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Microneedles: A Novel Approach in Transdermal Drug Delivery: Review Paper

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ABSTRACT

Transdermal drug delivery systems (TDDS) are a focus of drug delivery research due to their distinct advantages over oral and parenteral drug delivery systems. Researchers have focused on the use of microneedles to break through the stratum corneum barrier. The drug is delivered into the epidermis via microneedles, which do not disrupt nerve endings. This review discusses recent advances in the development of microneedles for the benefit of young scientists and to promote research in the field.Microneedles are made with a microelectromechanical system that includes silicon, metals, polymers, or polysaccharides. To pierce the superficial skin layer, solid coated microneedles can be used, followed by drug delivery. Advances in microneedle research have resulted in the development of dissolvable/degradable and hollow microneedles capable of delivering drugs at higher doses and engineering drug release. When used in conjunction with hollow microneedles, iontophoresis, sonophoresis, and electrophoresis can be used to modify drug delivery. Microneedles can deliver macromolecules like insulin, growth hormones, immunobiological, proteins, and peptides.

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INTRODUCTION

Microneedles, also known as Microarray patches, are micron-scaled medical devices used to administer vaccines, drugs, and other therapeutic agents[1]. While microneedles were initially studied for transdermal drug delivery, their applications have since expanded to include intraocular, vaginal, trans ungual, cardiac, vascular, gastrointestinal, and intracochlear drug delivery[2]. Microneedles are made using a variety of techniques, the most common of which involve photolithographic processes or micro-molding[3]. These methods entail etching microscopic structures into resin or silicon in order to cast microneedles. Microneedles are made of various materials such as silicon, titanium, stainless steel, and polymers[4]. Some microneedles are made of a drug that will be delivered to the body but are shaped like a needle to penetrate the skin. The size, shape, and function of microneedles vary, but they are all used as an alternative to traditional delivery methods such as hypodermic needles or other injection apparatus[5].

HISTORY

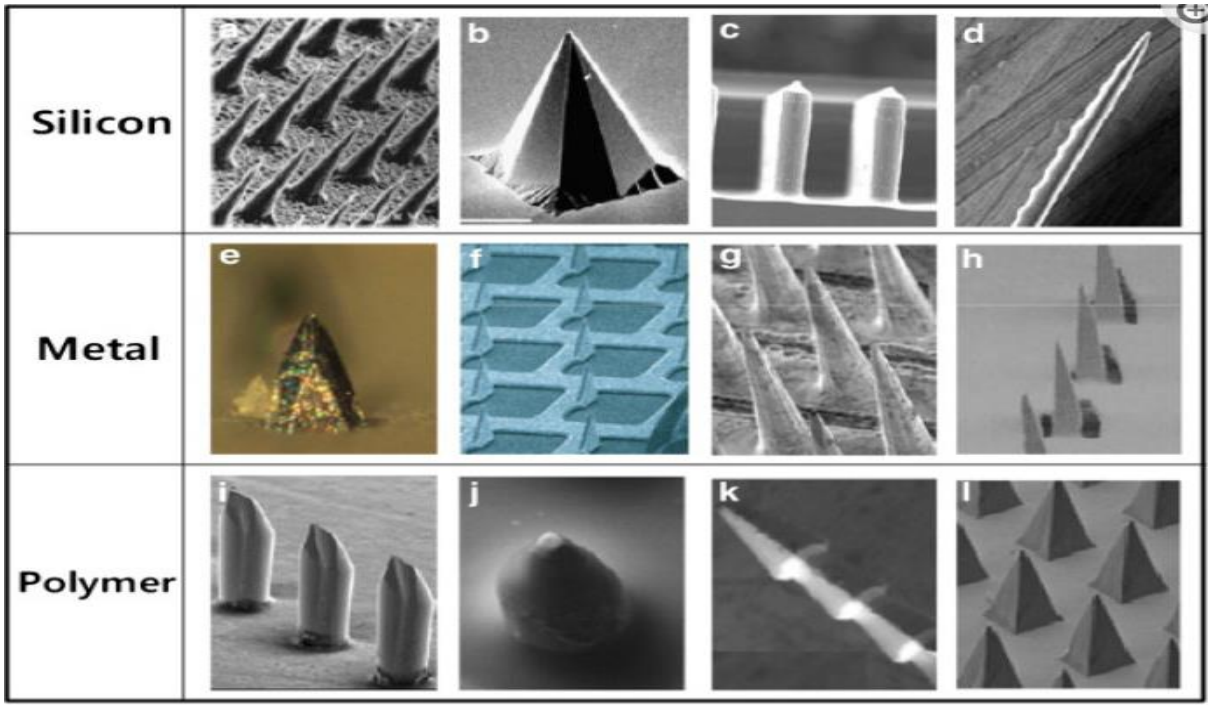
Microneedle concepts have evolved over time, beginning with the use of large needles and progressing to the current modern design of microneedles. Dr. Ernst Kromayer, a German dermatologist, used different sizes of motor-powered dental burs to treat scarring, hyperpigmentation, and other skin ailments in 1905[6]. Chambers published the first reference to microneedle use in 1921, when he injected the needle into the nucleus of an egg. In the 1960s, drug delivery via injection into the stratum corneum gained popularity. Following that, the microneedle concept was introduced in the 1970s; however, this concept was not experimentally demonstrated until the 1990s[7]. In 1979, the first transdermal system was approved for use in treating motion sickness by applying a three-day patch. Orentreich performed a subcision surgery in 1994, inserting a tri-bevelled hypodermic needle into the skin to release fibrous strands[8]. This surgery targeted the cutaneous defects located beneath the skin that caused depressed scars and wrinkles. The first transdermal microneedle was proposed in 1998 and was made from silicon wafers using ion etching and photolithography[9]. The research described the use of microfabricated microneedles to improve drug delivery across the skin. This paper sparked extensive research in the microneedle domain. Microneedles were created using a variety of materials including glass, ceramic, metal, and polymers. In 2004, a microneedle array was used to pierce holes into the skin for transdermal drug delivery, sparking interest in various TDD fabrication

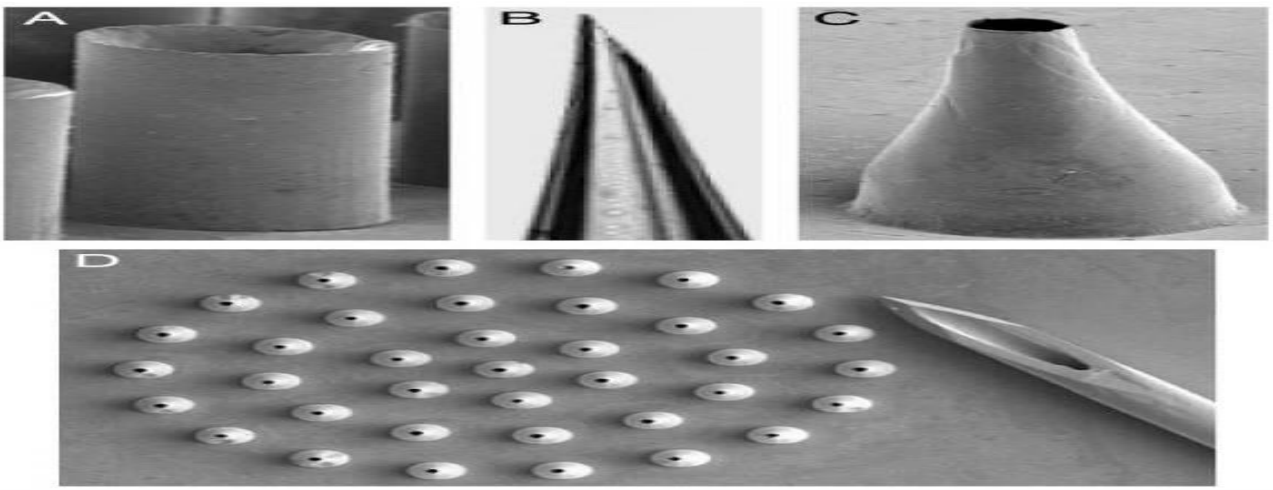
methods and materials[10]. MNs are classified as solid, coated, hollow, dissolvable, or hydrogel-forming. Furthermore, various manufacturing techniques such as laser ablation, photolithography, micro-injection moulding, and so on are available[11]. The first reports of a dissolvable microneedle used for TDD were published in 2005. According to the clinicalTrials.gov website, 43 clinical trials involving microneedles have been completed to date, with the first completed in 2007 (accessed on 30 June 2021, 5 p.m).To provide low-cost solutions for micro-mold manufacturing, additive manufacturing methods for MN mould fabrication were recently developed[12,13]. Reports demonstrating the use of commercially available 3D printers to fabricate the MN master mould heralded a new era in device fabrication and the possibility of custom-built high-volume MN manufacturing[14].

TYPES

Silicon, stainless steel, sugar, and polymers have all been used to create solid, coated, hollow, or dissolvable microneedles. Each microneedle has its own set of characteristics, advantages, disadvantages, applications, and material type.

- **Solid Microneedles**: This type of microneedle structure is intended to penetrate the stratum corneum in order to improve drug delivery to the dermis and kinetic transport across the skin[15]. In comparison to intramuscular delivery, the solid microneedle is better suited for vaccine delivery because it lasts longer and produces a stronger antibody response[16]. When compared to hollow microneedles, solid microneedles are easier to manufacture, have superior mechanical properties, and sharper tips[17]. Furthermore, the solid microneedle can be made of a variety of materials, including silicon, metals and polymers[18].



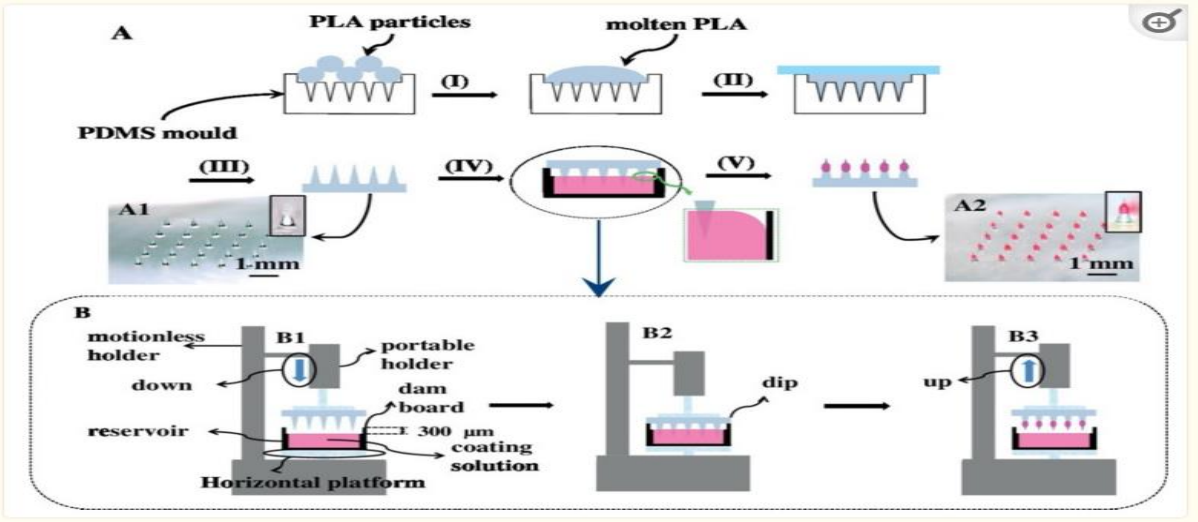


- **Hollow Microneedle:** A hollow/empty core/chamber into which drug fluid is injected/stored is present in the hollow microneedle[19].

  The hollow microneedle can handle a larger dose/amount of drug solution than the solid microneedle[20]. A hollow microneedle can also deliver drugs into viable epidermis or dermis, which is ideal for high molecular weight compounds. Furthermore, it regulates drug release over time, making it suitable for use with liquid vaccine formulations. Hollow microneedles are an active drug delivery system that forms a conduit for drug diffusion into the dermis based on a non-pressurized drug reservoir, as opposed to solid microneedles, which elutes drug primarily using the osmotic gradient Tuneable release kinetics can be achieved by using hollow microneedle material formulation and fabrication parameters. Higher concentration drugs may produce burst release drug profiles, whereas matrix-loaded drugs may produce steady-state drug release lasting days to weeks, depending on the application intent[21]. Hollow microneedles, like hypodermic needles, can be designed to allow for flow rate and pressure modulation. Other process parameters, such as the microneedle aspect ratio (height to base diameter ratio), can be tweaked to achieve rapid release, slow infusion, or time-varying delivery rate. The hollow microneedle has been used successfully in a variety of vaccine/inoculations over the years. However, because it is weaker and requires more care in terms of needle design and insertion method, this type of microneedle received less attention than the solid microneedle[22]. Furthermore, the hollow microneedle encounters technical difficulties such as leakage and clogging during the injection process.

Coated Microneedles: A coated microneedle is a solid-type MN that has been drug-coated. Depending on the thickness of the coating layer, it usually carries a smaller amount of the drug[23]. The ability to consistently coat a controlled drug layer onto MNs is critical to the success of drug delivery using a coated MN. A coated MN can deliver proteins and DNA in a non-invasive manner. The coated MN has the advantage of delivering the drug to the skin quickly; however, the remnant drug at the needle's tip may infect other patients[24]. Finally, the results of the vaccine delivery using coated MN were comparable to vaccines delivered via intradermal and intramuscular route.

- **Dissloving Microneedle:** Based on its characteristics, dissolvable MN first appeared in 2005 and is a promising technique. These features include facilitating the rapid release of macromolecules[25] and a one-step drug application that promotes drug administration ease[26]. This approach is considered superior to others due to the improvement observed in the application of dissolvable MNs following "poke-and-release[27]." A two-step casting method allows the dissolvable MN tip to be loaded quickly. When the dissolvable MN is inserted into the skin, the drug-load easily releases and diffuses due to needle tip dissolution. Water-soluble materials are best suited for the production of dissolvable MN[28]. Similarly, the micro-mold fabrication method is best suited for the production of dissolvable MN. A dissolvable MN array requires technical expertise to design and manufacture. However, this type of MN necessitates complete insertion, which is often difficult to achieve, as well as a delay in dissolution.



MECHANICAL CHARACTERIZATIONS

It is critical to consider the mechanical properties of the MNs as they are subjected to an applied force for epidural insertion during the MN design phase. To accomplish this, the MNs must be strong enough to prevent the MN array from failing[29]. According to Lutton *et al*., there is no single test that can simulate and observe the mechanical properties of the needle as well as the insertion of the MN *in vivo*. As a result, the MN should be subjected to a variety of mechanical tests for characterization. Mechanical tests performed on MNs

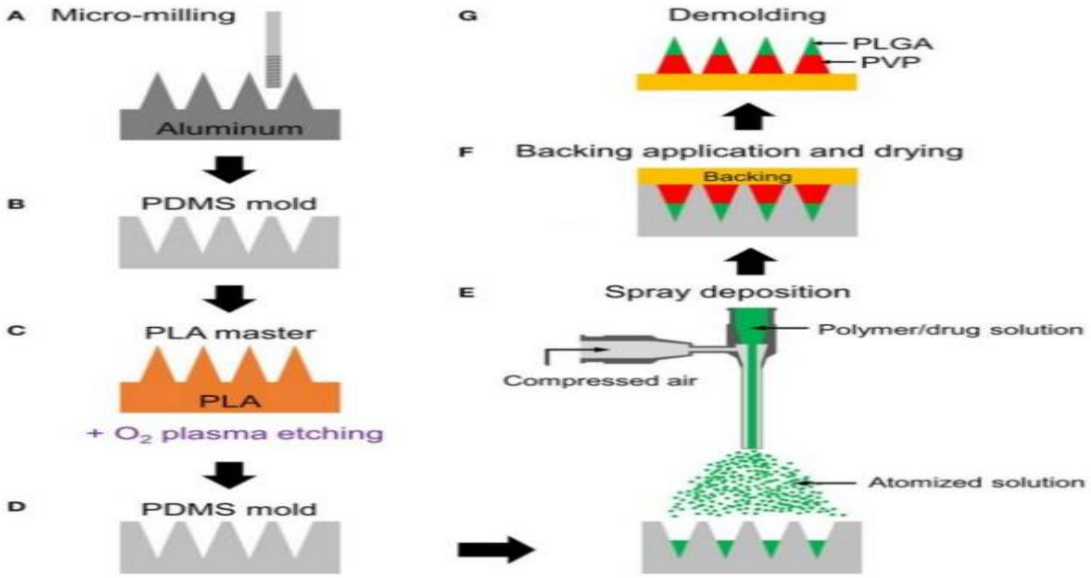
include axial force, transverse force, base plate break, and insertion force. Furthermore, several studies have been conducted to investigate the relationship between mechanical characterization and MN manufacturing parameters[30].

- **Axial Force**: The most common test is the axial force test, which involves applying force to the needle tips vertically and to the base of the MN array[31]. This mechanical test is important because it determines the needles' failure force. Knowing the needle failure force measurement is the most valuable information, also known as the safety point, because it provides an approximate range (expectation) of needle insertion force. Several axial force studies using various equipment and calculation methods have been conducted to determine the failure force of MNs. Davis et al. calculated force and displacement data to determine the failure (ScopeTest1, EnduraTEC, Minnetonka, MN, USA). Demir et al. also used a universal testing machine (Instron® Model 5969, Instron, Norwood, MA, USA) to measure the fracture force[32]. Furthermore, Khanna *et al* Axial fracture tests were investigated using a compression load cell (LCFA-500gF sensing capacity, Omega Co., Norwalk, CT, USA) and motorised actuators (Z600 series Thorlabs Motorised Actuators, Morganville, NJ, USA). and motorised actuators (Z600 series Thorlabs Motorised Actuators, Morganville, NJ, USA). Donnelly et al. used a TA-XT2 Texture Analyzer (Stable Microsystems, Haslemere, UK) in conjunction with a light microscope (GXMGE-5 digital microscope, Laboratory Analysis Ltd., Devon, UK) to conduct compression mechanical tests. Park and Prausnitz measured the failure test with a displacement-force test station (Model 921A, Tricor System, Elgin, IL, USA)[33].
- **Transverse Force:** In the transverse force test, a force parallel to the MN base plate with the y-axis is applied. Because skin surface irregularities can cause transverse bending of the MN, measuring the transverse fracture force is critical[34]. Furthermore, the transverse force, along with the axial force, completes the picture of the MN's mechanical property and thus predicts MN bending behaviour during insertion. The metal probe must be manually aligned with a defined length of the MN, which is a limitation of this test.Donnelly et al. used the TA.XT-plus Texture Analyzer (Stable Micro Systems, Surrey, UK) to calculate the transverse failure force of MN arrays[35]. Park et al. conducted another study to measure transverse force with a force-displacement station and a microscope[36]. A PDMS structure supported the MN vertically on a metal plate with perpendicular loading. The transverse force was applied until the MNs broke, implying that displacement increases linearly with MN base diameter. Demir et al. used a micromechanical tester (Instron® Model 5969; Instron, Norwood, MA, USA) to measure the transverse force of the MN.
- **Insertion Test:** The insertion test is more important than the axial force because the axial force does not provide an accurate measurement like the insertion test. This test also targeted different skin subjects, including pigs, rats, and humans. The ability to load the drug and deliver it to the skin is one advantage of using an MN. Despite the fact that several mechanical tests simulate the needle's fracture force, it is critical to validate the results with actual skin.The MN's imprints were then examined under a microscope (SZX12, Olympus, Bethlehem, PA, USA). Donnelly et al. implanted an MN on a movable cylindrical probe into the skin of a stillborn piglet. The skin surface was then examined under a digital microscope. Jun et al. used a zwickiLine material testing machine (Z5.0TN, Zwick/Roell, Ulm, Germany) to measure the transverse compression load[37]. Khan et al. also used a texture analyzer to study the insertion depth of different MN forces in neonatal porcine skin[38].

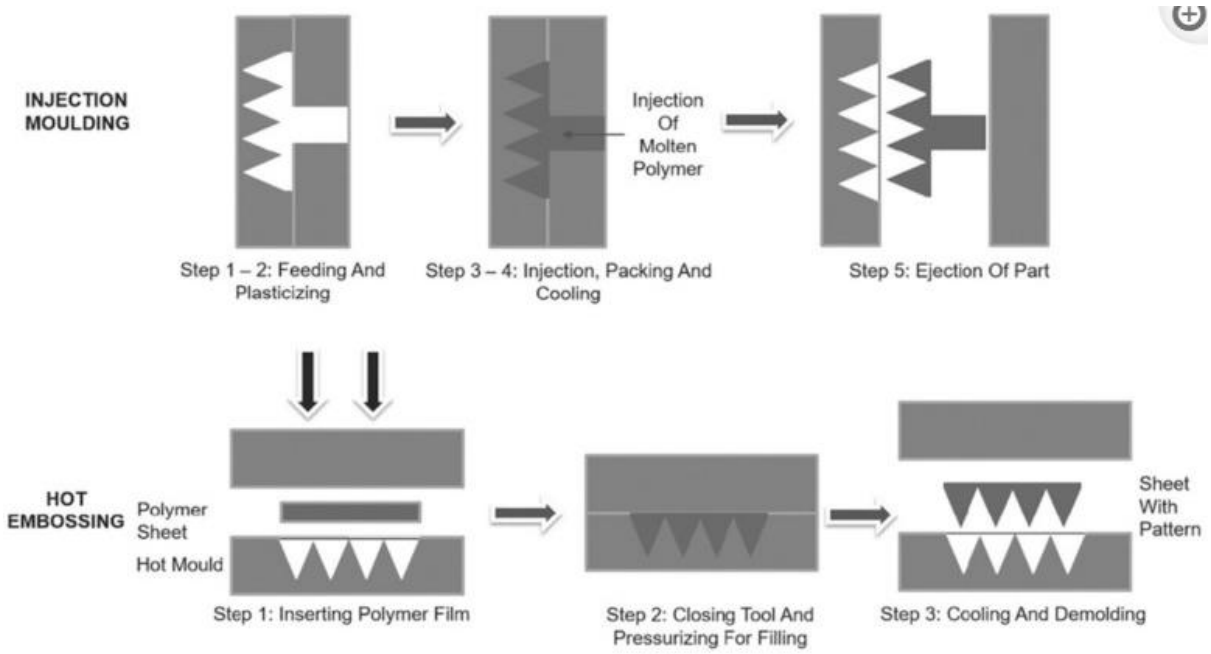
MANUFACTURING METHODS

There are several methods for creating MN arrays. Laser ablation, micro-moulding, additive manufacturing, injection moulding, chemical isotropic etching, surface/bulk micromachining, and lithography-electroforming-replication are the most common methods.

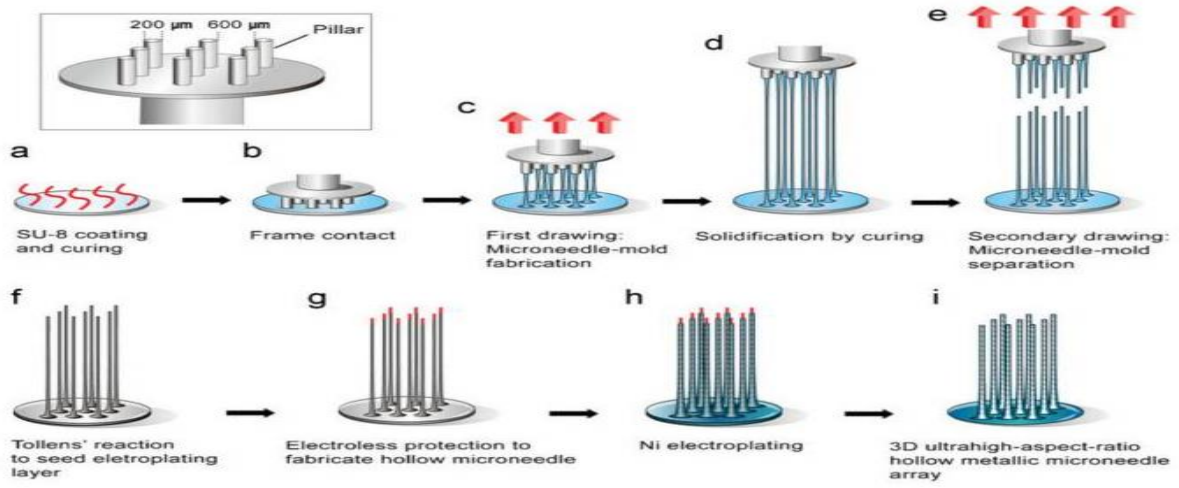
- **Micro-Molding:** The micro-molding process entails replicating the master mold. A polymer solution containing active pharmaceutical substances is used to cast the mold. Micro-molding is a low-cost method that is used for mass production[39]. For MN fabrication, micro-molding is commonly used with polymer material. In micro-molding techniques, PDMS has several advantages such as low cost, ease of use, low surface energy, and thermal stability[40]. The difficulties in controlling the depth of penetration, drug load capacity, and mechanical behaviour of the polymer are the limitations of this technique.



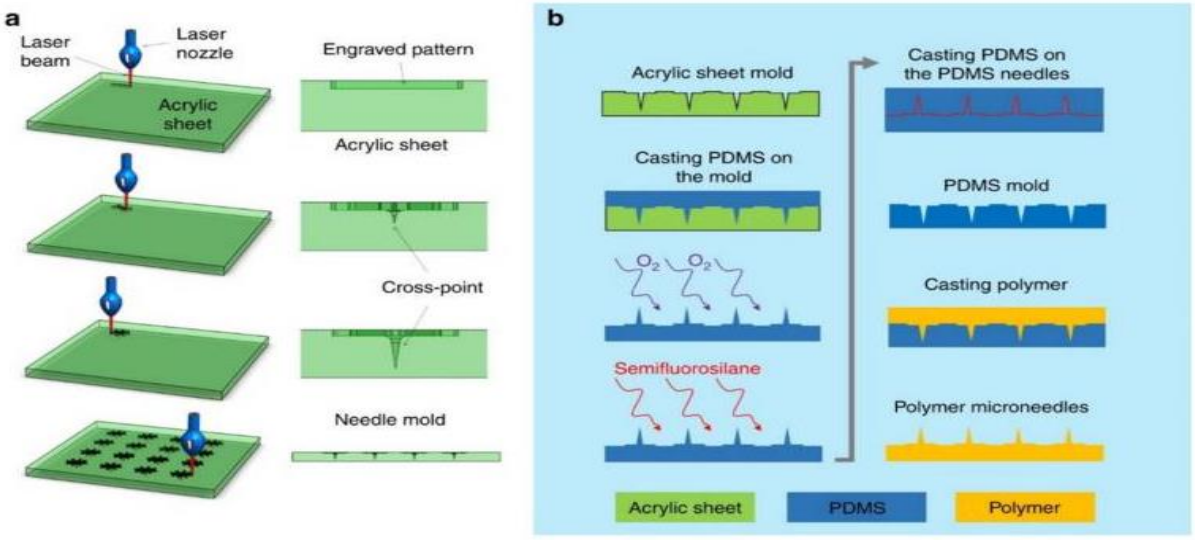
- **Injection Molding:** MNs are manufactured using injection moulding and the hot embossing technique. Lhernould *et al*. created a 4×4 hollow polymer MN array out of poly carbonate (PC)[41]. The MNs were shown to withstand high force and to be used for multiple insertions without blunting the needle. Another study created a solid MN using a micro-injection moulding process. These needles could deliver hydrophilic molecules with a high molecular weight. By moulding plastic material, Sammoura *et al*. created a polymeric MN[42]. The needles successfully penetrated a fresh chicken leg and a beef liver, extracting 0.04 L of liquid from each. The proposed method enables low-cost mass production of MNs.



- **Lithography:** The lithography technique is used to transfer the geometric shape master pattern onto the surface of a substrate[43]. Because of its wide applicability in the field of microelectronics, photolithography is primarily used for pattern transfer. Lithography is used as the first step in the fabrication of an MN in other techniques such as microelectronics and micromachining. Lithography necessitates precise photoresist processing[44]. This technique contributes roughly 30-35% of the cost of manufacturing integrated circuits. Lithography can create products from a wide range of materials, including glass, metal, ceramics, and plastics[45]. It also generates accurate geometries and smooth vertical sidewalls. However, this technique necessitates a sophisticated facility (cleanroom) and a lengthy production time.



- **Laser Ablation:** Laser ablation is the process of removing material from a substrate using a focused optical light beam to create MN arrays. Lasers have been used to process various materials at the micro- and nano-scale for a variety of applications[46].Several laser types have been investigated for use in the fabrication of MN arrays. CO_2, UV excimer, and femtosecond laser machines are examples of these[47]. Laser ablation is regarded as an efficient and quick method of producing MNs. It takes 10 to 100 nanoseconds for the laser beam to approach the burn point in the material sheet. Any metal could be shaped using a laser. This method is associated with thermal effects at the cutting surface, which cause changes in the structure and mechanical properties of MN[48]. In MNs, this may result in undesirable effects such as cracking or fatigue resistance. Laser ablation is a non-contact process that generates low heat loads on the substrate. The laser, on the other hand, is more expensive than other types of equipment. The laser ablation method is not suitable for mass production.



Merits

Microneedling has grown in popularity due to its growing list of advantages. It is said to rejuvenate and plump the skin with minimal discomfort and downtime, and it can be tailored to each individual's needs[49]

- Scar reduction, including acne scar reduction.
- Minimising the visibility of fine lines and wrinkles, minimising enlarged pores.
- Minimising the appearance of hyperpigmentation (dark spots).
- Evening out uneven skin tone.
- Enhancing skin elasticity.
- Promoting hair growth in alopecia patients[50].

Demerits

- Deep microneedling treatments may cause bruising or bleeding of the skin[51].
- Scarring is a possibility. Microneedling is not recommended for people who have keloids, which are skin scars that resemble large bubbles.
- Bleeding may also be more dangerous for people who have bleeding disorders or are taking blood thinners.

Before receiving this treatment, it is critical that you disclose this information to your doctor[52].

APPLICATIONS

MNs have piqued the interest of many researchers, scientists, and industry participants. Several studies have demonstrated MN's potential and ability to administer in a variety of fields. These include drug administration, vaccine administration, disease diagnosis, and cosmetics application.

- **Drug Delivery:** In 1998, a solid silicon MN was used for drug delivery for the first time[53]. Human growth hormone was delivered transdermally to hairless rat skin using a dissolvable MN patch. A caffeine-loaded dissolvable MN patch was found to be effective in controlling the weight of obese mice and serving as an anti-obesity treatment plan. Salmon calcitonin was delivered via a coated MN patch. A protein antigen (ovalbumin) was delivered into hairless guinea pig skin using a solid microneedle[54]. Calcine, BSA, and insulin were delivered using solid silicon and metal MNs .Drugs such as ibuprofen, ketoprofen, and paracetamol have also been transdermally permeated using MNs[55]. L-Ascorbic acid, riboflavin, aspirin, docetaxel, pilocarpine, lidocaine, hydrochloride, ketoprofen, and glycerol are some of the other drugs delivered via microneedles. Despite the fact that the majority of studies used a microneedle array to deliver drugs into mice, pigs, and human skin, other studies successfully demonstrated microneedle injection into chicken thigh and brain tissue[56].
- **Vaccine Delivery:** A dissolvable MN is a type of MN that is commonly used for vaccine delivery. The dissolvable MNs were used to replace the traditional hypodermic injection needles used to administer vaccines. Unlike other types of MN, soluble MNs are biocompatible, robust, scalable, and do not produce biohazardous waste[57]. Vaccines for malaria, diphtheria, influenza, Hepatitis B, HIV, and polio were delivered using soluble MNs[58]. Although dissolvable MNs are the most commonly used for vaccine delivery, coated MNs arrays have also been used successfully for vaccination. A study administered bacillus Calmette-Guérin (BCG) vaccine with a coated MN to improve the immune system of pigs in a simple, safe, and compliant vaccination method[59]. In another study, the hepatitis C virus protein was successfully encoded in a DNA vaccine coated on a microneedle. In mice, the microneedle effectively primed specific cytotoxic T lymphocytes (CTLs). Furthermore, a coated microneedle containing influenza virus antigen was used for vaccination of mice[60].
- **Diseases Diagnosis:** Several established bioassays that sample body fluids to assess and monitor health conditions can be used to monitor disease diagnosis and therapeutic efficacy. Current methods cause pain and necessitate specialised techniques, specialised equipment, and professional medical personnel[61]. Microneedle technology, on the other hand, provides a painless experience and simple implementation for bioassays. A hollow MN can detect several diseases, including cancer, diabetes, and Alzheimer's disease[62]. Another application of MNs is patient health monitoring. A hollow glass MN, for example, could be used to investigate the glucose level. In addition, O'Mahony et alproposed the MNs system for electrocardiography signal optimisation. Alcohol in artificial interstitial fluid was monitored using a microneedle-based enzyme. Microneedles containing nanoparticles were able to detect biomarkers in the early stages of osteoarthritis[63]. Microneedles were used as hydrogen peroxide, lactate, dissolved oxygen, and glutamate sensors.
- **Cosmetics:** MNs are commonly used in cosmetic applications such as skin care and hair growth. A hyaluronic acid-based dissolvable MN patch for intradermal delivery of ascorbic acid and retinyl retinoate was developed by Kim et al[64]. Kumar et al. used a solid MN to improve in vitro and in vivo local delivery of eflornithine (used to treat facial hirsutism)[65]. MN technology was also used to treat two patients with alopecia areata disease. Following treatment, these patients experienced hair growth. Using an MN, effective clinical trials in atrophic facial scarring, atrophic acne scars, and hypertrophic burn scars have been conducted[66].

CONCLUSION

Overcoming the stratum corneum barrier is critical for effective MN-mediated transdermal and intradermal delivery. This paper provides an overview of MNs technology in the transdermal drug delivery era. Because of the benefits, extensive studies and research have been conducted in the fabrication of MNs. This paper illustrates various MN design types, materials, and manufacturing methods. Several MN systems with distinct delivery mechanisms have been developed and used for the delivery of small or macromolecules over the last few decades. As highlighted in this comprehensive review, recent research has shown that temporarily disrupting the skin microchannel lifetime improves transdermal delivery efficiency of small molecular drugs, salt forms, excipients, and other formulation factors. The briefing covered intradermal and transdermal delivery of macromolecules such as therapeutic peptides and proteins, vaccines, and the synergistic effect of combined enhancement in addition to MN treatment. Furthermore, the literature investigates MN mechanical tests and their characterization.

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