

REVIEW ARTICLE

3D-printed microneedles in biomedical applications: Versatile approaches and clinical potential

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Abstract

Microneedles (MNs) are micron-scale structures that can painlessly penetrate the skin barrier to facilitate drug delivery, biomarker sampling, and biosensing. Although conventional molding techniques allow large-scale production, they have inherent limitations in rapidly and precisely customizing geometric structures—parameters that critically determine MN biomedical functionality and performance. As a next-generation manufacturing paradigm, three-dimensional (3D) printing offers novel opportunities for the development of personalized and intelligent MNs, leveraging its high precision, design flexibility, and integrated fabrication capabilities. This article reviews different types of MNs and their geometric characteristics, systematically summarizes the applications, advantages, and limitations of mainstream 3D printing technologies in MN fabrication, and focuses on recent research advances in 3D-printed MNs for drug delivery, biomarker extraction, and biosensor construction. Furthermore, it provides an in-depth overview of the application potential of 3D-printed MNs in treating various diseases. The article also discusses the emerging integration of 4D printing and artificial intelligence within this domain. Finally, we summarize and propose directions for future research.

Keywords: Three-dimensional printing; Microneedles; Personalized medicine; Biomedical applications

1. Introduction

In modern technology, additive manufacturing—commonly referred to as three-dimensional (3D) printing—is profoundly reshaping traditional manufacturing.¹ Unlike traditional subtractive or formative manufacturing methods, 3D printing transforms digital models into physical objects by layer-by-layer accumulation of material.² Fabricating complex structures via 3D printing typically begins with computer-aided design (CAD).

Designers create 3D models in CAD software and export them as Standard Tessellation Language files, which 3D printers can read. Subsequently, printer software slices the Standard Tessellation Language file into two-dimensional (2D) layers, guiding the printer to deposit material layer by layer to ultimately construct a 3D entity.³⁻⁵ Beyond CAD, 3D scanning technologies enable rapid acquisition of digital 3D images of objects or anatomical parts, providing essential data for designing customized medical devices.⁶ 2D images generated by medical imaging modalities such as X-ray, nuclear magnetic resonance imaging, and computed tomography scans can also be reconstructed into 3D models for fabricating personalized biological structures.⁷⁻⁹ 3D printing has found extensive application in producing customized medical supplies (such as wound dressings, implants, and prosthetics),¹⁰⁻¹³ personalized drug capsules and nanomedicine platforms,^{14,15} and the construction of organoids.^{16,17} In July 2015, the United States Food and Drug Administration (FDA) approved the world's first 3D-printed drug, Spritam (levetiracetam), for the treatment of epilepsy, developed by Aprelia Pharmaceuticals; this medication is manufactured using powder-binding technology.^{4,18} More recently, T21, a 3D-printed drug developed by the Chinese company Triastek for moderate-to-severe ulcerative colitis, received Investigational New Drug (IND) clearance from the FDA in November 2022.¹⁹ The first-in-human trial was completed in July 2023, with results confirming that T21 was precisely delivered to the target site in the colon, meeting the trial's endpoints. The FDA approvals of the aforementioned two drugs indicate the continued, rapid advancement of 3D printing technology in drug delivery, bringing new technological progress to this area.⁴

Microneedles (MNs) are micron-scale, needle-like structures typically ranging from 25 to 2,000 μm in height.²⁰ The concept of MNs dates back to the 1970s, and the first MN array designed for drug delivery was fabricated by Henry *et al.*²¹ in 1998.²² MNs can penetrate the stratum corneum—the skin's outermost layer—and create microchannels within the epidermis to facilitate effective drug delivery.²³ Regarding drug delivery mechanisms, MN technology offers a twofold advantage. First, unlike traditional hypodermic needles, MNs are precisely engineered to penetrate the stratum corneum without stimulating the nerve endings abundant in the dermis. Consequently, administration is virtually painless, significantly enhancing patient comfort and compliance.^{24,25} Second, by delivering therapeutics directly into the dermal tissue, MNs bypass the gastrointestinal tract and hepatic first-pass metabolism. This allows more drug to enter systemic circulation, enhancing therapeutic

efficacy, reducing required dosages, minimizing the risk of systemic side effects, and improving bioavailability.^{26,27} Furthermore, MNs enable continuous, painless sampling of interstitial fluid (ISF) from the skin, allowing rapid, real-time monitoring of biomarkers such as glucose, lactate, and alcohol. This capability establishes MNs as effective biosensors.^{28,29} The integration of MN-based monitoring and delivery systems holds promise for achieving closed-loop diagnosis and therapy.³⁰ In vaccine delivery, MN technology has opened new avenues for research and development. Results from a study on a measles-rubella vaccine MN patch demonstrated that the technology elicits immune responses comparable to those of traditional injectable vaccines in both adults and infants.³¹ Notably, MN technology exhibits unique potential in overcoming physiological barriers. Beyond penetrating the skin barrier, MNs can also effectively breach the blood-brain barrier (BBB). The BBB acts as a critical physiological barrier within the human body; while it effectively prevents the entry of harmful substances into the central nervous system, it simultaneously impedes the transport of therapeutic agents to pathological sites.³² Existing studies indicate that MN-mediated drug delivery across the BBB to target sites contributes to the treatment of Parkinson's disease and glioma.^{33,34}

The user-friendly nature of MNs allows for patient self-administration without the need for specialized training or additional tools.^{20,35} However, optimal therapeutic outcomes often require MNs with dimensions tailored to the individual patient—a level of personalization that traditional fabrication techniques, such as engraving, dipping, and molding, struggle to achieve.³⁶⁻³⁸ Capitalizing on the high precision and efficiency of 3D printing, this technology enables the rapid modulation of critical parameters governing MN performance, including tip diameter, aspect ratio, needle height, and needle density.^{39,40} Given the significant advantages of 3D printing in MN fabrication, publications in this field have increased in recent years (Figure 1A), and both articles and reviews show substantial academic impact (Figure 1B). This paper presents a comprehensive review of recent application scenarios of 3D printing in MN research (Figure 1C). First, different categories of MN systems and their intrinsic characteristics are introduced. Next, 3D printing technologies used in MN fabrication are summarized. Subsequently, recent research advances in 3D-printed MNs with different functions are discussed in detail. Finally, special types of MNs derived from common 3D printing technologies are reviewed to provide readers with a more in-depth and comprehensive understanding of this field.

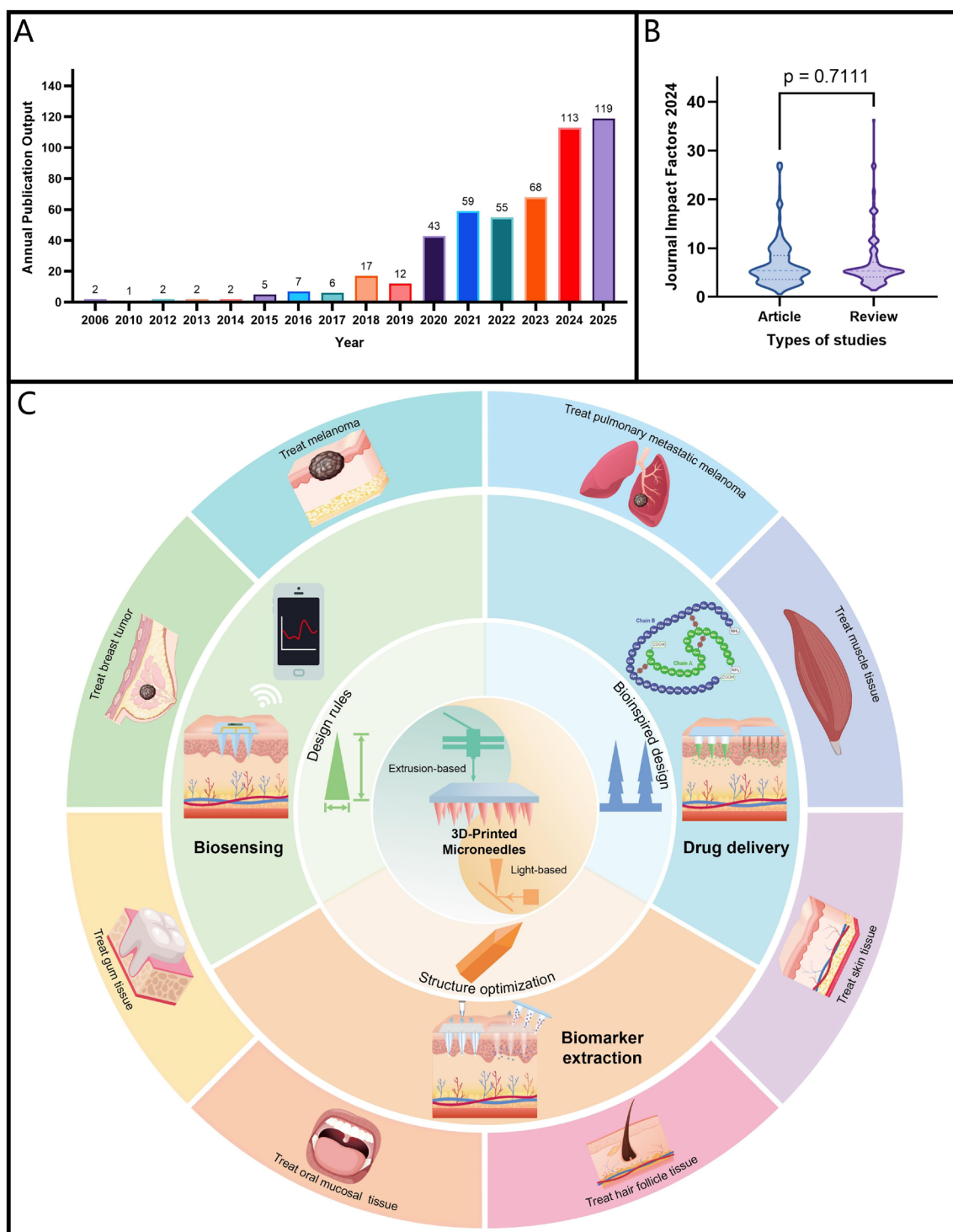


Figure 1. Bibliometric analysis of publications related to three-dimensional (3D)-printed microneedles (MNs). As of December 21, 2025, a literature search was conducted in Web of Science using the following search terms: (“3D printing” OR “3D-printed” OR “additive manufacturing”) AND (“microneedle*” OR “micro-needle*” OR “micro needle*”). The language was restricted to English, and the databases searched included Web of Science Core Collection and MEDLINE*. Article types were limited to articles and reviews. The retrieved literature was analyzed to obtain: (A) annual publication output of research articles on 3D-printed MNs up to 2025; (B) a comparative analysis of 2024 journal impact factors for article-type and review-type publications in 3D-printed MN research. Overview of this article (C): schematic illustration of MN structures designed by computer-aided design and fabricated using extrusion-based and light-based 3D printing technologies, as well as the biological functions and disease-treatment applications of 3D-printed MNs.

2. Overview of microneedle delivery systems

2.1. Classification of microneedles

Microneedles can be classified based on various criteria. By material composition, they are categorized as non-polymeric or polymeric MNs. Non-polymeric MNs encompass silicon, metal, glass, and ceramic varieties, whereas polymeric MNs are further divided into non-degradable and biodegradable types. Common materials for non-degradable polymeric MNs include polystyrene (PS), polymethyl methacrylate, and polydimethylsiloxane (PDMS). Biodegradable polymeric MNs are typically fabricated from synthetic polymers—such as poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), and polycaprolactone (PCL)—or natural polymers, including chitosan, gelatin, sodium alginate, and sodium hyaluronate.^{41–45} Beyond material composition, a more conventional classification system is based on structural characteristics and drug delivery mechanisms. This approach divides MNs into six major categories, as illustrated in [Figure 2](#) and reported in [Table 1](#). The following sections will provide a detailed introduction to these six types of MNs.

As the earliest category of MNs developed, solid MNs are typically fabricated from silicon, metals (e.g., stainless steel, titanium, tantalum, and nickel), or polymers (e.g., PLGA, PLA) and are often referred to as “poke and patch” devices ([Figure 2A](#)).^{22,46} Solid MNs do not inherently encapsulate therapeutic agents; their primary function is to puncture the skin barrier. The drug delivery process generally involves a two-step protocol: (i) the insertion of MNs into the skin surface creates a multitude of microchannels, establishing an ideal pathway for subsequent drug permeation; (ii) upon removal of the solid MNs, the pharmaceutical formulation is applied topically to the puncture site, where the drug penetrates the skin through the microchannels via capillary action.⁴⁷ Although solid MNs exhibit excellent skin penetration, their high material hardness and fine tip geometry result in significant brittleness. This susceptibility leads to a risk of tip fracture during administration, potentially causing needle fragments to be retained within the skin and posing safety hazards.⁴⁸ Furthermore, the rapid closure rate of the microchannels created by solid MNs can hinder the delivery of precise drug dosages.⁴⁹ Additionally, the reliance on the two-step “poke and patch” methodology renders the administration process relatively cumbersome and time-consuming, which may increase patient discomfort.⁴⁷

Coated MNs ([Figure 2B](#)) approach facilitates drug administration by incorporating a therapeutic layer

onto the surface of solid MNs.⁵⁰ Upon insertion into the skin, the drug coating rapidly dissolves within the tissue, releasing the therapeutic agent into the ISF for systemic or local delivery.⁵¹ Coated MNs are particularly effective for delivering water-soluble compounds, offering rapid drug release and high bioavailability, and are applicable to both small-molecule drugs and macromolecules. Furthermore, once the drug coating dissolves, the underlying solid MNs can be removed, allowing potential reuse.⁵² Drug-loading capacity is primarily governed by coating thickness and needle-shaft surface area; coating stability is also critical to ensure the formulation does not detach prematurely before insertion.⁵³ However, coated MNs present distinct limitations: the drug payload is restricted, typically not exceeding a few hundred micrograms.⁵² Moreover, the external coating may compromise the sharpness of the MN tips. During administration, friction and the dense structure of the stratum corneum can shear off some drug, which is retained in the outer skin layers rather than reaching the dermis, thereby reducing the effective delivered dose.

Hollow MNs ([Figure 2C](#)) are characterized by a microscopic lumen running along the needle axis; hollow MNs share dimensional similarities with solid MNs and function essentially as micron-scale hypodermic needles.⁵⁴ Typically fabricated from non-degradable materials such as metals, silicon, or polymers, these MNs exhibit robust mechanical properties.⁵⁵ Their mechanism of action involves pre-loading the therapeutic agent within the needle's hollow structure or reservoir; upon insertion, the drug is delivered into the body, driven by pressure or concentration gradients into the ISF. This modality is particularly advantageous for delivering high-molecular-weight compounds or administering larger dosages. Furthermore, the integration of external injection drivers allows for precise control over drug release, facilitating personalized dosing tailored to individual patient needs.⁵⁶ Beyond therapeutic applications, hollow MNs are utilized for the sampling of blood and ISF, enabling the monitoring of biochemical markers and biological signals.^{57,58} However, hollow MNs have specific limitations. Primarily, the minute aperture of the tip renders it susceptible to clogging by tissue debris during insertion.⁵⁹ Additionally, suboptimal needle geometry can cause leakage or backflow of the therapeutic solution onto the skin surface during administration.

Porous MNs ([Figure 2D](#)) are a more versatile alternative to hollow MNs; these devices are fabricated from materials with a porous structure, enabling seamless integration of MN and liquid-reservoir functions.⁶⁰ Common materials employed in their fabrication include silicon, metals (e.g.,

stainless steel, titanium, and alumina), and polymers (e.g., PLGA, PLA, and PDMS).⁶¹ Functionally analogous to hollow MNs, porous MNs operate via a mechanism reliant on the porous architecture of the needle shaft to facilitate fluid transport. Compared to hollow MNs, porous variants usually have higher liquid loading capacity and provide more uniform fluid transport.⁶² However, it is crucial to note that excessive porosity can compromise mechanical integrity, thereby impeding effective skin penetration.⁶³ Additionally, pore size imposes constraints on the range of loadable therapeutics; specifically, porous MNs with small pore diameters are ill-suited for accommodating high-molecular-weight drugs.⁶⁴

Dissolving MNs (Figure 2E) are constructed by combining biodegradable polymers with therapeutic agents; these devices represent a distinct class of MNs.^{44,45} Upon insertion into the skin, the needle matrix gradually dissolves via interaction with ISF, releasing drug molecules. These agents subsequently permeate the stratum corneum barrier and are absorbed through the subcutaneous tissue into the systemic circulation, achieving effective drug delivery. Compared to other MN variants, the “poke and release” mechanism of dissolving MNs offers significant advantages. On the one hand, because of their biocompatibility and biodegradability, no needle removal is needed after treatment, which improves safety and patient compliance while reducing the risk of needle breakage and retention in the skin.⁴⁵ On the other hand, dissolving MNs provide versatile drug-delivery modalities; bilayer dissolving MNs or regionally partitioned dissolving MNs loaded with different drugs in different areas can be designed to meet patient needs and disease conditions.^{65,66} However, limitations remain: the hydrophilic nature of the constituent polymers compromises mechanical stability in humid environments, necessitating storage under strictly desiccated conditions.⁶⁷ Additionally, precise control of drug-release kinetics is challenging, as dissolution depends on both material properties and the physiological environment at the application site.⁶⁸ Nevertheless, recent research has proposed encapsulating gas-generating microbes, such as *Enterobacter aerogenes* ATCC 13048, within the MNs to modulate the depth and spread of drug release. This mechanism relies on *Enterobacter aerogenes* fermenting glucose to produce gas; by regulating glucose concentration, researchers can precisely control microbial gas production, which in turn drives the encapsulated drug into deeper tissue layers.⁶⁹

Hydrogel MNs (Figure 2F) represent an advanced iteration of the dissolving MN concept; hydrogel MNs are typically fabricated from cross-linked hydrogels or super-swelling polymers.⁷⁰ These constituent polymers

may be derived from natural sources (e.g., hyaluronic acid, silk fibroin), synthetic materials (e.g., polyvinyl alcohol [PVA], polyvinylpyrrolidone [PVP]), or semi-synthetic derivatives (e.g., methacrylated hyaluronic acid [MeHA], gelatin methacryloyl [GelMA]).^{71,72} Drug loading in hydrogel MNs generally follows one of two strategies: (i) reservoir-based loading, where the drug is contained in the patch backing; upon skin insertion, the needle shaft absorbs ISF and swells to form a hydrogel conduit, allowing the drug to diffuse from the backing into the body, and (ii) matrix loading, where both the base and the needle shaft are prepared by mixing the drug with the polymer; following insertion, fluid ingress causes the matrix to swell, triggering drug release.⁷³ Post-delivery, the depleted polymer needles can be removed from the skin intact, leaving no residue. Beyond sharing the benefits of traditional dissolving MNs—such as high drug-loading capacity and excellent biocompatibility—hydrogel MNs offer the added capability of modulating drug release kinetics: hydrophilic polymers swell rapidly to facilitate immediate release, whereas hydrophobic polymers swell more slowly, enabling sustained release for prolonged therapy.^{48,70,74} However, upon absorbing body fluids, the mechanical strength and physical stability of these MNs are inevitably compromised.

2.2. Design of microneedles

2.2.1. Fundamental properties of microneedle structures

Any MN involves four key properties: tip diameter, aspect ratio, needle height, and needle density. This section explains how each property influences MNs.

The tip diameter primarily affects the force required for the MN to penetrate the skin. MNs with smaller tip diameters are sharper, and the variation in insertion force is smoother. Römgens *et al.*⁷⁵ prepared MNs with different tip diameters by stretching a 1 mm glass rod. The research team found that MNs with a tip diameter of 5 μm provided smoother skin penetration, while those with a tip diameter of 37 μm experienced a sudden reduction in resistance and a rapid increase in insertion depth during insertion.⁷⁵ This sudden breakthrough sensation can severely impact the control of the MN by medical personnel. However, MNs with smaller tip diameters also have the disadvantage of low mechanical strength and high liquid delivery resistance.^{76,77} In contrast, MNs with larger tip diameters have better mechanical strength, but their sharpness decreases, which may lead to the sudden increases in insertion depth observed by Römgens *et al.*⁷⁵ Interestingly, tip diameter does not affect the penetration depth; MNs with different tip diameters exhibit similar average penetration depths at

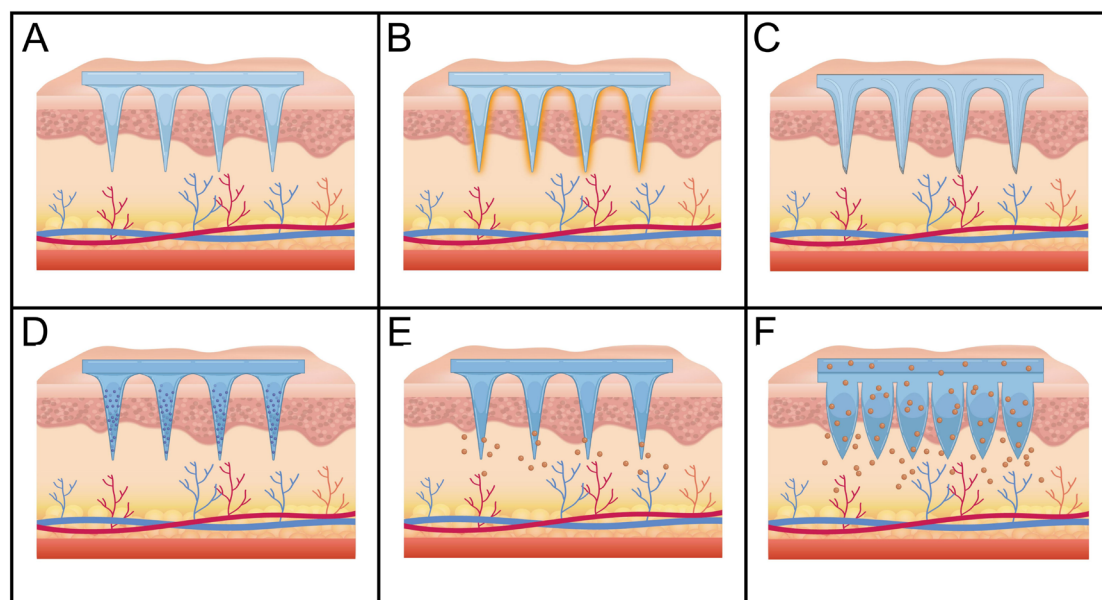


Figure 2. Schematic illustrations of different types of microneedles (MNs): (A) solid MNs; (B) hollow MNs; (C) porous MNs; (D) coated MNs; (E) dissolving MNs; and (F) hydrogel MNs. Created with Adobe Illustrator.

Table 1. Working principles of six types of MNs and comparison of their advantages and disadvantages

Type	Working principle	Advantages	Disadvantages	References
Solid MNs	The skin is punctured to form micropores, then the MNs are removed; the drug is absorbed through capillary action	High mechanical strength; simple to prepare	Brittle needle tips prone to fracture; potential retention of needle fragments in the skin; rapid closure of microchannels reducing drug diffusion; complex administration procedures	22,46-49
Coated MNs	After MN insertion, the drug coating quickly dissolves and enters the body	Fast drug release from coating; high mechanical strength; reusable needles	Limited drug loading capacity; drug coating affects needle sharpness; some drug residue in the stratum corneum	50-53
Hollow MNs	The needle is hollow, and the drug is injected through the needle hole or absorbed by tissue fluid	Can deliver large drug doses, collect blood and ISF; controllable fluid flow rate	Needle holes can clog; improper design can lead to drug leakage outside the skin.	54-59
Porous MNs	The drug or fluid is delivered through the MN pore structure	High liquid capacity; more even fluid diffusion	Excessive pores reduce mechanical strength; pore size limits drug types; not suitable for large molecule drugs	60-64
Dissolving MNs	MNs gradually dissolve after insertion, releasing the drug	Good biocompatibility; no need to remove the MN; high patient compliance; can be designed for multi-layer or segmented release	Poor mechanical stability (softens easily in humid environments); drug release is difficult to control precisely; limited drug loading capacity	44,45,65-69
Hydrogel MNs	MNs absorb water and expand to facilitate drug release	Good biocompatibility; high drug loading capacity; adjustable release rate (fast or slow release); no residue	Mechanical strength and stability deteriorate after absorbing body fluids	48,70-74

Abbreviation: MNs: Microneedles.

the same maximum displacement.⁷⁵

The aspect ratio refers to the ratio of the height of the MN to its base width, reflecting the MN's mechanical strength and the ease of insertion.⁷⁸ MNs with a higher aspect ratio are easier to insert into the skin because their tips are more slender, but they have lower mechanical strength. In contrast, MNs with a lower aspect ratio are more mechanically strong and stable, but more difficult to insert into the skin.⁷⁹ Additionally, penetration depth decreases as aspect ratio decreases, but only when it falls below a certain value does it significantly affect penetration depth. This was demonstrated in experiments by Cárcamo-Martínez *et al.*,⁸⁰ where the team prepared MNs with four different aspect ratios (2.5–4.5). They found that the penetration depth decreased as the aspect ratio decreased, and only when the aspect ratio was 2.5 did the penetration depth become significantly smaller than 80% of the needle length.⁸⁰

The needle height directly influences the distance over which the drug diffuses from the tip to the dermal microcirculation, as well as the level of pain experienced. The higher the needle height, the more efficiently the drug is absorbed by the dermal microcirculation, but excessively high needle heights can cause pain.⁸¹ Studies have shown that MNs 400 μm or less generally do not cause pain,^{82,83} while MNs 1,450 μm result in significant pain.²⁴ Furthermore, MNs with excessive height can also cause bleeding and stimulate skin redness and swelling.⁸² Needle height is not the only factor influencing penetration depth; MN material also plays a role. For example, MNs made of poly(methyl vinyl ether-co-maleic anhydride) with a height of 600 μm achieved a penetration depth of about 78% of the needle height, while MNs made from carboxymethyl cellulose of the same size achieved only 25–33% penetration depth.^{81,84}

The needle density is related to the total drug load of the entire MN patch. A higher needle density increases the total drug load but simultaneously reduces the penetration ability of the MN patch. This is because a higher needle density increases the total contact area between the needle tips and the skin, resulting in a decrease in the pressure per unit area under the same external force, which generates the “nail bed effect”.⁸⁵ Studies have shown that when the distance between adjacent MNs is less than 150 μm , the nail bed effect negatively impacts penetration.⁸⁶ Additionally, needle density is also associated with pain sensation; the higher the density, the stronger the pain. However, pain sensation does not increase linearly with needle density. Gill *et al.*²⁴ found that when a patch with only 5 MNs was compared with a patch with 50 MNs (10 times the former) for pain assessment in subjects, pain sensation increased

by only 2.5 times.

2.2.2. Geometric structure of microneedles

In addition to the basic properties of MNs, their geometric structure is also closely related to penetration force, mechanical strength, delivery efficiency, and tissue adhesion. Pyramid-shaped and conical-shaped are the most common needle body structures for MNs. A study by Lee *et al.*⁸⁴ indicated that pyramid-shaped MNs have twice the mechanical strength of conical-shaped MNs, and their failure force (the maximum force an MN can withstand before breaking or deforming) is also higher. This may be related to the larger cross-sectional area of pyramid-shaped MNs, which results in a smaller aspect ratio.⁸⁴ Base geometry also affects MN performance. Loizidou *et al.*⁸⁶ evaluated pyramid-shaped MNs with triangular, square, and hexagonal base geometries (Figure 3A). In terms of penetration depth, the MNs with triangular and square bases penetrated to depths of 340 μm and 343 μm , respectively, while the MNs with hexagonal bases had the shallowest penetration depth, at only 197 μm (Figure 3B). However, in terms of mechanical strength, the MNs with hexagonal bases performed the best (Figure 3C). The study suggests that MN mechanical strength increases as the number of vertices in the base geometry increases, but their ability to penetrate the skin decreases.⁸⁶ Therefore, to balance penetration depth and mechanical strength, pyramid-shaped MNs with square bases appear to be the best choice. In addition to these two common structures, several research teams have designed MNs with special geometric structures. For example, El-Sayed *et al.*⁸⁷ designed an MN with a structure similar to a “tanto blade” (Figure 3D). This MN has a square base and two different sloped surfaces: the slope near the tip is shorter and steeper to enhance sharpness, while the back slope is longer and flatter, similar to a knife handle, to increase the mechanical strength of the MN, making it more stable.⁸⁷ Furthermore, a structure resembling an “arrow” was designed, where the arrowhead is a drug-loaded soluble MN connected to a metal shaft (Figure 3E). Due to the high mechanical strength of the metal shaft, this design can effectively prevent skin deformation during insertion, allowing the drug-loaded arrowhead to fully embed into the skin. Once the arrowhead is inserted into the skin, the metal shaft can be manually separated quickly.⁸⁸ In recent years, certain biological structures have inspired researchers to design various special MN structures. Hard coral reefs protect internal coral polyps, which can feed through holes in the reef. This coral behavior inspired Liu *et al.*,⁸⁹ who designed a porous hydrogel MN with a hard outer shell (Figure 3F). Jiang *et al.*,⁹⁰ inspired by the serrated structure of a bee stinger, developed a hydrogel

MN with a serrated structure (Figure 3G). This biomimetic MN not only has excellent penetration performance but also exhibits high skin adhesion.⁹⁰ The spines of a cat's tongue can change their angles in different environments, enabling them to firmly grasp objects. Gan *et al.*⁹¹ used this characteristic of cat tongue spines to develop an MN with a similar structure, aiming to increase MN skin adhesion (Figure 3H). However, most of these special structures rely on 3D printing technology for fabrication. El-Sayed *et al.*'s⁸⁷ "Tanto blade" MN and Liu *et al.*'s⁸⁹ coral-inspired MN were both fabricated using digital light processing (DLP) 3D printing technology. The following section provides a detailed introduction to various 3D printing technologies used to manufacture MNs.

3. Overview of three-dimensional printing technology in microneedle fabrication

3.1. Material deposition

3.1.1. Fused deposition modeling

Fused deposition modeling (FDM) is one of the most cost-effective and widely used 3D printing methods.⁹² This technology uses thermoplastic polymer filament extrusion, where gears feed solid thermoplastic filament into the print head, heat it to a molten state inside the print head, and then extrude it through a nozzle (Figure 4A).^{93,94} The printer consists of a print platform that moves along the Y-axis and an extrusion head that moves along the X and Z axes.⁹⁵⁻⁹⁷ As the print head moves according to a preset 2D slicing pattern, the molten material is precisely extruded and deposited onto the print bed, forming a layer of structure.^{96,97} Since the new layer is deposited before the previous layer has fully cooled, fusion occurs between the layers, resulting in a solid structure.⁹⁶ This process is repeated, with the print head moving upward along the Z-axis layer by layer, ultimately constructing the complete 3D object based on the model in the CAD software.^{95,97,98} When the temperature drops below the polymer's melting point, the printed object solidifies and can be removed from the print bed. When using FDM to fabricate MNs, factors such as biocompatibility, mechanical strength, and melting temperature of the thermoplastic polymer need to be considered. PLA, PCL, PVA, and polyethylene glycol are commonly used choices due to these characteristics.^{92,98-101} Luzuriaga *et al.*⁹⁴ published a study in which they successfully used FDM 3D printing technology to fabricate PLA MNs for transdermal drug delivery. However, Luzuriaga *et al.*⁹⁴ noted that it is difficult to precisely manufacture high-resolution PLA MNs using FDM 3D printing alone. Due to the relatively low resolution and poor dimensional accuracy of FDM, the surface of the printed MNs is often rough, and FDM

offers the lowest precision compared to other 3D printing technologies. To address this issue, they first printed the MNs as cylindrical structures and then chemically etched them in a 5 M potassium hydroxide solution for nine hours. This reduced the needle tip diameter from 170–220 μm to 1–55 μm , achieving the ideal size for smooth skin penetration (Figure 5A). Mechanical characterization further demonstrated that the etched PLA MNs possessed sufficient strength for skin insertion. The axial fracture force of a single MN, which reflects its resistance to failure during vertical insertion, was 0.23 N, while the transverse fracture force, indicative of its lateral bending stability, was 0.64 N. Both values were higher than the force required for skin puncture, reported as 0.058 N. In addition, the authors indicated that the etching treatment did not adversely affect the mechanical performance or material properties of PLA. The requirement for FDM to heat polymer filament to a molten state limits the direct incorporation of drugs into the polymer filament during 3D printing. This is because drugs may decompose during the high-temperature melting process.^{102,103} Therefore, the research team needed to carefully analyze the drug's decomposition temperature and the polymer filament's melting temperature to ensure drug stability during printing. In addition to directly mixing the drug with the polymer filament for FDM printing, researchers have explored other drug-loading methods. For example, Khosraviboroujeni *et al.*¹⁰⁴ fabricated PLA MNs loaded with estradiol valerate by first printing PLA MNs with drug reservoirs using FDM. They then injected the drug solution into the reservoirs and used PLA sealing technology to close the filling holes (Figure 5B).¹⁰⁴ Finally, the research team also employed potassium hydroxide chemical etching to post-process the MNs, improving the sharpness of the needle tips. The resulting MNs exhibited an axial fracture force of 36.0 ± 0.48 N per needle, which was substantially higher than the measured puncture force of 0.16 ± 0.02 N, confirming their mechanical suitability for skin insertion. This method avoids drug thermosensitivity, preventing decomposition at high temperatures during FDM printing while ensuring high-quality PLA formation. However, this also means that the MN patch requires a large drug package, reducing the integration of the MNs with the drug.

3.1.2. Material jetting

Material jetting (MJ) is a 3D printing technology similar to FDM, using a layer-by-layer manufacturing principle to construct three-dimensional structures (Figure 4B). However, unlike FDM, MJ uses a print head driven by thermal or piezoelectric forces, enabling the high-speed jetting of liquid materials drop by drop.¹⁰⁵ MJ commonly employs ultraviolet (UV)-curable inks; after depositing

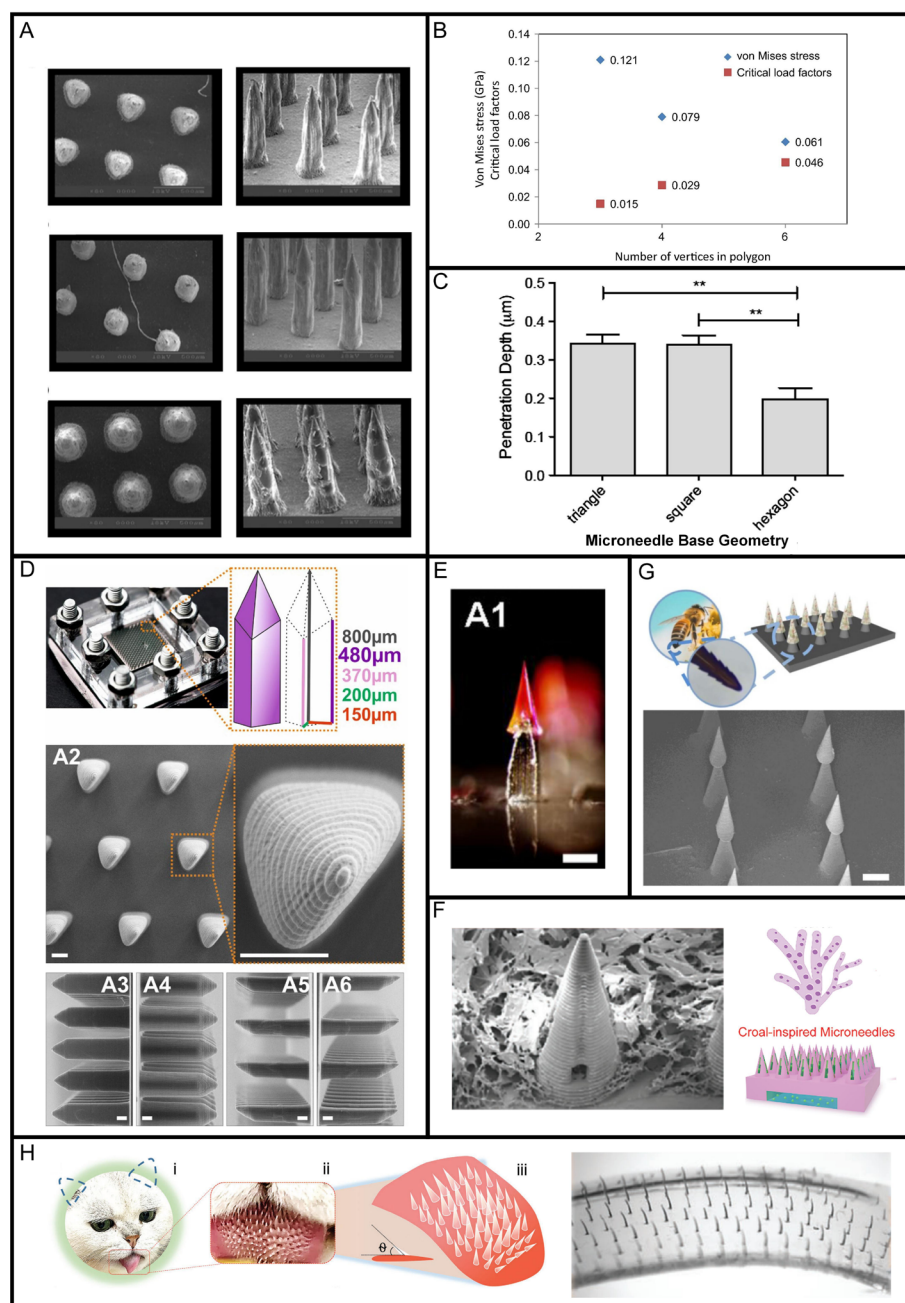


Figure 3. Different structural designs of microneedles (MNs). (A) Top-view and side-view scanning electron microscopy (SEM) images of MNs with three different base geometries; from top to bottom: triangular base, quadrilateral base, and hexagonal base. Scale bar: 600 μm ; magnification: 60 $\times$. Reproduced with permission from Loizidou *et al.*⁸⁶ Copyright © 2016, Elsevier. (B) Comparison of penetration depths of MNs with three different base geometries: triangular base: 0.340 ± 0.071 ; quadrilateral base: 0.343 ± 0.068 ; hexagonal base: 0.198 ± 0.087 (mean $\pm$ standard deviation, $N = 9$). Reproduced with permission from Loizidou *et al.*⁸⁶ Copyright © 2016, Elsevier. (C) Comparative analysis of von Mises stress and critical load factors of 3×3 MN arrays with three different base geometries. Reproduced with permission from Loizidou *et al.*⁸⁶ Copyright © 2016, Elsevier. (D) Design schematic of a “Tanto blade”-shaped MN and SEM images of the tip, back, front, and side views. Scale bar: 100 μm . Reproduced with permission from El-Sayed *et al.*⁸⁷ Copyright © 2020, Elsevier. (E) Front view of a detachable arrowhead MN, in which the red pyramidal structure represents the arrowhead and the brighter structure below represents the shaft. Scale bar: 300 μm . Reproduced with permission from Chu *et al.*⁸⁸ Copyright © 2011, Elsevier. (F) Schematic illustration and SEM images of coral-inspired porous hydrogel MNs. Reproduced with permission from Liu *et al.*⁸⁹ Copyright © 2024, John Wiley and Sons. (G) Schematic illustration and SEM images of bee-stinger-inspired MNs. Scale bar: 200 μm . Reproduced with permission from Jiang *et al.*⁹⁰ Copyright © 2025, IOP Publishing. (H) Schematic illustration and optical images of cat-tongue-inspired MNs. Reproduced with permission from Gan *et al.*⁹¹ Copyright © 2025, John Wiley and Sons.

each layer, a brief exposure to UV light is required to cure the material and prepare it for the next layer.⁹⁸ This process is repeated until the complete model is built. Droplet jetting is typically achieved through either the piezoelectric effect or heating elements. In the piezoelectric-driven system, a piezoelectric crystal deforms when a voltage is applied, generating acoustic pulses that propel the ink from the print head in tiny droplets in the range of 1–70 pL.¹⁰⁶ In the heat-driven system, heating forms small ink bubbles, and their expansion and rupture eject the ink from the nozzle.¹⁰⁷ MJ is typically not used for the fabrication of the MN body itself but rather for coating the surface of MNs with drugs. For example, Ross *et al.*¹⁰⁸ utilized inkjet printing technology to evenly coat the surface of stainless steel MNs with an insulin–polymer solution (Figure 5C).¹⁰⁸ They used a piezoelectric-driven nozzle (PicPip 300) to jet approximately 300 pL microdroplets at 1–5 m/s, depositing six droplets every 50 μm along the longitudinal axis of the MN, repeating the process 50 times to form a uniform coating. The puncture force of the entire MN patch was 7 N. Atomic force microscopy tests showed that the resulting insulin–polymer coating was evenly distributed, with no noticeable phase separation, and enabled rapid release within 20 minutes. Similarly, Economidou *et al.*¹⁰⁹ applied a similar technique to coat the surface of MNs with an insulin solution, successfully loading approximately 5 IU (175 μg) of insulin into MN arrays of three different geometries (conical, pyramidal, and spear-shaped) (Figure 5D).¹⁰⁹ Among these geometries, the pyramidal MNs showed the highest axial fracture force, reaching about 9.2 N per needle, followed by the conical MNs at about 7.5 N per needle and the spear-shaped MNs at about 2 N per needle. In terms of puncture force, the conical MNs required the lowest force of about 33.5 mN per needle, while the pyramidal and spear-shaped MNs required about 34.7 mN per needle and 35.2 mN per needle, respectively. Overall, the conical and pyramidal MNs exhibited more favorable mechanical performance. The resulting insulin–polymer coating showed good stability and consistent drug-release performance. However, material selection limitations remain a significant challenge in MJ development. Currently, available polymer materials on the market primarily include waxes and photosensitive resins, and the variety of materials is somewhat limited. Moreover, when printing large MNs, MJ precision is generally lower than that of light-based 3D printing technologies, as larger droplets must be used to improve printing efficiency for large components.¹¹⁰

3.2. Light-based three-dimensional printing

3.2.1. Stereolithography

Stereolithography (SLA) is a nozzle-free 3D printing

technology. It was invented by Charles Hull in 1984 and patented in 1986, and was later promoted for commercial use by 3D Systems, Inc. in 1988.^{111,112} In this technology, a UV laser with a wavelength of 355 nm is typically placed above a vat of liquid photosensitive resin. The laser scans a preset 2D cross-sectional path, causing the resin to undergo photopolymerization and solidify. After each layer is cured, the build platform is lowered by one layer thickness, and fresh liquid resin is evenly spread over the previous layer. The laser scanning and curing process is then repeated until the entire 3D object is built layer by layer (Figure 4C). After printing, the object generally requires cleaning to remove any uncured resin, followed by additional UV exposure to further enhance the object's mechanical strength and stability.^{18,111} Compared to the low resolution of FDM, the higher resolution of SLA has made it widely used in MNs¹⁰¹. For example, Economidou *et al.*¹⁰⁹ fabricated insulin-coated MNs using SLA technology. Additionally, Kundu *et al.*¹¹³ directly used SLA to manufacture MNs, designing an 81-needle array MN patch and employing acetone vapor polishing to reduce print-layer lines and improve MN penetration performance. However, Kundu *et al.*'s¹¹³ example raised an issue with needle-tip sharpness when printing individual MNs using SLA. This occurred because, during standard vertical (Z-axis) 3D printing, the cross-sectional area of each layer gradually decreases from the base to the tip, becoming very small at the tip and exceeding the printer's resolution limit. To address this, the printing direction can be tilted at a certain angle, thereby increasing the cross-sectional area of each layer and enhancing the tip sharpness (Figure 6A). Using this strategy, the MN patch achieved effective skin puncture at 10 N per patch, corresponding to approximately 0.123 N per needle. Tip damage began at around 30 N per patch, equivalent to about 0.37 N per needle, while complete failure occurred at approximately 40 N per patch, corresponding to about 0.49 N per needle. This approach has been adopted by most researchers, with Choo *et al.*¹¹⁴ indicating that adjusting the print angle to 60° can increase the layer stacking area to 22,187 μm^2 , improving the tip diameter from $155.2 \pm 1.3 \mu\text{m}$ (printed vertically) to $30.2 \pm 3.4 \mu\text{m}$ (Figure 6B). Another drawback of SLA is its relatively slow printing speed, typically only 1 to 3 cm per hour. This is mainly because the laser can only cure a limited surface area of resin at a time, and the layer-by-layer manufacturing method results in a longer production time.^{110,115} To overcome this issue when producing large quantities of identical MN patches, an indirect fabrication method can be used.¹¹⁶ This involves 3D printing a master mold of the MNs and then using PDMS to cast a reverse mold from the master mold. Once the reverse mold is cured, it can be used to fabricate MN patches (Figure 6C). By reusing

the pre-made mold for subsequent MN production, this method greatly facilitates large-scale MN production. However, a significant drawback of this method is the lack of customization. Additionally, when printing complex or uniquely shaped MNs with SLA, support structures must often be printed simultaneously and manually removed after printing.¹¹⁷ Because MNs are small, removing support structures carries a high risk of damaging their delicate structure. In summary, while SLA offers higher resolution than FDM, its resolution is still relatively low compared with DLP, continuous liquid interface production (CLIP), and two-photon polymerization (TPP).

3.2.2. Selective laser melting and selective laser sintering

Selective laser melting (SLM) is a powder bed-based metal 3D printing technology whose core mechanism is the interaction between the laser and the powder: rapid melting and solidification of metal powder under a high-energy laser (Figure 4D). First, the high-energy laser selectively scans the powder surface based on the sliced data of the 3D model, causing the powder in the specified area to melt and solidify. After each layer is completed, the build platform descends by one layer thickness, and the powder spreading and scanning process is repeated until the part is fully formed.^{118,119} Gieseke *et al.*¹²⁰ used 316L stainless steel powder and the selective laser micro-melting process to create hollow MNs with an inner diameter of approximately 160 μm and solid MNs with an outer diameter of 200 μm (Figure 6D). The research team used femtosecond laser etching to create small drug storage holes on the solid MNs and injected test liquid methanol using a piezoelectric nozzle.¹²⁰ This technology demonstrates the strong potential of SLM for personalized production of drug-releasing MNs. However, the drawbacks of SLM technology cannot be ignored. Because metal powder is used as the raw material, it is difficult to avoid rough surfaces during melting and solidification, often requiring polishing and grinding of the initially formed parts.¹¹⁹ Common methods include sandblasting or wire brushing, but these processes can easily damage the fine structure of the MNs. Gieseke's research team also pointed out this flaw.¹²⁰ Furthermore, although the high design freedom and ability to form complex structures are the most significant advantages of SLM technology, the need for support structures arises due to the thermal processing involved. At high temperatures, the metal hardness is relatively low, leading to insufficient support. Therefore, auxiliary support structures are often needed when manufacturing certain complex structures, which limits the preparation of specialized structured MNs to some extent.¹²¹

Selective laser sintering (SLS) is similar to SLM in its

core mechanism, also based on the interaction between the laser and the powder, and its production process similarly relies on repeated cycles of powder spreading and scanning (Figure 4E). However, unlike SLM, SLS does not require the powder to be fully melted; it only needs to soften or partially melt the surface of the powder particles, achieving particle bonding through surface tension. This process is called "sintering".^{118,122,123} As a result, products made by SLS do not require support structures (because the unsintered powder naturally supports the forming part),¹²⁴ which benefits manufacturing complex-structured MNs. Another difference is that SLS is not limited to metal materials for the raw materials; current research shows that SLS can use biocompatible polymers (such as PLA) for 3D printing,¹²⁵ which helps improve the biocompatibility of the fabricated MNs. Due to the similar principles of SLS and SLM, they share common drawbacks. The surfaces of SLS-printed products are also relatively rough.¹²⁴ Additionally, if drugs are to be directly incorporated into the 3D-printed raw materials, the thermal processing involved in SLS can cause the drug to decompose at higher temperatures, producing toxic by-products.¹²²

3.2.3. Digital light processing

Digital light processing is a surface-based photopolymerization printing method, also known as projection micro-stereolithography (PμSL).^{101,126} DLP works by polymerizing and solidifying liquid resin under UV light. After each layer is scanned, the platform moves up or down by one slice thickness, and after the resin is replenished, the next layer is cured. The newly solidified layer bonds tightly with the previous one, and the process repeats layer by layer to build the 3D structure (Figure 4F).¹²⁷ DLP is similar to SLA, but SLA cures resin point by point with a laser beam, while DLP projects the entire 2D cross-section with a laser, making DLP faster than SLA.¹²⁸ In fabricating MNs, DLP can be used both directly and indirectly. Justyna *et al.*¹²⁹ used the indirect method to prepare a soluble MN patch for treating animal gingival diseases. They first used DLP to print the main mold of the MN array (10 × 10 array, MN height 600 μm , base width 350 μm), then made a negative mold using PDMS and cast PVP and PVA polymers into it to produce the dissolvable MN patch (Figure 6E).¹²⁹ The resulting MNs showed a puncture force of approximately 0.4 N per needle, suggesting adequate mechanical strength for insertion into gingival tissue. Shin *et al.*¹³⁰ utilized DLP technology for one-step fabrication, directly printing a silk fibroin-based hydrogel MN (Figure 6F). This method used riboflavin as a low-cell-toxicity photoinitiator to trigger di-tyrosine covalent bond formation between tyrosine residues in the silk fibroin molecules, achieving photopolymerization. After

image grayscale anti-aliasing treatment, the printed MNs exhibited smoother slanted structures; after dehydration and drying, sharp tips were further obtained. The resulting MN patch showed good mechanical strength, requiring a puncture force of 300 mN per patch and withstanding an axial fracture force of more than 1000 mN. It also demonstrated effective transdermal performance in a pig skin model, with excellent biodegradability and successful delivery of the fluorescent molecule rhodamine B.¹³⁰ However, the current DLP workflow is often limited by the need to manually remove support structures, a flaw common to SLA and SLM, especially when manufacturing components with overhangs or internal joints. This limitation reduces automation in MN fabrication and increases production time and costs. However, solutions to this flaw have been proposed. Mason *et al.*¹³¹ introduced a multi-material DLP 3D printing technology based on wavelength-selective photopolymerization. The research team designed two photoinitiator systems. Photoinitiator System 1 used UV (365 nm) to trigger dual polymerization of acrylate/epoxy resin (thermoset), and violet light (405 nm) to trigger acrylate polymerization (thermoplastic). Photoinitiator System 2 used UV for epoxy crosslinking and blue light (460 nm) for acrylate polymerization. By adding chain transfer agents to control the thermoplastic molecular weight, the dissolution rate was optimized so the thermoplastic structures could dissolve within 10 minutes in ethyl acetate. In short, the team designed wavelength-selective photopolymer resins, using different light colors during printing to form an insoluble thermoset structural body and easily soluble thermoplastic support structures. After printing, the support structures were quickly dissolved using ethyl acetate, eliminating the need for time-consuming polishing or cutting¹³¹. Furthermore, although DLP accelerates printing by projecting the entire 2D plane with a laser, the printed model size is inversely proportional to pixel resolution: the higher the pixel resolution, the smaller the model size.¹³² Additionally, due to the layer-by-layer printing nature, the surface of the printed object is affected by the stair-step effect. However, this issue can be mitigated by anti-aliasing techniques (such as the image grayscale anti-aliasing treatment used by Shin *et al.*¹³⁰), where pixel brightness levels along curved edges are adjusted to create a gradual light-intensity transition, resulting in smoother surfaces or slanted structures.^{130,132}

3.2.4. Continuous liquid interface production

Continuous liquid interface production is a photopolymerization 3D printing technology based on continuous liquid surface growth. This technology relies on a special transparent and breathable window that allows both UV light and oxygen to pass through. The device can

precisely control the oxygen concentration and the time it enters the resin pool, using the oxygen at the bottom of the resin pool to inhibit curing in that area.^{133,134} Meanwhile, the light can cure the areas not inhibited by oxygen. In other words, oxygen creates a “dead zone” at the bottom of the resin pool with a minimum thickness of several micrometers (about 2–3 red blood cell diameters), within which the resin cannot undergo photopolymerization^{133,134}. As the platform rises, CLIP technology uses UV light to continuously project a series of cross-sections of the 3D model into the resin pool, achieving layer-by-layer curing and forming, a process similar to DLP technology (Figure 4G).^{134,135} CLIP technology has two major advantages: first, it offers extremely fast printing speeds, about 100 times faster than SLA;¹³⁵ second, CLIP models are finer and smoother. In comparison, SLA and DLP slice the 3D model and print it layer by layer, similar to playing slides one by one, which inevitably results in the stair-step effect. CLIP, by contrast, is more like playing a high-frame-rate 2D cross-sectional video of the 3D model, allowing continuous changes at the edges of the model, effectively eliminating the stair-step effect and creating smoother surfaces.¹³³ This high surface smoothness is particularly important for MNs, as it enhances skin penetration and reduces skin irritation and damage. Additionally, the “dead zone” prevents the printed model from sticking to the bottom of the resin pool, eliminating the need for manual detachment. A recent study has shown that CLIP technology can achieve an optical resolution as high as 1.5 μm .¹³⁶ Thanks to these advantages, researchers can use CLIP technology to fabricate MNs with various special shapes. The lattice MN patch (L-MAP) designed by Rajesh *et al.*¹³⁷ achieved a hollow lattice geometric structure that is difficult to create with traditional 3D printing methods. This structure consists of multiple fine support bars that form an open needle body with high surface area and lightweight properties (Figure 6G). This complex structure is difficult to form with layer-by-layer printing processes such as SLA or DLP because they require layer-by-layer curing, support structures, and are limited by mold-release requirements. However, CLIP’s continuous stretching-curing feature enables rapid, integrated formation of complex geometries. Moreover, this hollow lattice pyramid geometry enhances drug loading capacity and ISF exchange channels, holding promise for functional integration in transdermal drug delivery and fluid sampling.¹³⁷ However, the high cost of CLIP equipment limits its widespread application in MNs.¹¹²

3.2.5. Two-photon polymerization

Two-photon polymerization is a 3D printing technology based on two-photon absorption, suitable for the

fabrication of micro- and nanoscale structures. Two-photon absorption is a nonlinear effect where the absorption rate significantly increases with the energy density of the light, and extremely high light energy density is a critical condition for achieving two-photon absorption.¹³⁸ In TPP technology, the liquid resin molecules undergo polymerization only after experiencing two-photon absorption. Based on this property, TPP uses ultrashort pulse high-energy lasers, focusing the laser inside the photosensitive resin. Polymerization reactions can only be triggered in the extremely small volume at the laser focus center (where the light energy density is highest), thus enabling ultra-high precision 3D printing (Figure 4H).^{139,140} The printing resolution of TPP can reach an astonishing 100 nm.¹⁴¹ In MN fabrication, Szeto *et al.*¹⁴² used TPP technology to produce ultra-sharp hollow MNs to puncture the guinea pig round window membrane and collect 1 μ L of cochlear perilymph for proteomic analysis. These MNs had an outer diameter of only 100 μ m and an inner diameter of 35 μ m. Due to the extreme fragility of the round window membrane and the high precision required for sampling, traditional 3D printing methods could not meet the geometric accuracy and smoothness needed. However, the nanometer-level printing resolution and design flexibility of TPP allowed for precise control over the MNs' cone angle, tip morphology, and internal lumen path, enabling safe and highly reliable sampling of cochlear perilymph.¹⁴² However, the extremely high precision of TPP technology comes with trade-offs: high equipment cost and slower printing speeds. In the past, TPP printing speeds were generally considered to be below 1 mm/s. Recent studies have shown that the printing speed of TPP can be increased to several hundred millimeters per second, but this enhancement often depends on specific printing materials.^{143,144} To address the slow printing speed of TPP, many research teams have adopted an indirect method for fabricating MNs. This involves using TPP technology to print a high-precision MN master mold, then making a negative mold with PDMS, and finally casting the MNs from the negative mold. However, due to the shrinkage of PDMS during curing as the temperature increases, the size of the replicas made with PDMS molds is typically smaller than that of the master mold.¹⁴⁵ Additionally, the structural stability of PDMS negative molds is limited, making it difficult to replicate more complex structures such as sharp barbs or the internal cavities of hollow MNs, which contradicts the high-precision printing advantages of TPP technology.¹⁴⁶

A summary of these 3D printing technologies is provided in Table 2. Other printing methods, such as direct ink writing (DIW) and FDM, rely on nozzle extrusion of materials to achieve layer-by-layer deposition. The

difference between the two lies in the way DIW utilizes shear thinning properties, which enhances the fluidity of the ink under high shear forces, making it easier to extrude through the nozzle, while maintaining shape stability under low shear conditions.¹⁴⁷ As a result, DIW has fewer limitations regarding ink selection, as long as the ink exhibits suitable rheological properties. Due to the similarities between DIW and FDM principles, some have even suggested that FDM printers can be modified into DIW printers.¹⁴⁸ Given the limited application of DIW in MN fabrication, this section provides only a brief supplementary explanation of the technology. In addition, new 3D printing technologies evolving from traditional 3D printing methods continue to emerge. For instance, Liu *et al.*¹⁴⁹ developed a new technology named static optical projection lithography (SOPL) based on DLP technology (Figure 7). This technology uses static projection of UV light patterns to cure photosensitive resin, enabling rapid MN fabrication. Unlike traditional DLP, SOPL does not require the light source to move layer by layer; instead, it controls the curing region by using fixed light patterns and the spatial distribution of light intensity, effectively avoiding the stair-step effect common in DLP. As a result, SOPL produces smoother and more precise surface structures.

In addition to improvements in DLP projection strategies, volumetric additive manufacturing (VAM), which can overcome the conventional layer-by-layer fabrication paradigm, has also emerged in recent years based on DLP.¹⁵⁰ Unlike conventional DLP, which sequentially projects 2D cross-sectional patterns layer by layer, VAM projects a series of computationally generated 2D light patterns into a volume of photosensitive material from multiple angles. The light dose accumulates within the 3D space, and photopolymerization occurs only where the accumulated dose reaches the polymerization threshold, enabling the entire 3D structure to form in a single volumetric fabrication process.¹⁵¹ Bernal *et al.*¹⁵⁰ employed a rotating photosensitive resin container with a DLP modulator to project dynamic light patterns calculated using the Radon transform throughout the build volume, enabling volumetric bioprinting of complex hydrogel structures within tens of seconds. A major advantage of VAM is that it eliminates the need for layer-by-layer fabrication and can therefore effectively avoid the staircase effect associated with conventional layered manufacturing.¹⁵² In addition, this volumetric fabrication approach generally does not require support structures and enables complex 3D architectures to be produced in a relatively short time. Previous studies have shown that VAM can fabricate parts containing overhanging features of approximately 80 μ m and cavities of approximately 500

μm within about 25 seconds.¹⁵³ Moreover, VAM enables overprinting, in which a pre-existing device is placed in the photosensitive resin and new 3D structures are fabricated directly around it. This capability is particularly relevant to the secondary processing and functional modification of 3D-printed MNs.¹⁵⁴ However, VAM still faces several challenges. Commercial VAM printers remain scarce. Currently used systems mainly include the Tomolite v1.0, whose relatively prominent position in the market *also* reflects the limited supply of dedicated equipment in this field, potentially restricting the broader dissemination and application of VAM.¹⁵¹ Additionally, VAM imposes more stringent requirements on printing materials than conventional 3D printing technologies. Because the technique relies on the propagation, superposition, and precise spatial distribution of light throughout the entire resin volume, the resin generally needs to possess high optical transparency.¹⁵⁵ If the material exhibits substantial light absorption or scattering, the actual light-dose distribution may deviate from the theoretically calculated distribution, potentially resulting in localized over-curing or under-curing. Consequently, VAM may be limited for materials containing macromolecular drugs, nanoparticles, proteins, or cellular components. Because of these constraints, no publicly available original study has yet systematically evaluated VAM performance in fabricating 3D-printed MNs.

However, in light-based 3D printing technologies such as SLA, DLP, CLIP, and TPP, photoinitiators are essential for facilitating the photopolymerization reaction.¹¹² This is important because photoinitiators left in MNs may be cytotoxic, posing potential safety risks. Specifically, photoinitiator toxicity mainly arises from the free radicals generated during photocuring. Excessive free radicals can induce oxidative stress, disrupt cell membrane integrity, cause DNA damage and mitochondrial dysfunction, and ultimately induce apoptosis.¹⁵⁶ In addition, conventional photocuring processes require UV light, which can directly damage bioactive molecules. To mitigate the cytotoxicity of

photoinitiators, photoinitiators with good water solubility, high initiation efficiency, and favorable cytocompatibility should first be prioritized. For example, compared with the conventional photoinitiator Irgacure 2959, lithium phenyl-2,4,6-trimethylbenzoylphosphine exhibits better water solubility and higher photoinitiation efficiency, enabling hydrogel crosslinking at lower concentrations and with shorter exposure times.¹⁵⁷ Second, visible-light-initiated systems can replace UV-curing systems, reducing direct UV damage to bioactive molecules. Sun *et al.*¹⁵⁸ reported a photoinitiation system based on a water-soluble derivative of vitamin B2, flavin mononucleotide.¹⁵⁸ Under blue-light irradiation, FMN can undergo efficient electron-transfer reactions with potassium persulfate, thereby initiating various photocrosslinking reactions and achieving cell viability as high as 98%. Furthermore, to ensure the mechanical strength of MNs, the minimum effective photoinitiator concentration and the minimum effective exposure dose should be determined to minimize free radical generation. After printing, sufficient post-curing, washing, and vacuum drying should also be performed to remove residual monomers, photoinitiators, and photolysis byproducts. Meanwhile, novel photoinitiator systems should also be actively explored. For example, Rizzo *et al.*¹⁵⁹ proposed a photo-mediated crosslinking method based on ortho-nitrobenzyl alcohol. This method does not rely on traditional photoinitiators to generate free radicals; instead, under 365 nm irradiation, ortho-nitrobenzyl alcohol undergoes photolysis to generate reactive nitroso and benzaldehyde groups. These groups subsequently react with thiol groups to form dynamic N-semimercaptal bonds, or with amino groups to form indazolone bonds, enabling crosslinking of synthetic hydrogels and natural protein networks. The indirect method of fabricating MN molds allows for the use of various polymer materials (such as water-soluble and biocompatible polymers) to produce MNs, thereby avoiding toxic photoinitiators. This method helps mitigate the toxicity issues associated with certain printing materials to some extent.

Table 2. Comparison of common three-dimensional printing technologies used in microneedle fabrication and their advantages and disadvantages

Type	3D Printing technology	Highest resolution	Speed ^a	Materials	Advantages	Disadvantages	References
Material deposition	FDM	50 μm	Moderate	Thermoplastic polymers (e.g., PLA, PCL, PEG, and PVA)	The most cost-effective and widely used	The lowest resolution, rough surface of printed products; difficult to make high-precision needle tips; high temperatures may cause drug degradation	92,94,102,103, 160,161

(Cont'd...)

Table 2. (Continued)

Type	3D Printing technology	Highest resolution	Speed ^a	Materials	Advantages	Disadvantages	References
Light-based 3D printing	MJ	5 µm	Moderate	Waxes and photosensitive resins	Uniform and stable drug coating; controllable drug loading	Few available materials; limited print size; low print precision	106,107,110, 161,162
	SLA	25 µm	Moderate	Photocrosslinkable materials (e.g., GelMA, MeHA, and PEGDA)	Higher resolution than material extrusion printing	Slow printing speed; support structures required for printing products, removal can affect structural accuracy; needle sharpness still limited	101,110,113,115, 117,163
	SLM	50 µm	Moderate	Metal powders (e.g., 316L stainless steel and titanium alloys)	Can quickly form complex metal structures	Rough surface of products; high temperature during process can result in insufficient support strength, requiring additional support structures	118,119,120,121, 164
	SLS	45 µm	Moderate	Thermoplastic polymers (e.g., PLA, PCL, PEG, and PVA), bioceramics (e.g., hydroxyapatite), and metal powders (e.g., 316L stainless steel and titanium alloys)	No support structures required; more materials available compared to SLM	Rough surface of products; high temperatures may cause drug degradation and produce by-products	118,122-125,161
	DLP/PµSL	15 µm	High	Photocrosslinkable materials (e.g., GelMA, MeHA, PEGDA, acrylates, and epoxy resins)	Faster than SLA; higher resolution	Support structures required; resolution conflicts with product size; staircase effect in printed products	128,131,132,163
	CLIP	1.5 µm	High	Photocrosslinkable materials (e.g., GelMA, MeHA, PEGDA, and acrylates)	Extremely fast printing speed (much faster than DLP and SLA); smooth surface with no staircase effect; complex structures can be molded in one piece	High equipment cost	112,133,135,136
	TPP	< 25 nm	Low	Photocrosslinkable materials (e.g., GelMA, MeHA, PEGDA, and acrylates), and IP-S photoresist	Highest resolution (nano-scale); precise control of structure; suitable for micro/nano complex needles	Extremely high cost; slow printing speed and material limitations	141,143,144,165

Note: ^aSpeed (mm³/s): High (>10⁴), Moderate (>1 and <10⁴), Low (<1).

Abbreviations: 3D: Three-dimensional; CLIP: Continuous liquid interface production; DLP: Digital light processing; FDM: Fused deposition modeling; GelMA: Gelatin methacryloyl; MJ: Material jetting; MeHA: Methacrylated hyaluronic acid; PCL: Polycaprolactone; PEG: Polyethylene glycol; PEGDA: Polyethylene glycol diacrylate; PLA: Polylactic acid; PµSL: Projection micro-stereolithography; PVA: Polyvinyl alcohol; SLA: Stereolithography; SLM: Selective laser melting; SLS: Selective laser sintering; TPP: Two-photon polymerization.

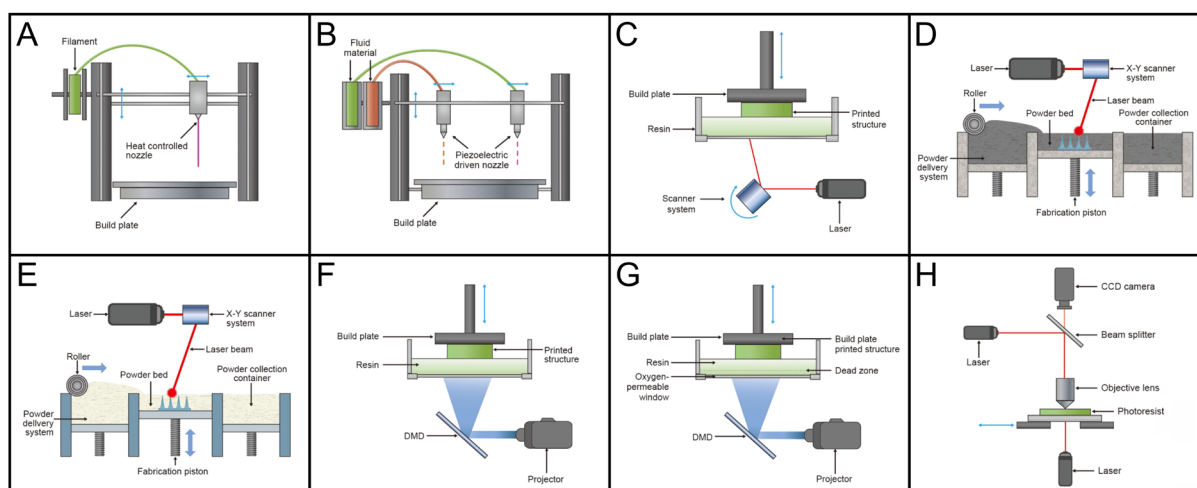


Figure 4. Three-dimensional printing technologies for the fabrication of microneedles. (A) Fused deposition modeling; (B) material jetting; (C) stereolithography; (D) selective laser melting; (E) selective laser sintering; (F) digital light processing; (G) continuous liquid interface production; and (H) two-photon polymerization. Created with Adobe Illustrator.

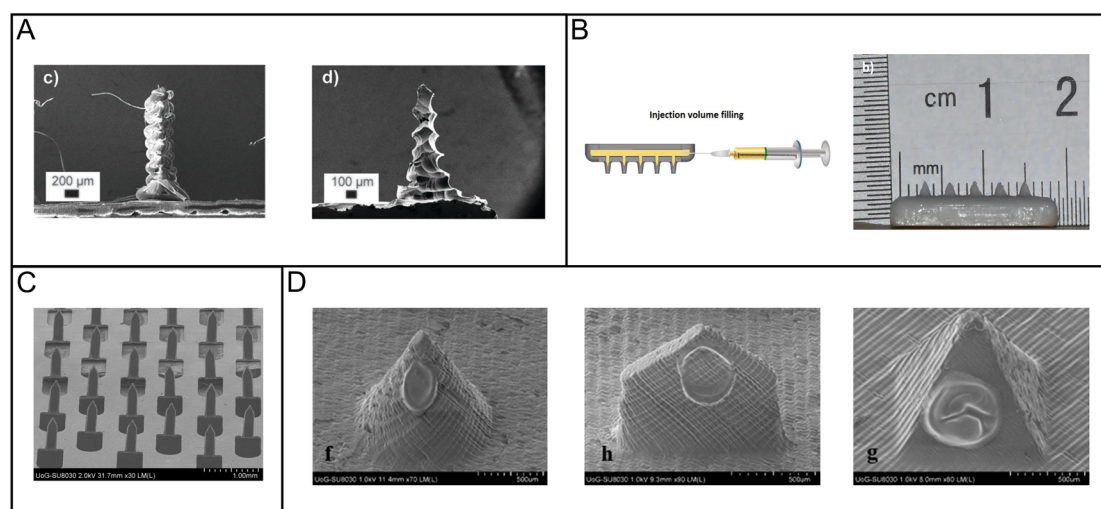


Figure 5. Microneedles (MNs) fabricated using fused deposition modeling technology. (A) Scanning electron microscopy (SEM) images showing changes in MN tip dimensions before and after potassium hydroxide chemical etching treatment. Scale bars: 100 μ m, 200 μ m. Reproduced with permission from Luzuriaga *et al.*⁹⁴ Copyright © 2018, Royal Society of Chemistry. (B) Schematic illustration and optical images of MNs with an integrated drug reservoir. Reproduced with permission from Khosraviboroujeni *et al.*¹⁰⁴ Copyright © 2021, Springer Nature. MNs fabricated using material jetting (MJ) technology. (C) SEM images demonstrating the uniform coating of an insulin–polymer solution on the surface of stainless-steel MNs via MJ technology. Scale bar: 1 mm; magnification: 30 $\times$. Reproduced with permission from Ross *et al.*¹⁰⁸ Copyright © 2015, Springer Nature. (D) SEM images showing insulin solution coatings on MN arrays with different geometries (conical, pyramidal, and spear-shaped). Reproduced with permission from Economidou *et al.*¹⁰⁹ Copyright © 2021, MDPI.

4. Biological functions of three-dimensional-printed microneedles

In this section, we categorized recent studies by biological function and summarize all cases in Table 3 to help readers better understand the progress of 3D-printed MNs.

4.1. Drug delivery

Because MN drug delivery is painless, has low infection risk, and can bypass the gastrointestinal tract and the liver's first-pass effect, it has become a popular method for transdermal drug delivery.^{24–27} Compared with traditional mold-based MN fabrication methods, 3D printing

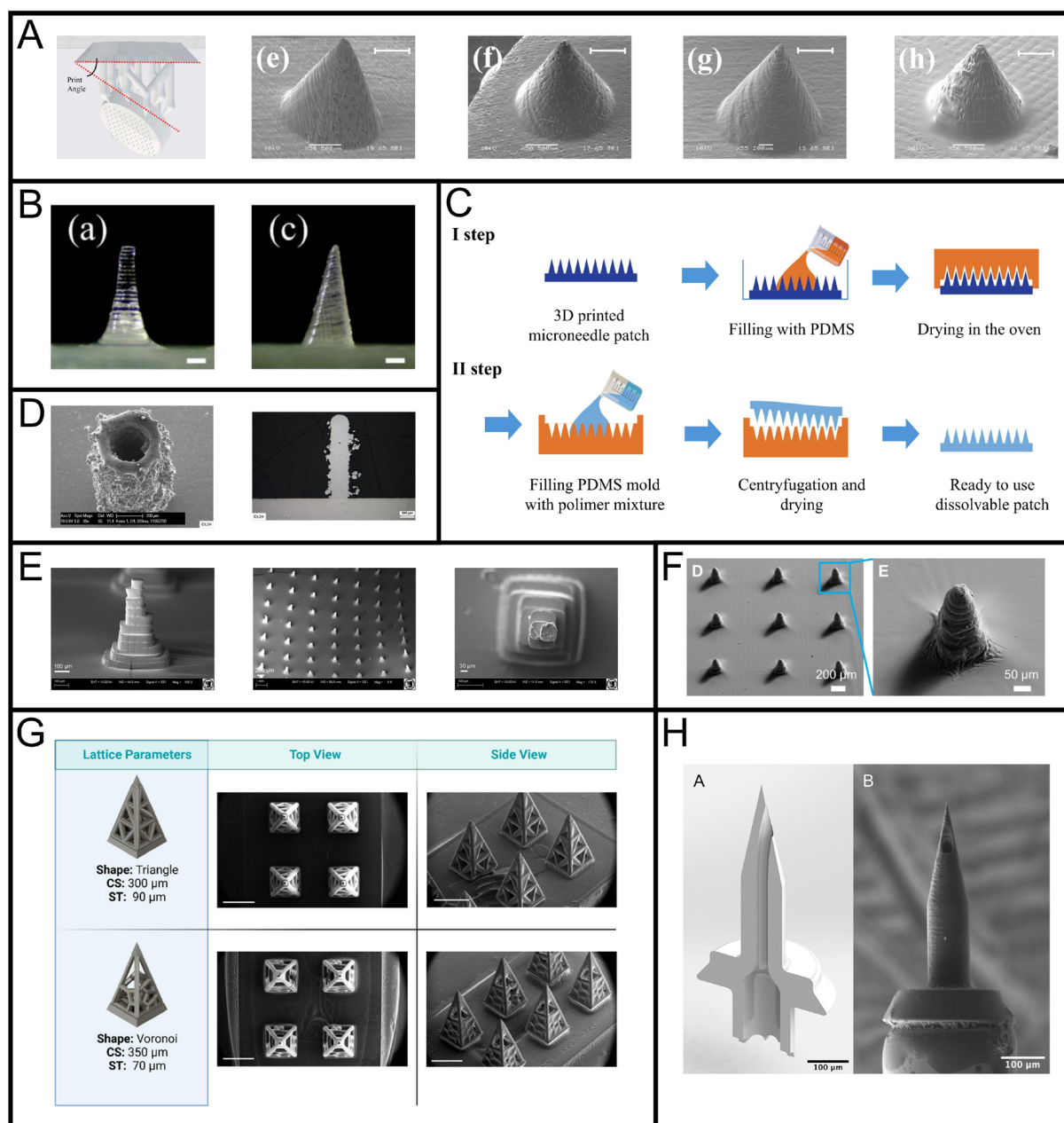


Figure 6. Microneedles (MNs) fabricated using stereolithography, selective laser melting, digital light processing, continuous liquid interface production, and two-photon polymerization technology. (A) Schematic illustration of MNs printed at a tilted angle and optical images of 3D-printed MNs at tilt angles of 0°, 45°, 60°, and 90°. Scale bar: 500 μm ; magnification: 50 $\times$, 55 $\times$. Reproduced with permission from Kundu *et al.*¹¹³ Copyright © 2018, MDPI. (B) Comparison of MN tip morphologies printed at 0° and 60° tilt angles. Scale bar: 0.3 mm. Reproduced with permission from Choo *et al.*¹¹⁴ Copyright © 2022, MDPI. (C) Schematic illustration of an indirect fabrication approach for MNs using 3D printing. Reproduced with permission from Justyna *et al.*¹²⁹ Copyright © 2025, Springer Nature. (D) Optical image of hollow MNs with an inner diameter of approximately 160 μm , fabricated from 316L stainless-steel powder, and a cross-sectional optical image of solid MNs with an outer diameter of approximately 200 μm . Scale bar: 200 μm ; magnification: 99 $\times$. Reproduced with permission from Gieseke *et al.*¹²⁰ Copyright © 2012, De Gruyter Berlin. (E) Scanning electron microscopy (SEM) images of polyvinyl alcohol/polyvinylpyrrolidone MNs fabricated via an indirect method, showing the morphology of a single MN, MN arrays, and the needle tip. Scale bar: 100 μm , 200 μm , 30 μm ; magnification: 100 $\times$, 9 $\times$, 175 $\times$. Reproduced with permission from Justyna *et al.*¹²⁹ Copyright © 2025, Springer Nature. (F) SEM images of silk fibroin hydrogel MNs directly printed using digital light processing technology. Scale bars: 50 μm , 200 μm . Reproduced with permission from Shin *et al.*¹³⁰ Copyright © 2021, Elsevier. (G) Top-view and side-view SEM images of lattice MN patches with two lattice geometries (triangular and Voronoi). Reproduced with permission from Rajesh *et al.*¹³⁷ Copyright © 2022, American Chemical Society. (H) Design schematic and SEM images of hollow MNs for cochlear perilymph collection. Scale bar: 100 μm . Reproduced with permission from Szeto *et al.*¹⁴² Copyright © 2021, Elsevier.

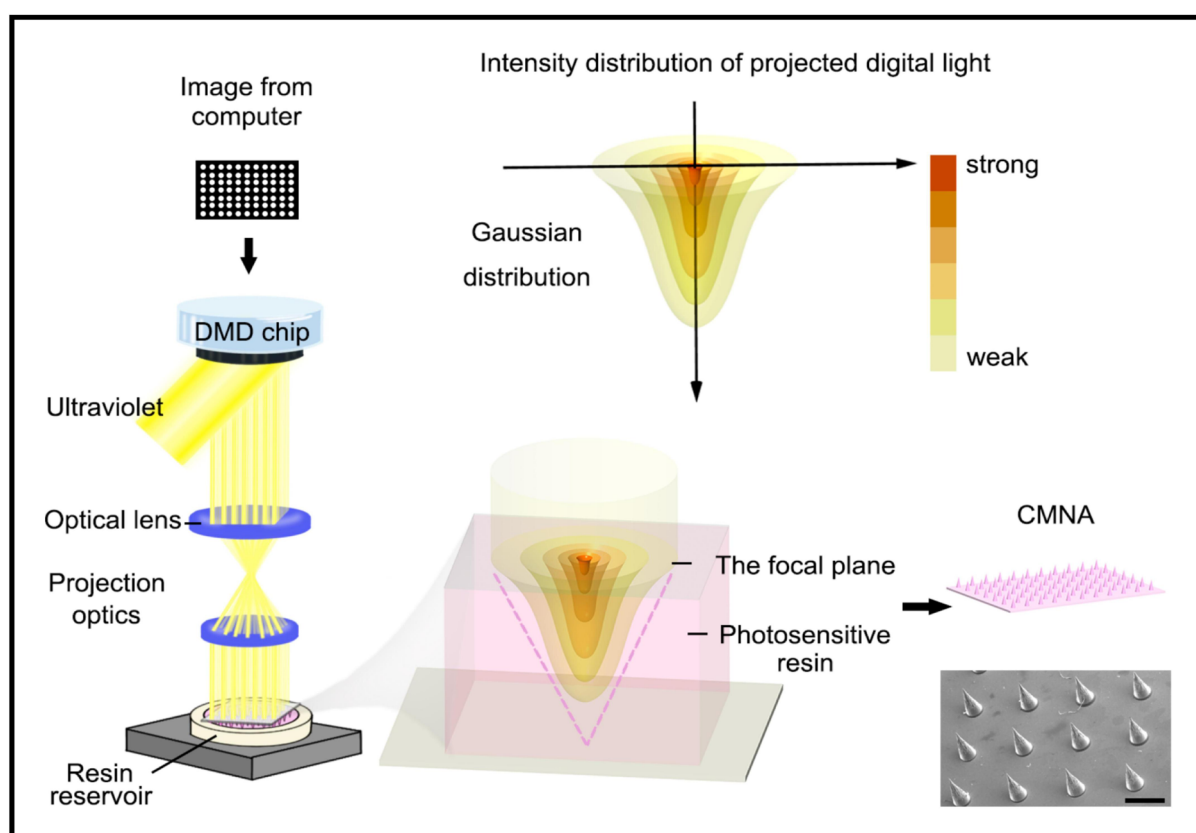


Figure 7. Schematic illustration of the static optical projection lithography principle for microneedle fabrication. Scale bar: 1 mm. Reproduced with permission from Liu *et al.*¹⁴⁹ Copyright © 2021, American Chemical Society.

technology significantly simplifies the preparation of complex geometric MNs, thanks to its high precision and diverse structural design. It also greatly enhances the personalization, intelligence, and multifunctionality of drug delivery. In recent years, research on 3D-printed MNs for drug delivery has become increasingly in-depth. Bahnick *et al.*¹⁶⁶ reported a dissolvable MN made using CLIP technology for the local delivery of dexamethasone (DXM), achieving local pain control (Figure 8A).¹⁶⁶ The study used poly(propylene fumarate-co-propylene maleate) with controllable degradation properties as the carrier, and precisely regulated the crosslinking density through thiol-ene click chemistry, optimizing both the mechanical properties of the MNs and the drug release rate. Thanks to the MNs' ability to achieve high local drug release concentrations and their controllable release rate (Figure 8B), this method effectively overcame the limitations of systemic side effects caused by high doses of DXM in clinical applications. The study showed that in a mouse tibia fracture model, DXM delivered via MNs achieved the same analgesic effect as intravenous administration at a lower drug dose, significantly improving the biosafety

of DXM usage. In addition to delivering small-molecule drugs, MNs can also deliver biomacromolecules in a stable manner. Uddin *et al.*¹⁶⁷ used SLA technology to fabricate hollow MNs and used an external syringe to deliver the osteoporosis drug denosumab (Figure 8C and 8D). Notably, the research team emphasized environmental protection by using a high-biomass-content photopolymer resin made from a mixture of pine resin-derived isobornyl acrylate and pentaerythritol tetraacrylate, significantly reducing the environmental impact of traditional petrochemical resin production and offering new ideas for sustainable, eco-friendly drug delivery. Rajesh *et al.*¹⁶⁸ further evaluated the carrying and release capabilities of solid ovalbumin (OVA) and mRNA lipid nanoparticles using the previously developed L-MAP (Figure 8E). The results showed that the L-MAP could carry up to twice as much of these two biomolecules as traditional MNs (Figure 8F and 8G), and over 50% of the mRNA lipid nanoparticles could be released within five minutes. Furthermore, by designing two different lattice structures on a single MN patch, differentiated rapid and sustained release effects for OVA were achieved. OVA and mRNA lipid

nanoparticles are key substances in vaccine development and immunological research. The L-MAP developed by Rajesh *et al.*¹⁶⁸ demonstrated excellent delivery capabilities for both biomolecules, providing important insights and strong potential for developing novel combination vaccines and personalized immunotherapy applications.

Some research teams have further improved the drug-delivery efficiency of 3D-printed MNs by applying external energy fields. Mo *et al.*¹⁶⁹ used DLP technology to fabricate porous MN patches and applied a direct current microcurrent (1 mA/cm²) to promote the directional diffusion of human parathyroid hormone (PTH) in subcutaneous tissue between the anode and cathode. This approach transiently and reversibly remodels the vascular endothelial cell cytoskeleton, increasing vascular permeability. As a result, it reduces drug exposure time, enhances cellular absorption of PTH, improves bone synthesis, and alleviates osteoporosis (Figure 8H and 8I).¹⁶⁹ In addition to external electric fields, external ultrasound has also been used. Chen *et al.*¹⁷⁰ integrated a cymbal-type ultrasound transducer with an MN array using PuSL technology to create a lightweight 3D-printed cymbal MN array weighing only 20 g. This MN includes a multi-channel structure connected to a drug reservoir, allowing for continuous drug delivery (Figure 8J). By using a 115 kHz ultrasound resonance to generate acoustic cavitation, this device promotes drug diffusion into deeper skin layers, enabling local insulin transdermal delivery. In a diabetic mouse model, it produced a blood glucose-lowering effect comparable to intraperitoneal injection (Figure 8K).

Three-dimensional-printed MNs based on intelligent, responsive systems have become a research hotspot. Intelligent response refers to the process in which MNs autonomously release drugs in response to changes in the physicochemical properties of the disease site in the body or when specific external signals are applied. Since such MNs often require complex geometric structures, they largely rely on 3D printing technologies for their fabrication. One example is the coral biomimetic MN developed by Liu *et al.*,⁸⁹ an intelligent MN designed to control wound infections. The team first replicated the solid structure of coral reefs using polycaprolactone methacrylate (PCLMA) as 3D-printing ink and created a porous outer shell for the MNs via DLP technology. This structure ensures that the MNs can penetrate tissues while allowing ISFs to permeate into the MNs. The team then replicated the coral polyp structure in the reef by loading minocycline-heparin hydrogel (HepMi) inside the PCLMA to create the HepMi-PCL MNs. When an infection occurs in the wound, the exudate keeps the hydrogel moist and uses phenol red to indicate the acidity

or alkalinity of the exudate, signaling infection status. Under acidic conditions, the glycosidic bonds of hyaluronic acid in the hydrogel hydrolyze more easily, while the hydrolysis rate is slower under alkaline conditions. As a result, in the early stages of infection, the MNs rapidly release minocycline in the acidic environment to suppress bacterial growth, while in the alkaline environment of chronic infection, the MNs switch to controlled release. When no exudate is present, the hydrogel dries out again, halting drug release (Figure 8L and 8M). Additionally, Zhou *et al.*¹⁷¹ used DLP technology to develop a triple-responsive hydrogel MN patch (Figure 8N). The MN patch uses 2-(dimethylamino)ethyl methacrylate (DMAEMA), N-isopropylacrylamide (NIPAM), acrylic acid, and acrylamide as functional monomers, with aluminum hydroxide nanoparticles as the crosslinking agent, forming a tough nanocomposite hydrogel, NAADx. The tertiary amine groups of DMAEMA can be protonated in acidic environments, increasing the hydrogel's hydrophilicity and promoting hydrogel expansion and drug release, giving it significant pH responsiveness under acidic conditions. By loading glucose oxidase (GOX), the MNs achieve glucose responsiveness: high glucose concentrations promote GOX-catalyzed conversion of glucose to gluconic acid, triggering a local pH drop and pH-responsive behavior. Additionally, NIPAM provides the MNs with notable temperature responsiveness, enabling temperature-controlled drug release. This triple-responsive MN system can respond precisely to physiological changes, enabling intelligent drug release with significant biomedical implications for personalized treatment of chronic diseases such as diabetes.

The drug-delivery system of 3D-printed MNs can also be used for wound healing and scar management, contributing to the development of plastic surgery and medical aesthetics. Li *et al.*¹⁷² used DLP technology to fabricate a hydrogel MN patch (GSPMNs) loaded with platelet-rich protein, using GelMA and silk fibroin methacrylate as the matrix (Figure 8O). This patch can quickly adapt to the precise size, depth, and shape of the wound. Platelet protein significantly accelerates re-epithelialization and collagen deposition, showing excellent wound-healing effects (Figure 8P). Zhao *et al.*¹⁷³ used FDM technology to fabricate a chitosan/PLA composite MN array (Figure 8Q), and combined it with finite element analysis to determine that a 0.2 chitosan/PLA ratio was the optimal material combination. MNs made from this material can effectively penetrate the dermis and collagen layers of scar tissue (Figure 8R), delivering loaded triamcinolone acetonide accurately and evenly to deeper layers of chest keloid tissue and improving scar treatment outcomes.

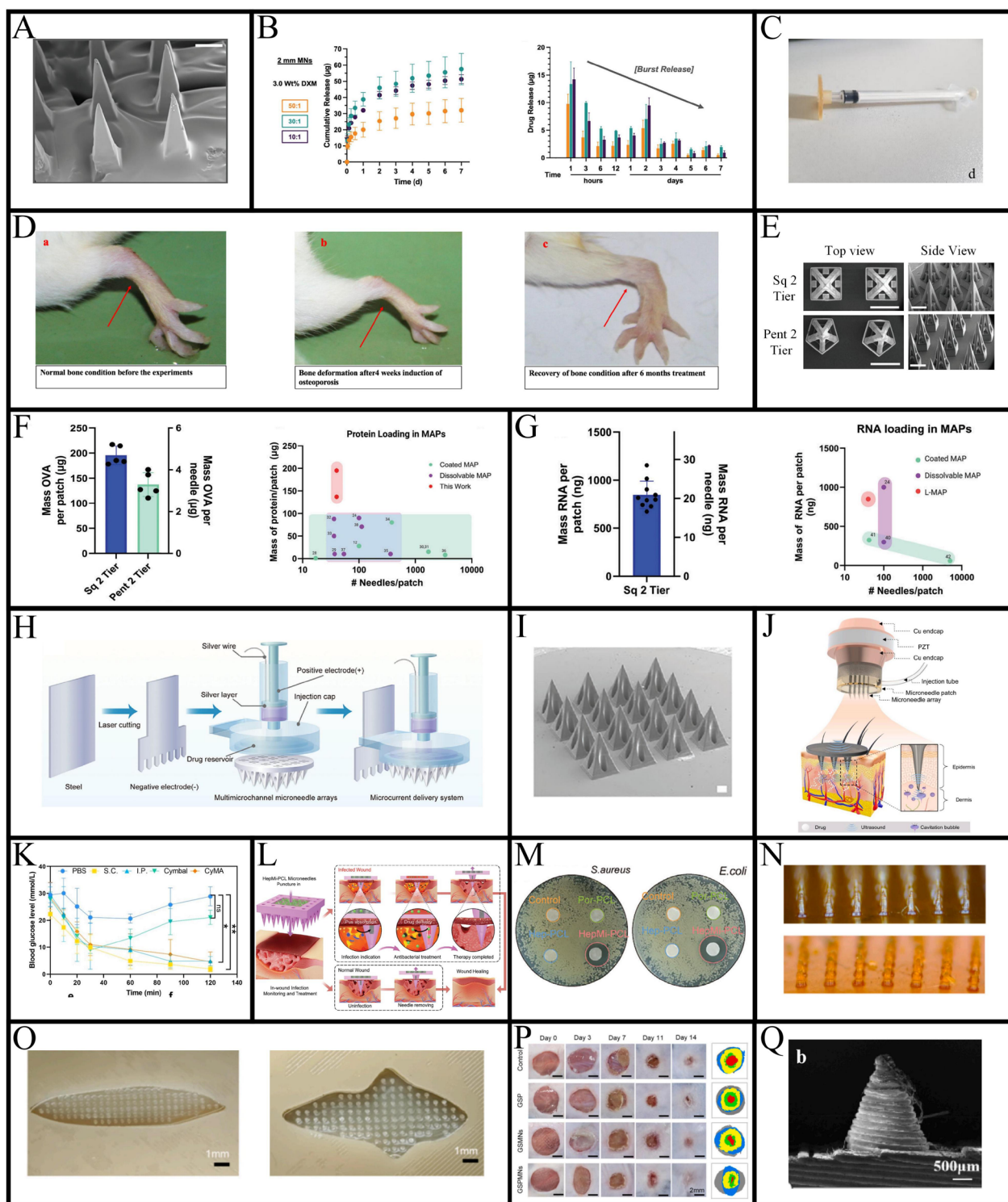
The development of MN-based vaccines has become increasingly mature, and some 3D-printed MN vaccines have already entered clinical trials.³¹ Tumor cell vaccines (TCVs) have shown great potential in cancer immunotherapy. Yang *et al.*¹⁷⁴ incorporated TCVs into 3D-printed MNs and proposed an innovative strategy based on an ice MN array. The research team used SOPL technology to fabricate personalized ice MN patches loaded with inactivated melanoma cells transfected with granulocyte-macrophage colony-stimulating factor plasmid, maintaining vaccine activity through freeze preservation (Figure 8S). Compared to traditional subcutaneous injection, this MN-based method could painlessly and efficiently deliver TCVs to the intradermal area, significantly enhancing the recruitment of dendritic cells at the vaccination site. It also promoted the infiltration of CD8⁺ T cells and CD4⁺ T cells into the tumor microenvironment, inhibited melanoma growth, and effectively prevented tumor recurrence (Figure 8T). The results of the study suggest that this MN provides a safe, efficient, and personalized innovative treatment for cancer immunotherapy, opening up new pathways for cancer treatment.

4.2. Extraction of biomarkers

Endoscopic examination, histopathological analysis, and biomarker detection have advanced disease diagnosis. However, these methods are costly and highly invasive. The skin, being the largest organ of the body, is rich in various biomarkers, with the dermis containing approximately 70% of the ISF.¹⁷⁵ ISF is the product of plasma that has passed through the capillary wall into the tissue interstitial space, and it is relatively easy to collect. It is rich in biomarkers, including metabolites, proteins, and nucleic acids. These biomolecules are related to both systemic and local physiology and have significant diagnostic value.¹⁷⁶ Therefore, the ability to collect sufficient ISF for pathological analysis with minimal skin damage is important for disease diagnosis. Existing methods for collecting ISF include blister aspiration, reverse iontophoresis, microdialysis, and open-flow microperefusion.¹⁷⁷⁻¹⁸⁰ However, each method has limitations. In contrast, MNs provide a less invasive, more convenient, and faster way to collect ISF, and 3D printing further enables the personalized customization of such MNs.

Jiang *et al.*¹⁸¹ used TPP to fabricate solid MN patches (Figure 9A). These MNs create micropores upon insertion into the epidermis, and a vacuum chamber then generates negative pressure to drain ISF from the dermis to the surface for manual collection (Figure 9B). An average of 20.8 μL of ISF can be collected in 25 minutes.¹⁸¹ The collected ISF contained over 600 proteins, with many disease-related

biomarkers strongly correlated with serum concentrations, validating ISF as a blood substitute for disease diagnosis. Furthermore, this method caused minimal pain during sampling, and any localized redness and swelling resolved within 24 hours, demonstrating good patient tolerance. The study shows that 3D-printed MNs can efficiently and minimally invasively collect sufficient amounts of ISF, which can be directly applied in subsequent experimental analyses such as liquid chromatography-tandem mass spectrometry, Western blot, enzyme-linked immunosorbent assay, and electrochemical sensing, providing a feasible technical path for non-invasive clinical diagnosis. Similarly, Xie *et al.*¹⁸² developed a hollow MN array combined with a vacuum sampling tube using P μ SL technology (Figure 9C). The MNs penetrate the skin and, with a negative pressure of approximately 75 Pa, drain the ISF from the dermis through the MNs into the vacuum sampling tube (Figure 9D).¹⁸² Unlike the traditional passive exudation method using solid MNs, this device is more integrated and can stably collect continuously flowing ISF in a short time. In five minutes, $18.42 \pm 1.02 \mu\text{L}$ of ISF can be obtained, with a single-needle rate of $0.0368 \mu\text{L} \cdot \text{min}^{-1}$, making it suitable for applications requiring real-time detection. In the study, the collected ISF was directly analyzed for glucose content using a commercial glucometer and could also be integrated with various detection platforms (such as lateral flow test strips, chemiluminescence, and colorimetric analysis) to enable rapid detection of corticosteroids, lactate, glucose, and pH. This strategy for collecting ISF with 3D-printed hollow MNs supports future on-site rapid screening and dynamic monitoring. Additionally, Li *et al.*¹³⁸ proposed a biomimetic solid MN array fabricated using P μ SL technology to create a template, and then MNs were made from the mold¹⁸³. Unlike the previous two examples, this MN does not rely on vacuum negative pressure to extract ISF; instead, it mimics the pitcher plant's trichome, with hierarchical microchannels designed on the needle surface to absorb ISF via capillary action (Figure 9E). The research team also integrated an ISF sensing system at the base of the hierarchical microchannel-MNs, enabling real-time electrochemical and colorimetric detection of various biomarkers (Figure 9F and 9G), including electrolyte ions (K^+ and Na^+), glucose, uric acid, reduced glutathione, and C-reactive protein. This integrated platform offers a simple, efficient solution for health monitoring, with potential applications in long-term monitoring of chronic diseases such as diabetes and metabolic disorders, and provides a novel approach for ISF sampling. Thanks to the excellent water-absorption properties of hydrogels, hydrogel MNs can directly absorb ISF. For example, Zhang *et al.*¹⁸⁴ developed a hydrogel-based MN array composed of HAMA and GelMA, fabricated using DLP (Figure



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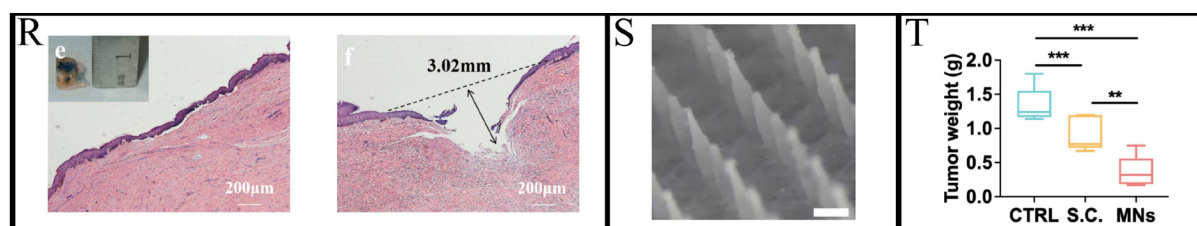


Figure 8. Three-dimensional-printed microneedles (MNs) for drug delivery. (A) Scanning electron microscopy (SEM) images of dissolving MNs fabricated using continuous liquid interface production technology for local dexamethasone (DXM) delivery. Scale bar: 500 μm. Reproduced with permission from Bahnick *et al.*¹⁶⁶ Copyright © 2024, John Wiley and Sons. (B) Cumulative drug-release profiles and DXM release at specific time points for MN patches containing 3 wt% DXM with three different alkene–thiol ratios (50:1, 30:1, and 10:1) in aqueous solution at 37 °C. Reproduced with permission from Bahnick *et al.*¹⁶⁶ Copyright © 2024, John Wiley and Sons. (C) Optical image of hollow MNs fabricated using stereolithography for denosumab delivery and integrated with an external syringe. Reproduced with permission from Uddin *et al.*¹⁶⁷ Copyright © 2024, American Chemical Society. (D) Skeletal conditions of mice before treatment and after 4 weeks and 6 months of treatment, demonstrating the therapeutic efficacy of MNs for osteoporosis. Reproduced with permission from Uddin *et al.*¹⁶⁷ Copyright © 2024, American Chemical Society. (E) Top-view and side-view SEM images of lattice MN patches (L-MAPs) with two different designs (Sq 2 Tier: two-tier L-MAP with a square base; Pent 2 Tier: two-tier L-MAP with a pentagonal base). Scale bar: 500 μm. Reproduced with permission from Rajesh *et al.*¹⁶⁸ Copyright © 2024, John Wiley and Sons. (F) Ovalbumin (OVA) protein loading of L-MAPs and comparison of OVA loading capacity among L-MAPs (labeled as “This Work”), coated MAPs, and dissolving MAPs. Reproduced with permission from Rajesh *et al.*¹⁶⁸ Copyright © 2024, John Wiley and Sons. (G) RNA loading of L-MAPs and comparison of RNA loading capacity among L-MAPs (labeled as “This Work”), coated MAPs, and dissolving MAPs. Reproduced with permission from Rajesh *et al.*¹⁶⁸ Copyright © 2024, John Wiley and Sons. (H) Design schematic of a porous MN patch fabricated using digital light processing (DLP) combined with an external microcurrent. Reproduced with permission from Mo *et al.*¹⁶⁹ Copyright © 2024, John Wiley and Sons. (I) SEM images of the porous MN patch fabricated using DLP technology combined with an external microcurrent. Scale bar: 100 μm. Reproduced with permission from Mo *et al.*¹⁶⁹ Copyright © 2024, John Wiley and Sons. (J) Design schematic of cymbal MN array (CyMA) fabricated using projection micro-stereolithography. Reproduced with permission from Chen *et al.*¹⁷⁰ Copyright © 2025, Elsevier. (K) Blood glucose levels of diabetic mice over time after different treatments, where phosphate-buffered saline (PBS) indicates mice receiving PBS injection only, S.C. indicates subcutaneous insulin injection, I.P. indicates intraperitoneal insulin injection, the Cymbal group indicates insulin delivery using only a cymbal-type ultrasonic transducer, and the CyMA group indicates insulin delivery using CyMA. Reproduced with permission from Chen *et al.*¹⁷⁰ Copyright © 2025, Elsevier. (L) Schematic illustration of the working principle of minocycline–heparin hydrogel (HepMi)–polycaprolactone (PCL) porous hydrogel MNs. Reproduced with permission from Liu *et al.*⁸⁹ Copyright © 2024, John Wiley and Sons. (M) Inhibition zone assays of HepMi–PCL porous hydrogel MNs, where Por–PCL represents porous MNs without any filling, and Hep–PCL represents MNs loaded with heparin hydrogel. Reproduced with permission from Liu *et al.*⁸⁹ Copyright © 2024, John Wiley and Sons. (N) Photographs and SEM images of triple-responsive hydrogel MN patches fabricated using DLP technology. Reproduced with permission from Zhou *et al.*¹⁷¹ Copyright © 2024, Elsevier. (O) Images showing hydrogel MNs customized to match wound geometries. Scale bar: 1 mm. Reproduced with permission from Li *et al.*¹⁷² Copyright © 2025, Elsevier. (P) Effects of GSPMNs on wound healing, where GSP represents platelet-rich plasma-loaded gelatin methacryloyl (GelMA)/silk fibroin methacrylate (SFMA) patches and GSMNs represent GelMA/SFMA hydrogel MN patches. Scale bar: 2 mm. Reproduced with permission from Li *et al.*¹⁷² Copyright © 2025, Elsevier. (Q) SEM images of chitosan/poly(lactic acid) composite MN arrays fabricated using fused deposition modeling. Scale bar: 500 μm. Reproduced with permission from Zhao *et al.*¹⁷³ Copyright © 2025, Elsevier. (R) Histological comparison of chitosan/poly(lactic acid) composite MN arrays before and after insertion into keloid tissue. Scale bar: 200 μm. Reproduced with permission from Zhao *et al.*¹⁷³ Copyright © 2025, Elsevier. (S) Optical image of ice MN arrays under a microscope. Scale bar: 500 μm. Reproduced with permission from Yang *et al.*¹⁷⁴ Copyright © 2024, John Wiley and Sons. (T) Tumor mass of tumor-bearing mice recorded on day 15 after treatment, where CTRL indicates the control group, S.C. indicates the subcutaneous vaccine group, and MNs indicate the ice MN vaccine group. Reproduced with permission from Yang *et al.*¹⁷⁴ Copyright © 2024, John Wiley and Sons.

9H). In an *in vitro* skin simulation experiment, this MN array successfully quantified glucose concentrations and extracted 8.5 mg of phosphate-buffered saline solution within one minute, indicating a theoretical ISF extraction efficiency of up to 8.5 μL·min^{−1}.

In addition to the molecules present in ISF, cellular components within individual cells and the skin microbiome are also more direct sources of biomarkers. As early as 2017, Kavaldzhiev *et al.*¹⁸⁵ demonstrated the potential of MNs for extracting cellular materials. They used TPP to fabricate MNs on a silicon substrate, with an iron coating applied to the surface (Figure 9I). This iron coating not only imparts magnetic properties to the MNs

but also forms an oxide layer on the surface, enabling the use of antibody-functionalized nickel nanowires for cell classification and identification. The study showed that these MNs could penetrate up to half the depth of colon cancer cells, with each MN corresponding to a single cell. This technology could be applied for single-cell content extraction and analysis, assisting in diagnosis. Liang *et al.*¹⁸⁶ used DLP to fabricate MNs with varying lengths, geometries, and needle densities to select the best structural MN patch (Figure 9J and 9K). The optimized MN patch efficiently extracted microbiota from human scalp skin. Notably, the Ascomycota phylum contains many opportunistic pathogens, and the MN patch demonstrated

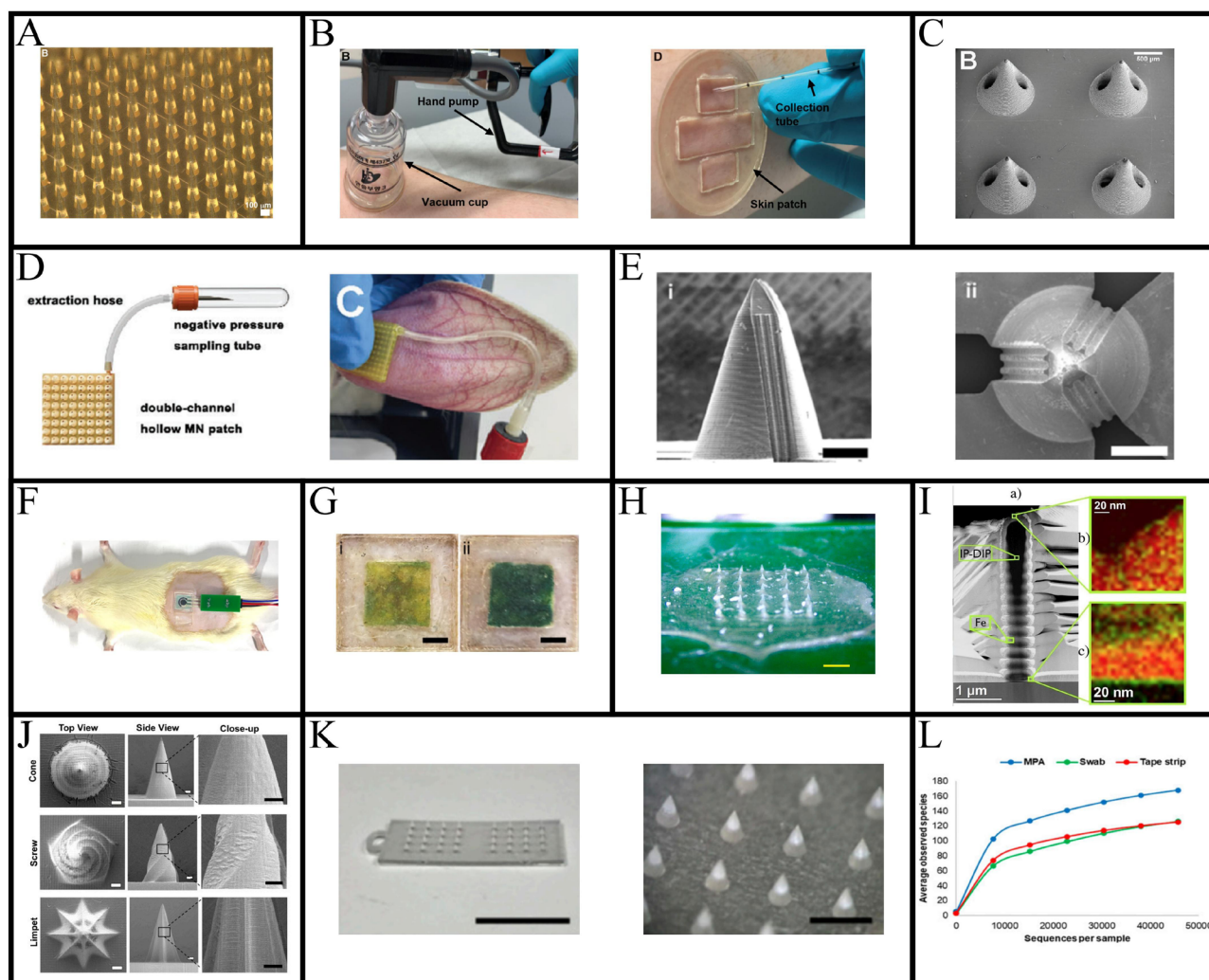


Figure 9. Three-dimensional-printed microneedles (MNs) for biomarker collection. (A) Locally magnified image of a solid MN patch fabricated using two-photon polymerization (TPP). Scale bar: 100 μm . Reproduced with permission from Jiang *et al.*¹⁸¹ Copyright © 2024, Elsevier. (B) Schematic illustration of the negative-pressure interstitial fluid (ISF) collection process using a vacuum chamber. Reproduced with permission from Jiang *et al.*¹⁸¹ Copyright © 2024, Elsevier. (C) Scanning electron microscopy (SEM) image of the hollow MN portion of a VT-MAP fabricated using projection micro-stereolithography (P μ SL). Scale bar: 500 μm . Reproduced with permission from Xie *et al.*¹⁸² Copyright © 2024, John Wiley and Sons. (D) Overall schematic illustration of the VT-MAP for ISF extraction and images of its practical application. Reproduced with permission from Xie *et al.*¹⁸² Copyright © 2024, John Wiley and Sons. (E) SEM images showing the lateral view of the MN shaft and the top view of the MN tip of hierarchical microchannel (HMC)-MNs fabricated using P μ SL technology. Scale bar: 200 μm . Reproduced with permission from Li *et al.*¹⁸³ Copyright © 2025, Royal Society of Chemistry. (F) Optical image of HMC-MNs attached to the dorsal skin of a rat for biomarker monitoring using an electrochemical sensor. Reproduced with permission from Li *et al.*¹⁸³ Copyright © 2025, Royal Society of Chemistry. (G) Optical images of the glucose colorimetric sensor integrated with HMC-MNs on (i) normal rats and (ii) diabetic rats. Scale bar: 2 mm. Reproduced with permission from Li *et al.*¹⁸³ Copyright © 2025, Royal Society of Chemistry. (H) Optical image of MN arrays composed of HAMA/gelatin methacryloyl composite hydrogels fabricated using digital light processing (DLP), captured with a handheld microscope. Scale bar: 1,000 μm . Reproduced with permission from Zhang *et al.*¹⁸⁴ Copyright © 2025, Elsevier. (I) Cross-sectional image of coated MNs fabricated using TPP and corresponding electron energy loss spectroscopy elemental mapping (red indicates iron and green indicates oxygen). Scale bars: 20 nm, 1 μm . Reproduced with permission from Kavalzhiev *et al.*¹⁸⁵ Copyright © 2015, IOP Publishing. (J) SEM images of MN arrays with different geometries fabricated using DLP. Scale bar: 100 μm . Reproduced with permission from Ref.¹⁸⁶ Copyright © 2022, PNAS. (K) Microscopic images of the C_{8x4} structure (i.e., a MN patch with conical MNs arranged in a configuration of eight MNs in length and four MNs in width), identified as the optimal structure for pathogen extraction; left image: scale bar: 1 cm; right image: scale bar: 1 mm. Reproduced with permission from Liang *et al.*¹⁸⁶ Copyright © 2022, PNAS. (L) Rarefaction curves of different fungal species obtained using different sampling methods (MN patch, swab, and tape strip). Reproduced with permission from Liang *et al.*¹⁸⁶ Copyright © 2022, PNAS.

higher sensitivity than traditional swabs and tape strips for detecting Ascomycota. Additionally, the fungal diversity was richer (Figure 9L), which is important for the clinical diagnosis of skin infections.

4.3. Biosensing

Since MNs can penetrate the dermis to extract ISF or cellular contents as biological markers, combining them with electrochemical sensors enables the direct, real-time monitoring of physicochemical signals generated within the body. This eliminates the need to send ISF or tissue samples to clinical laboratories for testing, greatly simplifying and shortening the detection process. It provides a wearable, minimally invasive solution for real-time monitoring of bodily conditions or rapid detection of diseased tissues.

Recently, Zhong *et al.*¹⁸⁷ applied the aforementioned characteristics by using PuSL technology to create a wearable MN patch capable of real-time monitoring of glucose, lactate, and alcohol (Figure 10A). This MN array consists of a three-electrode system: a working electrode (WE), a counter electrode (CE), and a reference electrode (RE). The surface of the WE's MNs is sequentially coated with Pt, PEDOT:PSS, an adhesive enzyme layer containing GOX, lactate oxidase (LOX), or alcohol oxidase (AOX), and a Nafion outer layer; the CE and RE's MNs are coated with Pt and Ag/AgCl, respectively. Under the catalysis of the corresponding oxidase, glucose, lactate, and alcohol undergo redox reactions with oxygen to form the respective oxidized products and hydrogen peroxide. At the same time, a constant voltage is applied between the WE and RE, and hydrogen peroxide is oxidized to O₂, releasing electrons that, with the help of the CE, complete the electrical circuit. The generated current signal can be synchronously transmitted to a smartphone via Bluetooth and uploaded to a cloud platform for further analysis. This device addresses the limitations of traditional wearable devices, which can only monitor physical metrics such as heart rate and step count and fail to reflect the body's metabolic status. It helps analyze energy supply and demand, exercise intensity and recovery rhythm, and the impact of alcohol on performance and recovery at the individual level, thus providing quantifiable evidence for training decisions and health risk management. However, Reynoso *et al.*¹⁸⁸ discovered that due to skin contraction, the MNs might be physically pushed out of the skin, leading to the loss of connection between the WE and RE, which could cause irreversible damage to the sensor. In subsequent studies, the research team designed a 3D-printed MN biosensor that relies on magnetic fixation¹⁸⁹. Specifically, a metal plate is implanted subcutaneously in animals, and the MN array is securely fixed to the skin surface using magnetic force,

preventing MN detachment due to skin contraction. While this method effectively secures the MNs, it still requires invasive implantation of the metal plate, which conflicts with the minimally invasive nature of the MNs. However, this approach remains inspiring. For example, an MN array could be integrated on one side of an earring, with a magnetic metal plate installed on the other side, enabling stable biomarker collection at the earlobe for biosensing.

Three-dimensional-printed MN biosensors can not only monitor biological metabolites in ISF but also track drug metabolites. Kadian *et al.*¹⁹⁰ developed a wearable MN biosensor capable of real-time monitoring of chlorpromazine concentrations. Chlorpromazine is widely used in the clinical treatment of mental disorders such as schizophrenia, and its plasma concentration that is too low can lead to insufficient efficacy, while too high a concentration may cause severe side effects. Therefore, personalized and real-time monitoring of its concentration is of significant biomedical importance. The research team first used PuSL technology to print the MN array, then coated the surface of the WEs and CEs with carbon layers, further modifying the WE with carbon dots and covering it with a Nafion layer to prevent certain substances from leaching from the MN surface. The RE was sequentially coated with tin and Ag/AgCl layers, and the entire assembly was encapsulated using 3D printing (Figure 10B and 10C). The results showed that the sensor could stably detect drug concentration signals while maintaining skin barrier integrity. When the chlorpromazine concentration was in the range of 5–120 μM, the microcurrent was linearly proportional to the drug concentration, with a minimum detectable concentration of 0.09 μM (Figure 10D). This device provides a new tool for personalized medication and efficacy management for patients with mental disorders. Diabetes has become one of the most severe and burdensome chronic diseases worldwide, with close monitoring of blood glucose levels and timely medication being crucial for diabetes treatment.^{191,192} To achieve dynamic and precise control of blood glucose levels and therapeutic drug concentrations in diabetes management, Yang *et al.*¹⁹³ developed an MN-based continuous biomarker/drug monitoring (MCBM) system. This system, centered on a wearable, minimally invasive MN array, integrates 3D-printed MNs, electrochemical nanoenzyme sensors, and a smartphone app analysis module, enabling synchronous, real-time, wireless monitoring of glucose and metformin in ISF (Figure 10E). The working principle of the MCBM system can be compared to a closed-loop diagnostic-feedback engine: two WEs, a RE, and a CE are integrated into the four sides of a single MN (Figure 10F), with the two WEs each carrying CuO/Fe₂O₃ and Fe₂O₃ nanoenzymes to oxidize glucose and metformin in the ISF.

The microcurrent generated by these oxidation reactions enables precise determination of glucose and metformin concentrations; the collected signals are wirelessly transmitted to the smartphone app via a low-power Bluetooth module. The app integrates pharmacokinetics (PK) and pharmacodynamics (PD) analysis algorithms to generate personalized drug absorption and response curves, offer dose-adjustment recommendations, and send alerts to patients or healthcare providers when abnormal risk-monitoring results occur (Figure 10G). The MCBM system costs only about \$19.15, and it not only enables dual-parameter monitoring of “glucose-therapeutic drug” but also provides a new, intelligent, and refined path for home-based diabetes management. In the future, we hope that such 3D-printed MN biosensors, which can simultaneously detect drug and pathogen-related biomarkers, will play a role in managing a wider range of chronic diseases, such as hypertension, and provide strong support for individualized and precise drug therapy for patients.

Integrating drug-release functionality into 3D-printed MN biosensors could create a closed-loop system for diagnosis, monitoring, and treatment. In recent years, Razzaghi *et al.*¹⁹⁴ developed a hollow MN array that combines biosensing and drug delivery functions, fabricated using DLP technology. The sensing component uses colorimetric methods for real-time monitoring of biomarkers such as glucose, lactate, and pH (Figure 10H), while an ultrasonic atomization device integrated at the base of the MNs facilitates drug release, enabling precise delivery through ultrasonic vibration (Figure 10I). The control center for this integrated system is a smartphone that detects color changes via the colorimetric sensor and monitors levels of various biomarkers. When abnormal results are detected, the smartphone can remotely control the ultrasonic atomization device to release drugs as needed, achieving personalized and dynamic therapeutic interventions.

In addition to obtaining information from ISF, 3D-printed MN biosensors can also sense basic physical information. For example, Wei *et al.*¹⁹⁵ developed a wearable 3D-printed MN temperature sensor (T-MN). This system used DLP to fabricate hollow MNs and filled the needle cavities with the conductive polymer PEDOT:PSS (Figure 10J). Unlike traditional skin surface temperature measurement methods, this device contacts ISF through the MNs and uses the linear relationship between resistance and temperature to continuously monitor dermis temperature (Figure 10K). This approach effectively avoids interference from environmental factors and sweat, providing a more accurate reflection

of the actual internal state.¹⁹⁵ The T-MN can serve as an independent diagnostic tool, helping reveal the relationship between dermal temperature and thermoregulation and providing a deeper understanding of dynamic changes in pathological processes such as local inflammation, infection, or ischemia. It can also be used for continuous temperature monitoring during general anesthesia to prevent hypothermia. Additionally, this temperature module can work with sensor units for glucose, lactate, pH, and other biomarkers, providing real-time temperature calibration and compensation for various MN biosensors, which can aid early monitoring of sepsis or assessment of peripheral tissue vascular health. Traditional knee joint motion sensors mainly monitor larger displacements, often overlooking subtle knee movements during daily activities that can be early indicators of joint injury. To address this issue, Zhang *et al.*¹⁹⁶ developed a non-invasive wearable MN sensor based on DLP using PAMS hydrogel (Figure 10L). This sensor, combined with an inclined push plate structure, innovatively uses a synergistic amplification mechanism of MN deformation and contact area (i.e., small knee-joint movements drive the inclined push plate, further causing the MNs to bend) (Figure 10M). It specifically captures non-axial stress information induced by rotational and lateral sliding movements, which are more likely to cause damage, enabling highly sensitive detection of 20 μm -level skin micro-displacement and overcoming the limitations of traditional sensors in detecting sub-millimeter displacements. With its ability to detect small movements, this sensor not only aids in the early diagnosis of diseases such as arthritis but also helps doctors track subtle knee joint movements in real time, providing more accurate data for developing and adjusting rehabilitation plans and demonstrating significant clinical application value.

It should be noted that, although the studies described above fully demonstrate the potential of 3D-printed MNs for monitoring biomarkers via ISF, previous research has shown that real-time biosensing results based on ISF do not necessarily correspond to synchronous blood test results, indicating the presence of a time lag.^{197,198} Therefore, when using ISF to monitor different biomarkers in the future, systematic comparisons with simultaneously paired blood samples will still be necessary to clarify the bias caused by such time lag. This is particularly important for drug monitoring that requires precise therapeutic dose adjustment, where even a slight response delay may seriously affect clinical decisions about whether to administer medication.

To further address the translational development of 3D-printed MN technologies, we also briefly consider the

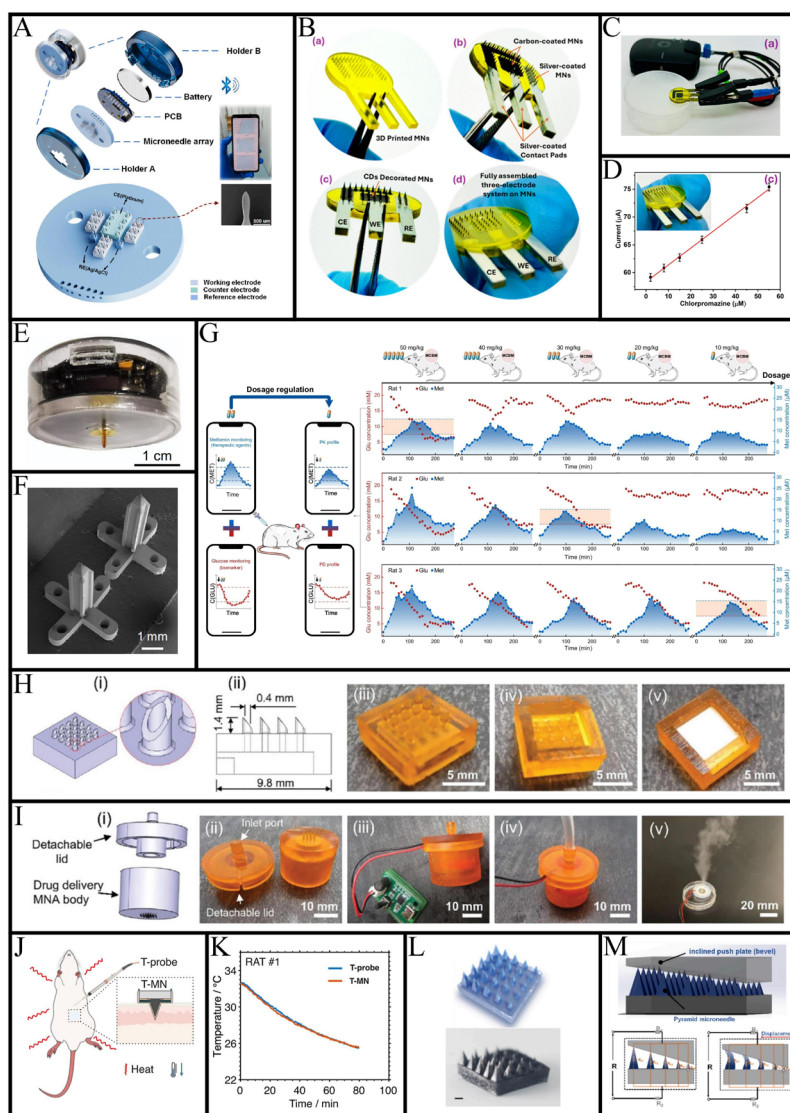


Figure 10. Three-dimensional-printed microneedles (MNs) for biosensing. (A) Overall design schematic and localized illustration of MN arrays of a wearable MN patch fabricated using projection micro-stereolithography (PμSL) technology for real-time monitoring of glucose, lactate, and alcohol; the inset shows bioelectrical signals transmitted to a mobile device via Bluetooth and a scanning electron microscopy (SEM) image of a single MN. Reproduced with permission from Zhong *et al.*¹⁸⁷ Copyright © 2024, Elsevier. (B) Exploded structural schematic of a wearable MN-based biosensor fabricated using PμSL technology for monitoring chlorpromazine concentration. Reproduced with permission from Kadian *et al.*¹⁹⁰ Copyright © 2024, Royal Society of Chemistry. (C) Photograph of the fully assembled MN biosensor for chlorpromazine monitoring. Reproduced with permission from Kadian *et al.*¹⁹⁰ Copyright © 2024, Royal Society of Chemistry. (D) Calibration curve showing the relationship between the MN biosensor peak current and chlorpromazine concentration. Reproduced with permission from Kadian *et al.*¹⁹⁰ Copyright © 2024, Royal Society of Chemistry. (E) Front-view image of the MCBM device fabricated using PμSL technology. Scale bar: 1 cm. Reproduced with permission from Yang *et al.*¹⁹³ Copyright © 2025, Springer Nature. (F) SEM image of the MN shafts of the MCBM device. Scale bar: 1 mm. Reproduced with permission from Yang *et al.*¹⁹³ Copyright © 2025, Springer Nature. (G) Personalized medication guidance provided by a smartphone app after receiving rat blood glucose and metformin data monitored by the MCBM system. Reproduced with permission from Yang *et al.*¹⁹³ Copyright © 2025, Springer Nature. (H) Structural schematic of the MN sensing module for biomarker monitoring via colorimetric analysis. Scale bar: 5 mm. Reproduced with permission from Razzaghi *et al.*¹⁹⁴ Copyright © 2024, John Wiley and Sons. (I) Structural schematic of the MN drug-delivery module with drug release regulated by an ultrasonic nebulization device. Scale bars: 10 mm, 20 mm. Reproduced with permission from Razzaghi *et al.*¹⁹⁴ Copyright © 2024, John Wiley and Sons. (J) Schematic illustration of T-MNs fabricated using digital light processing (DLP). Reproduced with permission from Wei *et al.*¹⁹⁵ Copyright © 2025, American Chemical Society. (K) Temperature–time curves obtained from body-surface temperature monitoring of euthanized rats using T-MNs and a commercial needle-type optical temperature probe (T-probe). Reproduced with permission from Wei *et al.*¹⁹⁵ Copyright © 2025, American Chemical Society. (L) Schematic illustration and corresponding microscopic images of a pyramidal hydrogel MN sensor fabricated by DLP to monitor subtle knee-joint displacement. Scale bar: 1 mm. Reproduced with permission from Zhang *et al.*¹⁹⁶ Copyright © 2025, Elsevier. (M) Schematic illustration of the synergistic amplification mechanism between MN deformation and contact area. Reproduced with permission from Zhang *et al.*¹⁹⁶ Copyright © 2025, Elsevier.

patent landscape. Patents reflect the ongoing efforts to protect and commercialize 3D-printed MN platforms for biomedical use. Representative patents are summarized in

Table 4 to complement the literature review and provide additional insight into current innovation trends.

Table 3. Summary of recent three-dimensional-printed microneedle research

Functional type	Involved 3D printing methods	MN types	Characteristics	Effects	Mechanism	Advantages	References
Drug delivery	CLIP	Dissolving MNs	Height: 1–2 mm; aspect ratio: 3:1; patch dimensions: 10 × 10 mm; number of MNs: 8 × 8 = 64; shape: pyramid; drug loading: 315.7 ± 53.5 µg/patch; drug release: cumulative release of approximately 50–60 µg over 7 days	Delivery of DXM, providing local pain relief	The PPFPS hydrolyzable crosslinked network is constructed via thiol-ene click chemistry, with DXM embedded within it. After the MNs absorb ISF and swell, they first release surface and shallow-layer drugs, forming a burst phase, followed by the slow release of remaining drugs through pore dissolution	Simultaneously achieving short-term analgesic effects while minimizing the systemic blood concentration of DXM, thereby reducing the drug's side effects	166
	SLA	Hollow MNs	Height: 1,000 µm; tip diameter: 100 µm; number of MNs: 2 × 2 = 4; shape: cone; puncture force: 35.9 ± 3.3 mN/needle; drug release: approximately 90% released within 60 min	Delivery of denosumab, treating osteoporosis	A drug delivery channel is established through the connection between the syringe and the hollow MN patch	The use of photocurable resin with a high biobased carbon content avoids traditional petrochemical resins, contributing to green healthcare	167
	CLIP	Coated hollow MNs	Height: 1,500 µm; base width: 550 µm; aspect ratio: 3:1; patch dimensions: 5 × 8.2 mm; number of MNs: 40; MN spacing: 1 mm; shape: lattice pyramid; fracture force: Sq 2 Tier ≈ 60 N/patch; Pent 2 Tier ≈ 37 N/patch; drug loading: 850 ng/patch, approximately 20 ng/needle; drug release: After 5 min, Sq 2 Tier released 7.1 µg and Pent 2 Tier released 7.5 µg	Delivery of immunotherapy-related substances (OVA and mRNA lipid nanoparticles)	Liquid drugs are adsorbed into L-MAP cavities via capillary action, and solid drugs are uniformly coated onto the grid scaffolds. When the patch is applied to the skin, ISF enters the L-MAPs, dissolving the solid drugs into liquid form for diffusion-controlled release	L-MAPs offer higher drug loading and release efficiency than traditional MNs and support the delivery of multiple drug combinations, providing important insights for developing new combination vaccines and personalized immunotherapies.	168

(Cont'd...)

Table 3. (Continued)

Functional type	Involved 3D printing methods	MN types	Characteristics	Effects	Mechanism	Advantages	References
	DLP	Porous MNs	Height: 850 μm ; tip side length: $18.2 \pm 2.4 \mu\text{m}$; base width: 600 μm ; aspect ratio: 1.42:1 (calculated); patch dimensions: circular patch, 8 mm in diameter; number of MNs: $4 \times 4 = 16$; MN spacing: 800 μm ; shape: pyramid; drug-loading volume: 200 μL /patch	Delivery of PTH, improving osteoporosis	The MN patch is connected to a syringe and a metal plate containing a silver coating. When an external microcurrent is applied, it creates a current pathway through the syringe's silver coating (+) - MN patch - ISF - metal plate (-), promoting the diffusion of positively charged PTH	Compared with subcutaneous injection, external microcurrent significantly increases PTH diffusion, and microstimulation reversibly enhances vascular permeability to facilitate PTH absorption	169
	P μ SL (only the MN base was 3D-printed)	Hollow MNs	Height: 12 mm; base diameter: 185 μm ; tip diameter: 180 μm ; aspect ratio: 64.9:1 (calculated); number of MNs: $5 \times 5 = 25$; MN spacing: 1 mm; shape: hollow tubular needle; drug loading: 0.3 IU/patch; drug diffusion: diffusion depth was approximately 1.5 mm at 90 min	Delivery of insulin, lowering blood glucose	The MN patch combines with a cymbal-type ultrasound transducer. Under the influence of ultrasound, the drugs in the drug reservoir diffuse through the needle body to deeper layers of the skin	CyMA's highly integrated and lightweight design makes it convenient for patient use. Insulin can achieve deeper, faster, and more uniform subcutaneous diffusion under the influence of ultrasound	170
	DLP	Hydrogel porous MNs	Height: 1,000 μm ; base diameter: 400 μm ; aspect ratio: 2.5:1 (calculated); number of MNs: 100; shape: cone; fracture force: 60 N/patch; drug release: approximately 20% released within 24 hours	Delivery of Minocycline, controlling wound infections	Wound exudate rehydrates the hydrogel, and phenol red indicators show exudate acidity, suggesting infection status. The MNs adjust minocycline release based on the pH environment, stopping drug release when no exudate is present and the hydrogel dries out	With pH-responsive characteristics, it automatically adjusts minocycline release based on the acidity or alkalinity of wound exudate, enabling adaptive treatment for infections at different stages, reducing medication overuse, and promoting efficient healing	89

(Cont'd...)

Table 3. (Continued)

Functional type	Involved 3D printing methods	MN types	Characteristics	Effects	Mechanism	Advantages	References
DLP		Hydrogel MNs	Height: 900 μm ; tip diameter: 20 μm ; base diameter: 300 μm ; aspect ratio: 3:1 (calculated); number of MNs: $13 \times 13 = 169$; shape: cone; fracture force: 14 N/patch; drug release: after 24 hours, $96.8 \pm 2.7\%$ was released at pH 2, $50.2 \pm 0.1\%$ in pure water, and $91.2 \pm 0.9\%$ in 16.7 mM glucose solution	Responsive drug delivery based on pH, glucose, and temperature changes	- pH-responsive mechanism: DMAEMA protonates in acidic environments, becomes more hydrophilic, promotes hydrogel MN swelling, and facilitates drug release - Glucose-responsive mechanism: GOX catalyzes glucose to produce gluconic acid, which lowers local pH and triggers the pH-responsive mechanism - Temperature-responsive mechanism: NIPAM exhibits temperature-responsive properties. When the temperature exceeds the critical solution temperature, the hydrophilic interactions between polymer chains weaken, causing the hydrogel to shrink and enabling slow drug release. Conversely, the drug is released rapidly at lower temperatures	The triple-responsive MN system can respond accurately to changes in the physiological environment, improving drug-release targeting and enabling treatment of diseases with pathological changes in pH, glucose, or temperature	171
DLP		Hydrogel MNs	Height: 500 μm (for the MN mainly used in the experiments); base diameter: 400 μm (for the MN mainly used in the experiments); aspect ratio: 1.25:1 (calculated); patch dimensions: circular patch, 8 mm in diameter; number of MNs: 100 shape: cone; drug release: sustained release for up to 72 hours, with a higher release amount during the first 24 hours	Delivery of platelet protein, promoting wound healing	After the MNs insert into the skin and absorb ISF, they release platelet proteins. These proteins interact with various growth factors, promote cell migration, accelerate wound re-epithelialization and collagen deposition, and enhance wound healing	The shape of the 3D-printed MNs can be customized to the wound shape, and the personalized design helps maximize the healing-promoting effects of the MN patch	172

(Cont'd...)

Table 3. (Continued)

Functional type	Involved 3D printing methods	MN types	Characteristics	Effects	Mechanism	Advantages	References
	FDM	Coated MNs	Height: 3.2 mm; base diameter: 2.5 mm; aspect ratio: 1.28:1 (calculated); shape: cone; drug loading: 254.97 ± 43.34 $\mu\text{g}/\text{needle}$; drug release: Rapid release during the first 8 h, followed by a plateau after 24 hours; cumulative release reached 72.44%	Delivery of Triamcinolone, improving existing scars	Triamcinolone, coated on the surface of the MNs, dissolves after the MNs penetrate chest scars and exerts its therapeutic effect	MNs can be 3D-printed and customized according to scar shapes; the optimal material ratio is determined through finite element analysis to ensure the best mechanical properties of the MNs; the chitosan component in the MNs exhibits antibacterial properties, reducing the risk of wound infection; with the help of MNs, triamcinolone can be delivered deep into the scar, enhancing the drug's effect	173
	SOPL (indirect fabrication)	Dissolving MNs	Height: 900 μm ; base diameter: 400 μm ; aspect ratio: 2.25:1 (calculated); number of MNs: $13 \times 13 = 169$; MN spacing: 1 mm; shape: cone; cell loading: 4×10^5 cells	Delivery of live TCVs, inhibiting melanoma growth	Inactive melanoma cells transfected with GM-CSF plasmids are used to construct TCVs, which are encapsulated in ice MNs. After insertion into the skin, the ice melts and releases the TCV, continuously secreting GM-CSF to recruit dendritic cells, activate CD4+ and CD8+ T cells, and trigger an anti-tumor immune response	Compared with traditional subcutaneous TCV injection, ice MN intradermal vaccine delivery generates a long-lasting, effective anti-tumor immune response against melanoma; combined with 3D printing technology, this ice MN vaccine offers a new strategy for personalized cancer therapy	174
Biomarker extraction	TPP (indirect fabrication)	Solid MNs	Height: 450 μm (for the MN with the best performance); base diameter: 200 μm ; aspect ratio: 2.25:1 (calculated); patch dimensions: 10×10 mm; number of MNs: $20 \times 20 = 400$; MN spacing: 400 μm ; shape: cone; ISF extraction: average extraction volume of 20.8 ± 19.4 μL within 25 min from human skin	Extracting ISF for biomarker detection and disease diagnosis	MNs create micro-pores in the skin, and a vacuum chamber generates negative pressure to drain ISF from the dermis to the surface for collection	The collected ISF can detect more than 600 diagnostic biomarker proteins; the MN patch is easy to use, well tolerated by patients, and can be used for disease diagnosis with low pain and low infection risk	181

(Cont'd...)

Table 3. (Continued)

Functional type	Involved 3D printing methods	MN types	Characteristics	Effects	Mechanism	Advantages	References
	P μ SL	Hollow MNs	Height: 1,000 μ m; patch dimensions: 21 $\times$ 21 mm; number of MNs: 10 $\times$ 10 = 100 (mainly used in the experiments); MN spacing: 2,000 μ m; shape: cone; ISF extraction: average extraction volume of 18.42 $\pm$ 1.02 μ L within 5 min in live animals	Extracting ISF for real-time detection of corticosteroids, lactate, glucose, and other biomarkers	The hollow MN patch connects to a vacuum collection tube, which uses negative pressure to draw ISF from the dermis, allowing direct collection via the tube	With high integration, easy operation, and no need for professional medical personnel, it can analyze ISF samples immediately when combined with various analytical sensors, making it suitable for fast, convenient point-of-care medical testing	182
	P μ SL (indirect fabrication)	Solid MNs	Height: 860 μ m; tip diameter: 20 μ m; patch dimensions: 8 $\times$ 8 mm; number of MNs: 2 $\times$ 3, 4 $\times$ 4, or 6 $\times$ 6; shape: cone; fracture force: 7.4 N/patch; ISF extraction: 2.50 $\pm$ 0.54 to 6.60 $\pm$ 0.54 mg/patch within 5 min for 2 $\times$ 3 to 6 $\times$ 6 arrays in live animals	Extracting ISF, integrating sensor systems for real-time biomarker detection	The surface of the MNs has micro-channels. After insertion into the skin, capillary action draws ISF into the MN patch's base sensor for detecting electrolytes (K ⁺ , Na ⁺), glucose, uric acid, reduced glutathione, and C-reactive protein	The MN patch does not rely on external devices to create vacuum negative pressure to absorb ISF, making the overall patch smaller and more convenient to use; it allows real-time monitoring of various biomarkers, particularly suitable for chronic disease monitoring	183
	DLP	Hydrogel MNs	Height: 510 $\pm$ 19.5 μ m; patch dimensions: 10 $\times$ 10 mm; number of MNs: 5 $\times$ 5 = 25; MN spacing: 1.5 mm; shape: cone; ISF extraction: 8.5 mg of PBS absorbed within 1 min in a simulation experiment	Extracting ISF, quantifying glucose concentrations rapidly	After insertion, MNs utilize hydrogel's water absorption properties to draw ISF from the dermis	Hydrogel MNs have excellent water-absorption properties, with a theoretical ISF extraction rate of up to 8.5 μ L $\cdot$ min ⁻¹	184
	TPP	Coated MNs	Height: 6 μ m; tip diameter: 580 $\pm$ 20 nm; base diameter: 630 $\pm$ 15 nm; aspect ratio: 10:1; number of MNs: 225; MN spacing: 12 μ m; shape: cylinder (for the MNs mainly used in the experiments)	Extracting single-cell contents for cell classification and identification	MNs can directly penetrate cells, contacting cell contents. The needle surface is coated with oxidation layers that modify specific biomolecules, such as antibodies targeting cell-content antigens, for cell classification and identification	One MN corresponds to one cell, and the needle body can penetrate half the depth of colorectal cancer cells, making it applicable for single-cell content extraction and analysis to aid in diagnosis	185

(Cont'd...)

Table 3. (Continued)

Functional type	Involved 3D printing methods	MN types	Characteristics	Effects	Mechanism	Advantages	References
Biosensing	DLP	Solid MNs	Height: 1,200 μm ; base diameter: 700 μm ; aspect ratio: 1.71:1 (calculated); patch dimensions: 22×11 mm; number of MNs: $8 \times 4 = 32$ (showing the best performance); shape: cone	Extracting epidermal microbes for skin infection diagnosis	After the MNs penetrate the scalp and enter the dermis, microorganisms adhere to the needle surface. The MN patch is then placed into a 2 mL EP tube, and buffer is added for DNA extraction, followed by microbial identification	MN sampling overcomes the limitations of swabs or tape sampling methods, which can only collect surface microbes; for detecting Ascomycota, MN sampling not only shows higher sensitivity than swabs or tapes, but also collects a broader range of fungal species, which is crucial for clinical diagnosis of skin infections	186
			Height: 1,200 μm ; base diameter: 500 μm ; aspect ratio: 2.4:1 (calculated); number of MNs/electrodes: 6 working electrodes + 8 counter electrodes + 2 reference electrodes = 16; MN spacing: 1.27 mm; shape: pointed cylinder; fracture force: 24 N/patch; detection range: glucose, 1–10 mM; lactate, 0.5–5 mM; alcohol, 1–10 mM	Monitoring glucose, lactate, and alcohol for personalized health management	The three WEs of the MNs are coated with GOX, LOX, and AOX. Glucose, alcohol, and lactate in ISF react with the enzymes, generating corresponding oxidation products and H_2O_2 . A constant voltage is applied between the working and REs, promoting the oxidation of H_2O_2 to O_2 and releasing electrons, which form a complete circuit with the auxiliary electrode, allowing concentration determination based on current magnitude	Real-time monitoring of various biomarker concentrations (glucose, lactate, alcohol) is possible, and data can be wirelessly transmitted via Bluetooth to a smartphone for real-time viewing and cloud upload for health analysis	187
			Height: 1,200 μm ; base diameter: 350 μm ; aspect ratio: 3.43:1 (calculated); number of MNs: 25 WE + 30 CE + 12 RE = 67; shape: cone; detection range: Chlorpromazine, 5–120 μM ; limit of detection: 0.09 μM	Monitoring Chlorpromazine drug levels for personalized medication in psychiatric patients	The potential of the MN's WE is first modified by applying voltage pulses. When the potential reaches the oxidation potential of chlorpromazine, it oxidizes at the WE surface, releasing electrons and generating current. By applying a series of voltage pulses, the sensor obtains the current peak at the corresponding concentration. The magnitude of the peak current is directly proportional to the chlorpromazine concentration, enabling the quantitative detection of chlorpromazine concentration	The MN sensor has high sensitivity to chlorpromazine, with a detection limit as low as 0.09 μM , suitable for rapid detection; even after 20 days of storage, the MN sensor retains 86% of its performance stability, making it suitable for long-term use; real-time monitoring ensures drug efficacy and safety	190

(Cont'd...)

Table 3. (Continued)

Functional type	Involved 3D printing methods	MN types	Characteristics	Effects	Mechanism	Advantages	References
	PμSL	Coated MNs	Height: 2,000 μm; tip diameter: 14.2 μm; base width: 900 μm; aspect ratio: 2.22:1 (calculated); shape: pointed cylinder; puncture force: 6 N/patch; detection range: glucose, 2–20 mM; metformin, 0–60 μM	Real-time monitoring of blood glucose and Metformin concentration, providing dosage adjustments	Voltage pulses modify the MN's WE potential. When the potential reaches the oxidation potential of glucose and metformin, CuO/Fe ₂ O ₃ nanocatalysts oxidize glucose, releasing electrons, while Fe ₂ O ₃ nanocatalysts oxidize metformin, also releasing electrons. By applying a series of voltage pulses, the system obtains the current peak corresponding to each concentration. The peak current is linearly related to the concentrations of both glucose and metformin, enabling the quantitative detection of blood glucose and metformin concentrations	This MN system can simultaneously monitor glucose and metformin, with real-time data transmission to smartphones via Bluetooth, enabling dynamic PK/PD assessment and providing precise dosing strategies for metformin, enhancing diabetes treatment outcomes and reducing the risk of side effects	193
	DLP	Hollow MNs	Height: 1,400 μm; number of MNs: 4 × 4 = 16; shape: syringe-needle; puncture force: 3 N/patch; detection range: pH 3–8; glucose, 0–16 mM; lactate, 0–3.2 mM	Real-time monitoring of pH, glucose, and lactate concentrations with integrated drug release function	After the MN patch is inserted into the skin, ISF in the dermis is drawn through capillary action along the internal channels of the hollow MNs to the colorimetric test strips for detecting different biomarkers. Subsequently, a smartphone can capture the colorimetric test strip's average RGB values, which are then used to calculate the concentration of the target substance. The MN patch's drug reservoir includes an ultrasonic diaphragm at the bottom, connected to a control circuit. The smartphone can remotely activate the ultrasonic diaphragm via Bluetooth. Under the influence of ultrasound, the drug is dispersed in an atomized form, enabling remote-controlled drug release	By integrating biomarker monitoring with drug release and using smartphones as the control center, this system enables dynamic, personalized, on-demand treatment interventions and strongly supports the development of closed-loop treatment MN patches	194

(Cont'd...)

Table 3. (Continued)

Functional type	Involved 3D printing methods	MN types	Characteristics	Effects	Mechanism	Advantages	References
			Height: 1,000 μm ; tip diameter: $<45 \mu\text{m}$; base width: 1,000 μm ; aspect ratio: 1:1 (calculated); number of MNs: 1; shape: pyramid; fracture force: $4.41 \pm 0.71 \text{ N}$ /needle; temperature detection range: $15\text{--}60^\circ\text{C}$; temperature resolution: 0.2°C	Monitoring dermal temperature for anesthesia or local inflammation	The hollow MNs are filled with temperature-sensitive conductive polymer PEDOT:PSS. Upon skin insertion, dermal temperature alters the carrier-transport characteristics of PEDOT:PSS, decreasing resistance and increasing conductivity as temperature rises. Real-time resistance measurement combined with a calibrated resistance-temperature relationship provides the dermal temperature	MNs directly monitor dermal temperature, avoiding environmental interference and continuously providing more accurate body temperature measurements	195
			Shape: pyramid; minimum detectable displacement: $5 \mu\text{m}$; response delay: 0.4 s	Detecting small knee joint displacements for early diagnosis of joint diseases and rehabilitation monitoring	Small knee-joint movements drive the motion of the inclined push plate, further causing the MNs to bend. This alters the contact area between the MNs and the inclined surface, as well as the connectivity of the conductive network in the MN region, resulting in measurable resistance changes. By detecting these resistance changes, the system can measure small knee-joint displacements	Non-invasive detection reduces operational complexity; its ultra-high precision allows for sub-millimeter-level knee joint displacement detection	196

Abbreviations: 3D: Three-dimensional; AOX: Alcohol oxidase; CE: Counter electrode; CLIP: Continuous liquid interface production; CuO: Copper oxide; CyMA: Cymbal microneedle array; DLP: Digital light processing; DMAEMA: 2-(Dimethylamino)ethyl methacrylate; DXM: Dexamethasone; EP: Eppendorf; FDM: Fused deposition modeling; GM-CSF: Granulocyte-macrophage colony-stimulating factor; GOX: Glucose oxidase; H_2O_2 : Hydrogen peroxide; ISF: Interstitial fluid; L-MAP: Lattice microneedle array patch; LOX: Lactate oxidase; MN: Microneedle; NIPAM: N-isopropylacrylamide; OVA: Ovalbumin; PBS: Phosphate-buffered saline; PEDOT:PSS: Poly(3,4-ethylenedioxythiophene):polystyrene sulfonate; PK/PD: Pharmacokinetics/pharmacodynamics; PPFPS: Poly(pentafluorophenyl acrylate); PTH: Parathyroid hormone; PuSL: Projection micro-stereolithography; RE: Reference electrode; SLA: Stereolithography; SOPL: Soft sacrificial-layer-based omnidirectional photolithography; TCV: Therapeutic cancer vaccine; TPP: Two-photon polymerization; WE: Working electrode.

Table 4. Summary of representative three-dimensional-printed microneedle patents

Patent no.	Title	Country	Involved 3D printing methods	Description
CN119792248A	A 3D printing-based analgesic microneedle patch and its preparation method and application	China	DLP	A 3D-printed hydrogel MN patch loaded with lidocaine for local anesthesia before radial artery puncture catheterization, designed to improve transdermal drug delivery efficiency and shorten onset time
US20250144387A1	Microneedle integrated 3D printed micropump combined with polymeric nanoparticles for rapid release transdermal drug delivery	United States	FDM and SLA	A 3D-printed MN-integrated shape memory alloy-triggered micropump system combined with polymeric nanoparticles for rapid transdermal drug delivery, enabling improved skin deposition and potential wearable insulin administration
US20250186754A1	Compliant Polymeric Structures Having Polymeric Microneedles and Methods for Making and Using Same	United States	CLIP	A compliant polymeric 3D-printed MN structure with stimulus-responsive elastic deformation for transdermal delivery of active agents or collection of biological fluid samples
CN116458931B	3D printing hollow microneedle array resin patch and its preparation and application, continuous blood glucose monitor, dynamic monitoring method of blood glucose concentration	China	Specific 3D printing modality not disclosed	A 3D-printed hollow MN resin patch with a well-shaped support and side-opening cone design that improves pore formation and body-fluid collection for continuous blood glucose monitoring and dynamic biomarker detection

Abbreviations: 3D: Three-dimensional; CLIP: Continuous liquid interface production; DLP: Digital light processing; FDM: Fused deposition modeling; MN: Microneedle; SLA: Stereolithography.

5. Three-dimensional-printed microneedles in disease treatment

The unique functions of 3D-printed MNs in the three major areas of drug delivery, biomarker extraction, and biosensing enable them to control disease progression more effectively and persistently. Unlike the previous section, which classified the biological functions of 3D-printed MNs, this section focuses on disease treatment and comprehensively showcases the integrated clinical applications of 3D-printed MNs in therapeutic contexts. Table 5 summarizes these applications.

5.1. Cancer treatment

Cancer, as one of the major public health issues faced globally, poses a serious threat to human life and health. According to statistics, cancer affects millions of patients annually and is the second leading cause of death worldwide.¹⁹⁹ In China, the cancer burden is particularly high, with the elderly population (over 70 years old) carrying a significantly higher cancer burden compared to younger groups.²⁰⁰ However, traditional treatment methods such as surgery, radiotherapy, and chemotherapy,

while effective to some extent, often come with limitations such as limited efficacy, severe side effects, and treatment restrictions due to patients' physical conditions. MNs, with their minimally invasive, efficient, and convenient features, combined with the personalized manufacturing advantages of 3D printing, provide an innovative technological pathway for cancer treatment. Earlier, we introduced a 3D-printed MN developed by Yang *et al.*¹⁹³ to deliver live tumor vaccines, which effectively inhibited melanoma growth. Similarly, Joo *et al.*²⁰¹ also approached cancer treatment from an immunotherapy perspective, developing a 3D-printed MN that modulates immune factors in the tumor microenvironment to suppress melanoma development. Structurally, this MN employs a “wide needle body-narrow base” geometry to achieve a “self-locking” effect, allowing it to be firmly fixed within the skin (Figure 11A). Regarding the drug delivery mechanism, once the MN is inserted into the skin, the hyaluronic acid-based needle body begins to dissolve, gradually releasing the loaded alpha programmed death-ligand 1 (αPD-L1) antibody and transforming growth factor beta receptor inhibitor SD-208. The αPD-L1 antibody binds PD-L1 on tumor cells, blocking its interaction with PD-1 on CD8⁺ T

cells, thereby relieving immune suppression of tumor cells on T cells and promoting the immune system's recognition and destruction of tumor cells. The transforming growth factor beta signaling pathway not only promotes tumor cell deformation and migration but also suppresses T cell immune function. SD-208 blocks this pathway, further enhancing the anti-tumor effect. Moreover, the research team compared MN delivery with intratumoral injection, and the results showed that MN delivery outperformed intratumoral injection, significantly inhibiting melanoma (Figure 11B). Interestingly, in addition to using immune substances, electrical stimulation (ES) can regulate endogenous cytokines in the immune system, modulating the tumor immune environment while directly killing tumor cells.²⁰² Pan *et al.*²⁰³ used this approach to develop a 3D-printed flexible MN-array-integrated interdigital electrode (FMIE), which can generate an electric field of approximately 1–3 V/cm at the tumor site, disrupt tumor cell calcium ion channels, increase Ca^{2+} influx, and cause mitochondrial Ca^{2+} overload. This causes mitochondrial damage, increased reactive oxygen species (ROS) generation, and ultimately tumor cell necrosis, releasing damage-associated molecular patterns (including ATP efflux, calreticulin exposure, and high-mobility group box 1 release). This process further matures dendritic cells, drives macrophages to chemotax from M2 to M1, and recruits CD8^{+} T cells, not only suppressing immune cell death *in situ* in tumors but also initiating sustained systemic anti-tumor immune responses (Figure 11C and 11D).²⁰³ FMIE cleverly combines the direct tumor-killing effects of ES with the indirect anti-cancer effects of immune microenvironment modulation, avoiding the toxic side effects of traditional drug therapies while providing an innovative and practical technological paradigm for non-drug-based anti-cancer treatments.

Unlike the previous two anti-cancer mechanisms, Xu *et al.*²⁰⁴ designed a 3D-printed hydrothermally responsive multi-round actuable MN. Its principle is similar to the hydrothermal system in self-heating hotpots, where a self-heating pack containing a mixed powder of CaO, Fe, activated carbon, NaCl, and MgSO_4 is loaded at the base of the MNs. The components work synergistically to release heat steadily: CaO releases a large amount of heat when it comes into contact with water, serving as the primary heat source; Fe undergoes oxidation in the air, assisting in the heat release process; the porous structure of activated carbon adsorbs CaO and Fe, not only slowing the overall heat release rate but also enabling even heat distribution, effectively preventing unnecessary burns due to localized overheating; NaCl, as an electrolyte, enables Fe and activated carbon to form a galvanic cell, further accelerating Fe oxidation; and MgSO_4 absorbs

trace moisture from the air to prevent the hydrothermal components from prematurely absorbing water before use, ensuring the stability of the self-heating pack. Additionally, this MN array is specially designed with three independent fan-shaped regions, allowing for ordered hydrothermal triggering. When each fan-shaped MN region is exposed to 100 μL of water, the self-heating pack can precisely raise the water temperature to 60–70 °C, a temperature that induces the glass transition of the PCL-based needle body, leading to the release of the loaded docetaxel from the needle body, effectively inhibiting tumor growth (Figure 11E and 11F). From an application advantage perspective, this hydrothermal response strategy effectively addresses the potential biotoxicity risks associated with photothermal agents used in mainstream photothermal response strategies and does not rely on complex equipment. It only requires adding water to enable on-demand drug delivery, making it convenient and fast and giving it strong clinical application potential. Furthermore, Yang *et al.*²⁰⁵ designed a 3D-printed porous MN patch with remotely controlled thermal responsiveness via a smartphone, made of fully flexible materials that exhibit excellent stretchability and can tightly conform to the skin's dynamic curves (Figure 11G). The built-in stretchable heater is made from MXene material and undergoes a pre-stretching process to form a micro-pleated structure, which effectively buffers the stretching stress and significantly suppresses resistance fluctuations during deformation, ensuring stable thermal conductivity performance. This heater, in combination with a flexible circuit board, forms a wireless system that receives instructions via Bluetooth from a smartphone, allowing the heater to trigger local heating of the skin in the tumor area to a preset temperature. When the temperature reaches the phase change threshold, the microcarriers embedded in the composite textile dressing of the MN patch (using tetradecanol as the phase change matrix and encapsulating doxorubicin) undergo a solid-liquid phase change, releasing doxorubicin through the porous MN channels to target the melanoma site, achieving synergistic anti-cancer effects through “heat-chemotherapy” (Figure 11H and 11I).

5.2. Tissue repair

Tissue injury is a common and complex clinical issue, involving various tissue types such as skin, muscles, and nerves. Traditional treatments for tissue damage often rely on surgical intervention or long-term medication, which are insufficient to meet the clinical demand for rapid, efficient, and minimally invasive treatment. For example, burn wounds vary significantly in healing speed and quality depending on depth and area. Severe burns are often accompanied by chronic inflammation and scar

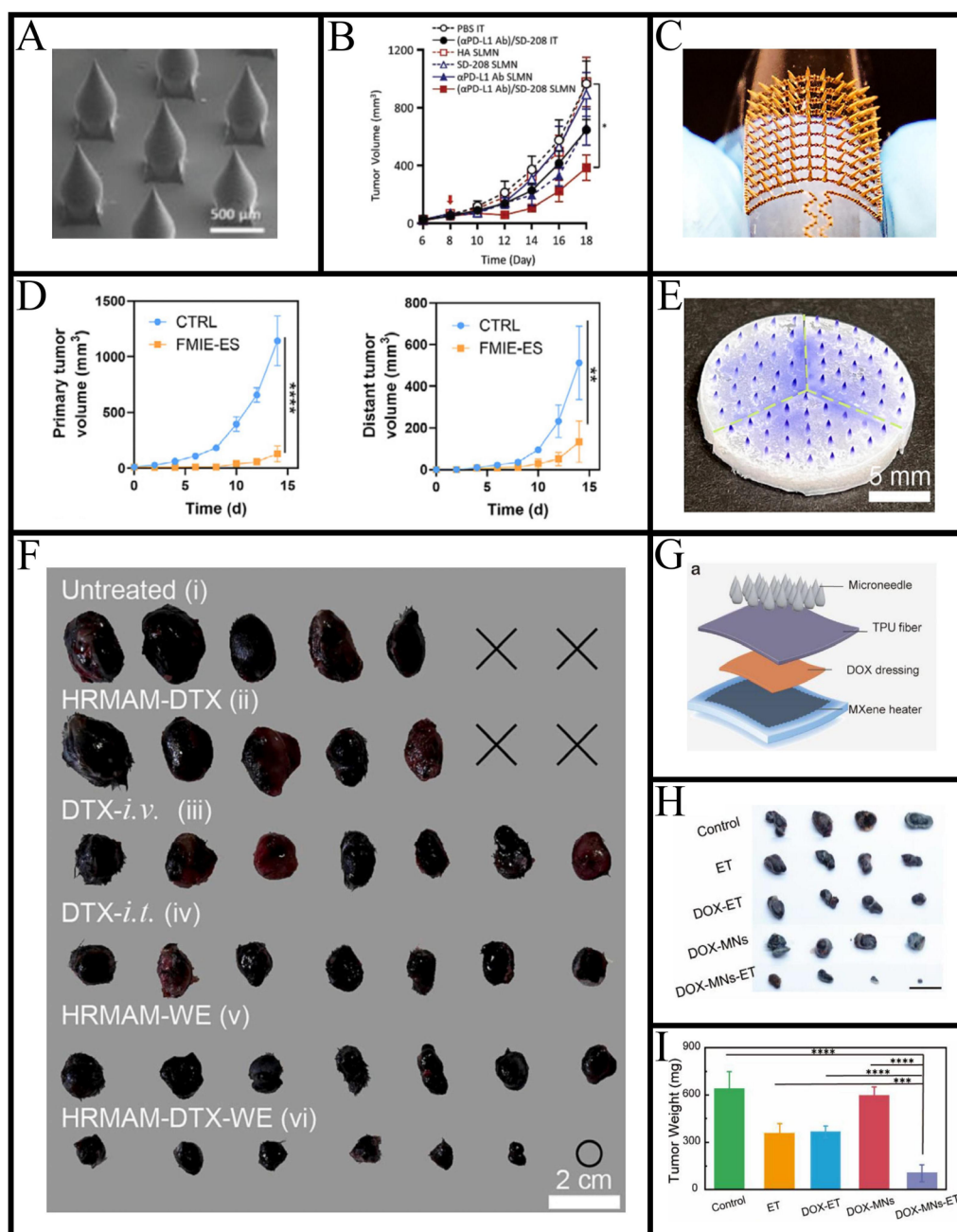


Figure 11. Three-dimensional-printed microneedles (MNs) for cancer therapy. (A) Scanning electron microscopy (SEM) images of self-locking MNs. Scale bar: 500 μm ; magnification: XX $\times$. Reproduced with permission from Joo *et al.*²⁰¹ Copyright © 2023, John Wiley and Sons. (B) Tumor volume measurements of an *in situ* melanoma mouse model after 18 days of treatment. Reproduced with permission from Joo *et al.*²⁰¹ Copyright © 2023, John Wiley and Sons. (C) Microscopic image of the fabricated flexible MN-array-integrated interdigital electrode (FMIE). Reproduced with permission from Pan *et al.*²⁰³ Copyright © 2023, Elsevier. (D) Time-dependent changes in primary and distant tumor volumes in the CTRL group (untreated) and the FMIE-ES group (treated with FMIE with alternating current). Reproduced with permission from Pan *et al.*²⁰³ Copyright © 2023, Elsevier. (E) Front-view digital image of hydrothermally responsive multi-round actuable MN. Scale bar: 5 mm. Reproduced with permission from Xu *et al.*²⁰⁴ Copyright © 2023, Elsevier. (F) Melanoma conditions of mice after 12 days of treatment under six different therapeutic modalities ($n = 7$ mice per group), where WE denotes water exposure. Scale bar: 2 cm. Reproduced with permission from Xu *et al.*²⁰⁴ Copyright © 2023, Elsevier. (G) Structural schematic of a stretchable 3D-printed MN patch. Reproduced with permission from Yang *et al.*²⁰⁵ Copyright © 2025, John Wiley and Sons. (H) Images of tumors collected from each mouse in different groups after 8 days of melanoma treatment, where ET denotes electrothermal therapy. Scale bar: 1 cm. Reproduced with permission from Yang *et al.*²⁰⁵ Copyright © 2025, John Wiley and Sons. (I) Tumor weights of mice in different groups after eight days of melanoma treatment. Reproduced with permission from Yang *et al.*²⁰⁵ Copyright © 2025, John Wiley and Sons.

hyperplasia, causing long-term pain and functional loss for patients.²⁰⁶ As previously mentioned, the customizable GSPMNs designed by Li *et al.*,¹⁷² which promote wound healing, already demonstrate how 3D-printed MNs provide innovative solutions to address issues such as large skin tissue damage and slow recovery. In the following section, we will focus on the disease perspective, specifically elaborating on the application of 3D-printed MNs in tissue repair.

Electrical stimulation can not only kill tumor cells and regulate the tumor immune environment but also simulate bioelectricity, prompting tissue cells to perform specific physiological activities. Hu *et al.*²⁰⁷ designed a 3D-printed MN for treating muscle atrophy caused by peripheral nerve damage. This MN mimics the physiological structure of a sea cucumber, with MNs on the outside and microchannels on the inside (Figure 12A). The materials include PCL, ZnO nanoparticles, and reduced graphene oxide (rGO). As the MN deforms with body movement, the piezoelectric properties of ZnO nanoparticles convert mechanical energy into microcurrents, while rGO enhances current conduction efficiency. The generated microcurrent is transmitted through the outer needle tips to the denervated muscle, replacing missing neural signals and inhibiting muscle fiber atrophy (Figure 12B). Meanwhile, the inner microchannels guide Schwann cell migration, and the piezoelectric-generated ES accelerates Schwann cell migration, promotes myelin regeneration, and supports axonal growth, ultimately achieving a synergistic biological effect of “inhibiting muscle atrophy—promoting nerve regeneration.” In addition, the mechanical stimulation produced by the MNs during skin penetration can also act as a repair signal. Li *et al.*²⁰⁸ designed a 3D-printed MN that promotes hair follicle tissue regeneration solely through needle body stimulation. This mechanical stimulation does not induce excessive inflammatory responses but can simulate physiological repair signals, thereby recruiting macrophages and inducing their polarization, releasing cytokines (such as human growth factor, insulin growth factor-1, and tumor necrosis factor alpha), and upregulating the Wnt/ β -catenin pathway—a key pathway for tissue regeneration—thereby activating hair follicle stem cell proliferation (Figure 12C and 12D). Compared with traditional drug treatments (such as minoxidil, finasteride, etc.), this new technology does not require drug intervention and can be customized through 3D printing to match the shape of MN patches to different patients’ hair loss areas, making it suitable for various types of hair loss and providing a more personalized and low side-effect treatment option for hair loss patients.

In the section introducing the biological functions

of 3D-printed MNs for drug delivery, we discussed several examples used to treat diabetes. However, diabetic patients often suffer from impaired wound healing mechanisms due to prolonged hyperglycemia, accompanied by peripheral neuropathy, vascular complications, and immune dysfunction.²⁰⁹ This makes diabetic foot ulcers one of the most common and severe chronic complications of diabetes.²¹⁰ To address skin tissue repair for diabetic wounds, Liu *et al.*²¹¹ designed a patch combining 3D-printed dissolvable MNs with a sticky anti-inflammatory backing (Figure 12E). The dissolvable MNs are loaded with glucose-responsive chitosan-based nanoparticles containing insulin, which can lower local blood glucose levels at the wound site and reduce the inhibitory effects of high glucose on wound healing. The backing contains tannic acid and curcumin; tannic acid provides broad-spectrum antibacterial effects to reduce the risk of infectious inflammation, while curcumin promotes cell migration and accelerates wound healing (Figure 12F). Additionally, the integrated patch, when combined with a sensor, can monitor movement: when movement in the wound area deforms the patch, the resistance signal changes, capturing motion data to monitor the real-time range and frequency of movement in areas like the fingers and wrists. Since wound infections affect a patient’s endurance and responsiveness (e.g., fatigue, discomfort, or pain during movement), this feature helps healthcare professionals monitor infection status or disease progression of diabetic patients’ wounds, while also providing a reference for personalized rehabilitation plans. Acne is a common inflammatory skin disease, affecting approximately 650 million people worldwide.²¹² Traditional topical treatments often have limited effectiveness due to difficulty penetrating deeper skin layers and may cause side effects such as skin redness, dryness, and peeling, in addition to increasing drug resistance. Park *et al.*²¹³ designed two “self-locking” 3D-printed MN patches with different heights to address the different stages of acne development (Figure 12G). For early-stage acne treatment, an antibacterial MN with a needle height of 450 μm is used, containing hyaluronic acid, salicylic acid, cannabis root extract, and anti-seborrheic agents, which target and inhibit the growth of *Propionibacterium acnes*, reducing inflammation. In later stages of treatment, an anti-inflammatory MN with a needle height of 300 μm is used, containing hyaluronic acid, salicylic acid, chamomile extract, glutathione, and niacinamide, to reduce oxidative stress and accelerate acne healing. This study enrolled 20 patients with mild to moderate acne for a 7-day treatment evaluation. By day 7, acne lesions in the experimental group were completely cleared, while only 71.2% of lesions were cleared in the control group (Figure 12H). This phased

treatment approach can precisely target different stages of acne development, achieving a synergistic therapeutic effect.

The oral cavity is one of the areas with the highest bacterial colonization density and most complex microbial communities in the human body, where many symbiotic bacteria coexist with pathogenic bacteria.²¹⁴ When the microbial community's balance is disrupted, infections can easily occur. Bacterial infectious stomatitis is an acute bacterial ulcer caused by pathogens such as *Staphylococcus aureus*, *Streptococcus viridans*, and *Escherichia coli*, which invade the oral mucosa. Current treatment strategies include medication and laser technologies, but they often fail to accelerate ulcer healing effectively, requiring complex and costly multi-treatment approaches. Hydrogels have opened broad prospects for ulcer treatment, but the continuously moist oral environment greatly affects their solubility and adhesion. To overcome these challenges, Qin *et al.*,²¹⁵ inspired by the structure of fruit fly tarsal claws, designed and developed a biomimetic 3D-printed hydrogel MN suction patch (Figure 12I). The suction part of the patch is made of PVA, ensuring stable adhesion in the moist oral environment. The MN part is prepared from a hydrogel composed of sodium carboxymethyl cellulose, hydroxypropyltrimethyl ammonium chloride chitosan (HACC), S-nitrosoglutathione (GSNO), and poly(N-isopropylacrylamide) (PNIPAM). Carboxymethyl cellulose gives the MNs excellent mechanical properties, enabling them to penetrate the oral mucosa effectively. HACC, a chitosan derivative, retains good biocompatibility, biodegradability, and hemostatic properties and also exhibits significant antibacterial activity. As an endogenous nitric oxide (NO) donor, GSNO stabilizes and continuously releases NO, preventing toxic NO accumulation. NO has multiple effects, including vasodilation, reduced pro-inflammatory cytokines, and enhanced macrophage phagocytic function, which can effectively control inflammation progression. Meanwhile, GSNO also scavenges reactive ROS and alleviates oxidative stress damage. PNIPAM is a temperature-responsive material that undergoes structural changes at around 32 °C. When the patch is applied to the affected oral mucosa, body temperature induces PNIPAM to reach its critical phase-transition temperature, transforming from a coiled structure to a spherical structure and enabling rapid GSNO release. The research team conducted experiments using a *Staphylococcus aureus*-induced bacterial infectious stomatitis rat model, and the results showed that the MN patch treatment group achieved complete ulcer healing by day six, while 32% of the ulcers in the experimental group treated with a commercially available gel remained unhealed (Figure 12J). This multifunctional MN, made

possible by 3D printing technology, can be flexibly applied to ulcers of various sizes, achieving precise treatment and significantly improving healing outcomes. In addition, bacterial infection is a major cause of periodontitis, and gum recession is a common clinical manifestation of periodontitis.^{216,217} Gum recession not only affects aesthetics but can also lead to issues such as dentin sensitivity and root caries.²¹⁸ Currently, surgical procedures are the most common treatment for gum recession, but due to significant trauma and pain, patient compliance is low.²¹⁸ To address this issue, He *et al.*²¹⁹ developed a PEGDA hydrogel 3D-printed MN patch loaded with madecassoside for promoting periodontal soft tissue regeneration (Figure 12K). The experiments showed that this MN patch effectively penetrates mucosal tissue and continuously releases the drug, significantly increasing gum thickness and type I collagen expression (Figure 12L and 12M), confirming its strong efficacy in a gum recession model. He *et al.*'s²¹⁹ study provides a novel periodontal tissue repair method that is more acceptable, less painful, and nearly non-invasive for patients with gum recession.

Among the 10 cases summarized in this section, only the self-locking 3D-printed MN patches developed by Park *et al.*²¹³ for acne treatment have been tested in human subjects, reaching clinical readiness. The remaining nine studies were validated only in animal models and thus represent preclinical feasibility. These examples indicate that, although the majority of 3D-printed MNs are still at the preclinical validation stage, future research should place greater emphasis on advancing the clinical readiness of these technologies to facilitate their translation into practical clinical applications.

6. Other technologies supporting the innovation of three-dimensional-printed microneedles

6.1. Four-dimensional printing

The concept of 4D printing was first introduced by Skylar Tibbits, founder and director of the Self-Assembly Lab at the Massachusetts Institute of Technology in February 2013.²²⁰ Essentially, 4D printing builds on 3D printing by adding a new dimension: "time." Through this technology, 3D-printed objects undergo structural changes in response to external stimuli such as temperature, pH, water, or light, which cause the objects to self-deform or change functionality as time progresses.²²¹ This additional dimension undoubtedly brings enormous potential to expand the applications of 3D printing technology.

In 2020, Han *et al.*²²² utilized PμSL technology combined with 4D printing strategies to fabricate an

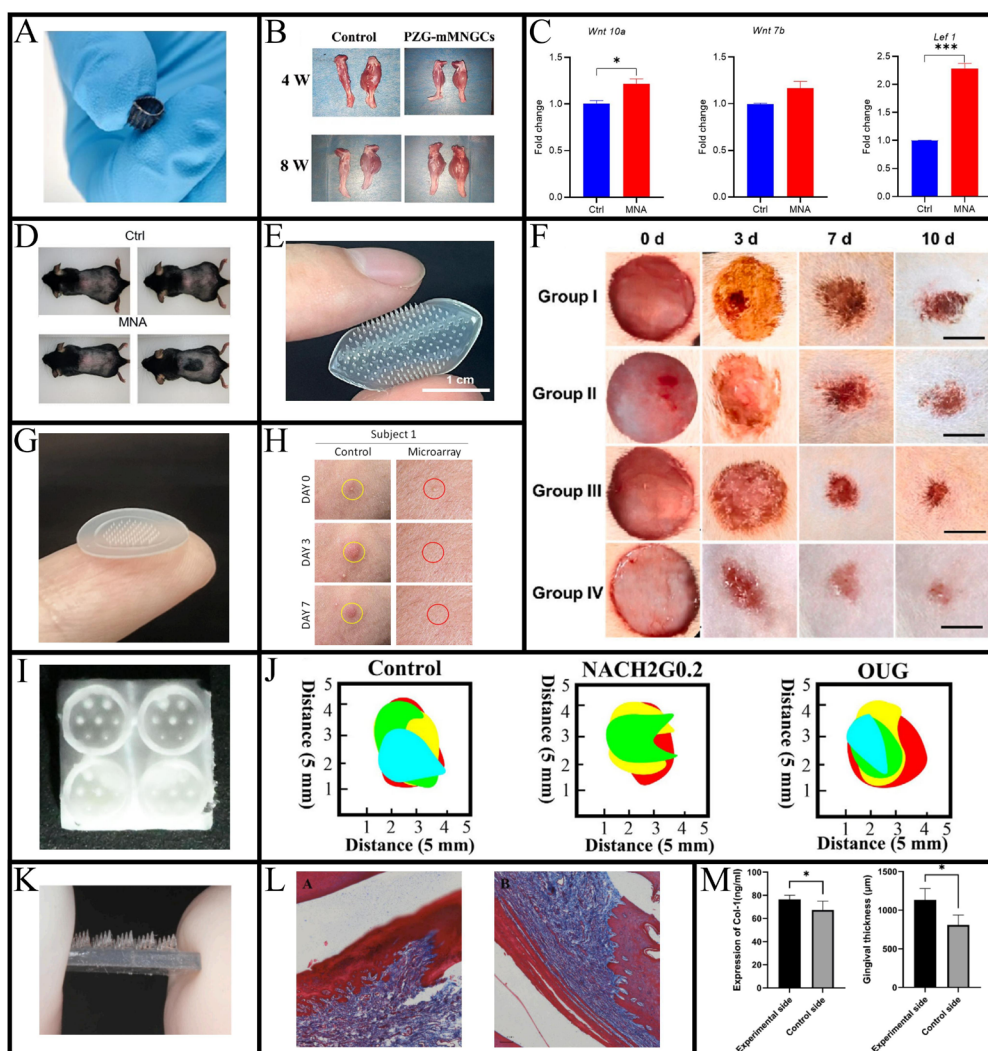


Figure 12. Three-dimensional-printed microneedles (MNs) for tissue repair. (A) Digital photograph of a sea cucumber-inspired MN patch. Reproduced with permission from Hu *et al.*²⁰⁷ Copyright © 2024, American Chemical Society. (B) Changes in the gastrocnemius muscle of rats at weeks 4 and 8 following treatment for gastrocnemius atrophy induced by peripheral nerve injury. Reproduced with permission from Hu *et al.*²⁰⁷ Copyright © 2024, American Chemical Society. (C) Real-time quantitative polymerase chain reaction results showing significantly elevated expression levels of *Wnt10a* and *Lef1* in the MNA group (MN patch-treated group). Reproduced with permission from Li *et al.*²⁰⁸ Copyright © 2023, Springer Nature. (D) Photographs of mice taken on day 0 (left) and day 28 (right) showing no hair regeneration in the control group, whereas pronounced hair regeneration was observed in the MNA group. Reproduced with permission from Li *et al.*²⁰⁸ Copyright © 2023, Springer Nature. (E) Digital image of 3D-printed MNs for treating diabetic wound ulcers. Reproduced with permission from Liu *et al.*²¹¹ Copyright © 2025, Elsevier. (F) Wound images of different treatment groups at various time points: Group I, control group; Group II, hydrogel backing containing tannic acid; Group III, hydrogel backing containing tannic acid and curcumin; Group IV, integrated patch composed of dissolving MNs loaded with insulin glucose-responsive nanoparticles combined with a hydrogel backing containing tannic acid and curcumin. Scale bar: 5 mm. Reproduced with permission from Liu *et al.*²¹¹ Copyright © 2025, Elsevier. (G) Digital image of a "self-locking" 3D-printed MN patch for acne treatment. Reproduced with permission from Park *et al.*²¹³ Copyright © 2025, American Chemical Society. (H) Digital images showing changes in facial acne at different time points after treatment. Reproduced with permission from Park *et al.*²¹³ Copyright © 2025, American Chemical Society. (I) Digital image of a bioinspired 3D-printed hydrogel MN suction-cup patch for treating bacterial infectious stomatitis. Scale bar: 5 mm. Reproduced with permission from Qin *et al.*²¹⁵ Copyright © 2025, John Wiley and Sons. (J) Comparison of wound-healing areas among different treatment groups on days 0 (red), 2 (yellow), 4 (green), and 6 (cyan), where OUG represents the experimental group treated with a commercially available therapeutic gel. Reproduced with permission from Qin *et al.*²¹⁵ Copyright © 2025, John Wiley and Sons. (K) Image of a 3D-printed hydrogel MN patch for promoting periodontal soft tissue regeneration. Reproduced from He *et al.*²¹⁹ (L) Masson's trichrome staining of gingival tissues from the control group (gingival recession model rabbits without MN patch treatment) and the experimental group (gingival recession model rabbits treated with MN patches), where blue indicates collagen fibers; the collagen area fraction was $48.7 \pm 2.04\%$ in the experimental group and $32.3 \pm 1.49\%$ in the control group. Reproduced from He *et al.*²¹⁹ (M) Left bar chart showing the relative expression of collagen type 1 between the experimental and control groups, and right bar chart showing gingival thickness in the experimental and control groups. Reproduced from Het *et al.*²¹⁹

Table 5. Summary of three-dimensional-printed microneedles for disease treatment

Disease type treated	3D printing method	Type of MN	Characteristics	Therapeutic agent	Treatment area	Mechanism	Advantages	References
	PuSL (indirect fabrication)	Dissolving MN	Height: 700 µm; tip diameter: 2 µm; base diameter: 250 µm; aspect ratio: 2.8:1 (calculated); number of MNs: $14 \times 14 = 196$; shape: cone-like with a self-locking structure; fracture force: 0.92 ± 0.21 N/needle; puncture force: 0.19 ± 0.08 N/needle	αPD-L1, SD-208	Melanoma	The released αPD-L1 antibody and SD-208 can relieve immune suppression and block the TGF-β pathway, inhibiting melanoma growth	Better anti-tumor effect than intratumoral injection; encapsulating active drugs in MNs improves drug storage stability, reduces cold-chain transportation requirements, and lowers treatment costs	201
Cancer treatment	PuSL	Coated MN	Height: 700 µm; number of MNs: $10 \times 10 = 100$; MN spacing: 800 µm; shape: cone; puncture force: 0.93 mN/needle	ES	Melanoma, Lung Metastatic Melanoma	ES causes tumor cell necrosis, releasing DAMPs that activate systemic anti-cancer immunity, achieving both local and systemic anti-cancer effects	ES directly kills tumors and regulates the immune microenvironment for indirect anti-cancer effects, avoiding drug side effects and providing a paradigm for drug-free cancer therapy	203
	DLP	Dissolving MN	Height: 900 µm; base diameter: 500 µm; aspect ratio: 1.8:1 (calculated); patch dimensions: circular patch with a radius of 8 mm; number of MNs: 75; shape: grooved-tip and conical-neck structure; fracture force: 2.4 N/needle	DTX	Melanoma, breast tumor	The self-heating pack generates heat upon contact with water, causing PCL to undergo glass transition, releasing DTX from the MNs, effectively inhibiting tumor growth	Water-triggered drug delivery without complex equipment, avoiding the biotoxicity of light-heat response agents, convenient operation, and high clinical potential	204
	DIW	Porous MN	Height: 600 µm; tip diameter: <8 µm; base diameter: 400 µm; aspect ratio: 1.5:1 (calculated); shape: cone; fracture force: 337 ± 18 mN/needle	DOX	Melanoma	Remote temperature control via smartphone triggers phase transition in the microcarriers, releasing DOX to inhibit melanoma	The fully flexible material conforms to skin contours; remote temperature-controlled drug release enables "thermal-chemotherapy" synergistic anticancer treatment	205

(Cont'd...)

Table 5. (Continued)

Disease type treated	3D printing method	Type of MN	Characteristics	Therapeutic agent	Treatment area	Mechanism	Advantages	References
	PuSL (indirect fabrication)	Solid MN	Height: 800 µm; base diameter: 600 µm; aspect ratio: 1.33:1 (calculated); shape: cone	ES	Muscle, nerve tissue	The piezoelectric effect generates microcurrents that stimulate denervated muscles, preventing muscle fiber atrophy. Simultaneously, the combination of ES and microchannels in the MN patch accelerates Schwann cell migration, promoting myelin regeneration and axonal growth	Uses the piezoelectric effect for ES, avoiding drug side effects, inhibiting muscle atrophy, and promoting nerve growth for dual repair	207
	SOPL	Solid MN	Shape: Cone	Mechanical stimulation of MNs	Hair follicle tissue	MNs mechanically stimulate hair follicle tissue, inducing macrophage polarization, releasing cytokines, activating the Wnt/ β -catenin pathway, promoting hair follicle stem cell proliferation, and promoting hair follicle regeneration for hair loss treatment	Mechanical stimulation alone without drugs to avoid side effects; personalized MN patch design for precise treatment based on the hair loss area	208
Tissue repair	DLP	Dissolving MN	Height: 600 µm (cone-shaped design); tip diameter: 20 µm; base diameter: 200 µm (cone-shaped design); aspect ratio: 4:1 (pyramid-shaped design); number of MNs: $10 \times 10 = 100$; shape: cone and pyramid; fracture force: 0.43 N/needle	Insulin, tannic acid, curcumin	Skin tissue	Release glucose-responsive chitosan-based nanoparticles containing insulin to reduce local blood glucose and counteract high-glucose inhibition of wound healing, with an anti-inflammatory backing that suppresses infection and accelerates healing	Glucose-responsive insulin release for on-demand drug delivery. The anti-inflammatory backing can also integrate with sensors to monitor movement, helping healthcare providers assess wound status and plan rehabilitation	211
	DLP (indirect fabrication)	Dissolving MN	Antibacterial MN height: 450 µm; anti-inflammatory MN height: 300 µm; number of antibacterial MNs: 69; number of anti-inflammatory MNs: 45; shape: cone-like with a self-locking structure; antibacterial MN fracture force: 0.42 ± 0.01 N/patch; anti-inflammatory MN fracture force: 0.24 ± 0.01 N/patch	Antibacterial phase MN (450 µm): salicylic acid, cannabidiol root extract, anti-seborrheic agents. Anti-inflammatory phase MN (300 µm): salicylic acid, chamomile extract, glutathione, niacinamide	Skin tissue	In the early stages of acne, antibacterial MNs target and inhibit <i>Propionibacterium acnes</i> growth, reducing inflammation; in later stages, anti-inflammatory MNs effectively reduce oxidative stress and accelerate acne healing	Stage-specific treatment for acne progression, achieving complete acne lesion clearance within 7 days	213

(Contd...)

Table 5. (Continued)

Disease type treated	3D printing method	Type of MN	Characteristics	Therapeutic agent	Treatment area	Mechanism	Advantages	References
	PμSL (indirect fabrication)	Hydrogel MN	Height: 700 μm; aspect ratio: 1.4:1 (calculated); patch dimensions: 1 × 1 cm; number of MNs: 4; shape: cone	HACC, GSNO	Oral mucosal tissue	The HACC in the MNs inhibits bacterial growth and controls bleeding; the thermoresponsive material PNIPAM releases GSNO, which clears ROS, releases NO, dilates blood vessels, reduces pro-inflammatory cytokines, and enhances macrophage phagocytosis. Collaborative treatment for bacterial oral inflammation-induced ulcers	Solves hydrogel solubility and adhesion issues in moist environments. Simultaneously inhibits bacterial growth, reduces infection risk, dilates blood vessels, alleviates inflammation, and accelerates mucosal recovery	215
	DLP	Hydrogel MN	Height: 1,143.97 ± 37.74 μm; tip diameter: 24.25 ± 2.87 μm; base diameter: 709.21 ± 53.5 μm; aspect ratio: 1.61:1 (calculated); number of MNs: 5 × 5 = 25; shape: cone; fracture force: 0.43 N/needle	Asiaticoside	Periodontal tissue	Asiaticoside-loaded MNs penetrate the mucosa for sustained drug release, increasing gum thickness and collagen type 1 expression, promoting periodontal soft tissue regeneration	Minimal trauma, nearly painless, offering a more patient-friendly method for periodontal tissue repair	219

Abbreviations: DAMPs: Damage-associated molecular patterns; DIW: Direct ink writing; DLP: Digital light processing; DOX: Doxorubicin; DTX: Docetaxel; ES: Electrical stimulation; GSNO: S-nitrosoglutathione; HACC: Hydroxypropyltrimethyl ammonium chloride chitosan; MN: Microneedle; NO: Nitric oxide; PCL: Polycaprolactone; PNIPAM: Poly(N-isopropylacrylamide); PμSL: Projection micro-stereolithography; ROS: Reactive oxygen species; SD-208: Transforming growth factor-β receptor 1 inhibitor SD-208; SOPL: Soft sacrificial-layer-based omnidirectional photolithography; TGF-β: Transforming growth factor-beta; αPD-L1: Anti-programmed death-ligand 1 antibody.

MN array with downwardly curved barbed structures (Figure 13A). They ingeniously leveraged the crosslinking-density gradient formed during photopolymerization: under light exposure, the crosslinking degree was higher in the upper layers, while the lower layers retained some unreacted monomers. When the printed MNs were treated with ethanol to remove residual monomers in the low crosslinking areas, uneven shrinkage during the drying process caused the lateral barbs to bend downward automatically, forming a hook-like structure similar to a bee sting, which significantly enhanced the mechanical interlocking between the MNs and tissue (Figure 13B). Compared with traditional MNs, this structure improved pull-out force by approximately 18 times, demonstrating stronger mechanical stability and drug-loading capacity and enabling stable, efficient transdermal drug delivery. In contrast, Che *et al.*²²³ proposed a different 4D printing strategy from the material perspective (Figure 13C). They used hydroxybutyl methacrylated chitosan, which exhibits both temperature- and light-responsive properties, as the printing ink and fabricated hydrogel MNs using DLP. At high temperatures, the hydrophobic segments of the material induced additional crosslinking and shrinkage, resulting in the MNs exhibiting a “self-sharpening” effect and enhanced mechanical properties (with a fracture force exceeding 50 mN and a minimum force of about 21 mN required to penetrate the skin’s stratum corneum); at low temperatures, the material absorbs water and swells, forming a loose structure. This temperature-driven response mechanism allows dynamic regulation of the MN structure and properties in a physiological environment. During the drug release process, the MNs rapidly shrink under the influence of body temperature, leading to an initial burst release of the drug, followed by slow drug release facilitated by the dense structure of the MNs. Experimental validation in a chicken breast muscle model showed that this system exhibited good penetration and controlled drug release properties, providing a new solution for non-transdermal drug delivery.

6.2. Artificial intelligence

Artificial intelligence (AI) is a broad, interdisciplinary field that includes machine learning and deep learning. Through these technologies, computer systems can simulate human intelligence and perform specific tasks autonomously with minimal human intervention.²²⁴ Machine learning, a subset of AI, refers to computers’ ability to analyze and identify patterns in large datasets, classify or cluster data, and make predictions on new data. It is particularly useful in scenarios involving large or complex data that are difficult for humans to analyze manually.²²⁵ Deep learning is a subset of machine learning that uses artificial

neural networks. It simulates the information-processing methods of the human brain through multi-layer neural networks, allowing automatic learning of complex features and patterns from data, thus enabling data analysis, prediction, or decision-making.²²⁶ In simple terms, any machine learning method that uses neural networks for modeling falls under deep learning, while methods that do not use neural networks belong to traditional machine learning. Deep learning algorithms include convolutional neural networks (CNN), fully convolutional networks, recurrent neural networks, and generative adversarial networks, with CNN being the most commonly used deep learning algorithm.²²⁷ In recent years, AI has contributed to 3D printing in various areas, including optimizing printing inks, constructing personalized models, and supervising print quality and adjusting printing parameters during the printing process.²²⁸ For 3D-printed MNs, Bagde *et al.*²²⁹ used CNN algorithms to analyze high-resolution images of MNs during printing, optimizing their geometric structures (e.g., needle tip radius and aspect ratio). Additionally, they combined machine learning with the quality by design (QbD) approach to identify key parameters, such as photoinitiator concentration in MN materials.²²⁹ Kadian *et al.*²³⁰ applied traditional machine learning methods to 3D-printed MN biosensors, inputting experimental current signals into a univariate linear regression model, and optimizing them through the least squares cost function. This process allowed them to determine the best-fit regression line and optimal regression coefficients to rapidly measure the submicromolar concentrations of buprenorphine in ISF.²³⁰ Xie *et al.*²³¹ used CNN for colorimetric analysis in a 3D-printed MN array designed for real-time detection of sodium ions and uric acid concentrations in ISF. The CNN was designed to address the effects of varying ambient light conditions on the colorimetric results, providing rapid and accurate classification. The system can effectively classify sodium ions and uric acid concentrations under different lighting and shooting angles, thereby improving detection accuracy and reliability. For 4D-printed MNs, AI can be extended beyond print-quality assessment to predict dynamic structural behavior and optimize processing parameters. Lee *et al.*²³² employed ML to optimize fabrication conditions and developed a 4D-printed MN system that promoted wound healing in diabetic mice. The MNs could vertically penetrate the wound and then curl automatically in response to body temperature to anchor in tissue. Specifically, Lee *et al.*²³² used photocrosslinker concentration, photocuring time, and shape-recovery time as input variables, with shape-recovery angle as the output variable, and built predictive models using support vector regression, extreme gradient boosting,

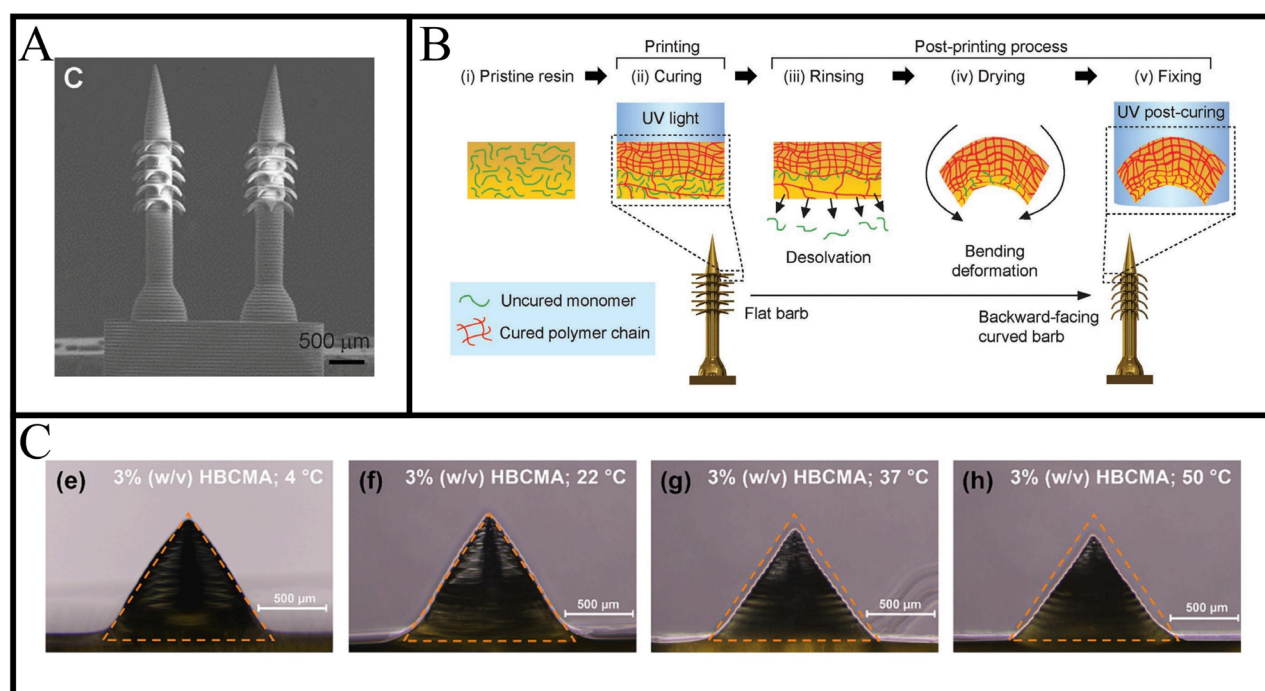


Figure 13. Four-dimensional-printed microneedles (MNs). (A) Scanning electron microscopy (SEM) images of MNs with downwardly curved barbed structures fabricated using projection micro-stereolithography technology in combination with a four-dimensional-printing strategy. Scale bar: 500 μm. Reproduced with permission from Han *et al.*²²² Copyright © 2020, John Wiley and Sons. (B) Schematic illustration of the fabrication principle of MNs with downwardly curved barbed structures. Reproduced with permission from Han *et al.*²²² Copyright © 2020, John Wiley and Sons. (C) Demonstration of the four-dimensional characteristics of MNs based on HCBMA material, showing enhanced self-sharpening behavior with increasing temperature. Scale bar: 500 μm. Reproduced with permission from Che *et al.*²²³ Copyright © 2024, Elsevier.

and Gaussian process regression. The results showed that Gaussian process regression achieved relatively high predictive accuracy and helped identify optimal fabrication conditions that balanced the thermoresponsive deformation capability and mechanical stability of the MNs. This study shows that AI in 4D-printed MNs is not limited to improving the dimensional accuracy of printed structures; more importantly, it can transform trial-and-error process screening into data-driven prediction of material–processing–stimulus response relationships. The ultimate functionality of 4D-printed structures depends on their spatiotemporal deformation under external stimuli. Therefore, even when the initial printed geometry conforms to the intended design, subtle variations in material composition or processing conditions may still affect the deformation rate and final configuration. Compared with 3D printing, 4D printing imposes more stringent requirements for manufacturing consistency and predictable dynamic responses. By learning the nonlinear coupling among material composition, printing parameters, and stimulus conditions, AI may predict the deformation trajectories and final functional states of 4D-printed MNs, improving reproducibility and reliability.

We believe AI is a key component for enabling personalized closed-loop therapy using 3D-printed MNs because it can simulate human reasoning, monitor and analyze changes in *in vivo* drug concentrations or physiological indicators in real time, and autonomously decide whether to release drugs when abnormalities are detected. However, once 3D-printed MN biosensors are integrated with mobile terminals, Bluetooth transmission, cloud platforms, and AI algorithms, the associated ethical and safety issues should not be regarded merely as general privacy concerns. Instead, they should cover the entire process of data acquisition, transmission, storage, modeling, and autonomous intervention. Firstly, wearable MN biosensors can continuously collect the concentrations of multiple biomarkers in ISF, and these dynamic physiological data are highly sensitive.²³³ If such data are transmitted to smartphones or cloud platforms via Bluetooth, Wi-Fi, or mobile networks, they may face risks such as unauthorized access, data interception, data tampering, device hijacking, communication interruption, and secondary use by third-party platforms. In fully automated drug delivery or real-time warning systems, data integrity, accuracy, and communication stability

directly affect AI models' judgment. Once sensing data or transmission links are disrupted, inappropriate drug administration may occur. Therefore, future 3D-printed MN biosensing systems should incorporate data security into the full life-cycle management of medical devices. Designers should consider data minimization, end-to-end encryption, identity authentication, access control, de-identification, abnormal communication monitoring, and fail-safe mechanisms. In addition, during scientific research and clinical translation, data flow, storage location, access permissions, and response plans for security incidents should be clearly defined. Secondly, AI-driven closed-loop decision-making also involves issues of patient-informed consent. Patient consent should not be limited to whether data are allowed to be used for algorithmic analysis or model training; it should also include what type of algorithm will process the data, whether algorithmic outputs will influence therapeutic decisions, whether human review is available, and whether patients can suspend or withdraw from automated decision-making. Complex deep learning models usually operate as a "black box," with limited transparency and interpretability, making their decision-making processes difficult to understand.²³⁴ This also complicates the determination of responsibility in the event of medical accidents.²³⁵ To reduce the uncertainty caused by "black box" models, future studies should improve model transparency and interpretability as much as possible, and ensure the reliability and fairness of AI systems across different populations and clinical scenarios through bias assessment and decision-logging records. For high-risk scenarios involving clinically meaningful interventions, AI is more suitable as an auxiliary decision-making tool rather than a complete replacement for shared decision-making between physicians and patients. Meanwhile, a "human-in-the-loop" supervision mechanism should be established, with clearly defined responsibility boundaries among patients, physicians, researchers, device manufacturers, and algorithm developers. Only when sensing accuracy, data security, patient authorization, algorithmic transparency, and clear accountability are improved simultaneously can 3D-printed MN-AI closed-loop systems progress from proof of concept to trustworthy clinical applications.

7. Discussion

In this review, we summarized the major types of MNs and their geometric characteristics, discussed the principal 3D printing technologies used for MN fabrication, and reviewed the major biomedical functions and applications of 3D-printed MNs. We also examined recent advances in integrating 4D printing and AI with 3D-printed MN technologies and provided perspectives on their future

development. During the preparation of this review, we identified several research directions that warrant further investigation. Although a clinical study involving 3D-printed MNs for ISF extraction has recently been registered (NCT0698075), it primarily evaluates the puncture performance and stability of 3D-printed MNs using human skin simulants, together with their fluidic performance in artificial ISF. Therefore, this study cannot yet be considered evidence of the clinical use of 3D-printed MNs in humans. More importantly, to date, the published literature contains no reported FDA Investigational New Drug applications or Investigational Device Exemption submissions for 3D-printed microneedle products. These observations suggest that the clinical translation of 3D-printed microneedles remains at an early stage and continues to face substantial challenges. The following section discusses these issues and outlines key priorities for future research.

7.1. Future research directions

Regarding cancer therapy, although this review discusses the potential of 3D-printed MNs, current studies mainly focus on melanoma. Future studies could expand the application of 3D-printed MNs to treat other tumor types. The high recurrence rate of tumors is one of the major threats to human health, especially for those with high postoperative recurrence rates, such as gliomas, ovarian cancer, and small-cell lung cancer.²³⁶⁻²³⁸ Dissolvable MNs, which have excellent biocompatibility, can be loaded with anti-tumor drugs and implanted into the post-surgical tumor cavity, providing a promising method to prevent local recurrence.²³⁹ However, there is currently limited research on the application of 3D-printed MNs for tumor cavity treatment. Thanks to the high flexibility of 3D printing in manufacturing complex geometric structures, researchers can design personalized MN structures based on the recurrence characteristics of different tumor types, achieving precise drug release during peak recurrence periods and reducing local recurrence rates. When selecting anti-cancer drugs for loading, researchers may not be limited to drugs recommended by traditional treatment guidelines and can explore nanoparticle-based drugs. Nanoparticles offer several advantages:

- (i) The small size of nanoparticles and their higher lipophilicity (for some types) can help certain macromolecules or poorly lipophilic drugs effectively cross biological barriers, such as the BBB.²⁴⁰
- (ii) The combination of nanoparticles with specific metal ions can synergistically enhance anti-cancer effects, providing efficacy beyond that of the individual agents alone. This synergistic effect has been applied in various treatment methods, including immunotherapy,

microwave hyperthermia, photothermal therapy, photodynamic therapy, and chemodynamic therapy.²⁴¹

For transdermal drug delivery, 3D-printed MNs offer considerable advantages, although several challenges remain. The drug release from dissolvable MNs is influenced by the dissolution rate of the material, and during the initial use, it may lead to a burst release of the drug due to rapid dissolution. To address this, researchers can design MNs with different geometric structures using 3D printing technology, optimizing the structure to reduce burst release. At the same time, improving *in vitro* drug-release models and selecting materials that better simulate human skin structure can improve the accuracy of drug-release curve predictions. Notably, future 3D-printed MNs may move beyond the limitations of conventional patch-based configurations. For example, Zhang *et al.*²⁴² developed spreadable 3D-printed microneedle particles, showing that MNs can shift from fixed patch structures to dispersed microparticulate formats, improving their adaptability to large-area skin regions. This concept suggests that future studies could further explore sprayable or spreadable 3D-printed microneedle particles to enhance the flexibility of MN applications in anatomically complex regions and personalized transdermal therapies. In addition, researchers can integrate 3D-printed hollow MNs with microfluidics technology. Microfluidics confines fluids within micron-sized channels, controlling very small fluid volumes (down to nanoliter levels).²⁴³ This makes 3D printing especially suitable for creating such high-precision microfluidic devices. Coates *et al.*²⁴⁴ used 3D printing to fabricate a single structure combining microfluidic networks and MN arrays, achieving the precision needed to deliver drug volumes at the microscale. With different microfluidic network structures, this device can deliver single-component liquid drugs, independently deliver two-component liquid drugs, mix and deliver two-component liquid drugs, and immediately reconstitute solid drugs for delivery. Microfluidics technology can be applied not only to drug delivery using 3D-printed MNs but also to extracting biological markers. In the future, researchers may focus more on deeply integrating microfluidic technology with 3D-printed MNs, fully leveraging microfluidics' precise fluid control to support their development.

Research on the functional integration of 3D-printed MN arrays remains relatively scarce. Future studies should focus more on combining AI with 3D-printed MN technology, fully leveraging AI's autonomous decision-making capabilities in the "biomarker extraction–biosensor–drug delivery" process to achieve a truly personalized "diagnosis–treatment" closed-loop system. This will greatly improve convenience for patients. In

addition, AI could help address the time-lag issue that may occur when 3D-printed MN biosensors monitor biomarkers through ISF. Research teams could collect large amounts of ISF monitoring data alongside synchronized blood test results and use machine learning models to analyze their dynamic relationship, thereby predicting and compensating for detection deviations caused by the time lag. When applying AI, researchers must take special care to avoid the ethical and safety issues discussed above to ensure it delivers maximum value.

7.2. Clinical translation challenges

Although 3D printing provides an important tool for the personalized design and high-precision fabrication of MNs, manufacturing reproducibility and quality control remain key barriers to further translational application.^{245,246} Traditional quality control largely relies on end-product testing, making it difficult to promptly identify and control quality fluctuations caused by the coupling of multiple factors during manufacturing. In contrast, the QbD concept emphasizes defining quality targets early in product development, systematically identifying critical variables that affect product quality, and reducing sources of variability through process control, thereby improving the predictability, reproducibility, and regulatory acceptability of product quality.²⁴⁷ Therefore, introducing the QbD concept and defining quality-control indicators during the development of 3D-printed MNs can help improve the controllability and consistency of the manufacturing process. For 3D-printed MNs, geometric dimensions, mechanical strength, insertion efficiency, skin adhesion, drug-loading uniformity, drug content and drug-release profiles, and swelling capacity should all be regarded as important quality-control indicators. First, the length, width, spacing, tip sharpness, and overall geometry of MNs directly affect their ability to penetrate the stratum corneum. Therefore, the appearance, dimensional accuracy, and tip integrity of MN arrays can be characterized using optical microscopy or scanning electron microscopy. Second, mechanical performance testing is essential to ensure that MNs do not bend or fracture during insertion, removal, or use, and can be evaluated by axial fracture force testing, transverse fracture force testing, and insertion force testing. In addition, dyes such as trypan blue can be incorporated into MN materials to visually indicate the microchannels formed during skin insertion experiments. After MNs penetrate the skin, the patch must maintain adhesion throughout the entire use period. Previous studies have evaluated adhesive strength by measuring the force required to peel the MN patch from the skin.²⁴⁸ For 3D-printed MNs used for drug delivery, drug-loading uniformity can be assessed by fluorescently

labeling the drug and observing its distribution within the MNs using fluorescence optical microscopy.¹²⁹ Moreover, 3D-printed MN patches can be placed in a 37 °C water bath to simulate drug release under *in vivo* conditions, allowing determination of the drug-release profile and drug content.¹⁶⁶ Similar methods can also be used to test the water-absorption and swelling capacity of hydrogel MNs, which is particularly important for hydrogel MNs designed for ISF extraction. During the fabrication of MNs by 3D printing, special attention should be paid to the actual reproducible precision of the printing technology used. Maximum resolution does not necessarily reflect stable manufacturing capability. For example, as mentioned above, CLIP technology can achieve a maximum resolution of 1.5 µm, but its reproducibly achievable structural precision is typically reflected by the ability to print 6 µm fine lines and 18 µm holes.¹³⁶ Researchers should not design MN structures based solely on the theoretical maximum resolution; otherwise, it may be difficult to ensure structural consistency across different batches.

Beyond geometric accuracy and batch-to-batch consistency, biosafety risks associated with materials and 3D printing processes are also critical determinants of successful clinical translation. It should be emphasized that good biocompatibility of the raw printing materials does not necessarily guarantee the same level of safety in the final 3D-printed MNs, because additional risks may be introduced during photopolymerization, thermal processing, powder fusion, and post-processing. Biosafety risks vary considerably across 3D-printing technologies. For light-based 3D-printing technologies, including SLA, DLP, CLIP, and TPP, the major shared risks arise from the potential cytotoxicity of residual photoinitiators, unreacted monomers, and photolysis by-products. Corresponding risk-control strategies include prioritizing photoinitiators with good water solubility, high initiation efficiency, and favorable cytocompatibility; determining the minimum effective photoinitiator concentration and minimum effective exposure dose; exploring novel low-toxicity or radical-free photoinitiation systems; and performing adequate post-washing and post-curing. Post-washing refers to the removal of unreacted monomers using solvents, with isopropyl alcohol being the most commonly used washing solvent. However, post-washing may also wash out drugs loaded within the MNs, thereby reducing drug loading and compromising therapeutic efficiency.²⁴⁹ Post-curing involves a secondary curing step after washing to promote further reaction of residual monomers; however, excessive post-curing may increase the crosslinking density of the material and consequently suppress drug release.²⁵⁰ The biosafety risks of FDM and MJ mainly involve drug degradation from high temperatures or ultraviolet curing

during printing, as well as the potential cytotoxicity of the resulting degradation products. Therefore, printing temperatures or curing conditions should be strictly controlled. For FDM, if chemical etching is required after printing, the etched 3D-printed MNs should be thoroughly rinsed to avoid local tissue irritation caused by residual etching solution. For MJ, attention should additionally be paid to issues related to photosensitive materials similar to those associated with SLA, DLP, CLIP, and TPP. The major shared biosafety risks of SLS and SLM arise from residual unsintered or unmelted powders. Residual particles may induce local foreign-body reactions and immune-inflammatory responses.²⁵¹ Common post-processing strategies include compressed-gas blowing, ultrasonic cleaning, and high-pressure rinsing. For metallic MNs fabricated by SLM, chemical acid pickling may also remove residual surface particles and oxides. However, after acid pickling, thorough washing with buffer solution or deionized water is essential to prevent residual acidic solution from causing local tissue irritation or even acid burns.

Sterilization is another critical issue for the clinical translation of MNs, because MNs penetrate the stratum corneum and reach the dermis. Currently, commonly used sterilization methods include autoclave sterilization, ethylene oxide (EtO) gas sterilization, and gamma-ray sterilization.²⁵² However, the applicability of different methods to MN materials varies substantially. Autoclave sterilization raises the environmental temperature to 121–134 °C. Under these high-temperature and high-humidity conditions, many polymeric materials are prone to softening, structural deformation, or degradation. Therefore, this method is generally more suitable for materials with relatively high thermal stability, such as stainless steel, titanium, and silicon.^{252,253} EtO gas sterilization is performed at relatively low temperatures, approximately 37–63 °C, and can be applied to polymeric MNs, such as PLGA, PLA, PVA, PVP, and PDMS; natural polymer MNs, such as chitosan, hyaluronic acid, and silk fibroin; and semi-synthetic hydrogel MNs, such as MeHA and GelMA. However, it should be noted that proteins or active functional groups may undergo alkylation reactions with EtO, thereby altering the chemical structure of the materials.^{254–256} Metallic and silicon MNs generally exhibit good stability under gamma-ray sterilization. This sterilization method can also be applied to polymeric MNs. However, gamma irradiation may cause polymer chain scission, thereby reducing polymer chain length and weakening mechanical strength. Some hydrogel materials may undergo yellowing after gamma-ray irradiation.²⁵⁷ In addition, previous studies have shown that gamma rays may affect the drug-loading performance of MNs and may

be particularly damaging to protein-based drugs.²⁵⁸ For light-based 3D-printed MNs, the tolerance of photocurable materials to different sterilization methods is also an important consideration. It should be noted that MeHA and GelMA mentioned above are also photocrosslinkable materials. In addition, the sterilization compatibility of commonly used photosensitive resins such as PEGDA and PCLMA has been investigated. For example, pure PEGDA has been reported to remain stable at temperatures below approximately 202 °C, suggesting its potential suitability for autoclave sterilization.²⁵⁹ Similarly, studies have shown that PCLMA-based systems can also be processed by autoclave sterilization.²⁶⁰ In comparison, EtO sterilization has relatively limited effects on PEGDA- and PCLMA-based systems, whereas gamma-ray sterilization may induce polymer chain scission and thereby alter material properties.²⁶¹ Overall, different sterilization methods may cause damage to MN materials (Table 6). Among them, autoclave sterilization causes relatively the greatest thermal damage, whereas EtO gas sterilization has a relatively smaller impact on MN materials and can be considered a preferred sterilization method. Implementing aseptic operation throughout the entire production process is the best strategy for preserving the material properties of MNs while ensuring the lowest risk of infection. To date, there are still few head-to-head comparative studies on the effects of different sterilization methods on MN materials, which provides a direction for future research. In addition, research teams are advised to systematically evaluate the performance of MNs before and after sterilization when developing MNs for biological applications, so as to promote the safe and effective clinical translation of MNs.

The electrochemical-based 3D-printed MN biosensors essentially rely on redox reactions occurring at the electrode surface, where the target biomarker in the ISF undergoes oxidation or reduction, releasing electrons to generate microcurrents. The variation in these microcurrents is then used to monitor the biomarker concentration. However, these MN electrodes typically experience wear during use, as redox reactions often require additional catalysts, such as oxidases, nanoenzymes, or applied voltages. Therefore, evaluating the impact of electrode wear on the accuracy of biomarker concentration monitoring is highly important, as it will help promote the translation of 3D-printed MN biosensors from short-term experimental feasibility to long-term clinical deployment. Among the factors associated with electrode wear, depletion of the sensing layer is an important issue affecting long-term stability. This issue was investigated in the study by Yin *et al.*²⁶² The study pointed out that conventional solid MN biosensors usually immobilize sensing materials, such as GOX, on the outer surface of MNs. Although this facilitates direct contact with

ISF, the sensing layer is prone to detachment due to friction with skin tissue during insertion and long-term wear, thereby weakening the long-term reliability and stability of the sensor. To mitigate this problem, the study immobilized GOX and carbon nanotubes inside the lumen of stainless-steel hollow MNs. This design not only protects the sensing layer within the lumen but also provides a larger internal space for loading more enzymes and conductive materials, thereby improving sensitivity while delaying the decay of the detection signal. The experimental results showed that this method enabled continuous and stable monitoring for 14 days, providing a potential strategy for the long-term clinical deployment of 3D-printed MN biosensors. Future studies are still needed to conduct standardized multi-day/multi-week wearing experiments and large-sample durability evaluations under real-life activity conditions, so as to further explore feasible pathways for advancing 3D-printed MN biosensors from short-term experimental validation to continuous clinical monitoring. The correlation between biomarker measurements in ISF and those in blood is also a critical issue that must be addressed for clinical translation. When developing new 3D-printed MN sensors to replace invasive blood sampling for biomarker monitoring, researchers should systematically evaluate the correlation between target-analyte concentrations in ISF and blood, their dynamic time-lag relationship, and interindividual variability. Such evaluations are essential to ensure the sensitivity, accuracy, and clinical interpretability of 3D-printed MN biosensors. Additionally, many 3D-printed MN biosensors transmit monitoring data remotely via Bluetooth to smartphones. Researchers must ensure the security and stability of this transmission process to prevent external factors from interfering with the Bluetooth data transfer, avoiding any deviations in the biological data received by smartphones.

From a regulatory perspective, 3D-printed MNs face more complex challenges in quality evaluation and clinical translation because they differ from both conventional transdermal patches and standard injection devices. In the European Union, the European Medicines Agency (EMA) classifies MNs containing cellular components as “advanced therapy medicinal products,” which are subject to strict regulation.²⁶³ In the United States, the FDA stipulates that MN products may be classified as medical devices when they are intended for use “in the diagnosis of disease or other conditions, or the cure, mitigation, treatment, or prevention of disease.”²⁶⁴ However, current EMA and FDA guidance documents on the development and quality information required for transdermal and topical delivery systems in new drug applications have not yet specifically covered MN products.²⁶⁴ Therefore, 3D-printed MNs still lack a clear, unified, and targeted regulatory framework.

In terms of MN types, the regulatory approval of non-dissolving MNs is relatively straightforward, with greater emphasis placed on mechanical safety and the safety of the MN matrix materials, so as to ensure that they do not cause harm to the human body, or that such harm is minimized, during long-term retention in or retrieval from the skin. In contrast, the regulatory approval of dissolvable MNs may be more complex, because in addition to the above-mentioned characteristics relevant to non-dissolving MNs, the safety of their biodegradation products and their drug-release behavior must also be demonstrated. However, most bioinks, such as GelMA, and photocurable resins, such as PEGDA, currently used for 3D printing have not yet been approved by the FDA or EMA. Only a few materials, such as medical-grade resins from Formlabs, have passed ISO 10993 biocompatibility testing.^{263,265} Therefore, major regulatory agencies worldwide need to collaborate to establish a globally unified classification and approval framework to address these issues. Meanwhile, relevant authorities should also establish pre-certified biomaterial libraries for materials such as photoinitiators and hydrogels, thereby reducing the cost of biomaterial testing for research teams. With respect to the application types of 3D-printed MNs, those used for biosensing require particularly careful evaluation, because they involve electronic components that may need to be embedded in the body for extended periods. Specifically, electronic components may induce immune rejection or local inflammation, affecting tissue tolerance and the safety of long-term implantation. Therefore, when developing such MNs, the material selection, encapsulation methods, insulation properties, and waterproof performance of embedded electronic components should be systematically evaluated, and their long-term stability and biocompatibility should be validated in both *in vitro* and *in vivo* models. In addition, when reviewing such composite MNs, regulatory authorities may require detailed data on immune-response assessment and long-term stability validation. Therefore, research and development teams should consider these factors in advance during the design and validation stages to ensure that the products meet the safety and reliability requirements for clinical translation. On the manufacturing side, as discussed above, research teams need to pay close attention to reproducibility and quality control during the fabrication of 3D-printed MNs, which imposes strict requirements on the printing process, photopolymerization parameters, post-processing procedures, and the stability of material batches. Therefore, future regulatory frameworks should provide unified guidance on process validation, batch traceability, and

quality consistency.

In addition, the economic feasibility of different 3D printing technologies is an important factor determining their potential for clinical translation, and their economic advantages are not necessarily the same at the laboratory prototyping and large-scale manufacturing stages. FDM offers the advantages of low equipment cost and simple operation, making it suitable for early-stage proof-of-concept studies and low-cost laboratory prototyping.²⁶⁶ However, its relatively low printing resolution necessitates additional surface-sharpening treatments to obtain sufficiently sharp MNs, thereby diminishing its cost advantage for the large-scale manufacture of high-precision MNs.⁹⁴ In contrast, TPP enables nanoscale control and is particularly suitable for laboratory studies requiring extremely high geometric complexity and precision. Nevertheless, its expensive equipment, limited build volume, and relatively slow printing speed currently make it more suitable as a laboratory prototyping tool.¹⁴¹ CLIP combines relatively high resolution with high-speed continuous fabrication and therefore shows greater potential for scale-up in terms of production throughput, although its high equipment cost still limits widespread commercial application.¹¹² Overall, current 3D-printing technologies remain more suitable for laboratory prototyping or personalized, small-batch manufacturing. For commercial markets that require both customization and relatively high production efficiency, CLIP has greater development potential. By contrast, for standardized, large-scale MN production, using 3D printing to fabricate high-precision master molds followed by replication using conventional molding represents one of the more economically viable manufacturing routes. Therefore, the economic feasibility of different technologies should not be evaluated solely on equipment cost or printing resolution. Instead, equipment investment, production throughput, and unit product cost should be considered comprehensively, and appropriate manufacturing strategies should be selected according to the differing requirements of personalized small-batch production and standardized large-scale manufacturing.

At the end of this review, we summarize the original studies on 3D-printed MNs discussed in Sections 4 and 5 to present the current stages of experimental validation, the disinfection or sterilization strategies employed, and the major challenges identified by the authors (Table 7). This summary aims to help readers better understand the current level of clinical translation of 3D-printed microneedles.

Table 6. Compatibility of common three-dimensional-printed microneedle materials with different sterilization methods

Material category for 3D-printed MNs	Autoclave sterilization	EtO sterilization	Gamma-ray sterilization
Metals: stainless steel, titanium	Suitable	Suitable	Suitable
Silicon	Suitable	Suitable	Suitable
Polymers: PLA, PLGA, PDMS, PVA, PVP	Not suitable	Suitable	Potential risk. May cause polymer chain scission.
Natural polymers: chitosan, hyaluronic acid, silk fibroin	Not suitable	Potential risk. Active functional groups may undergo alkylation	Not suitable
Photocrosslinkable hydrogels: MeHA, GelMA	Not suitable	Suitable	Potential risk. May cause polymer chain scission and yellowing
Photosensitive resins: PEGDA, PCLMA	Suitable	Suitable	Potential risk. May cause polymer chain scission
Drugs and bioactive substances	Not suitable	Potential risk. Active functional groups may undergo alkylation	Not suitable

Abbreviations: EtO: Ethylene oxide; GelMA: Gelatin methacryloyl; MeHA: Methacrylated hyaluronic acid; PCLMA: Polycaprolactone methacrylate; PDMS: Polydimethylsiloxane; PEGDA: Polyethylene glycol diacrylate; PLA: Polylactic acid; PLGA: Poly(lactic-co-glycolic acid); PVA: Polyvinyl alcohol; PVP: Polyvinylpyrrolidone.

Table 7. Summary of original studies on three-dimensional-printed microneedles and their current stages toward clinical translation

No.	<i>In vitro</i> studies	<i>Ex vivo</i> studies	Animal studies	Human studies	Disinfection/ Sterilization strategy	Main remaining barriers	Ref
1	Yes	Yes	Yes	Not reported	EtO	Printing resolution still needs to be improved; drug delivery efficiency needs to be increased; post-processing may cause drug loss	166
2	Yes	Yes	Yes	Not reported	Autoclave	The long-term pharmacokinetic mechanisms of MN-mediated drug delivery require further investigation; the bio-based carbon content of current bioresins can be further increased	167
3	Yes	Yes	Yes	Not reported	UV	Delivery efficiency under short application times needs to be improved; the relationships among structure, loading, and release still require validation; actual therapeutic efficacy in humans needs to be validated	168
4	Yes	Yes	Yes	Not reported	Not reported	Not explicitly stated by the authors	169
5	Yes	Yes	Yes	Not reported	Not reported	Limited coverage area; waterproof and electrically insulating encapsulation is still required for oral applications	170
6	Yes	Not reported	Yes	Not reported	Not reported	Batch-to-batch consistency; balance between porosity and mechanical strength; MNs are difficult to remove after fracture within tissues; rapid and visual staging of infection remains to be achieved	89
7	Yes	Yes	Not reported	Yes	Not reported	Limited printer precision may cause minor geometric errors; hydrogel dehydration may cause slight dimensional deviations	171

(Cont'd...)

Table 7. (Continued)

No.	<i>In vitro</i> studies	<i>Ex vivo</i> studies	Animal studies	Human studies	Disinfection/ Sterilization strategy	Main remaining barriers	Ref
8	Yes	Not reported	Yes	Not reported	Not reported	Not explicitly stated by the authors	172
9	Yes	Yes	Not reported	Not reported	Not reported	Differences in scar mechanics among patients require individualized selection of material composition; MN structural parameters still require optimization	173
10	Yes	Not reported	Yes	Not reported	UV	Not explicitly stated by the authors	174
11	Yes	Yes	Not reported	Yes	Not reported	ISF sampling volumes vary both within and between individuals; more studies involving more demographically diverse populations are needed; MN parameters and sampling procedures require further optimization to reduce sampling variability; adverse skin reactions limit the duration of vacuum-assisted extraction.	181
12	Yes	Yes	Yes	Not reported	75% ethanol	Not explicitly stated by the authors	182
13	Yes	Yes	Yes	Not reported	Not reported	Resistance to contamination from sweat is required; ISF diffusion rates <i>in vivo</i> limit sampling efficiency; further structural optimization is required to enable continuous monitoring of multiple biomarkers; some biomarkers exhibit a blood-to-ISF transport delay	183
14	Yes	Yes	Not reported	Not reported	Not reported	Material preparation is time-consuming; cost, production consistency, and biosafety still require evaluation; the actual puncture morphology cannot currently be determined	184
15	Yes	Not reported	Not reported	Not reported	75% ethanol	Not explicitly stated by the authors	185
16	Yes	Yes	Not reported	Yes	Not reported	Puncture tests using <i>ex vivo</i> porcine skin cannot fully represent living skin; the specific reason for the increased fungal detection rate remains unclear; deep-tissue sampling requires further validation; the quantity of microorganisms obtained by sampling is limited	186
17	Yes	Yes	Yes	Yes	Not reported	The time lag between biomarkers in ISF and blood needs to be reduced; the range of detectable biomarkers should be further expanded	187
18	Yes	Yes	Not reported	Not reported	Not reported	Simultaneous detection of multiple biomarkers; greater integration is required to form a complete wearable patch	190
19	Yes	Yes	Yes	Not reported	Not reported	ISF glucose shows an approximately 20 min delay relative to blood glucose; interindividual differences in metformin absorption occur at the same dose	193
20	Yes	Yes	Not reported	Not reported	Not reported	Long-term use remains challenging; sensor sensitivity and durability need improvement; higher integration is required; the range of detectable biomarkers should be expanded; comprehensive <i>ex vivo</i> and <i>in vivo</i> validation is still required	194
21	Yes	Yes	Not reported	Not reported	Not reported	Insufficient post-curing may result in cytotoxicity; long-term stability has not been adequately validated; the long-term performance of PEDOT:PSS is affected by environmental conditions	195

(Cont'd...)

Table 7. (Continued)

No.	<i>In vitro</i> studies	<i>Ex vivo</i> studies	Animal studies	Human studies	Disinfection/ Sterilization strategy	Main remaining barriers	Ref
22	Yes	Not reported	Not reported	Yes	Not reported	The experimental sample size is small; ethical constraints prevented validation under exercise conditions; interpretation of complex motion signals requires further investigation; a single sensing unit has limited information capacity, requiring integration of multiple sensors	196
23	Yes	Yes	Yes	Not reported	Not reported	Not explicitly stated by the authors	201
24	Yes	Yes	Yes	Not reported	Not reported	The surface gold coating may crack after more than five repeated uses; the electrical stimulation voltage has an upper safety limit	203
25	Yes	Yes	Yes	Not reported	Not reported	Not explicitly stated by the authors	204
26	Yes	Yes	Yes	Not reported	Not reported	Not explicitly stated by the authors	205
27	Yes	Yes	Yes	Not reported	75% ethanol + UV	The underlying mechanism by which electrical stimulation alleviates muscle atrophy remains unclear; the mechanism by which microchannels promote nerve regeneration remains unclear	207
28	Yes	Yes	Yes	Not reported	75% ethanol	The detailed mechanism underlying hair regeneration requires further elucidation; it is ineffective for cicatricial alopecia	208
29	Yes	Yes	Yes	Yes	NA	Long-term efficacy and safety require further validation; clinical trials are needed	211
30	Yes	Not reported	Not reported	Yes	NA	Detailed antibacterial activity requires further evaluation; larger-scale and longer-term clinical studies are needed; the synergistic effects of the active components still require dose-response studies	213
31	Yes	Yes	Yes	Not reported	NA	The conditions for using frozen MNs are restricted, and transportation is difficult; the operational window is only approximately 20 s, requiring rapid handling and strict storage conditions; the mechanism by which nitric oxide (NO)-mediated vasodilation promotes healing requires further investigation	215
33	Yes	Not reported	Yes	Not reported	75% ethanol	The effect of drug concentration on COL-I expression requires further clarification; validation with a larger animal sample size is required	219

Notes: *In vitro* studies refer to experiments involving materials, mechanical testing, cells, or artificial membranes. *Ex vivo* studies refer to experiments performed on excised tissues obtained from animals or humans. Animal studies refer to experiments conducted in living animals, such as mice and rabbits. Human studies refer to studies involving human participants.

Abbreviations: EtO: Ethylene oxide; ISF: Interstitial fluid; MN: Microneedle; NO: Nitric oxide; PEDOT:PSS: Poly(3,4-ethylenedioxythiophene); polystyrene sulfonate; UV: Ultraviolet.

8. Conclusion

Overall, 3D printing technology has created unprecedented opportunities for the fabrication and application of MNs. It not only enables the customization of MNs but also shows great potential in areas such as drug delivery, biomarker extraction, and biosensing. With continued technological advances, the application prospects of 3D-printed MNs across a wide range of medical fields are becoming increasingly broad. In particular, their use in personalized medicine, noninvasive diagnosis, and treatment is expected to substantially improve patients' quality of life.

List of abbreviations

Abbreviations	Full form
AI	Artificial intelligence
AOX	Alcohol oxidase
BIS	Bacterial infectious stomatitis
CE	Counter electrode
CLIP	Continuous liquid interface production
DAMPs	Damage-associated molecular patterns
DIW	Direct ink writing
DLP	Digital light processing
DMAEMA	2-(dimethylamino)ethyl methacrylate
DXM	Dexamethasone
EMA	European Medicines Agency
EtO	Ethylene oxide
FDM	Fused deposition modeling
FMIE	Flexible MN-array-integrated interdigital electrode
GelMA	Gelatin methacryloyl
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GOX	Glucose oxidase
GSNO	S-nitrosoglutathione
HepMi	Minocycline-heparin hydrogel
HMCs	Hierarchical microchannels
ISF	Interstitial fluid
LOX	Lactate oxidase
MCBM	Mn-based continuous biomarker/drug monitoring
MJ	Material jetting
NIPAM	N-isopropylacrylamide
OVA	Ovalbumin
PCLMA	Polycaprolactone methacrylate
PDMS	Polydimethylsiloxane

PLA	Poly(lactic acid)
PLGA	Poly(lactic-co-glycolic acid)
PNIPAM	Poly(N-isopropylacrylamide)
PTH	Parathyroid hormone
PVA	Polyvinyl alcohol
PVP	Polyvinylpyrrolidone
P μ SL	Projection micro-stereolithography
rGO	Reduced graphene oxide
ROS	Reactive oxygen Species
SLA	Stereolithography appearance
SLM	Selective laser melting
SLS	Selective laser sintering
SOPL	Static optical projection lithography
TCVs	Tumor cell vaccines
UV	Ultraviolet
WE	Working electrode

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have

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Further disclosure

During the preparation of this manuscript, the authors used ChatGPT to assist with language translation. After using this tool, the authors carefully reviewed and edited the content as needed and take full responsibility for the content of the published article.

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