug delivery dates back to the year 1976 when Gerstel and Place patented solid and hollow needle-like projections with 5–100 µm length for local or systemic drug delivery (Gerstel & Place, 1976). It then took around 20 years to eventually demonstrate how to create a microneedle-based drug delivery device using microfabrication techniques (Henry *et al.*, 1998). Henry *et al.* constructed an array of silicon microneedles using microfabrication technology to enhance the transport of calcein through human skin and conduct in-vivo testing. Since then, the

use of microneedles has rapidly expanded to allow the administration of a wide range of medications, genetic material, vaccines, macromolecules, and nanoparticles through the skin (Henry *et al.*, 1998; Lopez-Ramirez *et al.*, 2020; Qu *et al.*, 2020). In 2005, Miyano *et al.* developed the first dissolving sugar microneedles for the delivery of ascorbate-2-glycoside into the epidermis and dermis (Miyano *et al.*, 2005). In the same year, Fernandes *et al.* used the microneedle roller for cosmetic applications for tightening the skin and reduction of wrinkles (Fernandes, 2005). Furthermore, this year, the diagnostic application of microneedles was also established by Wang *et al.* (Wang *et al.*, 2005) Following that, Donnelly *et al.* prepared a hydrogel-forming polymeric microneedle arrays, for exhibiting antimicrobial properties in 2014. According to the studies, this technology is a desirable and optimistic method of treating and diagnosing dermal infections and various other diseases. As a result, many of these microneedle delivery devices have been permitted by the FDA or are now undergoing clinical testing.

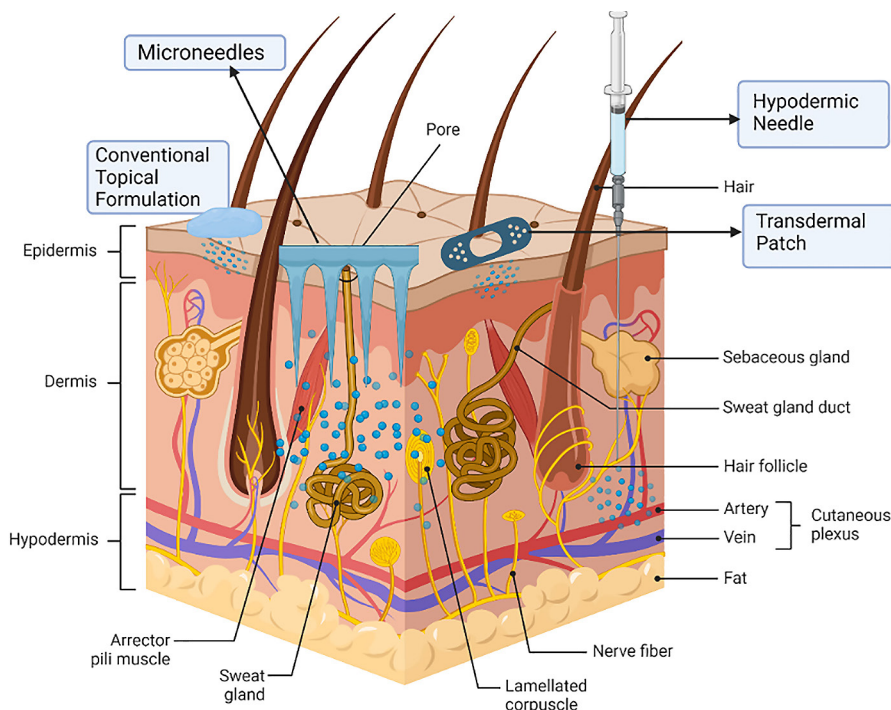


Fig. 1. Structure of skin with the application of various topical dermal formulations vs microneedles with emphasizing its penetration to skin with delivery of drug to systemic circulations

This review elaborates on all the current advances and techniques in the making of painless microneedles for the control and detection of skin infections. The review begins with an overview of

dermal infection and its contributing factors before focusing on the many hurdles that might arise during the management of skin infections. In-depth explanations of the fabrication of the microneedle,

especially in the management of dermal infections, will be explained, followed by their characterization and drug release mechanism. The review focuses on the biological application of microneedles in the management of dermal infections, ongoing clinical trials, and a patented microneedle product. The assessment of recent developments in microneedles, along with their difficulties and constraints, is another goal of this work. The review aims to enable future research opportunities.

2. BARRIERS TO SKIN INFECTIONS

2.1. The structure and purpose of skin

The skin is the largest organ of the human body, its surface area covering two meters squared and its weight equalling 20 percent of an adult's total body weight. The epidermis and the dermis, parted by a basement membrane, form the three primary layers of skin histology. The epidermis is classified into four layers based on the morphology of keratinocytes and the level of differentiation into cornified cells such as stratum corneum, stratum granulosum, stratum spinosum, and stratum basale (Gilaberte *et al.*, 2016). The hard outermost layer of the epidermis, known as the stratum corneum, comprises layers of dead cells called corneocytes that are joined by Corne desmosomes, folds of tight junctions, and intercellular lipids (Dragicevic & Maibach, 2017; Ishida-Yamamoto *et al.*, 2018; Matsui & Amagai, 2015) The main purpose of the epidermis is to guard the body against external dangers such as infections, UV radiation, and hazardous substances. The dermis, found beneath the epidermis, contains cells such as macrophages, fibroblasts, collagen, and mast cells. Sweat glands, hair follicles, and blood vessels are all in the dermis. It is separated into an upper stratum papillae and a lower stratum reticular, which contain thin collagen fibers accordingly, based on the thickness of its collagen content (Nie *et al.*, 2013). Skin infections of the dermis are very challenging to treat because of several obstacles that prevent the medication from reaching the infection site. Intradermal delivery is the term used to describe drug transport targeted at deeper skin layers (Aulton & Taylor, 2013). Subcutaneous tissue, consisting mostly of adipose tissue, is beneath the skin's outermost layer. It acts as insulation and padding for the body, effectively keeping heat and regulating body temperature in the skin's crevices (Tareen *et al.*, 2018).

2.2. Various types of barriers or hurdles present during the management of dermal infections

The anatomy of the skin revealed that the management of dermal infections can be problematic because of several barriers or hurdles that impede successful intradermal drug delivery. The skin shields the inside of the body against chemical, physical, and microbiological hazards; as a result, it blocks the entry of drugs (Naik *et al.*, 2000; Proksch *et al.*, 2006; Singh Malik *et al.*, 2016; Tareen *et al.*, 2018). The stratum corneum, the tight connections in the interfollicular epidermis, and the hair follicles are the key components of the skin that prove to be physical challenges in the treatment of dermal infection (Bäsler *et al.*, 2016; Lee, 2020; Patzelt & Lademann, 2020). Because of its rigidity, the stratum corneum appears to be an obvious barrier to passing most medications from the outside to the inside. Structurally, the second important barrier present in the epidermis is tight junctions, which make it difficult for molecules to cross through the para-cellular barrier and infiltrate deeply inside the skin. Transmembrane proteins called claudins, occludins, and tricellulin, as well as junctional adhesion molecules, make up these tight junctions. Claudins play a crucial role in determining how well-defined tight junctions serve as barriers (Gorzellany *et al.*, 2020; Günzel & Yu, 2013). Hence, the structure of the skin is the first barrier that makes it difficult for topical treatments to penetrate the site of infection. Additionally, the presence of hair follicles and sweat glands can provide reservoirs for pathogens, making it challenging to fully eradicate an infection. Furthermore, foreign objects, such as splinters or embedded debris, can act as physical barriers by preventing topical medications from reaching the infected area (Schroeder *et al.*, 2010) (Fig. 2).

Besides the physical structure, the chemical barriers present in the skin can indeed pose challenges to treating dermal infections. Human skin has a pH between 5.4 and 5.9, making it an unfriendly habitat for infections (Nguyen & Soulika, 2019). However, this low pH can also influence the stability and activity of certain drugs, making them less effective. The presence of sebum, an oily substance produced by the sebaceous glands in the skin, limits the solubility and absorption of water-soluble medications. Furthermore, the skin contains various enzymes like cytochromes P450,

flavin monooxygenase, glutathione-S-transferases, N-acetyltransferase, and sulfotransferases that can degrade or metabolize certain drugs, reducing their effectiveness (Svensson, 2009).

The skin has a strong immunological barrier system to protect our body from microbial attack. Dermal dendritic cells, mast cells, macrophages, CD4+ T memory cells, and innate lymphoid cells are just a few of the innate immune cells that make up the immunological skin barrier and scour the dermis for pathogens. Immunoglobulins, cytokines, and inflammatory mediators are released once Langerhans cells and dendritic cells are exposed to a particular antigen (Jamaledin *et al.*, 2020). These components can prove to be a hurdle in the management of dermal infections. Also, the immune system's response to an infection can cause inflammation and tissue damage, which can impede the delivery and effectiveness of treatments.

Besides this, the drug molecule itself should have appropriate physicochemical properties to penetrate deep into the skin. The drug should remain unionized for permeation through different strata of the skin since passive diffusion accounts for most of the drug's delivery through this pathway. The features of the drug molecule, such as the partition coefficient, molecular weight, diffusion coefficient, level of ionization, size of the molecule, and physicochemical structure, determine how deeply the drug

permeates the dermal layer. The molecular weight of the drug is a very important element in determining the diffusivity of the drug molecule through the skin. The drugs that have molecular weights under 500 Da exhibit excellent permeability. The studies have revealed that the relationship between molecular weight and absorption rate is inverse. Furthermore, the drug's penetration into the dermis is also significantly affected by the vehicle through which the formulation penetrates the skin.

Furthermore, the presence of biofilm, which are communities of bacteria encased in a protective extracellular matrix, can impede the penetration of antibiotics and other antimicrobial agents. Finally, the development of antibiotic resistance among pathogens can limit the effectiveness of traditional treatment options. Bacteria and fungi tend to develop resistance to antimicrobial agents, both naturally and through the overuse or misuse of antibiotics. These resistant strains can create biological barriers that limit the effectiveness of treatment options (Ventola, 2015). This can also lead to the use of more expensive and toxic medications, further exacerbating economic barriers. Lately, understanding the barriers to the treatment of skin infections has become very important given the ongoing rise of antibiotic resistance in human pathogenic microorganisms and the high morbidity and death rates linked to infectious illness (Gallo & Nizet, 2008).

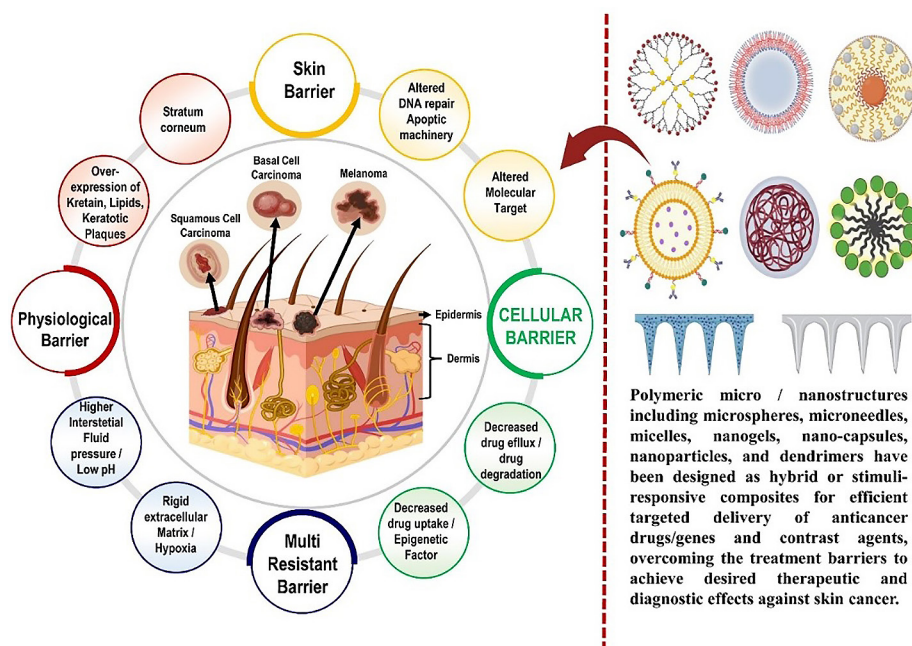


Fig. 2. Anatomy and function of skin emphasizing the various obstacles during the management of dermal infections (adapted and reproduced with permission from (Khan *et al.*, 2022).

3. FABRICATION METHOD OF MICRONEEDLE

In recent years, researchers have been using many techniques to generate a diversity of MNs. When designing an MN, one must consider the type, concentration, and desired pharmacokinetic profile of the medication, as well as the characteristics of the materials used. The primary aim in the production of MNs is to have needle geometrical uniformity and accuracy at the micron-scale level, which will make it possible for the needle to penetrate the skin effectively. The study has shown that several methods, such as photolithography, microfabrication, electro-spinning, and 3D printing, can be used for making microneedles (Zhu *et al.*, 2016). Critical attributes of microneedles in the management of dermal infections is presented in table 1.

3.1. Photolithography

By preferentially exposing a photoconductive composite material to light through a mask, a latent image is created in the polymer, which can then be preferentially solubilized to allow sequence access to a surface underneath. This patterning process is known as photolithography. The production of microneedles in any shape or size is made possible using this method. Some techniques that are included in this process are X-ray lithography, electron beam lithography, and ion beam lithography. The common method for achieving this is through the use of silicon microneedles (Dharadhar *et al.*, 2019). A wafer is formed with the desired pattern through a process with an optical mask and an opaque template. Constructed with a quartz plate or flat piece of glass, this mask allows only a certain sequence of light to enter. Distinct HMNs have already been created using two distinct kinds of photolithographic masks. Mask S had a 500 m outer diameter and 380 m inner diameter for the symmetrical circles that were used to create symmetrical HMNs as a “volcano” (Dardano *et al.*, 2021).

Etching is typically carried out following photolithography during the manufacturing process. This technique uses an excision to leave a mark on the substrate’s surface. Photo-resistant substances like silicon dioxide and silicon nitride are employed to mask the surface. It is a difficult procedure that requires a variety of tools, along with expert guidance. Using organic solvents, the organic material is etched. This technique of microneedle has accurate

structure and dimensions. Raw physical etching methods typically involve the relative movement of kinetic exposure particles to remove the surface. Wet etching and dry etching are two methods that are employed based on the physical properties of the etching process (Lim & Kim, 2022).

3.2. Microfabrication

Using microengineering methods to produce highly accurate and precise microscopic-level objects is known as microfabrication. The basic stages of a microfabrication process are material selection, layout, geometric patterns, engraving, bond formation, and arrangement. The selection of components is crucial when producing microneedles; they need to be structurally durable, easily predictable, and exhibit good biocompatibility. The most frequently utilized materials in the manufacture of microneedles are rich in silica (Ahmed Saeed Al-Japairai *et al.*, 2020). Silicon microneedles can be produced using microfabrication methodologies like photolithography, deep reactive ion etching (DRIE), and liquid embossing. In the process of photolithography, a photosensitive material that has been embedded with a photomask and exposed to UV light is used. A formed layer is left on the silicon substrate after the exposure to photoconductive areas becomes immiscible and is eliminated with an emerging solution. After being engraved with DRIE or wet etching, the formed silicon surface is produced into microneedles (Tao & Desai, 2003).

3.3. Three-dimensional printing

The computer-aided design (CAD) component is the basis of 3D printing, also known as adjuvant producing (AP), which uses the gradual placement of materials to create parts with a customizable, intricate shape. Different 3D printing strategies, including material extrusion, powder bed fusion processes, photopolymerization, substance and adhesive jetting, have been suggested over the past decade to produce adjustable doses of medication precisely for various purposes, such as for oral administration (Yang *et al.*, 2021) (Fig. 3).

The field of biodegradable polymer and pharmaceutical sciences has significantly been advanced by three-dimensional (3D) printing, also known as additive manufacturing. The biomedical and pharmaceutical industries often employ 3D printing, a method that utilizes computerized modeling to produce 3D models with various geometric shapes.

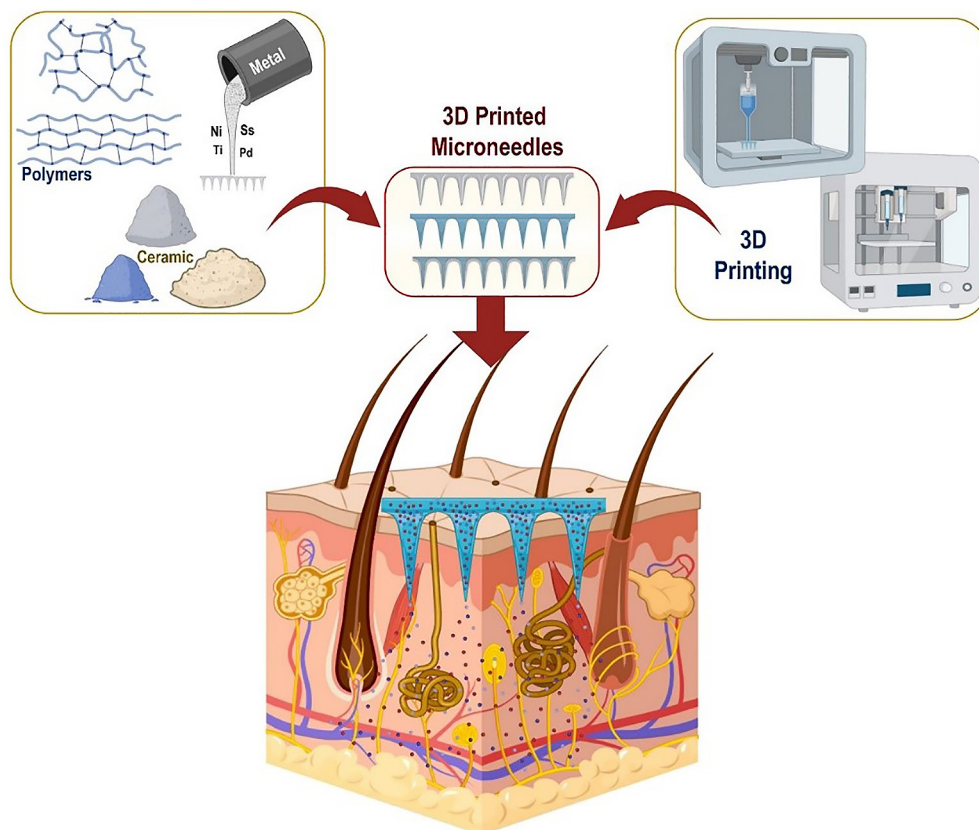


Fig. 3. Microfabrication using 3D Printing. (adapted with permission from (Elahpour *et al.*, 2021).

3.3.1. Fused deposition model

The Fused filament fabrication (FFF) method, commonly referred to as the fused deposition model (FDM), operates by deforming hot, molten state materials through a nozzle. In this process, material transforms into filaments as it reaches the nozzle, and the extruder generates slim strands as a product. They crystallize when they contact the fundamental bed, and the final shape is created by applying layers one after the other. With the help of a nozzle, consumers of fused deposition modeling technology can extrude molten thermoplastic materials to build three-dimensional objects layer by layer. Three steps make up the FDM process: first, a 3D model is designed employing specialized software; second, a prototype is divided into tiny layers; and third, every surface is printed using an FDM printer. Whenever the nozzle is warmed, the biopolymer-based melts can be extruded, resulting in the formation of a solid bond between the layers and the creation of three-dimensional objects. Thermoplastic materials with high strength, adaptability, and good thermal stability are being used, including ABS, PLA, PETG, and nylon (Elahpour *et al.*, 2021).

3.3.2. Stereolithography

In this methodology, a laser system is used to solidify resin into the desired structure layer by layer. The SLA procedure is based on a computer-aided design (CAD) file that has been broken down into smaller layers. The SLA device employs a laser to detect every surface, which is followed by the liquid resin in the vat being crystallized into the desired form. SLA 3D printing is frequently used to create solid microneedles. The primary solid microneedles were created using SLA 3D printing and were utilized as a mold for agarose gel casting. The isotropic shrinking of agarose gel kept the microneedles' structural integrity. The agarose gel was therefore used as a mold cavity to make microneedles from the polydimethylsiloxane (PDMS) polymer using the dried agarose gel. Under the research, the settlement of microneedles might be generated about five times more accurately once SLA 3D printing was combined with a hydrogel's isotropic deformation. Additionally, the PDMS microneedles framework may create PDMS molds (Detamornrat *et al.*, 2022).

3.3.3. TPP: A technique for two-photon polymerization

The two-photon polymerization (TPP) or 2PP technique enables the layer-by-layer production of conformations from solid, liquid, or powder intermediates for microscopic-level and nano-sized frameworks, making it one of the most precise 3D advanced technologies. Through the help of a near-infrared laser pulse, TPP can generate

highly precise, arbitrarily defined 3D microstructures, boasting a lateral resolution of 100 nm and an axial resolution of 300 nm. Two-photon absorption serves as the core of the innovation. Succinctly, the process involves positioning a drop of resin on a glass substrate, followed by the precise focusing of an ultrafast laser light ray (e.g. femtosecond) on a photosensitive material, inducing two-photon permeation within the focal region to start the polymerization reaction (Sirbubalo *et al.*, 2021) (Fig. 4).

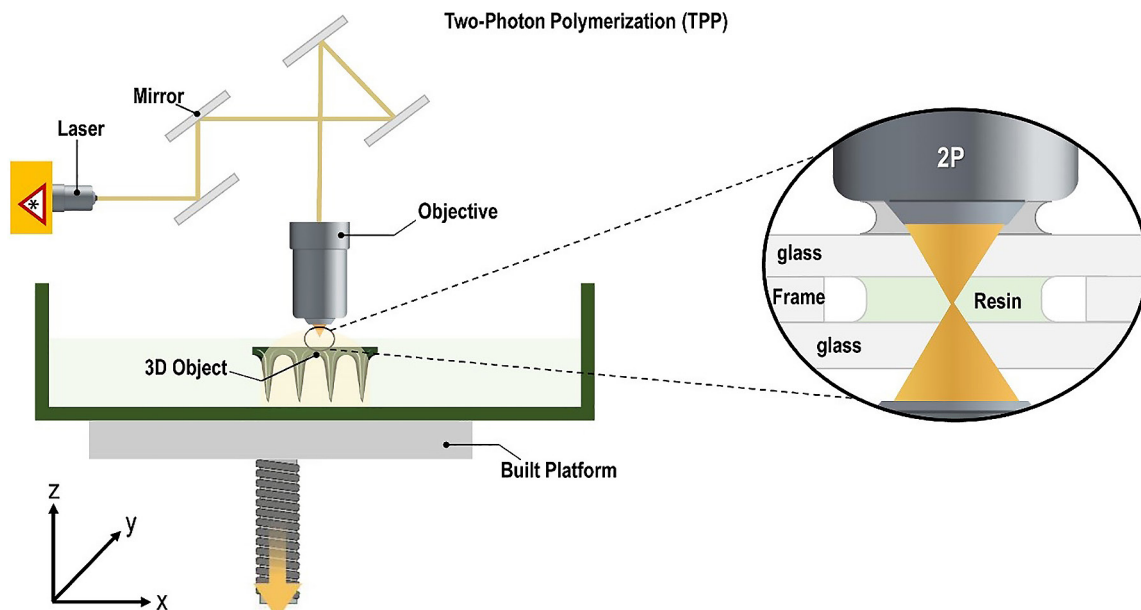


Fig. 4. Depicts the operational principle of the Two-Photon Polymerization (TPP) technology, adapted and reproduced in adherence to the Creative Commons Attribution (CC BY) license 4.0 (Sirbubalo *et al.*, 2021).

3.3.4. Digital light processing

Digital light processing (DLP) is an innovation that is based on photopolymerization and differs from SLA only in terms of its light source. DLP technology is notably faster than SLA because of the employment of the Digital Micromirror Device (DMD) in high-resolution intelligent projectors, which stresses the display. The volumetric pixel resolution of the material's cross-section and the entire layer is conventional and complementary. Using digital light processing (DLP) in 3D printing is a field that is widely recognized for its enormous technological and financial potential (Mu *et al.*, 2017).

An energetic source of light serves as the form of energy for the scanning process, a mechanical printing framework is known as the response container, and photo-curable components are used as the reaction medium. In traditional DLP, the light

field has a repaired amplitude, which causes the components to cure uniformly. It can also be helpful to produce a product with uneven characteristics that improve the degree of content manipulation. The development of evaluated materials using grey-scale digital light processing (g-DLP) is a promising method (Zhao *et al.*, 2020).

The two most prevalent forms are the nozzle-based and light-based 3D printing techniques. Both extrusion printing and inkjet printing are classified as nozzle-based 3D printing techniques. The printed materials are extruded or jetted in these printing processes before being accumulated over onto a framework. DLP printing, beam printing, selective laser melting (SLM), and selective laser sintering are light-based 3D printing (SLS). The DLP-based printing framework is essential for performing synthetic operational processes. Vats for storing printing precursors and motorized

phases for adjusting the printing stance make up a typical printing framework. The printing platform sets the reaction parameters besides regulating the printing's velocity and position (J. Zhang *et al.*, 2020).

3.5. Four-dimensional printing

An advanced iteration of 3D printing, referred to as 4D, employs intelligent materials that autonomously assemble or transform when subjected to environmental factors like temperature, moisture, or light. In microneedles, 4D printing produces needles that could change in shape or relieve drugs over time, improving their performance and efficiency. 4D printing microneedles may be more effective at puncturing the skin and delivering medications because they can adapt to variations in temperature or pH. They may also release medications progressively, which would reduce the need for repeated dosing and improve patient adherence (Han *et al.*, 2020).

4. TYPE OF MICRONEEDLE

4.1. Solid microneedle

By implanting and then eliminating solid microneedles, micron-scaled pores can be formed on the layers of the skin, allowing these needles to serve as a skin pretreatment. The “poke and patch” theory is how they make micro channels. These microchannels increase drug permeation by enabling direct subcutaneous surface propagation from a composition. Research findings on rat skin have demonstrated that, when allowed to hold under occlusive circumstances, the micropores caused using microneedles persisted for at least 72 hours. The “scrape and patch” technique, in which microneedles, micro-projections, or micro-blades are scratched over the skin to create micro-abrasions, is a modification of a typical solid microneedle method. Use of a solid microneedle roller that repeatedly penetrates the epidermis as it rotates on the skin. Based on this idea, commercially available Derma-rollers are used in skin pore opening treatments, conducted research to yield medications for high blood pressure utilizing cylindrical surface Microneedle Systems. Transdermal flux values have been demonstrated to rise 5 to 8 times after using microneedle rollers on porcine skin (Nagarkar *et al.*, 2020)

4.2. Hollow microneedle

As the name implies, hollow microneedles (HMNs) are hollow in nature that serve as pipework structures and are solely utilized to inject fluid and liquid dosage forms. Therefore, poke and flow are the names of the drug delivery process that is used by HMNs. With HMNs, molecules can be delivered continuously, and the drug solution can move through the MNs bore in a variety of ways, including by permeation, force, or electrically driven flow. Bolus injections can be executed quickly because of the attenuation of flow rate brought about by HMNs characteristics, i.e., a slow infusion or a time-varying response time. Compared to other types of MNs, HMNs drug formulation has some drawbacks, such as low stability, a short shelf life, and low patient compliance. HMNs have the disadvantage of the potential for needle blockage during skin implantation (Cárcamo-Martínez *et al.*, 2021).

Silicon, metal, glass, polymer, and ceramic are among the materials used to make HMNs. Hollow conductive microneedles were used to develop an electric field in the surface layers of the skin that was strong enough for electroporation, allowing for needle-free microinjection and implementing electric pulses. The microneedle array and vibratory insertion were employed to penetrate the stratum corneum (Daugimont *et al.*, 2010) (Fig. 5).

4.3. Coated microneedle

The “Coat and Poke” framework is utilized in this drug delivery technique and is made with titanium and stainless steel. A single-step process involves coating the MNs with the medication before injecting them under the skin. The drug coating on MNs may be absorbed by the skin. MNs are then completely eradicated after dissolution. Only a specific quantity of drug can be coated onto the tip and shaft of MNs. The thickness of the polymer solution and needle dimensions affects drug dosage. The coating improves target quantitative measurements and microneedle performance. Additionally, it enhances the microneedles' mechanical attributes, boosting its durability and breakage tension. Coating materials made of ceramic materials, metal, polymer, and other substances for target-oriented medication delivery. Using coated microneedles to deliver multiple factors using the same preparation has also been investigated. Each microneedle was coated with various pharmaceutical formulations, enabling the

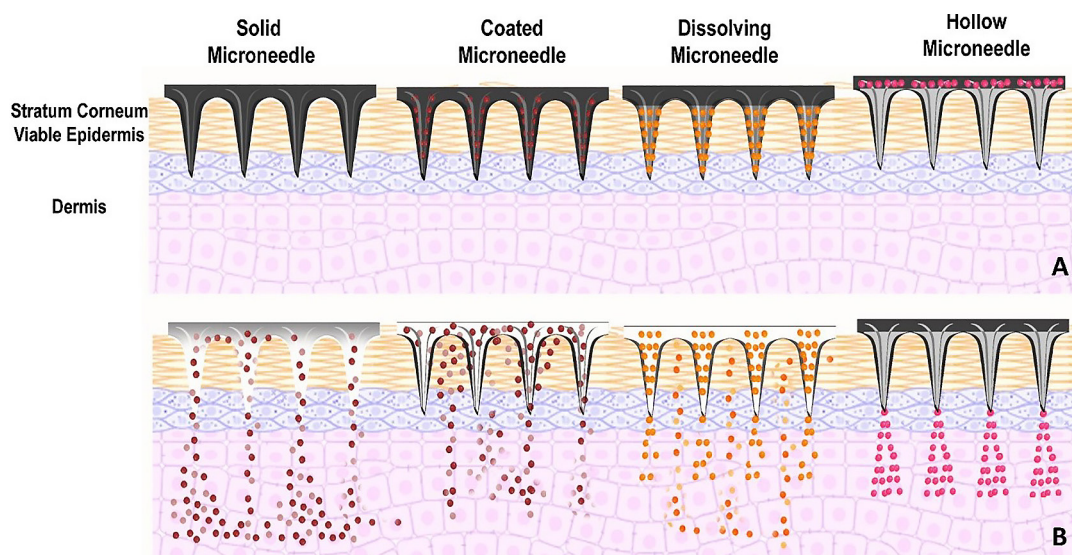


Fig. 5. Different microneedles: solid, coated, dissolving and hollow (adapted with permission under CC BY (Kim *et al.*, 2012).

co-delivery of several agents with various properties. Such concurrently delivered water-soluble and water-insoluble dyes (Waghule *et al.*, 2019).

Gas jet drying and EHDA innovation are two additional techniques used in microneedle coating. Coated microneedles make it possible to deliver medications, such as proteins and peptides, with minimal invasion. Coated MNs allow self-administration with no hospitalizations, skilled personnel, or costs involved.

4.4. Dissolving microneedle

Biodegradable polymers are used to make dissolving microneedles by trapping the drug inside of them. After insertion and dissolution of the microneedle, the medication disperses. The implementation takes only one step, regardless of whether the microneedle is inserted. The polymer disintegrates within the skin and controls the release of the medication. It is one of the most biocompatible materials because the polymer dissolves inside the skin for long-term therapeutic interventions that will increase patient compliance (Zhu *et al.*, 2016).

Challenges exist for effectively distributing drugs by dissolving microneedles. Therefore, an essential part of this process is combining the polymer and the drug. The research team created tip-disposing microneedles that demonstrated quick release of the drug without causing contact dermatitis. Dissolving microneedles is complicated to insert completely. Rapidly separating microneedles assembled

on solid surfaces was created by Zhu *et al.* throughout 30 microneedles, adequate mechanical strength and roughly 90% drug delivery efficiency were noticed (Waghule *et al.*, 2019).

4.5. Hydrogel microneedle

Microneedles have been recently invented. Super-swelling polymeric materials are used to make microneedles. The water-loving structure of the polymers lets them absorb huge amounts of water into their three-dimensional cement matrix. These polymers swell when they are inserted into the skin, thanks to the intercellular fluid. The outcome is the formation of networks between the medication patch and capillary blood vessels. These microneedles break down the skin barrier before needling. The swelling of the cells acts as a barrier that regulates speed. They can differ in terms of shape and size. Hydrogel microneedles used to deliver drugs are created with cross-linked polymeric materials. TDD, which is based on super-swelling HF MNs, is gaining a lot of attention because there's no need for an invasive procedure and it can deliver a variety of drugs. The HF MNs take in the interstitial skin fluid (ISF), increase in size, and help drugs move from the reservoir at the base to the epidermis without dissolving the polymer. It is essential to have a deep understanding of the drug transport framework to create HF MNs for applications, making it possible for controlled TDD and geometrical optimization (Ranjan Yadav *et al.*, 2022).

Critical Attributes	Description
The geometry	The geometric structure of microneedle arrays affects the mechanical strength and penetration characteristics of MNs.
Tip diameter and Sharpness	MNs with relatively blunt tips (with tip diameters ranging from 60 to 160 μm) cause a relatively high insertion force (ranging from 0.08 to 3.04 N) for precise applications and are directly proportional to the frontal area of the tip.
Application velocity and force	The depth of penetration of MNs arrays varies between 10% to 80% and escalates with the velocity and force of the application.
Length	Because of the variance in skin layers' thickness among individuals, the insertion depth of particles may also differ.
Interspace (centre-to-centre spacing)	The presence of a high-density microneedle array causes the generation of a substantial number of distinct punctures. (e.g., over 500/cm ²)

Table 1. Critical attributes of microneedles in the management of dermal infections

5. BIOLOGICAL APPLICATIONS AND BIOCOMPATIBILITY OF MICRONEEDLES

Microneedles are made of biodegradable or non-biodegradable materials and can be coated with drugs, vaccines, or other therapeutic agents. They have been used for various applications, including transdermal drug delivery, vaccination, and sampling of interstitial fluid. However, the use of microneedles in the management of dermal infections has gained significant attention because of the advantages offered by them. Due to focused distribution to a specific spot and decreased germ resistance, microneedle technology allows for a reduction in therapeutic dosage with fewer adverse effects. Additionally, it lessens the labor, discomfort, expense, and risk of infections brought on by the injections (Jamaledin *et al.*, 2020). Additionally, to deliver therapeutic chemicals to specific infection sites, microneedles have the potential to break through the thick physical barriers created by bacterial and fungal biofilm. Omolu *et al.* employed solid microneedles to improve the transdermal delivery of doxycycline, to treat chronic wounds (Omolu *et al.*, 2017). Research on untreated porcine skin revealed that solid microneedles increased the percutaneous penetration of tiagabine hydrochloride by almost seven times when compared to passive permeation (Nguyen *et al.*, 2016; Omolu *et al.*, 2017). Another study revealed that the delivery of clindamycin-containing gelatin nanoparticles was more effective in eradicating *Vibrio vulnificus* biofilm than drug solution (Xu *et al.*, 2019). Using microneedles to deliver amphotericin B allowed for more effective treatment of fungal infections, as it augmented the rate of *Candida albicans* biofilm removal in pig skin (Peng *et al.*, 2021).

Photodynamic, photo-thermal, chemotherapy, chemo-dynamic, photocatalytic, biotherapy, and a combination of these therapies have all been effectively administered through microneedles to treat skin infections. Combination therapy can improve the efficacy of antimicrobial activity by initiating complementary killing mechanisms. Zhao *et al.* developed microneedle patches of a novel cascade of silver (Ag) nanoparticles/ Glucose oxidase nano-capsules / apramycin nanocomposite for combinational antimicrobial therapy. The process of converting glucose into hydrogen peroxide via glucose oxidase nano-capsules accelerated the release of Ag⁺ from silver nanoparticles, thereby expediting a combined antimicrobial effect that encompasses starvation therapy, metal ions, and antibiotic activity (Zhao *et al.*, 2022). The microneedle-mediated nanocomposite delivery attained speed and scarless skin recovery in the animal models.

MNs have the potential to concurrently combat microorganisms and mitigate inflammation by encapsulating therapeutic agents with anti-bacterial, antioxidant, anti-inflammatory, and angiogenic properties. Separable MNs were developed by Zhang and his co-authors, and they were integrated with black phosphorus to facilitate photothermal-responsive oxygen delivery. This methodology was employed to address non-healing diabetic wounds. The exposure of BP quantum dots to NIR led to a rapid increase in local temperature and a corresponding decrease in the oxygen-binding capacity of hemoglobin. This resulted in a controlled oxygen delivery mechanism that expedited wound healing, accelerating wound closure, tissue regeneration, and angiogenesis. The practical

performance of such MNs has been demonstrated by treating the full-thickness cutaneous wounds of a type I diabetes rat model, indicating their potential value in wound healing and other related biomedical fields (X. Zhang *et al.*, 2020). Lee *et al.* aimed to tackle the issue of inadequate therapeutic efficacy and low migration ability of injected MSCs. The intradermal delivery of MSCs has been made possible with the development of a detachable hybrid MN depot (d-HMND). An array of microneedles constitutes the system and is comprised of an outer poly(lactic-co-glycolic) acid shell and an internal mixture of gelatin methacryloyl (GelMA)-MSC (GMM). The GMM is characterized and optimized for cell viability and the mechanical strength of the d-HMND required to penetrate mouse skin tissue is also determined. (Lee *et al.*, 2020). Sun and colleagues developed MNs integrated with MXene to attain temperature-responsive delivery of adenosine when exposed to NIR irradiation. This led to improved angiogenesis and expedited wound healing. There is evidence of the potential of microneedle patches in wound healing. (Sun *et al.*, 2021).

The primary chemotherapeutic agent, Cisplatin, has the potential to cause side effects such as nephrotoxicity, neurotoxicity, ototoxicity, electrolyte disruption, and hemolytic anemia. To prevent these detrimental effects, formulated lipid-coated cisplatin nanoparticles (LCC-NPs) using pH-responsive lipid nanoparticles that target tumors and embedded them into dissolvable microneedles to facilitate transdermal administration (Lan *et al.*, 2018). The summary of microneedles-based research reports for the mitigation of dermal infections is given in Table 2.

Microneedles have both diagnostic and therapeutic uses. Three major components of diagnostics that involve microneedles are the extraction of bio-fluids, the capture of target analysis, and electrochemical sensing *in situ* (Dixon *et al.*, 2020; Liu *et al.*, 2020). There has been comparatively little exploration of microneedle devices for infectious disease diagnosis (Rachael V. Dixon *et al.*, 2021).

Microneedles such as solid, hollow, swellable, hydrogel, and sponge-forming types can extract interstitial fluid. Solid microneedles cannot extract interstitial fluid directly but can be integrated with other techniques like suction, pressure-driven convection, diffusion, etc., for extraction of the fluid with minimum invasion (Samant & Prausnitz,

2018). The integration with other processes restricts the use of solid microneedles since it makes the interstitial fluid sample for diagnosis more difficult. Hollow microneedles are the preferable choice for drawing the interstitial fluid because of the presence of internal channels for direct withdrawal. The sampling process in hollow microneedles is much faster than micropore systems made of solid microneedles. Tran *et al.* used hollow microneedles for the collection of dermal interstitial fluid from healthy volunteers for clinical monitoring and diagnosis purposes. It was concluded that this technique can be an alternative to plasma or serum sampling, because of the least invasiveness of the microneedles (Tran *et al.*, 2018). A study performed by Strambini *et al.*, revealed that, by increasing the number of microneedles in an array, it is possible to achieve rapid sampling of interstitial fluid (Strambini *et al.*, 2015).

Porous and hydrogel microneedles have lately become popular new microneedle designs for interstitial fluid extraction. Porous microneedles are a combination of solid and hollow microneedles. The manner they are made allows for the formation of big, interconnected pores in the microneedle's body while preserving structural integrity. A simple capillary force may then remove the fluid from the skin, and centrifugation can collect it from the microneedles (Gholami *et al.*, 2019). In contrast, when inserted into the dermal interstitium, hydrogel microneedles expand like a sponge and absorb interstitial fluid utilizing a diffusion gradient (J. Chen *et al.*, 2019). Eltayib *et al.* developed hydrogel-forming microneedle arrays for lithium monitoring (Eltayib *et al.*, 2016). In a different study, scientists fabricated an osmosis-powered hydrogel microneedle patch for the *in situ* swelling mechanism-based removal of skin interstitial fluid. The developed patch's connection with electronic glucose sensors made it possible to analyze the collected glucose quickly and directly (Zheng *et al.*, 2020). The detection of Covid-19 infection testing represents a breakthrough in the diagnostic application of microneedles. Chen *et al.* proved that the use of microneedle-based oropharyngeal swabs can reduce the false negative results in Covid-19 testing. Additionally, this designed swab is expected to be helpful in the diagnosis of oral or respiratory disease (Chen *et al.*, 2020). Summarize report on outcome microneedles-based research reports in the diagnosis of dermal infections Table 3.

Investigation	Outcome	References
<p>Prepared Dissolvable polymeric microneedles to lower the risk of infection in clinical applications and avoid microbial contamination of the formulation during storage and transportation</p>	<p>The proliferation of <i>Staphylococcus aureus</i> and <i>Escherichia coli</i> was impeded upon exposure to graphene oxide-doped microneedles. However, the suppressive effect of hyaluronic acid/carboxymethyl cellulose was comparatively weaker than poly vinyl pyrrolidone.</p>	<p>(Y. Chen <i>et al.</i>, 2019)</p>
<p>A hybrid microneedle has been created, comprising two layers: an outer water-soluble layer loaded with vancomycin, and an inner near-IR photo-thermal core that is water-insoluble.</p>	<p>The findings indicate that the hybrid microneedle-based formulation can effectively suppress the growth of methicillin-resistant <i>Staphylococcus aureus</i>, owing to the synergistic interaction of heat with vancomycin</p>	<p>(Ziesmer <i>et al.</i>, 2023)</p>
<p>Development of dissolving Self-sterilizing antibacterial silver-loaded microneedle patches</p>	<p>Silver nanoparticle-loaded microneedles were more effective in suppressing microbial pathogens than simple silver nanoparticles.</p>	<p>(García <i>et al.</i>, 2019)</p>
<p>Itraconazole containing dissolving microneedles for fungal infections</p>	<p>The formulations exhibited growth inhibition zones when incubated with agar plates containing <i>Candida albicans</i> cultures.</p>	<p>(Boehm <i>et al.</i>, 2016)</p>
<p>Biofilm penetration enhancement using a combination of bacterial-sensitive nanoparticles and dissolving microneedles of doxycycline.</p>	<p>Results indicated a reduction of bacterial bio burdens of up to 99.99%.</p>	<p>(Permana <i>et al.</i>, 2020)</p>
<p>Hyaluronic acid and diatomaceous earth-based anti-acne microneedle patches of clindamycin.</p>	<p>The bio-responsive patch that has been prepared can facilitate the healing process of the skin by absorbing dead cell debris and pus.</p>	<p>(Zhang <i>et al.</i>, 2018)</p>
<p>Preparation of living <i>Bacillus subtilis</i>-encapsulated microneedles for fungal infection treatment.</p>	<p>Microneedles have the potential to prevent the release of <i>Bacillus subtilis</i> and consistently secrete different antifungal agents that can bind directly to fungal cell surface proteins, damaging the fungal cell membranes and not causing drug resistance.</p>	<p>(Wang <i>et al.</i>, 2020)</p>
<p>Physiologically based pharmacokinetic model to simulate nifedipine and cabotegravir loaded, dissolving microneedle array patches for HIV therapy.</p>	<p>The microneedle patches were utilized to estimate the optimal dosage and release rates of anti-HIV drugs using this model.</p>	<p>(Rajoli <i>et al.</i>, 2019)</p>
<p>Bleomycin containing micro needling pen device to treat vital warts</p>	<p>Patients who were treated with bleomycin with a microneedle had complete clearance of warts as compared to the patients treated with intralesional bleomycin.</p>	<p>(Biglic & Akman-Karakas, 2019)</p>
<p>Dissolving polymeric microneedle containing acyclovir to treat herpes labialis</p>	<p>Microneedles could permeate 16 times more drug inside the skin as compared with a commercial cream formulation of acyclovir.</p>	<p>(Pamornpathomkul, Ngawhirunpat, <i>et al.</i>, 2018)</p>
<p>Cationic niosome and hollow microneedles were used to administer plasmid DNA-encoding ovalbumin to mice.</p>	<p>This technique achieved a better immune response as compared to subcutaneous injections with no infection or bleeding, which proves the safety of the system</p>	<p>(Pamornpathomkul, Niyomtham, <i>et al.</i>, 2018)</p>
<p>Hydrophobic drug cyclosporin A delivered dermally using dissolving microneedles of high molecular weight.</p>	<p>According to the study, the needed amount of cyclosporin A for psoriasis treatment was delivered within the skin without being solubilized.</p>	<p>(Jeong <i>et al.</i>, 2018)</p>

Table 2. Summary on outcome microneedle-based research reports for mitigation of dermal infections.

Study	Outcome	Discussion	References
Comparison of biomarkers in ISF and plasma samples using mass spectrometry.	Develop a solid microneedle-based method to sample interstitial fluid from human skin	The study provided a method to use microneedles for the withdrawal of dermal interstitial fluid by using it as a source of biomarkers.	(Samant <i>et al.</i> , 2020)
Extracting glucose through minimally invasive microneedles.	Develop solid microneedles to extract dermal interstitial fluid for monitoring glucose	The results revealed the capability of microneedle devices to extract interstitial fluid for painless glucose monitoring	(Wang <i>et al.</i> , 2005)
Extracting glucose through minimally invasive microneedles.	Fabrication of silicon hollow microneedles to explore its feasibility for monitoring biomarkers in skin fluid	These microneedles proved to robust in penetrating the porcine skin and transporting biomarkers of clinical interest for the diagnosis purpose.	(Wang <i>et al.</i> , 2005)
Detection of Anti-SARS-CoV-2 IgM/IgG antibodies through a patch sensor with porous microneedles and a paper-based immunoassay.	Fabrication of novel patch sensors integrating porous biodegradable microneedles for the rapid detection of anti-SARS-CoV-2 IgM/IgG in dermal interstitial fluid	The results proved the efficiency of the developed device for rapid screening of various infectious diseases, including COVID-19.	(Bao <i>et al.</i> , 2022)
Rapid diagnostic testing without blood using microneedle skin patch.	Microneedle-based dermal patch for blood-free quick diagnostic testing	The device could detect very low concentrations of biomarkers for malaria infection and the test was completed in less than 20 minutes	(Jiang & Lillehoj, 2020)
Biomarker monitoring is made possible with a wearable microneedle array.	Wearable microneedles patch with the wireless and nonstop real-time sensing of metabolites in interstitial fluid	The developed device was attached with a smartphone app and it helped in providing the continuous monitoring of essential biomarkers.	(Tehrani <i>et al.</i> , 2022)

Table 3. Summarize a table on outcome microneedles-based research reports in the diagnosis of dermal infections.

6. ONGOING CLINICAL TRIALS

Several clinical studies are exploring the possibility of using microneedles to treat skin infections. A phase two trial involving a microneedle patch containing imiquimod is being conducted to treat cutaneous warts. The research aims to assess the safety and effectiveness of the microneedle patch compared to the topical imiquimod cream. A microneedle patch containing chlorhexidine is being studied in a Phase 1 trial to prevent surgical site infections. Healthy volunteers will undergo evaluation to determine the safety and tolerability of the microneedle patch. Positive results were obtained by Zosano Pharma and Corium companies during the phase II clinical trials which tested the safety of microneedles on repeated skin application (Chandran *et al.*, 2019). The efficacy of a microneedle patch against psoriatic plaques was evaluated in a pilot clinical trial involving 10 patients with psoriasis. Promising patch results improved the psoriatic patient's treatment outcome (Men *et al.*, 2022). Microneedles are currently the subject of several ongoing clinical trials. Microneedles are showing promise for vaccine delivery. COVID-19 vaccines can be administered through microneedle-based delivery systems being developed. The University of California, Los Angeles, is conducting a clinical trial to test the Moderna COVID-19 vaccine delivery via a microneedle patch. Microneedles' clinical trials show their potential and versatility in drug delivery technology. Microneedles are poised to become a crucial tool for delivering various therapeutics as research advances.

7. PATENTED MICRONEEDLE PRODUCTS

Several companies have patented microneedle products for the management of dermal infections. Companies like Anger, Corium, Vaxxas, Becton-Dickinson, LTS Lohmann, Zosano Pharma, and NanoPass Technologies are playing a very important role in commercializing the microneedle-based transdermal delivery systems (Rzhevskiy *et al.*, 2018). Vaxxas, has developed a microneedle patch for the delivery of vaccines and drugs. The patch comprises an array of thousands of micro-sized needles that can penetrate the skin and deliver the drug or vaccine. Corium microneedle patch is a patented product that uses microneedles technology for the delivery of terbinafine to treat fungal nail infections. The patch comprises an array of microneedles coated with terbinafine, which can penetrate the nail plate and

deliver the drug directly to the site of infection. The company has received FDA approval for the product and has partnered with Mylan for the commercialization of the product. The 3M microneedle patch is another patented product that uses microneedle technology for the delivery of lidocaine for local anesthesia (Zhang, 2012.03.06). The 3M microneedle patch has shown promising results in preclinical studies and is currently being evaluated in clinical trials. The GentleWaves microneedle device is a patented product that uses microneedle technology to treat acne scars, fine lines, and wrinkles (Microneedling, 2023). The device uses a micro-needling roller system to create micro-channels in the skin, which stimulates collagen production and improves the appearance of the skin. The GentleWaves microneedle device has received FDA approval and has been commercialized by Lightwave Medical.

Commercial microneedles-based skin treatment

Metallic microneedles, DarmaRoller® is used to treat stretch marks, acne, and hair loss. These microneedles also can increase the absorption of the drugs like minoxidil, hyaluronic acid, etc. A skin patch called MicroHyal® , which contains hyaluronic acid and is made of dissolvable microneedles, is sold on the market to address wrinkles. Micro-Trans® and Drugmat® are the microneedle patches available for delivering the drug into the dermis (Halder *et al.*, 2021).

Latest biological contexts employing microneedles

Many studies since 1976 have illustrated the utilization of microneedles. There are two primary areas in which microneedles are applied in biomedicine: therapy and diagnosis. Microneedles can administer certain medications through the skin. Multiple studies have demonstrated that microneedles can be employed for transdermal administration of lidocaine (Shakya *et al.*, 2017), and metformin. (Vora *et al.*, 2017) , insulin (Schipper *et al.*, 2017), vaccines, human growth hormone (hGH) (Donnelly *et al.*, 2014) and nanoparticles (NP) (Hardy *et al.*, 2016) (Fig. 6) in the treatment of wounds (Mills *et al.*) (Li *et al.*, 2017), diabetes therapy tumors (Omolu *et al.*, 2017), etc. The diagnosis of various medical conditions has been heavily researched using microneedle-based biosensors for the collection and analysis of interstitial fluid and blood, as well as the detection of skin melanoma (Polomska *et al.*, 2019).

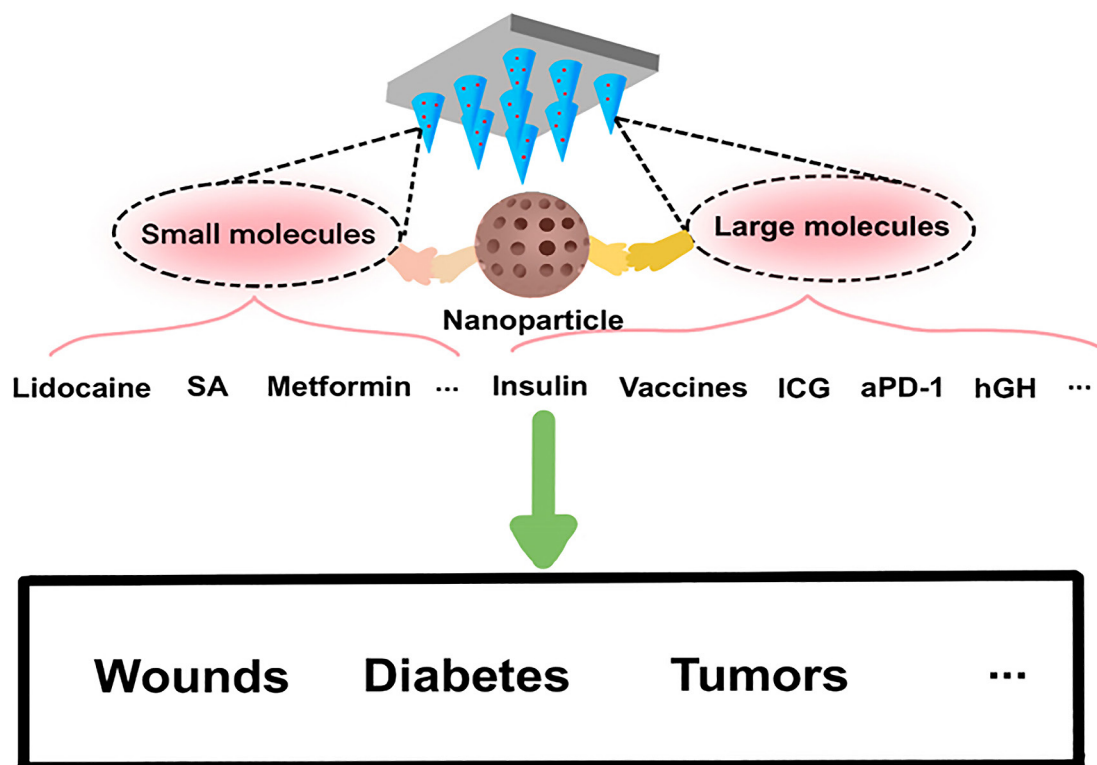


Fig. 6. Schematic of the combination of small and large molecules for the use in wound healing, diabetic care, and tumour treatments. (Adapted and reproduced from under CC BY license 4.0 (Xu *et al.*, 2021))

7.1. Compatibility with biological systems, decomposition and reliability

The biocompatibility of MNs systems is an essential security feature when used in clinical settings. To ensure that MNs products are acceptable for human exposure, several tests are required to evaluate their biocompatibility based on contact periods of less than 24 h, between 24 h and 30 h, and over 30 h (Shu *et al.*, 2021). For the prior two cycles, the applicable assessments are cytotoxicity, sensitization, inflammation, and intracutaneous reactivity tests. For the latter period of use, it is suggested to perform additional genotoxicity and subacute/sub-chronic systematic toxicity tests. Using biodegradable materials when creating microneedles is helpful, as these materials can break down and be removed from the body without harm. As a result, the construction of MNs using biodegradable polymeric systems has been investigated in recent years. Polymeric microneedles offer the major benefit of having the capacity to include medication into its matrix to be delivered into the skin through decomposition or dissolution of the skin's bodily fluid.

It may be a significant gain to maintain the stability of a combined medication, particularly for therapies involving proteins and peptides, to fabricate microneedle structures from aqueous polymeric mixtures with no heating step at room temperature. Analyzing the reliability of MNs cargo is imperative to guarantee that fragile and quickly decomposable therapeutics are safeguarded during storage. This method entails the maintenance of MNs and their cargo at temperatures of $-25\text{ }^{\circ}\text{C}$, $4\text{ }^{\circ}\text{C}$, $20\text{ }^{\circ}\text{C}$, $40\text{ }^{\circ}\text{C}$ and $60\text{ }^{\circ}\text{C}$ before evaluation. The solid glassy microneedle matrices inhibit molecular movement and stop oxygen from the atmosphere, resulting in the protein contents of MNs having a more dependable protective state and a prolonged shelf-life (Zvezdin, Kasatkina, *et al.*, 2020). Using stabilizers, such as trehalose and sucrose, can enhance the capability of this. In situations where a vacuum is not present, great care must be taken regarding the amount of water, as it can damage the loaded cargo and the physical features of the MNs (Ono *et al.*, 2017). The sensitivity of MNs to the humidity levels of their environment affects their dissolution.

7.2. Latest developments and difficulties of the microneedle delivery system

Making it possible for MNs to move from research laboratories to the relevant industries soon is an invigorating but strenuous task. To take this inventive technology from the lab bench to workable products in the markets, some essential questions and

difficulties should be addressed immediately. We will look at these challenges and active strategies to deal with these problems, which could decide the fate of the field and its commercial applications. Figure 7 highlights the primary challenges associated with the development of a microneedle-based delivery system, which will be further discussed in the subsequent sections.

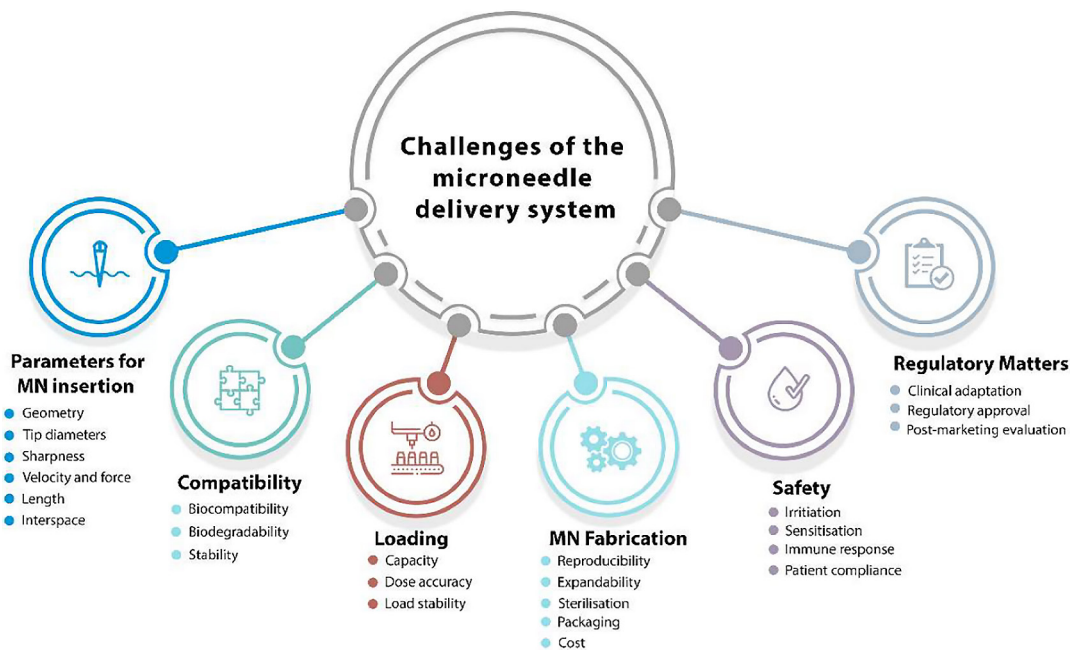


Fig. 7. Challenges of the microneedle delivery system (adapted and reproduced from under Creative Commons Attribution (CC BY) license 4.0 (Avcil & Çelik, 2021).

7.2.1. Parameters affecting microneedle insertion

It is essential that MNs patches can puncture the skin properly. In discussing this matter, the skin’s characteristics, which may be different in different locations on the body and different people, should be kept in mind. Many factors, like geometry, base and tip diameters, length, and interspace (center-to-center spacing), impact the insertion and permeation behavior of MNs as they try to overcome the skin’s elasticity. [43]. It’s impossible to use a “one-size-fits-all” strategy when designing and developing any MNs application. The success of infiltration and active delivery of MNs is largely determined by the geometry of individual MNs and the array, the materials used for the MNs, the MNs management technique, and the properties of the skin tissue (Zvezdin, Kasatkina, *et al.*, 2020). The mechanical strength, insertion depth and drug

release characteristics of the microneedle can be changed by altering its shape and composition, depending on the target medicines and applications.

It is essential to pay attention to the geometry of MNs when first creating MNs for medical use. A recent investigation demonstrated that the strength and penetration ability of MNs are affected by the layout of microneedle sets.

The tip size and its sharpness must be considered when inserting MNs. Insertion of MNs that are relatively blunt (tip diameters of 60-160 μm) needs a considerable amount of force (0.08-3.04 N) for precise applications, and this is linked to the size of the tip frontal area.

The velocities and forces at which the MNs delivery system is applied are closely linked to the tip diameters and should be considered. Studies have shown that MNs arrays can penetrate to depths ranging from 10% to 80%, and the depth increases as the application velocity and force increase.

The depth to which the particles are inserted may vary because of the differences in the thickness of the SC and other skin layers between individuals. The amount of material that can be transported through the skin after an MNs patch has been applied will depend on how deep the tissue is pierced. A drug of small size and a high diffusion capacity should be able to have its therapeutic function fulfilled by creating surface pores through microneedle application.

The skin is a surface with many hills and valleys that can take on a lot of change before being pierced. A significant number of distinct punctures must be generated when there is a high-density array of microneedles (e.g., over 500/cm²).

7.2.2. Compatibility with biological systems, degradability, and durability

The biocompatibility of MNs systems used in clinical practice is a key safety consideration. To ensure that MNs products are acceptable for human exposure, several tests are required to evaluate their biocompatibility based on contact periods of less than 24 h, between 24 h and 30 h, and over 30 h (Shu *et al.*, 2021). During the preceding two-time frames, it was necessary to conduct cytotoxicity, sensitization, irritation, and intracutaneous reactivity tests. During the later period of use, genotoxicity and subacute/ sub chronic systematic toxicity tests should be conducted. Using biodegradable materials is desirable for microneedles because these materials can be degraded and removed from the body safely. Recently, researchers have investigated the use of biodegradable polymeric systems to produce MNs. using polymeric microneedle systems has the benefit of loading medication into the microneedle matrix for release in the skin through the process of biodegradation or dissolution of the skin's body fluid. Manufacturing microneedle structures from aqueous polymers without heating could ensure the stability of medications. Despite this, it is imperative to evaluate the steadiness of MNs cargo to make sure that delicate and easily decomposable therapeutics are safeguarded during storage. This is typically achieved by keeping MNs and their freight at different temperatures, which can range from -25 °C to 60 °C, then completing analytical evaluations. The helpful storage stability and extended shelf-life of protein cargo held within microneedle matrices are because of their rigid and glassy nature, which restricts molecular movement and access to

atmospheric oxygen. (Zvezdin, Peno-Mazzarino, *et al.*, 2020). Including stabilizers, such as trehalose and sucrose can further extend this. Paying attention to the water content is especially important when non-vacuum storing conditions are present, as it can ruin not only the reliability of the product being carried but also the mechanical property of the MNs (Ono *et al.*, 2017). Dissolvable MNs are highly prone to the humidity of their surroundings.

7.2.3. Loading capacity and accuracy of dosage

Accurate calculation of loading capacity is paramount in microneedle technology due to its direct influence on treatment efficacy, safety, and consistency. Microneedles deliver therapeutic agents directly to the skin, making precise loading essential. This accuracy ensures therapeutic effectiveness, uniform dosing across microneedles, and minimizing adverse effects. Regulatory compliance, formulation optimization, cost-effectiveness, customization, and informed research and development are also facilitated by precise loading calculations. In essence, accurate loading capacity calculations are pivotal for achieving targeted and effective drug delivery while maintaining safety and regulatory standards.

The maximum amount of medicine that can be loaded into a coated microneedle device is approximately 1 mg. Hollow microneedles provide an opportunity for uninterrupted infusion or “as-needed/on-demand” dosage. However, the central exits could be blocked by pressed skin tissue after microneedle insertion. Whether MNs are successful in overcoming the barrier properties of the skin is contingent upon the passive diffusion of the biological formulation into the skin. The administration of large dosages can be hampered by the amount that is lost on the skin's surface.

Dosage accuracy: Careful consideration must be given to the accuracy of dosage when using MNs delivery systems for continuous drug delivery. Suggestions for minimizing patch-wearing time and quickly removing the formulation from the microneedles have been put forward using separable microneedles. Presenting and conveying protein drugs, for example, insulin, erythropoietin, glucagon, growth hormones, and parathyroid hormones, is a laborious process, as bio-macromolecules are susceptible to rapid deterioration and deactivation. (Han *et al.*, 2012).

7.2.4. Skin ailment and recuperation

Microneedles-based delivery of therapeutic agents is highly effective on the skin because of its immunogenic nature. Depending on the size, material and sort of medication given, there could be a minor and transient redness as an effect. It is necessary to evaluate skin irritation, sensitization, and immune response when conducting safety assessments of MNs products in clinical trials. Animal testing is imperative to assess this safety concern before any human clinical trials (Nagarkar *et al.*, 2020).

7.2.5. Expense of microneedle fabrication

It is necessary to change the current microneedle production methods to achieve mass production so that microchip-based microneedles can be effectively used for therapeutic purposes. To this point, there has not been a comprehensive economic assessment of the technology, however, it is unsurprising that, as with all new technology, the clinical application of MNs can be relatively costly because of the intricate fabrication and storage procedures and the slow and comprehensive approval process.

7.2.6. Sterilization of the microneedle patches

When aiming for commercial application of MNs-based products, MNs patch sterilisation is a challenge that should be addressed from the start. If sterilization is needed, the method of choice must be taken into consideration, as the most commonly used methods, including moist heat, gamma or microwave radiation, and ethylene oxide may have a negative effect on any cargo with delicate ingredients, such as biomolecules, vaccines, peptides, and even the microneedles themselves. The material utilized in MNs fabrication will influence the approach for sterilization. Sterilizing solid MNs comprised of metals, silicon, and glass is a straightforward process.

7.2.7. Regulation of the microneedle patches

The US Food and Drug Administration has been concerned about the quality of submissions originating from combination products with microneedles, especially in stability testing, content consistency, risk analysis, sterility validation, and production. Using MNs is an effective method of delivering

therapeutic agents, such as hormones, vaccines, enzymes, mRNA, and small molecules difficult to administer through the skin. The regulatory body must be presented with cell studies, animal testing, and clinical trials to demonstrate thoroughly the repeatability and efficacy of microneedle devices for clinical applications. Moreover, gaining a comprehensive knowledge of human physiological circumstances, analyzing clinical requirements, and the portability and simplicity of microneedle devices can all contribute to the advancement of such clinical translations. The number of medicinal products produced in Minnesota that are used for medical therapy is skyrocketing. Submitting to the FDA for authorization is tiresome, as the submissions must be combination products that use microneedles. Entries must include satisfactory material for item investigation, examining, and affirming, such as danger examination, consistency, steadiness testing (formulation/API relocation/mechanical properties), sterilization validating, and assembling (Brown *et al.*, 2020).

Regulations that govern microneedle patches within the Indian and broader Asian context encompass a combination of national frameworks, international guidelines, and evolving standards that are pertinent to medical devices and pharmaceutical products. The approval, production, and distribution of microneedle patches are influenced by regulatory bodies and overarching principles, though regulatory nuances may differ among Asian countries, including India. (Manu & Anand, 2022).

The Central Drugs Standard Control Organization (CDSCO) operates as the central regulatory authority for medical devices in India, functioning under the Ministry of Health and Family Welfare. The endorsement procedure for microneedle patches conforms to the Medical Device Rules, 2017, necessitating substantiation of safety, effectiveness, and quality through clinical trials, directed by regulations such as Good Clinical Practices (GCP) and Good Manufacturing Practices (GMP). In addition, microneedle patches that incorporate drug delivery capabilities fall under the purview of the Drug Controller General of India (DCGI), who is responsible for overseeing pharmaceutical regulations. The therapeutic effectiveness and safety of these patches would be established through clinical trials under the protocols specified in Schedule Y of the Drugs and Cosmetics Act. (Radhadevi *et al.*, 2012).

Regulatory agencies commonly cite international standards and guidelines to uphold quality

and safety. Comprehensive documentation, which covers technical details, manufacturing processes, quality control procedures, preclinical and clinical data, and safety evaluations, is required for the registration and approval process of microneedle patches. This compiled information provides evidence of the device's performance, safety, and efficacy, which is essential for regulatory approval. Vigilance programs are comprised of adverse event reporting, quality control measures, and compliance with regulatory standards to guarantee continuous patient safety and product quality. The protection of intellectual property rights through patents is essential for companies involved in the development of microneedle patches. Patents provide legal safeguarding for the novelty, blueprint, and efficacy of the patch, fostering innovation and promoting market competitiveness.

7.2.8. Societal impact of microneedle in dermal infections

The integration of microneedle technology within the context of dermal infections has a significant impact on society. The utilization of microneedles offers possibilities for improved patient adherence and increased treatment accessibility through a less invasive and user-friendly approach. The drug delivery capabilities that they possess are precise and targeted, thereby reducing the probability of systemic side effects and minimizing cross-contamination. (Ganeson *et al.*, 2023). This technology has the potential to alleviate the strain on healthcare systems by allowing for self-administration, thereby enabling prompt intervention and infection prevention. Furthermore, microneedles can contribute to public health outcomes by mitigating the spread of infections and associated complications. (R. V. Dixon *et al.*, 2021). Moreover, this innovation promotes research and improvements in the field of dermatology, assuring a change in the management of dermal infections and contributing to the general health and well-being of patients and the community.

8. FUTURE PROSPECTIVE

Over the last two decades, MN-based product development and regulation of larger peptides, proteins, vaccine compounds, and other traditional molecules for transdermal delivery have become a significant area of interest to those researching in

this area. Various commercial MNs products are eagerly awaited on a global scale. MNs may have an impressive influence on clinical medicine in the forthcoming period. The materials employed in the construction of microneedles have developed from metals to silicon and then polymers. The techniques for making microneedles have been enhanced and optimized. The fabrication techniques of microneedles have been enhanced and optimized. The generation of polymeric MNs for diagnostic purposes is an ongoing area of research, and its further advancement can significantly enlarge the toolset. The investigation of polymeric MNs for medical testing is a vigorous field of study, and further progress in this area can significantly extend the range of resources. Using biocompatible polymers may pave the way for the creation of microneedle systems that are both biocompatible and have good solubility. Various drug delivery techniques will be improved by microneedles, which will have a greater impact on clinical medicine and further boost human health.

9. CONCLUSION

Taking everything into account, it can be concluded that the prospects for the advancement and methodologies used in producing microneedles that are painless, and that are effective in both diagnosing and mitigating dermal infections, hold a lot of promise. The potential benefits of continuing research and development in this field include groundbreaking breakthroughs in materials innovation, sensing capabilities, and integration with digital health technologies. To make painless microneedles a reality, we need to tackle regulatory challenges and guarantee scalability and cost-effectiveness. These advancements have revolutionized the way dermal infections are managed and diagnosed, and their impact cannot be overstated. By investing more time and resources in research and development and by implementing novel perspectives, painless microneedles have the potential to revolutionize the field of dermatology and take patient care and outcomes to unprecedented levels.

Abbreviations

MNs: microneedles; HMNs: hollow microneedles; TPP: two-photon polymerization; DLP: Digital light processing; FDM: Fused deposition model; DMD: Digital Micromirror Device.

FFF: Fused Filament Fabrication; CAD: Computer-aided design; 3D printing: Three-dimensional printing; FDA: Food and Drug Administration; CDSCO: Central Drugs Standard Control Organization; DCGI: Drug Controller General of India; GCP: Good Clinical Practices and GMP: Good Manufacturing Practices.

Authors contributions

Conceptualization: Sudarshan Singh; Supervision: Bhupendra Prajapati and Popat Mohite; Writing original draft: Meenakshi Bhavesh Patel, Popat Mohite, Abhijeet Puri, and Anil Pawar; Formal analysis and validation: Bhupendra Prajapati and Popat Mohite; Reviewing and editing: Sudarshan Singh and Popat Mohite.

Conflict of Interest

The authors declare that there is no conflict of interest.

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