

## REVIEW ARTICLE

# Microneedle Array Patches: The Tiny Next Generation Approach to Transdermal Drug Delivery

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### ABSTRACT

Microneedle technology has emerged as a revolutionary approach in transdermal and intradermal drug delivery, offering a minimally invasive, painless, and efficient alternative to traditional injection methods. The stratum corneum layer of the skin acts as a barrier for the drug molecules and only a small number of them may reach the site of action, the majority of therapeutic medicines have a restricted effect and micro-scale needles can enhance drug permeability through the skin. A novel delivery method known as microneedles aids in improving drug distribution via this pathway and resolving a number of issues with traditional formulations. The main idea is that the skin layer is disrupted, which creates microchannels that take the medicine straight to the epidermis or higher dermis, where it can enter the systemic circulation without encountering any barriers. This review provides a comprehensive overview of microneedle classifications, fabrication techniques, materials and diverse applications, including vaccine delivery, peptide delivery, cosmetics, cancer therapy, and gene therapy. Numerous microneedle products have entered the market in recent years. However, before the microneedles can effectively enter the market, a great deal of study is required to address the numerous obstacles.

**Keywords:** Microneedles, transdermal drug delivery, bioavailability, penetration enhancer, targeted drug delivery

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### INTRODUCTION

The most popular methods for delivering drugs through the skin are topical lotions and hypodermic needles but they suffer from drawbacks of lower bioavailability of lotions and associated pain of needles. When a medicine is applied topically, the skin acts as the main barrier. The outermost stratum corneum, middle epidermis, and thickest layer, dermis, are the three primary layers of skin. Because it only permits specific chemicals, such as lipophilic and low molecular weight medications, to get through, the stratum corneum layer functions as a primary barrier. When creating topical formulations, the low permeability of skin layers poses numerous challenges [19, 34].

Numerous transdermal or topical delivery methods have been investigated to enhance medication penetration through skin. Transdermal drug delivery (TDD) is a painless, non-invasive method for self-administering medication through the skin. Additionally, compared to subcutaneous injection, the pharmacokinetics of medications delivered transdermal are more consistent and have a lower drug peak concentration. TDD can thereby reduce the possibility of adverse effects [23, 24]. By reducing the hepatic first pass effect of medications, bioavailability can also be increased [1]. Notwithstanding these benefits, transdermal patches have many disadvantages, such as poor drug delivery effectiveness and restrictions on the medications that can be utilized due to the stratum corneum (SC) in the skin. The SC is the main barrier for TDD and is a superficial layer of skin that is 10–15  $\mu\text{m}$  thick [39]. Furthermore, TDD is not appropriate for biopharmaceuticals, such as protein medicines and vaccines, because of their high molecular weight [6].

An innovative transdermal patch featuring arrays of microneedles is called a microneedle array patch (MAP). To get beyond the drawbacks of traditional TDD, the idea of microneedles was first presented in 1976 [11, 13]. The SC is physically punctured by the MAP's tiny, pointed needles, creating a medication delivery channel. In other words, the medication is not held in the SC but is instead administered straight into the dermis or epidermis. Because its needles are typically smaller than 1 mm, they only slightly stimulate blood vessels and nerve fibres found in the dermis or epidermis. Therefore, compared to conventional parenteral routes such subcutaneous injection, a MAP can achieve better patient compliance as with improved drug delivery efficiency. Comparative drug administration of drug via different delivery system is shown in figure 1.

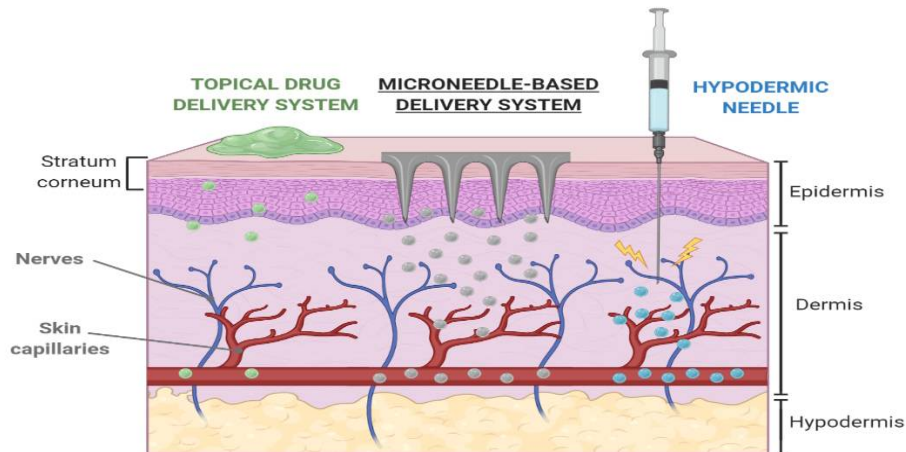


Figure 1: Comparative drug administration via different delivery system

The materials used in MAPs, as well as their size and form, determine how well they distribute drugs. The target area of the skin, the level of manufacturing precision, and the quantity of medication placed into the patch can all affect size of MAP. For instance, longer needle lengths or more microneedles per patch result in higher medication concentrations. Skin penetration is also influenced by a MAP's form. Drug delivery may be more significantly impacted by specialised shapes. The contents pertain to the different kinds of MAPs, the effectiveness of medication delivery, safety, mechanical strength, and special tactics of this delivery system.

### CLASSIFICATION OF MAPs

Various types of microneedles have been developed and explored for drug delivery applications, including solid, coated, dissolving, hollow, and hydrogel microneedles. Each type possesses distinct characteristics that influence its drug delivery mechanism as illustrated in figure 2. While some microneedles function by creating microchannels in the stratum corneum, others are coated with drug formulations, dissolve upon application, or contain preloaded drug solutions for controlled release [20, 21, 5].

#### Solid MAPs

A variety of materials, such as silicon, titanium, and stainless steel can be used to create solid MAPs. They can be made via electroplating, casting, ultraprecision machining, laser micromachining, and mechanical/chemical etching [4, 41, 42, 12]. Solid MAPs typically possess high mechanical strength and can readily pierce the SC barrier to create reversible microchannels in the skin. Subsequently, medications placed to the skin's surface can passively penetrate the microchannels and progressively penetrate the skin. However, because of their still dubious biocompatibility and the potential for skin damage from fractured metal or silicon MAPs, pretreatment of human skin with these solid MAPs can provide challenges [10]. Inaccurate doses can easily result from the dynamic recovery of the microchannels created by solid MNs [13].

#### Coated MAPs

A coated MAP is composed of a solid microneedle backbone covered with a biocompatible matrix that contains drugs. Strong mechanical strength is provided by the solid structure during application, and the coated layer quickly dissolves in the skin. The needle-body materials and fabrication techniques used for coated MPAs are comparable to those used for solid MPAs. Fabricated MPAs are then further coated with the medication solution or dispersion using either inkjet printing technology or a micron-scale dip-coating method to create a thin layer with a therapeutic agent on the needle-body surface. Following skin

entry, the coating layer separates from the needles, allowing the medicines to be released. One advantage of coated MPAs over solid MPAs is their easy one step application for full drug delivery [28, 3, 35].

The extended shelf life is another benefit of coated MPAs. During six months of nitrogen storage, the full performance of Desmopressin coated MPAs stayed at 98% (Cormier et al, 2004). In general, the coating efficiency is affected by the excipients, specific active medications, formulations, and coating procedure [11]. Furthermore, just the outside of the coated needle bodies can be loaded with medication molecules. Consequently, the thickness of the coating layer and the geometrical dimensions of the needles have a significant impact on the amount of drug loading [34, 21].

#### **Dissolving MAPs**

The medication is encapsulated within biodegradable polymers to create dissolving microneedles. Dissolution occurs after the microneedle has been inserted into the skin and will release the medication. The polymer controls the release of the medicine and breaks down in the skin. The polymer is one of the finest options for long-term therapy with better patient compliance because of its bioacceptability and skin-dissolving properties [19, 31, 4]. Fast-separating microneedles that were fixed on solid microneedles were prepared as dissolving microneedles take time in complete insertion [43]. In order to stop drug diffusion throughout the dissolving microneedles, bubbles were added to the device [38]. Rapid drug distribution with controlled release kinetics was made possible by forming separable arrowhead to dissolving microneedles [7].

#### **Hollow MAPs**

The catheter aperture, height, and needle tip all affect the hollow MAPs stability and performance. Usually, they are composed of ceramic, glass, metal, and silicon. A number of variables, such as tip size, length, pressure, inner diameter, insertion, and depth retraction, might affect the flow of medications through hollow MAPs. These are tiny, usually measuring only 1 mm. A few microns to several hundred microns can be the range of the diameter and length. To create hollow microneedles, fabrication techniques like photolithography, laser ablation, and micromolding can be employed [17, 18].

#### **Hydrogel MAPs**

A new method for overcoming the drawbacks of conventional medication delivery is hydrogel-forming MAPs. To make it, swellable polymers and hydrogels are crosslinked. This type of microneedle causes skin to inflate when it comes into contact with the hydrogel, which leads to water swallowing. There are minimally intrusive methods for delivering drugs. Proteins and vaccinations can be administered transdermally with the aid of hydrogel MAPs. Because it delivers medications without causing discomfort, many people like this practical alternative method. Hydrogel MN allows for controlled and extended medication release delivery. Hydrogel-forming MNs are made using a variety of techniques, including laser drilling, polymer casting, micromodeling, and a prospective approach [9]. Different types of microneedles based on their mechanism of drug release are shown in figure 2.

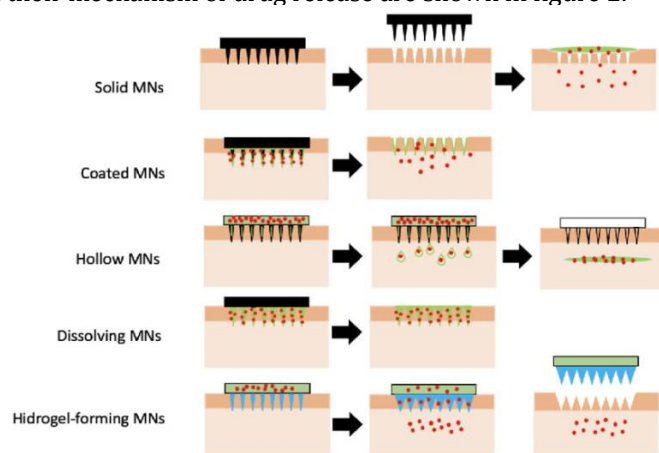


Figure 2: Types of microneedle based on their drug delivery mechanisms

#### **APPLICATIONS OF MAPs**

The MAPs are widely employed in many medical sectors in comparison to traditional administration methods since they are painless, simple to administer, safe, and can prevent gastrointestinal and hepatic first pass metabolism, deterioration and comparatively lower the expense of healthcare.

### **Vaccine therapy**

The DNA vaccine was administered using microneedle patches. The observed immune responses were much superior to those of standard injections [27]. There has also been an attempt to create a microneedle patch that can be used to administer influenza vaccine [26]. Additionally, the use of hollow microneedles to administer rabies and anthrax vaccines were investigated [20]. Immunity is improved by the drug's precise delivery in the upper dermis. On the fifteenth day following the vaccination, intradermal vaccination with microneedles produced noticeably larger antibody titers than subcutaneous injection [29, 32].

### **Cancer therapy**

Numerous anticancer drugs have been investigated for microneedle delivery. In order to cure melanoma, self-degradable microneedles that deliver anti-PD-1 (aPD1) continuously were studied. Using a microneedle, pH-sensitive dextran nanoparticles loaded with glucose oxidase and anti-PD-1 were administered [37, 38]. To treat basal cell carcinoma, a topical cream containing 5-fluorouracil is used. The application of the cream to skin treated with solid microneedles increased the permeability of 5-fluorouracil by up to 4.5 times. The enhanced effectiveness of microneedles was further validated by a significant suppression of tumour growth (Naguib et al., 2014). In order to treat breast cancer, Microneedles were used to deliver the gemcitabine and tamoxifen. Adverse effect of these drugs were found less due to localized delivery [2]. Skin cancer and localized delivery of anticancer medications were also studied using polymeric microneedles [42].

### **Melasma therapy**

Melasma is a disorder characterised by symmetric hyperpigmentation that can be caused by a number of factors, including hormone imbalances or UV exposure. Increased cutaneous pigmentation and larger melanocytes are seen in melasma histology. Although hydroquinone or corticosteroid creams are used as part of the traditional treatment for melasma, their effectiveness is limited because to their weak transdermal penetration. Microneedling's improved transdermal penetration and effective drug distribution have made it one of the more beneficial melasma treatment methods (Ogbechie-Godec et al., 2017).

### **Peptide delivery**

When peptides are taken orally, they are broken down by enzymes. Although transdermal administration circumvents this, less peptide can get through the skin. Microneedles for the delivery of peptides can aid in overcoming inadequate peptide skin penetration. Desmopressin is a synthetic version of the powerful peptide hormone vasopressin. Low vasopressin levels are replaced by it. Haemophilia A, diabetes insipidus, and bedwetting in young children are all treated with this drug. Research on the use of microneedles to deliver desmopressin revealed that these methods were safer and more effective than other approaches (Mdanda *et al.*, 2021).

### **Acne vulgaris therapy**

A persistent skin condition, acne vulgaris affects more than 80% of people worldwide. Increased sebum production, inflammation, propionibacterium acnes colonisation, and obstruction of the sebaceous duct in hair follicles are all associated with it (Tuchayi et al., 2015, Youn et al., 2005). By producing long-term dermal remodelling without the negative effects of retinoic acid, fractional radiofrequency microneedles (FRMs) have been developed for the treatment of acne and skin rejuvenation [14, 33].

### **Psoriasis therapy**

Recurrence and treatment resistance make it challenging to totally eliminate psoriasis, even if biotherapy has recently created new treatment options, particularly for moderate and severe cases. Anti-TNF- $\alpha$  Ab, a tumour necrosis factor-specific antibody, has been shown to efficiently block tumour necrosis factor and treat a number of inflammatory conditions. The dissolving MAPs were used for local intradermal delivery of anti-TNF- $\alpha$  Ab [16].

## **CONCLUSION**

The field of microneedle mediated transdermal drug administration has advanced remarkably. Through the formation of mechanical micropores in the skin, microneedles can significantly improve transdermal medication delivery. This method has distinct advantages over oral and injection administration, including low invasiveness, painless application, self-administered ease, and prevention of the first-pass effect. Microelectronics, materials science, and microfabrication technology have advanced recently, making it possible to make MAPs in a variety of sizes, shapes, and materials. Research indicates that when compared to hypodermic needle puncture, microneedles considerably lessen the amount of microbiological penetration across skin pores. It is necessary to ensure the safety of the materials used in microneedle manufacture, and new research indicates that optimised MAPs are biocompatible once

applied to human skin. The majority of microneedles intended for treatment are still in the development phase, necessitating greater work and close overlook. The microneedle technology has been the subject of numerous clinical investigations. Apart from administering medications, microneedles have been successfully used to administer vaccines, biotherapeutics like insulin and parathyroid hormone, and diagnostic techniques like gathering physiological fluids. In order to attain optimal therapeutic efficacy, it is critical to create appropriate treatment strategies for the numerous skin disorders.

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