Original Article

# Newly Developed Microneedles Can Dissolve in The Skin to Deliver Drugs

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## Abstract

Microneedles were first created for medication delivery many decades ago, but serious study on them did not commence until the mid-1990s. Microneedles, skin creams, and transdermal patches are the most extensive treatments for the transdermal administration of medications. Due to the stratum corneum layer of the skin, which acts as a barrier for the particles, multiple particles can appear at the site of action, limiting the effectiveness of the vast majority of supportive specialists. Microneedles are a further type of drug delivery device that aids in working on the transport of pharmaceuticals through this course and overcoming the numerous challenges associated with conventional nuances. The essential rule comprises interruption of the skin layer, so creating micron-sized routes that lead the drug plainly to the epidermis or higher dermis region, from which it can enter the central course straight without encountering a restriction.

**Keywords:** Microneedles, Vaccines, Delivery, Micromolding, Absorption

## 1. INTRODUCTION

An infusion needle, or hypodermic, is used to administer most biotherapeutics and vaccinations. Infusion provides a low-effort, rapid, and direct method of delivering nearly any particle into the body at a low cost.(1) Unfortunately, most people aren't comfortable using hypodermic needles on their own, so they're typically only used in hospitals or by patients at home after they've received special training on proper infusion technique, safe needle removal, and other related topics. Pain and needle-fear, experienced by many patients, also limit patient consistency. Needle reuse, which can spread blood-borne pathogens, is also a major problem, especially in non-industrialized countries. (2),(3) While oral administration typically solves these problems, many drugs cannot be administered orally due to poor absorption or drug breakdown in the gastrointestinal tract or liver. (4) Various methods of administration have also been studied, but none have shown the widespread efficacy of direct infusion with a needle. (5)

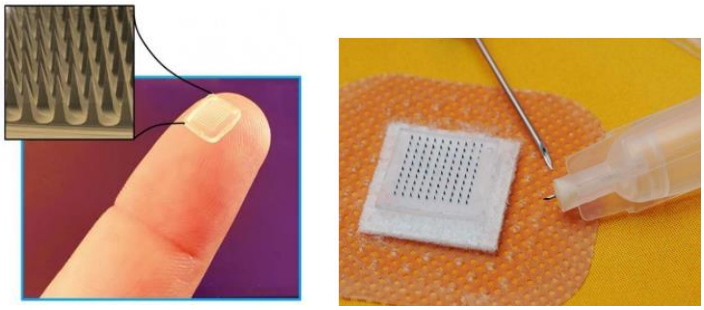

**Figure 1:** Microneedles

Microneedles (MNs) have been lauded by a variety of researchers as a means of transdermal drug delivery that can overcome the limitations of more conventional methods. Devices with micron-sized needles organised on a miniature fixture are known as microneedle devices. The microneedle drug conveyance framework was developed to address the shortcomings of both the hypodermic needle and the transdermal patch. One major drawback of transdermal innovation is that many medications fail to penetrate the skin at the adequate rate necessary for their therapeutic effect. The stratum corneum can now be penetrated by hydrophilic, high-subatomic-weight mixtures thanks to a refined innovation developed by scientists using microneedles. When drugs are organised with a microneedle device, drug particles are able to pass through the stratum corneum and into the skin. Faster startup time, improved quiet consistency, self-organization, and enhanced penetrability and adequacy are among the hallmark features of this innovation.

Microneedles, three-layered (3D) microstructures with microscale length (usually 1000 m), can penetrate the stratum corneum and produce temporary micro channels through which particles from the outside can latently infiltrate into the skin. The entrance depth of microneedles could be designed to be shallow enough to avoid nerve receptors in the lower

reticular dermis. This results in an uncomplicated drug business. This microneedle-based transdermal delivery method has the potential to provide a self-administering, patient-friendly, and efficient method for medication delivery. [6]
Solid microneedles for tissue pre-treatment, drug-coated microneedles, dissolving microneedles, and hollow microneedles are all distinct types of microneedles. As depicted in, each of these microneedle designs facilitates drug administration via distinct processes.

## 2. FIVE MAIN TYPES

(A) Solid Microneedles
(B) Coated Microneedles
(C) Hollow Microneedles
(D) Dissolving Microneedles
(E) Hydrogel Microneedles

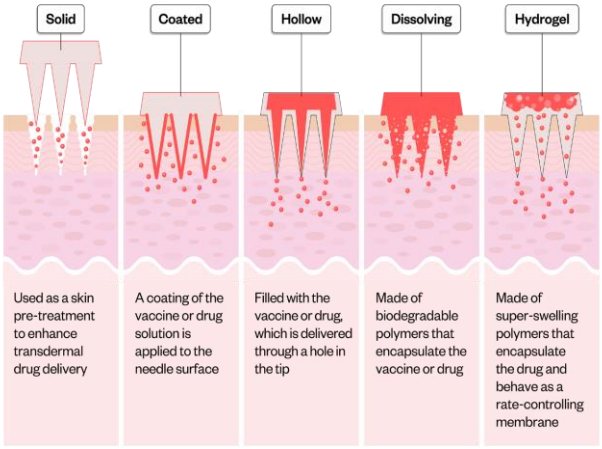


**Figure 2:** Types of Microneedles

The problems encountered with solid and coated microneedles have spurred the development of new types of microneedles. The hollow nature of microneedles makes it possible to transport fluids rather than dry details and to channel disproportionately large amounts. The advantages of dissolvable microneedles include their low cost of production (albeit testing has only been done on a large scale), precision and consistency in dosage, generally larger antibody amount limit, controlled drug conveyance, and ease of removal. Hydrogel microneedles are the most recent type of microneedle; they deliver moderately higher doses than previous dry microneedle measuring structures and, in theory, don't leave any polymer build-up under the skin.

### SOLID MICRONEEDLES

Micron-sized pores are created on the skin's surface by solid microneedles, which are inserted into the skin and have sharp, microscale tips made of a single substance with little to no excipients or drugs. The greatest skin barrier, the stratum corneum, is easily penetrated by the medication when it is applied to the treated area through these poncreasing the medication's bioavailability [7]. The medication is thus easily transported to the vessels in the shallow dermis. The expert could be identified as a traditional transdermal repair or as efficient skin detailing [8]. By adding chemicals that maintain the pores open for a longer period of time, medications can be delivered over and extended in time [9].

### COATED MICRONEEDLES

Coated microneedles are microneedles that have had the exterior layer of a robust microneedle covered with a water-dissolvable framework, allowing the drug to penetrate the skin swiftly [10]. The covering scheme should create a film on the microneedle's outer layer and maintain grip during insertion into the skin. The covering plan needs to be sufficiently thick to achieve this goal. It is important to consider where the covering detailing will be placed. Generally speaking, it is effective to apply the drugs right where the microneedle enters the actual skin. On account of plunge covering, the medication covered region can be controlled by means of managing the profundity to which the microneedle is dunked into the covering detailing [11]. The medication covered region still up in the air by controlling the surface pressure of the covering detailing, accordingly managing the spreading of the microneedle. In covered microneedles, the medication can rapidly break up in the skin, bringing about a quick beginning of medication activity [12]. The thickness of the covering can be expanded by rehashing the definition covering; in any case, it isn't reasonable for drug conveyance as it requires an enormous portion because of portion constraints [13] .

### DISSOLVING MICRONEEDLES

The actual microneedles can be made from biodegradable or water-soluble materials that deliver the drugs and have the required mechanical strength to pierce the skin [14]. When a dissolving microneedle is inserted into the skin, no sharps waste is produced because it instantly dissolves or disintegrates upon contact with the skin fluid [15],[16],[17]. The majority

of dissolving microneedles are produced by solvent casting a water-soluble biodegradable polymer. Utilized commonly are biodegradable cellulose-based polymers such as carboxymethyl cellulose (CMC) and methyl cellulose. Saccharides (such as trehalose and sucrose) are also included into the microneedles; they enhance formulation disintegration and stabilise biomolecules [18],[19]. The formulation of the drug-containing tip must be compatible with the drug, have mechanical strength, and have a viscosity low enough to fill the microscale mould space without air pockets.[20]

### HYROGEL MICRONEEDLES

In hydrogel microneedles, the drug is incorporated in every component of the microneedle tip, base substrate, and fix backing, and is slowly released as the fix is applied to the skin. The microneedle patches are mostly composed of hydrogel, and when they come into contact with liquids in the skin, they become hydrated without degrading [21],[22]. Through dispersion, a significant amount of the drug in the hydrogel is delivered to the skin [23],[24]. Since the medication may be incorporated into the entire microneedle fix, this system is suitable for large dose delivery; however, its disadvantage is that the fix wearing duration is long since the drug delivery rate is slow.

### HOLLOW MICRONEEDLES

As seen in Figure 2, hollow microneedles feature a bore on the needle tip and an empty hollow inside each needle. This permits the subcutaneous injection of minute volumes of medicinal solutions using a "poke and flow" technique. Microneedles made of glass, silicon, ceramics, and metal have all been created [15]. It becomes evident when one of the well-known issues with the "poke and patch" technique is juxtaposed with the benefit of hollow microneedles. When the solid microneedles are removed and the microchannels that were generated collapse, the skin recovers rapidly. In addition to avoiding the stratum corneum, hollow microneedles provide non-collapsible microchannels that can be left in situ for as long as necessary to administer the desired treatment. Although the creation of microneedles with an off-center hole can prevent this, microneedles with a hollow interior can occasionally experience microchannel blockage. [25]

## 3. MN MATERIAL

The ability of MNs to penetrate the skin without breaking or bending was the primary motivation for their development. A number of factors, including material, manufacturing technique, and design, have been considered to overcome the MN manufacturing problem. Diverse materials have been used to make various MN variants. Silicon, metals, ceramics, and polymers are examples of these materials. In the disciplines of medicine administration, tissue engineering, and biomedical implants, numerous distinct types of materials have been mixed. [26]

### MICRO-MOLDING

During the micromolding process, duplicates of the master mould are produced. A solution containing a polymer and active pharmaceutical substances is poured into the mould. Micro-molding is used for mass production and is considered a cost-effective process. Micro-molding with polymer material is frequently applied in the production of MN. The PDMS offers several advantages over other micromolding materials, such as its price, use, low surface energy, and thermal stability. Controlling the depth of penetration, drug load capacity, and mechanical behaviour of the polymer are difficulties inherent to this technique. [27]

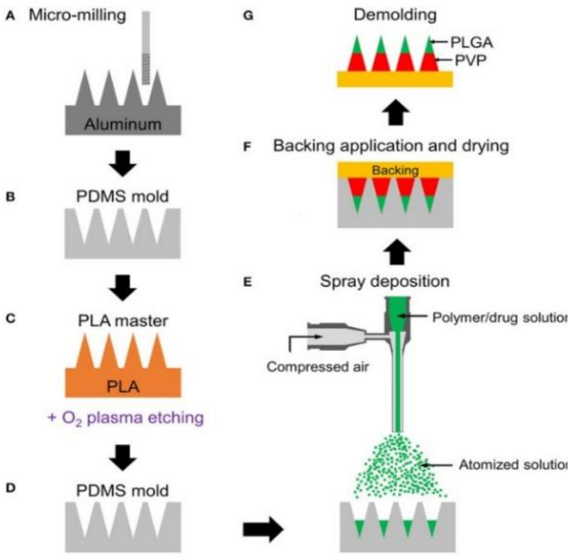


**Figure 3:** Micromolding Process

Multilayer MN manufacturing technique illustrated schematically: A micro-milling process is utilised to produce the aluminium master. (B) Replicating the PDMS mould from its original form. Micromolding and tip-sharpening with oxygen plasma to generate a PLA master. (D) PDMS duplicate of the PLA master mould. (E) Spraying a polymer solution

containing a medication into the mould cavity to fill it. Sequential polymer solution deposition resulted in the creation of multilayer MN. (F) Applying the backing material (yellow) to the mould and letting it to cure at room temperature so that the polymer can harden. (G) Removing the hardened multilayer MN array from the mould. Layers of PVP and PLGA are seen in green and red, respectively.

## 4. POLYMER USED IN MICRONEEDLE FORMULATION

In order for the drug to be delivered correctly, the microneedle must be inserted into the epidermal layer without breaking, so the needle's strength is the most important factor in microneedle manufacturing [28]. Additionally, the microneedles must have a sharp tip and be the right size and shape. Additionally, the needles must be biocompatible with the biosystem [29]. As a result, selecting the appropriate polymer for the production of microneedles is crucial. Glass, silicone, metals like stainless steel, titanium, solid or coated gold over nickel, palladium, cobalt, platinum, and synthetic and natural polymers are some of the components utilized in the production of microneedles [30]. The ideal polymer ought to be biocompatible and capable of providing sufficient mechanical strength for the microneedles.

## 5. IDEAL CHARACTERISTICS OF MICRONEEDLE PATCH

Newly developed microneedles must be able to penetrate the skin deeply without breaking, and their length or height can range from 50 to 900 meters [6], [31]. MNs ought to have a maximum size. In addition, they are intended for controlled drug delivery at a predetermined rate and must be mechanically stable and able to withstand an insertion force of approximately 10 N [28].These ought to be able to quickly and effectively deliver drugs, just like a hypodermic needle. These products must have a longer lifespan and be leak-proof when delivering drugs in a liquid state [13]. The goals of these are self-medication as well as personalized medication at various dose levels. In order to be comparable to standard transdermal patches, these patches must adhere well.

## 6. TECHNIQUES

The majority of dissolving microneedles are produced by micro casting or micro moulding, which is filling a microneedle mould with a solution, slurry, or suspension of a substance and allowing it to dry and harden prior to removal [32].

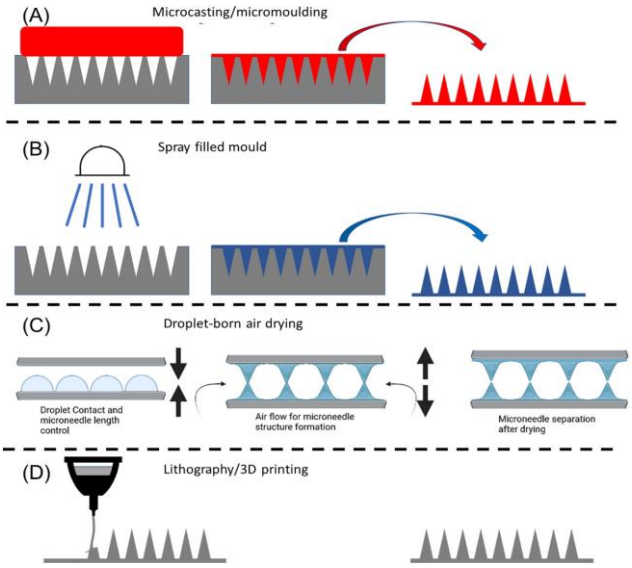


**Figure 4:** Techniques to Create Microneedles

The following techniques are used to create dissolvable microneedles:
(A) Micromolding / Microcasting,
(B) Spray Micromolding
(C) Droplet-born air drying,
(D) Lithograhy/3D printing

## 7. APPLICATIONS OF MICRONEEDLES

1067 applications remained after safety and fabrication applications (n = 436) were omitted from the study of target applications for microneedle research. Not unexpectedly, microneedle cosmetic operations were the most prevalent in general. With rising interest in cancer treatment, pain management, diabetes diagnosis/monitoring, and vaccine delivery studies, there is a clear upward trend.

Solid microneedles (64%) and hollow microneedles (19%) are the most common types of microneedles being studied in clinical studies at present. This is understandable considering that these microneedles are simpler to manufacture and would be subject to less regulatory scrutiny than coated or dissolving alternatives. According to the findings of the clinical investigations (n = 10), 7% of prior and contemporary trials utilised dissolvable microneedles. Between 1998 and 2018,

dissolvable microneedles comprised 11.1% of industry-based literature and 27.9% of scientific articles. This demonstrates that both academia and industry have a strong interest in dissolvable microneedles. Growing interest in the study of dissolvable microneedles will almost surely result in the anticipated increase of dissolvable microneedles undergoing clinical trials. [27]
Microneedles are mostly used in the cosmetics business to treat skin problems, which is consistent with previous research. In addition, there is evidence of a recent surge in the use of microneedles for the administration of vaccines.

### 7.1. VACCINES/ANTIBODIES
Vaccinations are frequently provided solely by subcutaneous injection today. Recently, it has been examined if microneedles containing vaccines can produce an immunological response with antibodies. In contrast to injectable formulations, microneedle vaccinations allow for better local immunity because antigen presentation to skin-resident dendritic cells is induced. Currently, vaccine delivery is often dependent on transport and cold storage. With vaccine production using microneedles, the patch's immunogenicity may be maintained throughout time, and storage conditions can be modified. Due to the fact that they target specific cells and affect the immune system, monoclonal antibodies are also beneficial in a variety of diagnostic and therapeutic procedures. To alleviate undesirable effects and prevent excessive autoreactive T cell stimulation, microneedle-based local injection of monoclonal antibodies was utilised. [33]

### 7.2. MN AND COVID19
Because the consequences of the coronavirus (Covid19) pandemic are felt globally, the MN method is a good option for battling the epidemic. Chen et al. developed an MN-based oropharyngeal swab to assist reduce the frequency of false negative COVID-19 test findings. Using this concept, physicians can differentiate between positive and negative samples by efficiently encapsulating the virus. Given that the COVID-19 immunisation is now available, MNs could carry it and administer it to patients who are capable of self-administration. [26]

### 7.3. HORMONES DELIVERY
The hormone insulin is a peptide. To lower the elevated blood sugar levels, medication is recommended. Using a microneedle to inject insulin has been demonstrated to reduce blood glucose levels more effectively [34]. Using a microneedle enhanced the skin's permeability to insulin, leading in a reduction of blood glucose to 29% of the initial level after 5 hours.

### 7.4. COSMETICS
The use of microneedles in cosmetics is growing rapidly, notably for improving the appearance of the skin and healing scars and blemishes. Several cosmetic active compounds, such as ascorbic acid, eflornithine, and retinyl retinoate, were administered via microneedles. Phosphatidylcholine nanoliposomes (nanoliposomes) with enhanced lipid solubility were modified with melanin. On application with an e-roller, it was found that more pigment penetrated deeply near hair structures [35]. Also investigated [36] was the use of microneedles to enhance the distribution of melanostatin, rigin, and pal-KTTKS.

### 7.5. CANCER THERAPY
Each year, millions of people throughout the world are diagnosed with cancer, and cancer treatment is extremely challenging. Microneedles have been researched for the administration of various anticancer medications. In order to treat melanoma, the ability of biodegradable microneedles to deliver anti-PD-1 (aPD1) over an extended period of time was evaluated. Anti-PD-1 and glucose oxidase loaded pH-sensitive dextran nanoparticles delivered via microneedle [37]. The treatment for basal cell carcinoma is topical 5-fluorouracil cream. When the cream was applied to skin punctured with solid microneedles, 5-fluorouracil permeability was raised by up to 4.5 times.[38] Additional evidence for the greater efficacy of microneedles was supplied by the prevention of tumour growth. Bhatnagar et al. explored the use of microneedles to administer tamoxifen and gemcitabine in the treatment of breast cancer. Localized delivery of these drugs could reduce their adverse effects [39]. Also investigated are polymeric microneedles for the localised administration of anticancer drugs and skin cancer [40].

## 8. FUTURE POTENTIAL
The skin is a promising organ for the development of therapeutic and preventative genetic therapies since it is an easily accessible, highly regenerative, and directly examinable tissue. Chabri et al. shown that microneedling may be used to transport a nonverbal vector intradermally, which can be used to treat epidermolysis bullosa and other inherited diseases locally. [41]

## 9. PATIENT COMPLIANCE AND SAFETY
### 9.1. SKIN HEALING PROCEDURE
When a microneedle device is inserted into the skin and removed after treatment, it leaves behind microscopic holes. It may take some time to reseal these pores. To prevent infection, these holes must be patched immediately. The time required for the skin to recover its barrier functions is crucial. The pore resealing process can be examined using electrical impedance testing. Depending on the needle's shape and whether or not the skin is occluded, the recovery time could range from 2 to 40 hours. Pore resealing can also be studied using TEWL and tissue staining [42], [20]

### 9.2. SKIN IRRITATION AND INFECTION

As a result of exposure to numerous environmental stimuli, the skin is equipped with a variety of self-defence systems. People with sensitive skin may have mild to moderate skin irritation or allergies when using microneedles. Redness, pain, and swelling are visible. Patients may report itch-related discomfort [43]. If the needles are not sterile, skin punctures created by microneedles can become sites of infection. Although the pores formed by microneedles are far smaller than those produced by hypodermic needles, microbial penetration is still less [42].

### 9.3. PAIN

Microneedles are less painful than hypodermic needles because they do not penetrate the deep skin pain receptors. The quantity of microneedles, their length, and the angle or form of their tips all affect how painful a patch feels to the patient [42]. Gill et al. claim that 26-gauge hypodermic needles are more painful than microneedles. The length and quantity of the patch's microneedles are inversely related to how uncomfortable the therapy is [44].

## 10. CLINICAL TRIALS AND SAFETY

Many pre-clinical studies on microneedles were successful from a variety of perspectives, but only a few achieved success with human subjects. In 2001, Kaushik et al. directed the first review for microneedles in a long time. The goal was to determine whether silicon microneedles, as opposed to a 26-millimeter hypodermic needle, are small enough to prevent pain. The 12 male and female sound workers chosen for the review had the microneedles inserted into their lower arms. The review argued that the agony caused by microneedles was distinct from that caused by hypodermic needles [45]. Preliminary research was conducted by Arya and colleagues to determine whether or not microneedles produce local skin responses and are accepted by patients.15 people participated in the study. The review showed that the patch's use of microneedles did not result in any swelling, pain, or erythema. The patients could manage the patches on their own without the help of a tool. These were preferred by human subjects over standard needles [46].The randomized clinical trial was conducted on 21 men to investigate the improved delivery of lidocaine following microneedle pretreatment. Skin 4% lidocaine cream conveyed sedation later 60 min of the application. The pre-treatment with microneedles resulted in sedation within 30 minutes. [47]. In order to investigate the beneficial effects of hyaluronic corrosive-based microneedle fix on the treatment of psoriasis, an open preliminary was conducted on ten patients. A balm containing calcipotriol and betamethasone was put on the skin. Over this, microneedle fix was applied once per day for seven days. When compared to the usual cream application, the one-week application was deemed effective [48]. As a result, the psoriatic plaques were significantly reduced.

## 11. CONCLUSION

The microneedle approach is now utilised to administer a variety of pharmaceuticals, but it must first overcome a number of obstacles before it can be commercialised. In order to obtain clinical approval, substantial research is necessary. Skin allergies, rashes, and irritation are the primary difficulties with microneedles technology. There is a maximum amount of medication that a microneedle can hold. Large and hydrophilic chemicals have a difficult difficulty penetrating the skin. These needles must be made from a material with sufficient insertion force and mechanical strength. The primary goal is to enhance penetration without creating discomfort. After pricking the region with a needle, it may be difficult for the patient to apply the patch. After application, if the skin pores do not seal, there is a risk of infection. Various technologies are being explored to administer medication through the skin. The conventional microneedles have undergone numerous modifications. The 3M hollow microneedle is one of these. This innovative technique is versatile enough to inject several hundred milligrams of proteins into the systemic circulation [49]. A combination of transdermal medication delivery and ultrasonography is being studied to increase drug permeability further [50]. Several modifications can be made to microneedles in order to distribute medication through the skin successfully.

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