Microneedles in biomedicine: Innovations, challenges, and future prospects

Xinrui Li, Chi Zhang, Yuxin Zhang, Zhijing Liu, Jiaxin Li, Ying Meng, and Peng Zhang*

ABSTRACT

The effective delivery of therapeutic drugs is fundamental to modern medical practice. However, conventional administration methods, primarily oral and parenteral injection, exhibit numerous limitations, including the suboptimal bioavailability of macromolecules and challenges related to patient compliance. The advent of microneedle (MN) technology is reshaping strategies in the biomedical field, effectively overcoming the constraints of traditional drug delivery and diagnostic approaches. Research indicates that MNs can penetrate the stratum corneum to form transient microchannels, facilitating the transdermal delivery of therapeutic agents while bypassing gastrointestinal and hepatic barriers. This customizable and personalized drug delivery system holds significant potential for clinical application. Beyond drug delivery, MNs also have the capacity to transform healthcare models through real-time biomarker monitoring enabled by contact with interstitial fluid. This technology demonstrates considerable promise in managing chronic conditions such as diabetes, while also opening avenues for applications in vaccination, tissue regeneration, and cancer therapy. Recent innovations include the development of stimulus-responsive MNs for precision medicine and their integration with wearable devices to achieve closed-loop therapeutic diagnostics. Despite the substantial promise of this field, challenges remain regarding clinical translation, particularly in relation to biocompatibility, mechanical strength, and drug stability. This review outlines MN classifications, design principles, and applications, emphasizing their expanding role not only in healthcare but also in precision medicine, global health, and food safety. By overcoming current barriers and integrating emerging technologies, MNs have the potential to transform diagnostic and therapeutic paradigms, delivering scalable, patient-centered solutions to a broad range of biomedical challenges.

Keywords:
Transdermal delivery system; Microneedle; Personalized medicines; Polymeric microneedles; Biomedical application

***Corresponding author:**
Peng Zhang,
peng.zhang@ytu.edu.cn

How to cite this article:
Li X, Zhang C, Zhang Y, *et al.* Microneedles in biomedicine: Innovations, challenges, and future prospects. *Biomater Transl.* 2025, 6(4), 373-388.

doi: 10.12336/bmt.25.00122

1. Introduction

The effective delivery of therapeutics to their target sites at controlled rates and concentrations is a cornerstone of modern pharmacology, profoundly influencing therapeutic efficacy, patient safety, and clinical outcomes. The choice of administration route governs a drug's pharmacokinetic and pharmacodynamic profiles, shaping its practical utility and patient acceptance.[1] For decades, pharmaceutical practice has relied on two dominant strategies: Oral administration and parenteral injection. Oral delivery, due to its convenience, cost-effectiveness, and high patient compliance, remains the preferred route for systemic delivery of small-molecule drugs. However, its efficacy is severely limited for various classes of biologic drugs, including peptides, proteins, and nucleic acids.[2] The gastrointestinal tract's environment, characterized by pH variations and enzymatic degradation by proteases and nucleases, coupled with extensive hepatic first-pass metabolism, often reduces the bioavailability of these macromolecules to below 10%. Parenteral routes—intravenous, intramuscular, and subcutaneous injections—bypass these barriers, achieving near-complete bioavailability and rapid onset of action. Nevertheless, their invasive nature presents several limitations, such as causing physical discomfort for patients, increasing the risk of

infectious complications, and producing sharp biomedical waste that requires hazardous material handling. Moreover, injectable administration typically requires professional healthcare providers, making frequent injections impractical for chronic conditions such as diabetes, rheumatoid arthritis, or multiple sclerosis.[3,4]

Transdermal drug delivery systems emerged in the 1980s as a non-invasive alternative, aiming to combine the simplicity of oral administration with the systemic access provided by parenteral routes.[5,6] Transdermal patches, exemplified by formulations for nicotine, scopolamine, and fentanyl, offer sustained drug release, bypass gastrointestinal and hepatic barriers, and enhance patient compliance through ease of use. However, their utility is constrained by the stratum corneum (SC), a 10–20 μm thick lipid-rich barrier with a "brick-and-mortar" architecture comprising corneocytes surrounded by an extracellular lipid matrix comprising ceramides, cholesterol, and free fatty acids.[7,8] This structure limits passive diffusion to lipophilic, low-molecular-weight compounds, effectively excluding most biologics and hydrophilic drugs. Efforts to enhance transdermal transport using chemical penetration enhancers, iontophoresis, or sonophoresis have achieved limited success, often requiring complex devices and posing risks of skin damage or allergic reactions.[9-12]

Microneedle (MN) technology, first conceptualized in the 1970s and practically realized in the 1990s through advances in microfabrication, offers a potential solution to overcome the SC barrier.[13] MN arrays consist of micron-sized projections ranging from 25 to 2000 μm in height, engineered to breach the SC and create temporary aqueous pathways into the viable epidermis or upper dermis.[14] These microchannels, approximately 50–100 μm in diameter, facilitate efficient drug diffusion while bypassing the SC's lipid matrix. Crucially, MN lengths are optimized to avoid dermal nerve endings and blood vessels, minimizing pain, bleeding, and infection risk compared to hypodermic needles. Studies have demonstrated that MNs can enhance transdermal flux by up to 100-fold for small molecules and enable the delivery of macromolecules such as insulin and monoclonal antibodies, which cannot penetrate intact skin.[15]

Advances in materials science and microfabrication techniques, including photolithography, laser ablation, and 3D printing, have increased the versatility of MN systems. MNs are fabricated from a wide range of materials, including metals (e.g., stainless steel, titanium), polymers (e.g., hyaluronic acid, polyvinylpyrrolidone), and ceramics (e.g., calcium phosphate), each tailored to specific therapeutic needs.[16-20] Common types of MNs include solid MNs (SMNs), coated MNs (CMNs), dissolving MNs (DMNs), hydrogel-forming MNs (HFMNs), and hollow MNs (HMNs).[21] These designs have expanded MN applications beyond traditional transdermal delivery to include targeted administration to the gastrointestinal tract, oral mucosa, myocardium, and ocular tissues, broadening their therapeutic scope. In addition to drug delivery, MNs have become valuable tools for diagnostics and biosensing. They enable the minimally invasive extraction of dermal interstitial fluid (ISF) through microchannels, allowing for real-time monitoring of biomarkers like glucose or inflammatory cytokines. MN-based glucose sensors integrated with wearable devices have demonstrated sensitivity comparable to subcutaneous sensors, offering a transformative approach to diabetes management.[22,23] MNs have also been explored in tissue engineering for delivering live cells in regenerative therapies and in non-medical fields such as food safety testing for pathogen detection.

The evolution of MN technology reflects a convergence of pharmaceutics, materials science, and biomedical engineering, positioning MNs as a novel modality for clinical application. This review presents a comprehensive overview of MN-based systems for drug administration and biological sensing, with a focus on their structural categories, fabrication methodologies, and advancements in material composition. We explore their therapeutic applications, including chronic disease management, vaccination, and emerging areas like gene therapy, alongside their diagnostic potential. By synthesizing recent advancements and identifying future directions, this review aims to examine the paradigm-shifting capabilities of MNs in biomedicine applications.

2. Classification of MNs

The functional versatility of MN technology stems from its diverse architectural designs. Based on their structural and functional properties, MNs are mainly classified into five categories: SMNs, HMNs, CMNs, DMNs, and HFMNs (shown in **Figure 1**). Each type is engineered to address specific clinical needs by balancing mechanical performance, drug-loading capacity, and delivery kinetics. The primary materials and diverse applications characterizing the five MN types are outlined in **Table 1**.

2.1. Solid MNs

Solid MNs, the foundational technology of MN systems, are fabricated from robust materials such as stainless steel, titanium, silicon, ceramics, or insoluble polymers (e.g., polycarbonate) using microfabrication techniques like photolithography, chemical etching, deep reactive ion etching, laser ablation, or thermoembossing.[24-27] The operational principle of SMNs is a two-step "poke-and-patch" strategy: the procedure involves piercing the SC to form temporary micropores, after which a drug-loaded patch is applied to facilitate passive permeation.[28,29] The mechanical strength of SMNs (Young's modulus of 50–150 GPa for silicon-based designs) ensures reliable skin penetration, while their relatively simple fabrication supports cost-effective, large-scale production. These advantages make SMNs particularly valuable in medical aesthetics, where they enhance the delivery of anti-aging agents and promote skin rejuvenation.[30]

Key Laboratory of Molecular Pharmacology and Drug Evaluation of the Ministry of Education, Collaborative Innovation Center of Advanced Drug Delivery System and Biotech Drugs in Universities of Shandong, School of Pharmacy, Yantai University, Yantai, Shandong, China

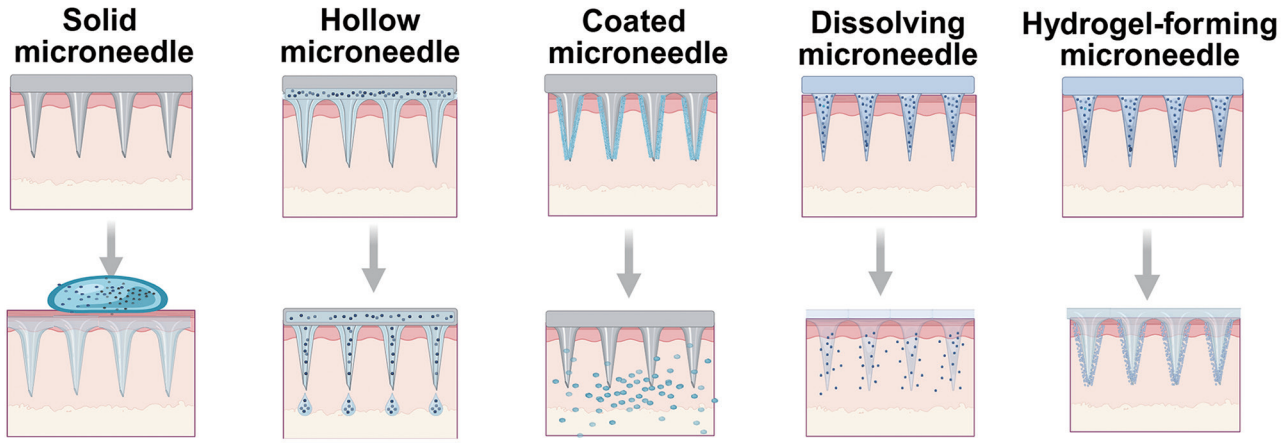

Figure 1. Classification of microneedles and schematic diagram of their mechanism of action. Created in BioRender. lili, l. (2025) https://BioRender.com/nhawu31.

Table 1. Materials of various microneedles and their application fields

Types of microneedles	Materials	Scope of application	References
Solid microneedles	Titanium	Administration of iloperidone for the treatment of schizophrenia	83
	Titanium	Enhancement of the doxycycline transdermal transport	84
Hollow microneedles	SU-8	Transcutaneous biosensing and drug administration	41
	Aluminum oxide	Insulin delivery	85
	Silicon	Minimally invasive diagnostics	86
Coated microneedles	Steel	siRNA delivery	87
	Steel	Cutaneous vaccination	56
	Steel	Glucose biosensing	88
Dissolving microneedles	PLA	Local analgesic action	89
	PVA	Treatment of Parkinson's disease	90
	HA	Inflammation regulation and acceleration of ulcer healing	91
Hydrogel-forming microneedles	HAMA	Glucose detection	92
	PVA/PVP	Cortisol testing and monitoring	93
	Dex-MA	Monitoring physiological status in animals via interstitial fluid sampling	94

Abbreviations: Dex-MA: Dextran-methacrylate; HA: Hyaluronic acid; HAMA: Methacryloyl hyaluronic acid; PLA: Polylactic acid; PVA: Polyvinyl alcohol; PVP: Polyvinylpyrrolidone; siRNA: Small interfering RNA.

Despite their utility, SMNs face significant limitations. Their reliance on passive diffusion results in low drug-loading capacity and variable delivery efficiency, particularly for biologics requiring precise dosing. Metallic SMNs also carry the risk of needle tip fracture, which may lead to local irritation, erythema, or swelling, posing safety concerns. To address these challenges, porous silicon (pSi) MNs have emerged as an advanced variant.[31,32] Featuring a nanoporous structure with a surface area of up to 500 m^2/g, pSi MNs serve as drug reservoirs, enabling the delivery of diverse payloads, including therapeutic agents, macromolecular proteins, and nucleic acids. Their biodegradability—degrading into non-toxic silicic acid *in vivo*—eliminates the need for removal, reducing infection risks and disposal costs.

2.2. Hollow MNs

To overcome the indirect, diffusion-dependent nature of SMNs, HMNs were engineered for active drug delivery. HMNs feature a microcavity within the needle tip and substrate that allows direct injection of drug solutions or suspensions into the dermis (**Figure 2A**).[33,34] Driven by external pressure from devices such as syringes or micropumps, their "poke-and-flow" mechanism supports high-dose delivery, making them ideal for rapid-onset applications such as vaccination, insulin administration, and local anesthesia.[35-37] Clinical trials have demonstrated that HMNs achieve immunogenicity comparable to intramuscular injections for influenza and SARS-CoV-2 vaccines, with seroconversion rates exceeding 95%.[38-40] In diabetes management, HMNs enable precise insulin delivery, reducing dosing frequency and improving patient adherence.[41-46] In addition, integration with microfluidic systems allows dynamic monitoring of biomarkers in ISF, with detection sensitivities as low as 1 μM for glucose, bridging therapeutic and diagnostic applications.[47-49]

However, HMNs face challenges related to mechanical fragility and delivery reliability. Early designs reported fracture rates of up to 5% during insertion, and microchannel clogging—particularly by dermal tissue and/or viscous drugs—can reduce delivery efficiency.[50] Recent advancements, including reinforced needle designs using materials like polyimide and anti-clogging coatings, have improved performance by 26%.[51] Ongoing research aims to integrate

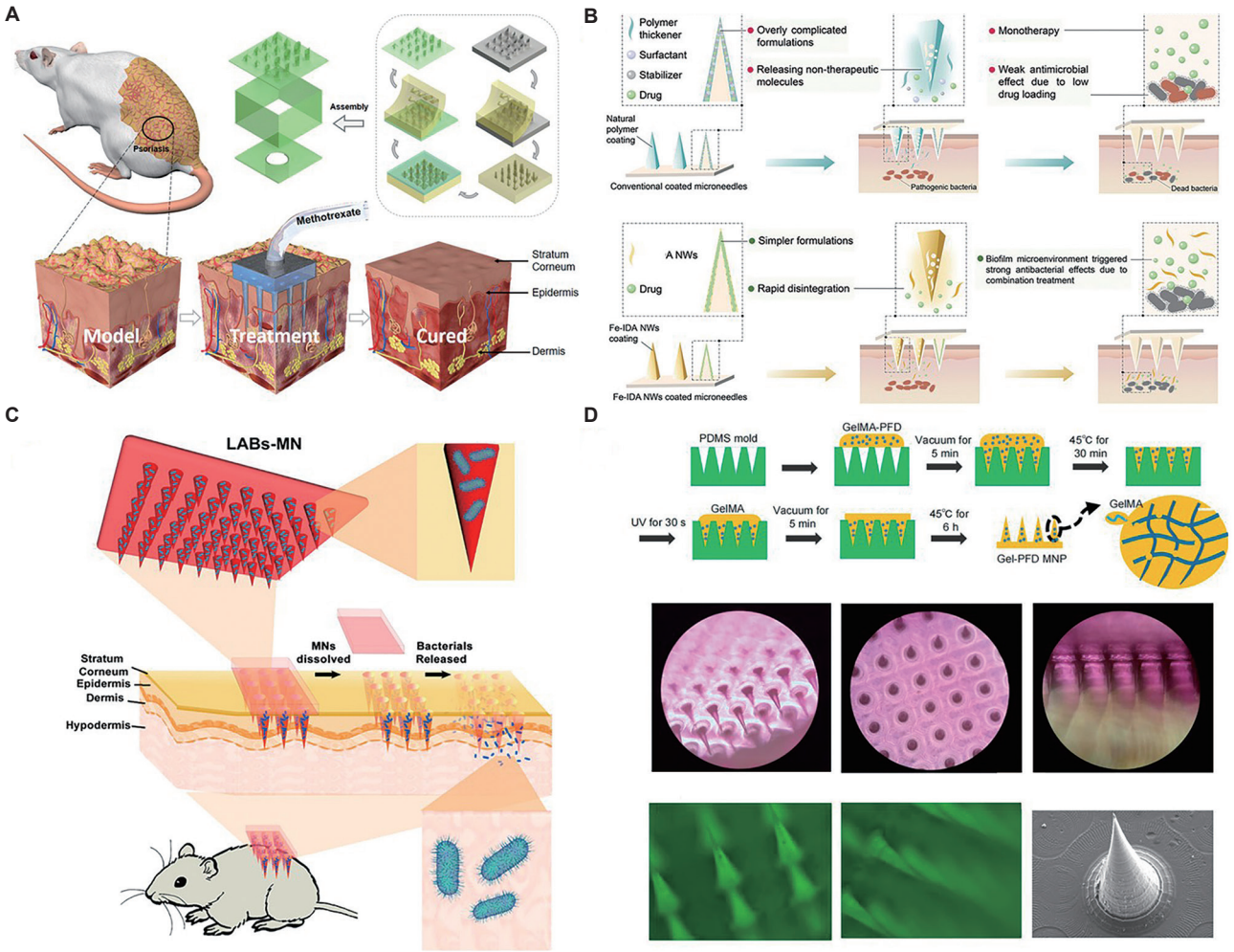

Figure 2. Therapeutic applications of various types of microneedles for different diseases. (A) Schematic diagram of hollow microneedles prepared using a dual-mode molding process and their use in the treatment of psoriasis in mice. Adopted with permission from Ren *et al.*[34] Copyright 2023 John Wiley and Sons. (B) Schematic of the advantages of a spiderweb-shaped iron-based coordination polymer nanowire network (Fe-IDA NWs) coated microneedles for transdermal drug delivery against infectious wounds. Reprinted with permission from Fu *et al.*[55] Copyright 2024 John Wiley and Sons. (C) Schematic of a dissolving microneedle patch facilitating the transdermal administration of viable and bioactive probiotics. Adopted with permission from Chen *et al.*[66] Copyright 2018 American Chemical Society. (D) Gel-PFD microneedle patch fabrication process and structural characteristic: preparation scheme of Gel-PFD microneedle patch, stereoscopic microscope photos, fluorescence stereoscopic microscope photos, and scanning electron microscopic (SEM) photo. Reprinted with permission from Gu *et al.*[74] Copyright 2023 Elsevier.
Abbreviations: IDA: 4,5-imidazoledicarboxylic acid, LABs-MNs: LABs-MNs: Lactobacillus microneedles; PFD: Pirfenidone; PDMS: Polydimethylsiloxane.

microvalves for precise flow control, potentially transforming HMNs into versatile platforms for personalized medicine.[52]

2.3. Coated MNs

Coated MNs offer a streamlined approach to rapid drug delivery, balancing simplicity with efficacy. CMNs combine a solid needle core or polymer substrate with a thin (1–5 μm) and water-soluble filming drug–excipient coating, typically composed of biocompatible materials such as polyvinyl alcohol or chitosan (**Figure 2B**).[53-55] Their "coat-and-poke" mechanism involves penetration of the SC, followed by the rapid disintegration of the coating in ISF to release the drug. This single-step process simplifies delivery, making CMNs suitable for rapid-onset applications such as vaccination[56,57] and local anesthesia.[58] For example, CMNs delivering influenza vaccine antigens elicit neutralizing antibody titers above 1:40 in 90% of subjects, which is comparable to intramuscular injections.[59,60] In medical aesthetics, CMNs deliver anti-aging agents like hyaluronic acid, offering immediate, minimally invasive results.

The primary limitation of CMNs is their constrained drug-loading capacity (0.1–1 μg per array), making CMNs unsuitable for therapies requiring high doses. Coating detachment during insertion can further reduce the dose by up to 30%.[61] Recently, multilayer CMNs have been reported to increase loading to 2–5 μg and improve stability, retaining 90% of the drug after 3 months at 25°C.[62] Future developments in nanostructured coatings aim to enhance adhesion and optimize release kinetics, potentially broadening the applicability of CMNs to higher-dose therapies.[63,64]

2.4. Dissolving MNs

Dissolving MNs are designed to be soluble in aqueous environments and undergo biological degradation. Materials such as hyaluronic acid and polylactic acid are commonly used to encapsulate drugs within the needle matrix (**Figure 2C**).[65,66] On penetrating the SC, the needles dissolve in ISF, releasing the payload through a "poke-and-release" mechanism. This approach supports high drug-loading capacities (up to 100 μg per array), as the entire needle serves as a drug reservoir, and ensures painless delivery, which could maximize both delivery efficiency and patient safety. Fabrication techniques such as microcasting, micromolding, and 3D printing have improved precision and reduced production time by up to 50%.[67] DMNs show particular promise for vaccine[68] and insulin delivery,[69] with preclinical studies demonstrating 99% bacterial clearance in localized infections using antibiotic-loaded DMNs.[70,71]

Compared to CMNs, DMNs offer superior drug-loading and release efficiency, with release profiles ranging from minutes to hours. However, premature dissolution in tissue fluid can lead to dose variability. Optimized formulations, such as cross-linked hyaluronic acid, have reduced variability to 5%.[72] Ongoing research is exploring multi-compartment DMNs to enable sequential or triggered release, enhancing their versatility for complex therapeutic regimens.[73] Furthermore, DMNs must possess sufficient mechanical strength to penetrate the skin without breaking while preserving the stability of encapsulated biologics. In addition, uncontrolled dissolution kinetics in the skin can lead to dose variability, posing potential therapeutic risks.

2.5. Hydrogel-forming MNs

Hydrogel-forming MNs, also known as swelling MNs, are constructed from cross-linked hydrophilic polymers that do not dissolve in the skin. After penetrating the SC, the hydrogel matrix of HFMNs rapidly imbibes ISF, causing the needles to swell and form continuous, porous channels between the attached drug patch and the dermal microcirculation. The therapeutic agent then diffuses through these aqueous channels in a highly controlled and sustained manner (**Figure 2D**).[74-77] The unique advantage of HFMNs is their ability to achieve long-term, zero-order release kinetics over hours or even days, making them exceptionally well-suited for managing chronic conditions, such as the continuous delivery of growth factors for wound healing or hormonal therapies. For instance, HFMNs delivering vascular endothelial growth factor accelerated diabetic foot ulcer healing by 50% in preclinical models.[78] Their ability to deliver large molecules, such as antibodies, with a 70% reduction in systemic side effects highlights their potential in cancer therapy and vaccination.[79]

Fabrication of HFMNs involves micromolding or photopolymerization, requiring precise control of the cross-linking ratio to balance the mechanical rigidity for insertion with the desired swelling kinetics for release.[80,81] Stimuli-responsive HFMNs, such as those that react swiftly to glucose or pH, dynamically adjust release based on the physiological environment, with glucose-responsive systems achieving 80% insulin release within 30 min of hyperglycemia.[82]

3. Applications of MNs

After decades of development, MNs have evolved from a transdermal drug delivery tool into a multifunctional platform integrating therapeutic, diagnostic, and interdisciplinary applications. By facilitating painless access to ISF and enabling the targeted delivery of diverse therapeutics—from macromolecules and biologics to living cells—MNs have demonstrated important applications in fields such as precision medicine, global health, as well as food safety and environmental monitoring.

3.1. Monitoring and diagnostics

MNs offer a minimally invasive alternative to conventional blood draws by accessing ISF, a rich reservoir of biomarkers such as glucose, hormones, electrolytes (e.g., calcium ions, potassium ions, sodium ions), cytokines, and nucleic acids. This innovative approach enables real-time, continuous monitoring of physiological parameters, significantly reducing patient discomfort and infection risks compared to conventional venipuncture. The compatibility of MNs with wearable diagnostic platforms enhances their utility for early diagnosis and long-term health monitoring, particularly for chronic conditions like diabetes and cardiovascular diseases.

3.1.1. Biomarker monitoring

Hollow MNs and HFMNs are primarily studied in biomarker detection, offering high sensitivity and integration with wearable platforms. HMNs act as direct conduits for the active extraction of ISF, while HFMNs operate through a different principle, swelling on insertion to passively absorb and sample fluid from the surrounding tissue. For instance, an HMN-based alcohol monitoring system employs a three-electrode configuration (platinum/silver electrodes with ethanol oxidase) to detect hydrogen peroxide in ISF, achieving a detection limit of 0.1 mM within 2 min (**Figure 3A**). This system supports real-time monitoring of alcohol levels, aiding the management of alcohol-related disorders.[95] In diabetes, HFMNs swell to extract ISF, integrating with glucose oxidase for continuous glucose monitoring. These systems achieve accuracy comparable to commercial devices (mean absolute relative difference <10%) and have been validated in clinical settings for Type 1 and Type 2 diabetes management (**Figure 3B**).[96] Beyond glucose, the applications of MNs have been extended to detect inflammatory markers (e.g., C-reactive protein) and tumor markers (e.g., carcinoembryonic antigen) with sensitivities down to 1 ng/mL, enabling early diagnosis of conditions like rheumatoid arthritis and cancer.[97,98] To overcome signal instability in biosensors, researchers developed a self-calibrating multiplexed MN electrode array (SC-MMNEA). This device facilitates simultaneous tracking of multiple biomarkers—such as glucose, lactate, ionic concentrations, and reactive oxygen species—in real-time and in a continuous manner. SC-MMNEA actively corrects for signal drift caused by long-term enzyme degradation and tissue variations *in vivo*, significantly enhancing sensor accuracy. This work also confirms that MNs can be applied for comprehensive, long-term physiological monitoring.[99]

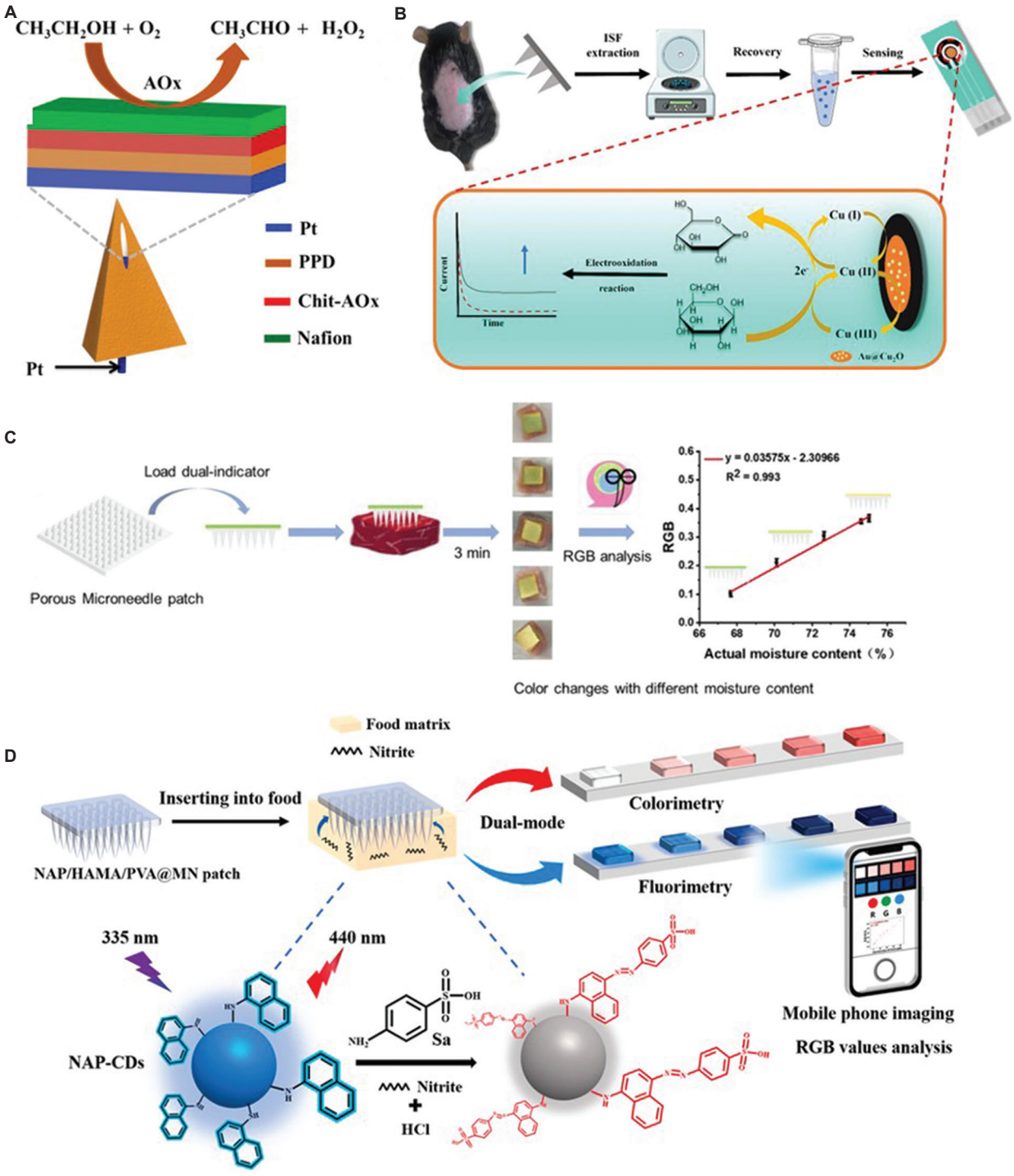

Figure 3. Efficacy of microneedles in early diagnosis and health monitoring. (A) Schematics demonstrating the construction of an alcohol biosensor. Adopted with permission from Mohan *et al.*[95] Copyright 2017 Elsevier. (B) Schematic diagram of glucose monitoring in the mouse interstitial fluid (ISF). Reprinted with permission from Jin *et al.*[96] Copyright 2024 Elsevier. (C) Schematic diagram illustrating the principle of using a porous polymer microneedle patch based on colorimetry to determine the moisture content of meat. Adopted with permission from Yang *et al.*[104] Copyright 2025 Elsevier. (D) Schematic illustration of a dual-mode (colorimetric/fluorescent) naphthylamine (NAP)/methacryloyl hyaluronic acid (HAMA)/polyvinyl alcohol (PVA) microneedle (MN) patch utilizing the Griess reaction was developed for non-invasive nitrite monitoring. Reprinted with permission from Xu *et al.*[105] Copyright 2025 Elsevier.
Abbreviations: Au: Gold; CDs: Carbon nanodots; Chit-AOx: Chitosan-alcohol oxidase; Cu: Copper ion; HCl: Hydrochloric acid; H_2O_2: Hydrogen peroxide; PPD: Poly(*o*-phenylenediamine); Pt: Platinum; RGB: Red, Green, and Blue; Sa: p-aminobenzene sulfonic acid.

3.1.2. Clinical diagnostic applications

MN-based diagnostics are pivotal in point-of-care testing, particularly in resource-limited settings. Indeed, MNs greatly facilitate the monitoring of chronic diseases. To circumvent the inherent constraints of conventional closed-loop diabetes systems, Liu et. Al.[100] developed an integrated, wearable MN

patch. This rapidly manufacturable system includes a sensor printed from a stable graphene composite ink on hollow MNs, combined with a polyethylene glycol (PEG)-functionalized micropump for insulin delivery. The graphene ink streamlines fabrication, while the pump's antifouling coating ensures long-term stability, maintaining over 70% of its initial flow for more than 3 weeks. The system demonstrated excellent glycemic control in diabetic animal studies, showcasing advantages in wearability and cost. Similarly, Yang *et al.*[101] reported a wearable MN sensing device for real-time and wireless glucose monitoring in human ISF. By integrating both a glucose sensor and a differential sensor on a single patch, the suppression of common-mode interference led to a notable enhancement in detection precision. During animal experiments, the system exhibited strong agreement with blood analyses, confirming its utility as an integrated system for highly accurate wearable sensing. Xu *et al.*[102] developed a wearable MN patch for the real-time monitoring of cytokine storm *in vivo*. This MN patch used functional carbon nanotube to boost the detectability and operational stability, with a detection limit of 0.54 pg/mL and 5-day stability with a 4.0% coefficient of variation. Gao *et al.*[103] developed a multi-target MN sensor for blood-free detection of inflammatory cytokines, including interleukin (IL)-6, IL-1β, tumor necrosis factor alpha, and C-reactive protein, enabling comprehensive profiling of the inflammatory cytokine signature within 30 min.

3.1.3 Food safety

Beyond disease monitoring, MN technology has been extended into non-medical applications, such as food safety and environmental monitoring. A porous polymer MN patch was developed to detect water in meat. This MN patch was fabricated with cobalt (II) chloride as a color-change indicator. When applied, the MNs extract tissue fluid without the need for sample preparation, causing the patch color to visibly shift from green to yellow with increasing moisture within 3 min and with sensitivities down to 1% water content, enabling rapid quality control in food processing (**Figure 3C**). The system demonstrated a regular, linear colorimetric response to moisture content in the 66.9–75.7% range.[104] Another notable study involved using an MN patch for non-destructive nitrite detection in foods. The MN patch was produced using methacryloyl hyaluronic acid and polyvinyl alcohol, and integrated highly fluorescent α-naphthylamine-based carbon dots (NAP-CDs) with a high quantum yield. Designed to penetrate food matrices, the patch efficiently extracts nitrite-containing tissue fluids. These samples then interact with NAP-CDs incorporated in the backing layer through the Griess reaction, resulting in the formation of a magenta azo dye accompanied by quenching of blue fluorescence (**Figure 3D**). Compared to traditional methods, these MN platforms offer a portable, user-friendly solution for on-site food safety assessments.[105]

3.2. Therapeutic applications

MNs can precisely administer payloads, including small molecules, biologics, and even living cells.[106-114] By circumventing hepatic first-pass metabolism, MNs significantly enhance drug bioavailability, minimize systemic toxicity, and improve patient adherence, offering transformative solutions for chronic disease therapeutics, prophylactic vaccination, tissue regeneration, and anticancer therapy.[115] Their minimally invasive nature allows for targeted, controlled release, optimizing therapeutic efficacy for clinical applications.

3.2.1. Diabetes management

As a painless delivery platform, MNs technology can directly deliver therapeutics into the dermal microcirculation, enhancing patient compliance and reducing medical waste. Furthermore, disposable MN patches fabricated from biocompatible polymers can lower the risk of infection. This makes MNs suitable for managing chronic conditions such as diabetes.

Several DMN patches have been reported for painless insulin delivery in diabetes management. These DMNs incorporate insulin into a biodegradable polymer network—composed of materials like hyaluronic acid or polyvinyl alcohol—that undergo rapid dissolution (within 5–10 min) after skin insertion, thereby facilitating insulin release into systemic circulation.[116-119] An innovative patchless default mode network drug delivery system, termed the Film Triggered Administerer (FTA), has been developed. *In vivo* trials revealed that the FTA group achieved a bioavailability of 93%, comparable to the injection group (100%). Preclinical studies have demonstrated that DMNs can achieve glycemic control comparable to subcutaneous injections, with the added benefits of eliminating pain and simplifying administration for patients requiring multiple daily doses.[120] Another advancement in MNs-based insulin delivery is the development of glucose-responsive "smart" patches designed to emulate the dynamic insulin secretion of a healthy pancreas. A study by Wang *et al.*[121] introduced a smart insulin patch integrating insulin-loaded nanovesicles within a glucose-sensitive polymer matrix embedded in MNs (**Figure 4A**). This MN patch features a solid core of insulin powder with a high payload capacity (over 70% by weight) and an outer polymer coating responsive to glucose. During hyperglycemia, the formation of negatively charged glucose–boronate complexes increases the charge density in the shell matrix, leading to matrix swelling and subsequent accelerated insulin release from the core. In both mice and minipigs rendered diabetic through experimental induction, the glucose-responsive patch demonstrated sustained regulation of blood glucose levels, highlighting its potential for long-term diabetes management.

3.2.2. Vaccination

By delivering antigens directly to the skin's immune-rich dermal layer, MNs target antigen-presenting cells, such as dendritic cells, eliciting robust immune responses. Compared to intramuscular injections, which rely on passive antigen diffusion in muscle tissue, MNs can significantly enhance immunogenicity.[122] In addition, various MN vaccine formulations, prepared as solid and dry-state patches, exhibit exceptional thermal stability, maintaining potency at ambient temperatures.[123]

Choi *et al.*[124] developed a dissolving MN patch for adjuvant-free hepatitis B surface antigen (HBsAg) vaccination to enhance the birth dose. This DMN patch delivered HBsAg at 5, 10, and

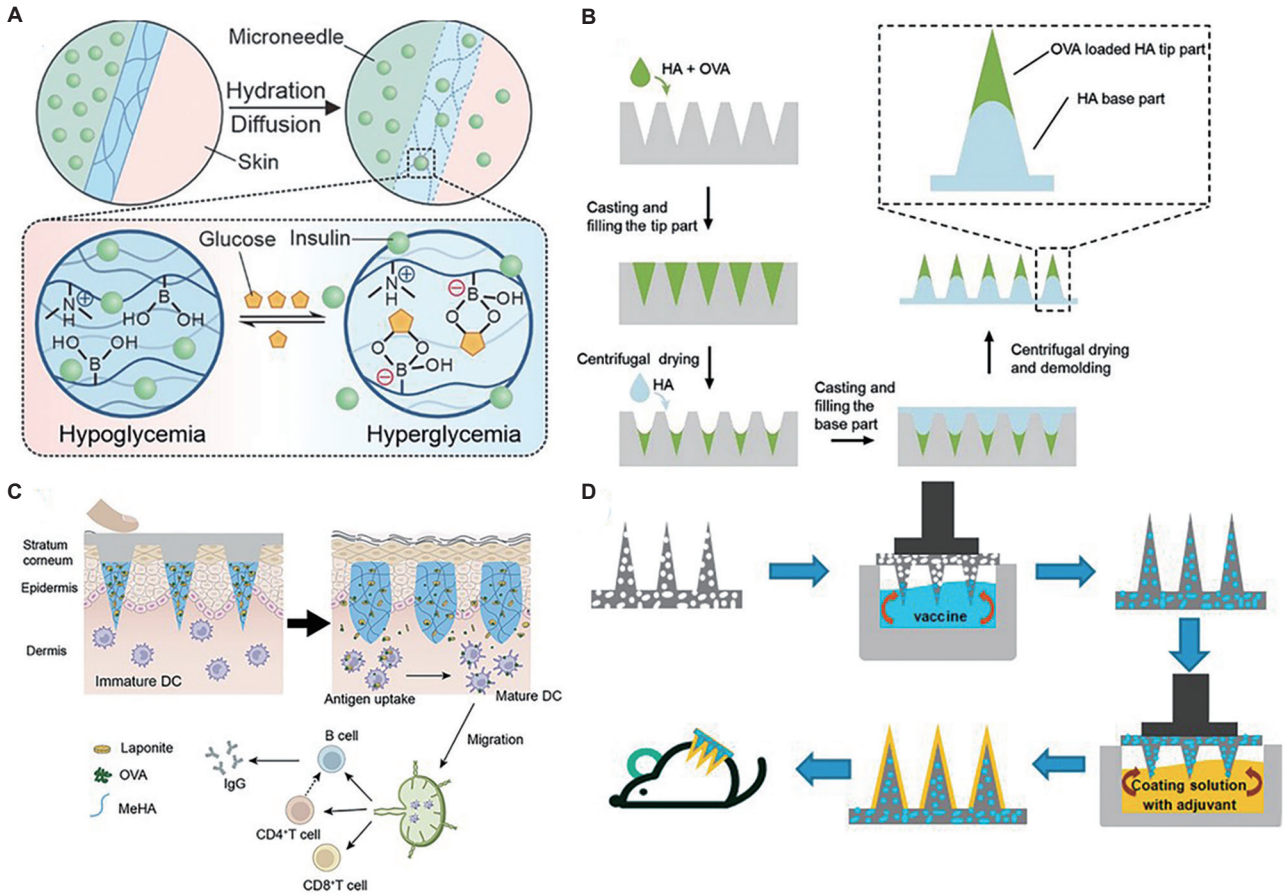

Figure 4. Schematic diagram illustrating the application of microneedles in diabetes management and vaccination. (A) Mechanism of glucose-triggered insulin release from the solid microneedle patch. Adopted with permission from Wang *et al.*[121] Copyright 2024 American Chemical Society. (B) Schematic illustration of the fabrication process of the proposed dissolving microneedle patch with tip-accumulated antigens (ovalbumin [OVA]). Reprinted with permission from Zheng *et al.*[125] Copyright 2023 John Wiley and Sons. (C) Schematic of intradermal immunization with an OVA-loaded methacrylated hyaluronic acid (MeHA)-laponite nanocomposite hydrogel microneedle patch to induce adaptive immune responses. Adopted with permission from Zheng *et al.*[126] Copyright 2024 Elsevier. (D) Schematic of a coated porous microneedle delivering an influenza vaccine. Reprinted with permission from Zhang *et al.*[127] Copyright 2023 American Chemical Society.
Abbreviations: CD: Cluster of differentiation; DC: Dendritic cell; HA: Hyaluronic acid.

20 μg; a robust immune response was observed, characterized by anti-hepatitis B antibody concentrations above the protective threshold (10 mIU/mL) in mice and macaques. Compared to a 10 μg intramuscular adjuvant-free vaccine, the DMN patch elicited stronger antibody responses. HBsAg-specific T cell responses and similar signaling pathways were also observed in the study groups. The DMN patch retained 67% HBsAg potency after 6 months at 20–25°C, offering a scalable solution for Hepatitis B vaccination.[124] Another DMN patch was developed by Zheng's group[125] for vaccine delivery. Utilizing a sequential casting process combined with centrifugal drying, the DMN patch (fabricated from hyaluronic acid) concentrated ovalbumin (OVA) in the needle tips to optimize antigen delivery. The use of low-temperature centrifugal drying enhanced antigen accumulation, ensured adequate mechanical properties for effective skin insertion, and allowed rapid antigen release within 3 min. *In vivo* studies demonstrated that OVA-loaded DMNs elicit superior enhanced immunogenicity compared to traditional hypodermic and intramuscular administration routes (**Figure 4B**).[125] Zheng *et al.*[126] also described an MN system based on a nanocomposite hydrogel (NHMN) for the prolonged administration of OVA, designed to improve vaccine efficacy. This OVA-loaded NHMN patch was fabricated using a methacrylated hyaluronic acid and laponite composite that was photo-cross-linked and reinforced with a dissolvable hyaluronic acid matrix. Laponite enhances mechanical strength and extends OVA release up to 15 days *in vivo*. An *in vitro* study confirmed that NHMNs activated dendritic cells without compromising viability. Once inserted into the cutaneous tissue, the MNs detached as the backing dissolved in ISF, serving as antigen reservoirs for targeted delivery to skin dendritic cells (**Figure 4C**).[126] In the application of MNs for vaccine delivery, ensuring the needles demonstrate the necessary rigidity to pierce the SC without fracturing during insertion is of critical importance. Zhang *et al.*[127] developed biocompatible cellulose acetate porous MNs (pMNs) using non-solvent-induced phase separation for influenza vaccination. To enhance the structural integrity of the pMN coating, an aqueous dispersion of biocompatible carboxymethyl cellulose was applied, achieving a mean peak stress value of 32.89 N. The microporous structure and coating enabled synergistic intradermal release of vaccine and induced robust immune responses in Wistar rats (**Figure 4D**).[127]

3.2.3. Tissue regeneration and localized therapy

Bio-inspiration provides a foundation for innovation in MNs, enabling enhanced performance for localized and sustained therapeutic delivery. By emulating structures like porcupine quills, researchers have engineered MNs with superior tissue anchoring capabilities, ensuring continuous delivery of growth factors to accelerate chronic wound healing, such as in diabetic foot ulcers (**Figure 5A**).[128] Similarly, optimized MN tip geometries inspired by shark teeth have improved penetration efficiency while minimizing tissue trauma and the required insertion force.[129] HFMNs play a pivotal role in ophthalmic drug delivery, leveraging their swellable, 3D network to deliver therapeutics directly to target tissues, thereby minimizing systemic exposure and toxicity. A biocompatible HFMN system capable of inducing suprachoroidal space formation (denoted as SI-HFMNs) has been developed to achieve targeted drug delivery to the posterior segment of the eye. SI-HFMNs, designed with a candlelit shape, swell by 356 ± 28% to separate the sclera and choroid. Formulated with 20% (w/w) poly(methyl vinyl ether-alt-maleic acid) cross-linked with 7.5% (w/w) PEG, SI-HFMNs exhibit robust mechanical strength (5.1 ± 0.7 N) and high drug absorption (101 ± 9 μg/mg). *In vitro* and *in vivo* studies confirmed effective drug delivery to the posterior segment of the eye through the induced suprachoroidal space, offering an innovative, minimally invasive approach for treating posterior eye disorders.[130] Liu *et al.*[131] developed dissolving MNs for treating dry age-related macular degeneration. These DMNs incorporated biomimetic nanoparticles, loaded with resveratrol and cloaked in retinal pigment epithelial cell membranes. On skin penetration, the DMNs rapidly dissolved and released nanoparticles that leveraged the retinal pigment epithelial membrane coating for homologous targeting and enhanced cellular uptake. In a dry age-related macular degeneration rabbit model, the DMNs significantly mitigated oxidative stress, inflammation, and retinal degeneration, preserving retinal architecture with excellent biocompatibility (**Figure 5C**).[131]

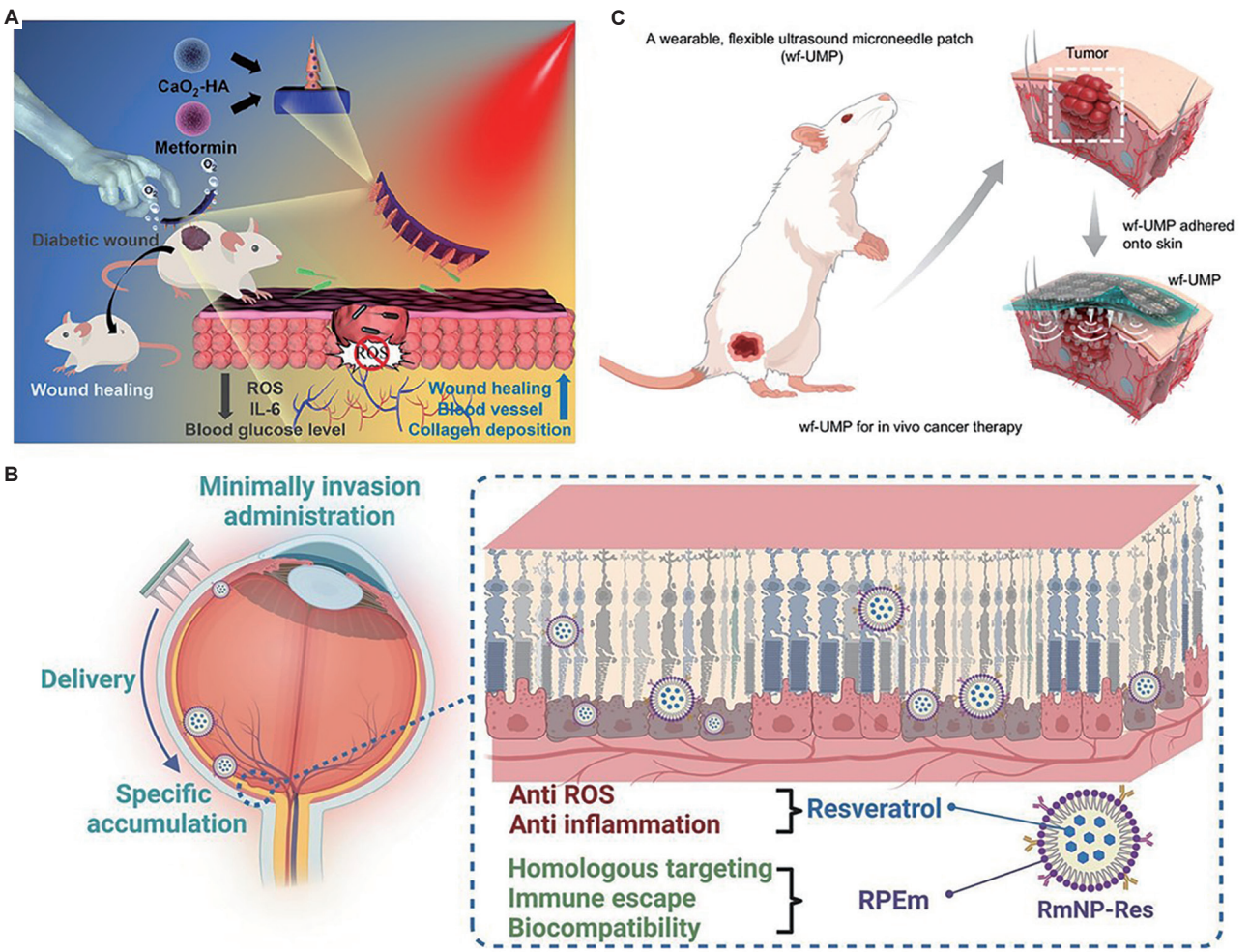

Figure 5. Schematic diagram illustrating the application of microneedles (MNs) in tissue regeneration, localized therapy, and tumor-targeted therapy. (A) Schematic illustrations of MN patches for glycemic wound management. Adopted with permission from Choi *et al.*[130] Copyright 2023 Elsevier. (B) The MN-mediated biomimetic nanoparticles for minimally invasive targeted therapy for age-related macular degeneration. Reprinted with permission from Chen *et al.*[133] Copyright 2025 Elsevier. (C) Schematic illustration of a wearable flexible ultrasound microneedle patch (wf-UMP) application for cancer therapy. Adopted with permission from Xue *et al.*[134]

Abbreviations: CaO_2: Calcium peroxide; HA: Hyaluronic acid; IL-6: Interleukin 6; RmNP-Res: Retinal pigment epithelial membrane biomimetic nanoparticle-resveratrol; ROS: Reactive oxygen species; RPEm: Retinal pigment epithelial membrane.

3.2.4. Cancer therapy

Due to their localized drug delivery potential, MNs can achieve high therapeutic concentrations at tumor sites while minimizing systemic toxicity. This approach is particularly effective for treating skin cancers (e.g., melanoma) and for targeting the tumor microenvironment.

Ma *et al.*[132] developed a hyaluronic acid-based MN patch (DPTC-MNs) incorporating 1,2-distearoyl-sn-glycero-3-phosphoethanolamine–PEG–tirapazamine (TPZ) micelles with chlorin e6 for synergistic photodynamic therapy (PDT) and hypoxia-activated chemotherapy. DPTC-MNs enhanced tumor infiltration and suppressed PDT tolerance factors under laser irradiation, demonstrating potent antitumor effects against melanoma and squamous cell carcinoma both *in vitro* and *in vivo*. This combination of PDT and TPZ exhibited excellent biocompatibility and significantly improved therapeutic efficacy, offering a promising, minimally invasive strategy for skin cancer treatment.[132] Another hyaluronic acid-based MN patch was reported for the co-delivery of a nanomotor cancer vaccine and doxorubicin to enhance melanoma treatment. On MN dissolution, the nanomotor released nitric oxide, inducing immunogenic cell death, while OVA activated T cell responses. Combined with doxorubicin, this MN patch significantly improved antitumor efficacy for synergistic cancer immunotherapy and chemotherapy.[133]

Dissolvable MNs can directly deliver chemotherapeutic drugs or immune checkpoint inhibitors (e.g., anti-programmed cell death protein 1 [aPD-1] antibodies). Studies demonstrate that this localized delivery achieves higher drug concentrations at tumor sites compared to systemic administration (**Figure 5B**).[134] Huang *et al.*[135] reported a dissolving MN patch (αNP-RNP@DMN) co-encapsulating Toll-like receptor 7/8 agonist R848 and aPD-1 for enhanced immunotherapy of triple-negative breast cancer. This transdermal system efficiently delivered drugs to tumor sites, maturing tumor-infiltrating dendritic cells and promoting cluster of differentiation 8-positive T cell infiltration through R848, while aPD-1 blocked PD-1/programmed death-ligand 1 (PD-L1) checkpoints, reversing triple-negative breast cancer's immunosuppressive microenvironment.[135] An MN array system encapsulating ligand-directed, lipid-based nanocarriers was also developed for the combinatorial administration of aPD-1 and cisplatin (CDDP) to enhance cancer immunotherapy. By penetrating the immunologically active epidermal layer, the patch enabled precise transdermal delivery to tumor sites, boosting T-cell responses. Research conducted in live organisms demonstrated that aPD-1/CDDP@NPs synergistically enhanced tumor regression by blocking PD-1/PD-L1 interactions, increasing CDDP cytotoxicity, and overcoming immunotherapy resistance.[136] Beyond chemotherapeutic drugs and aPD-1 inhibitors, MNs can also deliver other macromolecules, such as proteolysis targeting chimera drugs.[137]

4. Future prospects

4.1. Smart-responsive MN systems for precision medicine

In the last decade, researchers have increasingly focused on stimuli-responsive MN systems for applications in precision medicine. These advanced MNs can react to various physiological and external cues, such as changes in glucose levels, pH, and light exposure. By introducing boronate-based polymers, glucose-responsive MNs are believed to be capable of smart insulin release. For example, an innovative MN patch has been designed using a glucose-responsive shell, insulin powder payload, and a colored, osmotic pump-inspired core. This system releases insulin in response to blood glucose levels, offering high drug loading, near-complete release, and sustained normoglycemia for 24 h.[138] When compared to healthy skin, which maintains a pH between 4 and 6.5, acute wounds show a mildly acidic environment (pH 5–6), whereas chronic wounds typically display alkaline conditions with a pH ranging from 7 to 9. Acidic environments promote angiogenesis, epithelialization, oxygen release, and commensal bacteria maintenance. Elevating the pH to convert chronic wounds into acute wounds could facilitate healing.[139] Eudragit S100, a polymer that dissolves under alkaline pH, was applied as a coating on the MNs. This coating exhibited pH-dependent release behavior both in an *in vivo* rat abrasion wound model and an *ex vivo* porcine skin model at a wound-relevant pH of 7.5.[140] Beyond responding to endogenous physiological stimuli, drug release from MNs can also be triggered on demand through the application of external stimuli, such as light, heat, or ultrasound.[141-143] These MNs, responsive to exogenous stimuli, enable precise drug release at specific sites, offering high spatiotemporal control. On-demand release achieves peak drug concentrations at critical time points, thereby maximizing therapeutic efficacy.

4.2. Wearable and personalized MN systems

Wearable MN systems integrate biosensors and drug reservoirs, enabling closed-loop theranostics that combine real-time diagnostics with precise drug delivery. This concept has shown early success in the management of diabetes. For example, a sequential deposition technique for immobilizing nanoscale enzymatic components was reported for diabetes management. This system utilized a dual-sensor MN array with a stepwise assembly approach to immobilize nanoscale enzymes, enabling highly precise and selective detection of glucose and metformin within ISF. By continuously monitoring glucose level, the system enabled real-time data interpretation coupled with immediate feedback, supporting personalized treatment adjustments.[144] However, for long-term monitoring and therapeutic systems, the stability of MNs and their total drug loading capacity remain significant challenges.

Three-dimensional printing technology has profoundly impacted MN development. By enabling high-resolution, layer-by-layer fabrication, 3D printing allows precise control over MN dimensions, shapes, and geometries, meeting individualized therapeutic needs. It supports diverse biocompatible materials (e.g., photosensitive resins, polymers, metals), which can enhance MN functionality.[145] In addition, 3D printing accelerates the design-to-testing process and facilitates a rapid transition from design to small-scale production. Despite these advantages, high costs and resolution limitations remain significant challenges.

5. Limitations

Despite their minimally invasive design, MNs require rigorous clinical safety and biocompatibility validation. While generally well-tolerated, biodegradable fragments may trigger localized inflammation.[146] Designing MNs requires balancing mechanical strength and drug stability. Polymer-based MNs often exhibit low fracture stress (<10 MPa), risking tip breakage during SC penetration.[147] Dissolving MNs may release payloads prematurely due to ISF exposure, particularly for biologics. Stabilizing proteins or nucleic acids during fabrication and storage remains challenging, as degradation occurs at temperatures above 40°C. Although lyophilization can extend vaccine stability for up to 6 months at 40°C, it also increases production.

Concurrently, MNs face challenges in standardization and regulatory frameworks during development. To achieve genuine clinical application, it is essential to establish uniform standards for MNs. However, variations exist both across batches and within the same batch in terms of dimensional specifications, materials used, and internal construction. These seemingly minor distinctions directly influence penetration depth into the skin and the efficiency of tissue fluid collection, ultimately leading to inconsistent drug delivery outcomes and test results. As a nascent medical device, MNs function within a regulatory landscape that is still evolving. The current lack of industry-wide standardization and guidance for MN-based products complicates large-scale manufacturing. For instance, in the context of monitoring physiological changes in cancer, standardization is imperative to ensure safety and reliability. Consequently, the development of standardized protocols is imperative for the full integration of MNs into clinical practice.[148]

6. Conclusions

MNs have fundamentally transformed approaches in biomedical science, serving as adaptable tools that reduce invasiveness while enabling enhanced administration of therapeutics and monitoring of physiological conditions. By overcoming the SC barrier, MNs allow for the efficient delivery of therapeutics (e.g., insulin, vaccines) with high bioavailability in preclinical models, while also facilitating real-time biomarker monitoring for chronic disease management. Beyond clinical applications, MNs have been extended to other fields like food safety. However, challenges such as ensuring biocompatibility, optimizing mechanical strength, and stabilizing biologics during fabrication and storage hinder widespread clinical translation. MNs must possess sufficient mechanical strength to achieve effective skin penetration while maintaining excellent biocompatibility, making the development of novel materials crucial. At present, the uniformity of MNs in the manufacturing process presents a significant challenge, calling for enhanced industry standards to improve product consistency and reliability. The continuous advancement of 3D printing technology and smart materials holds the potential to drive major progress in the personalized, intelligent, and highly uniform design and production of MNs. This will propel the technology toward greater safety, efficiency, and broader application. Future research is focusing on developing smart-responsive MNs that react to physiological cues such as glucose or pH, as well as integrating these MNs with wearable systems to achieve personalized, closed-loop theranostics. With advancements in materials science and nanomedicine, MNs are poised to transform precision medicine, enhance global health accessibility, and redefine patient-centric care, positioning them as a cornerstone of next-generation biomedical solutions.

Acknowledgement

We would like to thank Prof. Gangqiang Yang, Sha Liu, and Aiping Wang from Yantai University for their valuable assistance in the manuscript writing.

Financial support

This study was supported by the Science and Technology Support Plan for Youth Innovation of Colleges and Universities of Shandong Province, China (Grant No. 2022KJ344), the Yantai Science and Technology Bureau (Grant No. 2024JCYJ063), and the National Science Foundation of China (Grant No. 82001961).

Conflicts of interest statement

The authors affirm the absence of any financial or personal affiliations that could be construed as influencing the research presented in this study.

Author contributions

Conceptualization: XL and PZ; *Formal analysis:* XL, CZ, and YZ; *Funding acquisition:* PZ; *Visualization:* XL; *Writing–original draft*: XL; *Writing–review & editing*: XL, ZL, JL, YM, and PZ. All authors have read, agreed with the contents, and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Jeong SH, Jang JH, Lee YB. Pharmacokinetic comparison of three different administration routes for topotecan hydrochloride in rats. *Pharmaceuticals (Basel)*. 2020;13(9):231. doi: 10.3390/ph13090231
2. Ouyang J, Zhang Z, Deng B, *et al.* Oral drug delivery platforms for biomedical applications. *Mater Today*. 2023;62:296-326. doi: 10.1016/j.mattod.2023.01.002
3. Ait-Oudhia S, Chen J, Li J, van der Graaf PH. Subcutaneous biologics: Clinical pharmacology and drug development. *Clin Pharmacol Ther*. 2024;115(3):385-390. doi: 10.1002/cpt.3179
4. Jin JF, Zhu LL, Chen M, *et al.* The optimal choice of medication administration route regarding intravenous, intramuscular, and subcutaneous injection. *Patient Prefer Adherence*. 2015;9:923-942. doi: 10.2147/PPA.S87271
5. Brown MB, Martin GP, Jones SA, Akomeah FK. Dermal and transdermal drug delivery systems: Current and future prospects. *Drug Deliv*. 2006;13(3):175-187. doi: 10.1080/10717540500455975
6. Sabbagh F, Kim BS. Recent advances in polymeric transdermal drug delivery systems. *J Control Release*. 2022;341:132-146. doi: 10.1016/j.jconrel.2021.11.025
7. Xiao Z, He S, Huang X, *et al.* Preparation and transdermal performance study of a new S-(-)-nicotine-loaded nano flexible liposome hydrogel patch with long-lasting and sustained drug-release effects. *ChemistrySelect*. 2024;9(37):e202401440.

doi: 10.1002/slct.202401440
8. Pensado A, Hattam L, White KAJ, *et al.* Skin pharmacokinetics of transdermal scopolamine: Measurements and modeling. *Mol Pharm.* 2021;18(7):2714-2723. doi: 10.1021/acs.molpharmaceut.1c00238
9. Park J, Lee H, Lim GS, Kim N, Kim D, Kim YC. Enhanced transdermal drug delivery by sonophoresis and simultaneous application of sonophoresis and iontophoresis. *AAPS PharmSciTech.* 2019;20(3):96. doi: 10.1208/s12249-019-1309-z
10. Karve T, Banga AK. Comparative evaluation of physical and chemical enhancement techniques for transdermal delivery of linagliptin. *Int J Pharm.* 2024;654:123992. doi: 10.1016/j.ijpharm.2024.123992
11. Vaidya J, Shende P. Potential of sonophoresis as a skin penetration technique in the treatment of rheumatoid arthritis with transdermal patch. *AAPS PharmSciTech.* 2020;21(5):180. doi: 10.1208/s12249-020-01725-w
12. Ita KB, Popova IE. Influence of sonophoresis and chemical penetration enhancers on percutaneous transport of penbutolol sulfate. *Pharm Dev Technol.* 2016;21(8):990-995. doi: 10.3109/10837450.2015.1086373
13. Gerstel MS, Place VA. Drug delivery device. Google Patents. US Patent No. US3964482A; 1976.
14. Chiu TM, Hsu PC, Khan MY, *et al.* A perspective on imiquimod microneedles for treating warts. *Pharmaceutics.* 2021;13(5):607. doi: 10.3390/pharmaceutics13050607
15. Cheng Y, Yang J, Han S, Lu Y. Near-infrared triggered biodegradable microneedle patch for controlled macromolecule drug release. *Macromol Biosci.* 2024;24(7):e2400105. doi: 10.1002/mabi.202400105
16. Nejad HR, Sadeqi A, Kiaee G, *et al.* Low-cost and cleanroom-free fabrication of microneedles. *Microsyst Nanoeng.* 2018;4(1):17073. doi: 10.1038/micronano.2017.73
17. Yang S, Feng Y, Zhang L, Chen N, Yuan W, Jin T. A scalable fabrication process of polymer microneedles. *Int J Nanomedicine.* 2012;7:1415-1422. doi: 10.2147/IJN.S28511
18. Oh NG, Hwang SY, Na YH. Fabrication of a PVA-based hydrogel microneedle patch. *ACS Omega.* 2022;7(29):25179-25185. doi: 10.1021/acsomega.2c01993
19. Ghanbariamin D, Samandari M, Ghelich P, *et al.* Cleanroom-free fabrication of microneedles for multimodal drug delivery. *Small.* 2023;19(29):e2207131. doi: 10.1002/smll.202207131
20. Mizuno Y, Takasawa K, Hanada T, *et al.* Fabrication of novel-shaped microneedles to overcome the disadvantages of solid microneedles for the transdermal delivery of insulin. *Biomed Microdevices.* 2021;23(3):38. doi: 10.1007/s10544-021-00576-x
21. Li X, Xie X, Wu Y, Zhang Z, Liao J. Microneedles: Structure, classification, and application in oral cancer theranostics. *Drug Deliv Transl Res.* 2023;13(9):2195-2212. doi: 10.1007/s13346-023-01311-0
22. Lin S, Ouyang Y, Lin W, *et al.* Microenvironment-optimized GelMA microneedles for interstitial fluid extraction and real-time glucose detection. *Surf Interfaces.* 2024;45:103847. doi: 10.1016/j.surfin.2024.103847
23. Bollella P, Sharma S, Cass AEG, Antiochia R. Minimally-invasive microneedle-based biosensor array for simultaneous lactate and glucose monitoring in artificial interstitial fluid. *Electroanalysis.* 2019;31(2):374-382. doi: 10.1002/elan.201800630
24. Liu TT, Chen K, Wang Q. Skin drug permeability and safety through a vibrating solid micro-needle system. *Drug Deliv Transl Res.* 2018;8(5):1025-1033. doi: 10.1007/s13346-018-0544-2
25. Li QY, Zhang JN, Chen BZ, Wang QL, Guo XD. A solid polymer microneedle patch pretreatment enhances the permeation of drug molecules into the skin. *RSC Adv.* 2017;7(25):15408-15415. doi: 10.1039/C6RA26759A
26. Eş I, Kafadenk A, Gormus MB, Inci F. Xenon difluoride dry etching for the microfabrication of solid microneedles as a potential strategy in transdermal drug delivery. *Small.* 2023;19(27):e2206510. doi: 10.1002/smll.202206510
27. Es I, Kafadenk A, Inci F. A high-precision method for manufacturing tunable solid microneedles using dicing saw and xenon difluoride-induced dry etching. *J Mater Process Technol.* 2024;325:118268. doi: 10.1016/j.jmatprotec.2023.118268
28. Abdullah AC, Ahmadinejad E, Tasoglu S. Optimizing solid microneedle design: A comprehensive ML-augmented DOE approach. *ACS Meas Sci Au.* 2024;4(5):504-514. doi: 10.1021/acsmeasuresciau.4c00021
29. Anbazhagan G, Suseela SB, Sankararajan R. Design, analysis and fabrication of solid polymer microneedle patch using CO_2 laser and polymer molding. *Drug Deliv Transl Res.* 2023;13(6):1813-1827. doi: 10.1007/s13346-023-01296-w
30. Chen BZ, Liu JL, Li QY, *et al.* Safety evaluation of solid polymer microneedles in human volunteers at different application sites. *ACS Appl Bio Mater.* 2019;2(12):5616-5625. doi: 10.1021/acsabm.9b00700
31. Tabassum N, Rudd D, Yan L, *et al.* Porous silicon microneedle patches for delivery of polymyxin-based antimicrobials. *Nano Select.* 2024;5(7-8):2300116. doi: 10.1002/nano.202300116
32. Tabassum N, Alba M, Yan L, *et al.* Porous silicon microneedles for enhanced transdermal drug delivery. *Adv Ther.* 2023;6(1):2200156. doi: 10.1002/adtp.202200156
33. Dardano P, De Martino S, Battisti M, Miranda B, Rea I, De Stefano L. One-shot fabrication of polymeric hollow microneedles by standard photolithography. *Polymers (Basel).* 2021;13(4):520. doi: 10.3390/polym13040520
34. Ren Y, Li J, Chen Y, *et al.* Customized flexible hollow microneedles for psoriasis treatment with reduced-dose drug. *Bioeng Transl Med.* 2023;8(4):e10530. doi: 10.1002/btm2.10530
35. Vinayakumar KB, Kulkarni PG, Nayak MM, *et al.* A hollow stainless steel microneedle array to deliver insulin to a diabetic rat. *J Micromech Microeng.* 2016;26(6):065013. doi: 10.1088/0960-1317/26/6/065013
36. Parrilla M, Detamornrat U, Domínguez-Robles J, Donnelly RF, De Wael K. Wearable hollow microneedle sensing patches for the transdermal electrochemical monitoring of glucose. *Talanta.* 2022;249:123695. doi: 10.1016/j.talanta.2022.123695
37. Resnik D, Možek M, Pečar B, *et al. In vivo* experimental study of noninvasive insulin microinjection through hollow Si microneedle array. *Micromachines (Basel).* 2018;9(1):40. doi: 10.3390/mi9010040
38. Driskill MM, Coates IA, Hurst PJ, *et al.* Lyophilized SARS-CoV-2 self-amplifying RNA vaccines for microneedle array patch delivery. *J Control Release.* 2025;384:113944. doi: 10.1016/j.jconrel.2025.113944
39. Tran KTM, Gavitt TD, Le TT, *et al.* A single-administration microneedle skin patch for multi-burst release of vaccine against SARS-CoV-2. *Adv Mater Technol.* 2023;8(3):202200905. doi: 10.1002/admt.202200905
40. Rouphael NG, Paine M, Mosley R, *et al.* The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch (TIV-MNP 2015): A randomised, partly blinded, placebo-controlled, phase 1 trial. *Lancet.* 2017;390(10095):649-658. doi: 10.1016/S0140-6736(17)30575-5
41. Mishra R, Maiti TK, Bhattacharyya TK. Feasibility studies on nafion membrane actuated micropump integrated with hollow microneedles for insulin delivery device. *J Microelectromech Syst.* 2019;28(6):987-996. doi: 10.1109/JMEMS.2019.2939189
42. Xenikakis I, Tsongas K, Tzimtzimis EK, *et al.* Transdermal delivery of insulin across human skin *in vitro* with 3D printed hollow microneedles. *J Drug Deliv Sci Technol.* 2022;67:102891. doi: 10.1016/j.jddst.2021.102891
43. Smith F, Kotowska AM, Fiedler B, *et al.* Using oscillation to improve the insertion depth and consistency of hollow microneedles for transdermal insulin delivery with mechanistic insights. *Mol Pharm.*

2025;22(1):316-329.
doi: 10.1021/acs.molpharmaceut.4c00942

44. Li R, Liu X, Yuan X, *et al.* Fast customization of hollow microneedle patches for insulin delivery. *Int J Bioprint.* 2022;8(2):553.
doi: 10.18063/ijb.v8i2.553
45. Zhang S, Sims J, Mehochko I, Zolovick R, Kwak T, Staples A. Design and characterization of 3D-printed hollow microneedle arrays for transdermal insulin delivery. *AIP Adv.* 2024;14(6):e065123.
doi: 10.1063/5.0204216
46. Davis SP, Martanto W, Allen MG, Prausnitz MR. Hollow metal microneedles for insulin delivery to diabetic rats. *IEEE Trans Biomed Eng.* 2005;52(5):909-915.
doi: 10.1109/TBME.2005.845240
47. Xiao N, Li H, Fan Z, *et al.* An electrochromism-equipped enzymatic biofuel cell system combined with hollow microneedle array for self-powered glucose sensing in interstitial fluid. *Mikrochim Acta.* 2025;192(4):224.
doi: 10.1007/s00604-025-07096-y
48. Yin S, Yu Z, Song N, *et al.* A long lifetime and highly sensitive wearable microneedle sensor for the continuous real-time monitoring of glucose in interstitial fluid. *Biosens Bioelectron.* 2024;244:115822.
doi: 10.1016/j.bios.2023.115822
49. Luo F, Li Z, Shi Y, *et al.* Integration of hollow microneedle arrays with jellyfish-shaped electrochemical sensor for the detection of biomarkers in interstitial fluid. *Sensors (Basel).* 2024;24(12):3729.
doi: 10.3390/s24123729
50. Chen J, Cheng P, Sun Y, *et a*l. A minimally invasive hollow microneedle with a cladding structure: Ultra-thin but strong, batch manufacturable. *IEEE Trans Biomed Eng.* 2019;66(12):3480-3485.
doi: 10.1109/TBME.2019.2906571
51. Unver N, Odabas S, Demirel GB, Gul OT. Hollow microneedle array fabrication using a rational design to prevent skin clogging in transdermal drug delivery. *J Mater Chem B.* 2022;10(41):8419-8431.
doi: 10.1039/d2tb01648f
52. Datta A, Biswas S, Dhar R, Kanti Bhattacharyya T. Design and development of a piezoelectric driven micropump integrated with hollow microneedles for precise insulin delivery. *J Micromech Microeng.* 2023;33(7):075003.
doi: 10.1088/1361-6439/acd25f
53. Lee HS, Ryu HR, Roh JY, Park JH. Bleomycin-coated microneedles for treatment of warts. *Pharm Res.* 2017;34(1):101-112.
doi: 10.1007/s11095-016-2042-x
54. Jeong HR, Jun H, Cha HR, Lee JM, Park JH. Safe coated microneedles with reduced puncture occurrence after administration. *Micromachines (Basel).* 2020;11(8):710.
doi: 10.3390/mi11080710
55. Fu X, Zhang T, Xia C, *et al.* Spiderweb-shaped iron-coordinated polymeric network as the novel coating on microneedles for transdermal drug delivery against infectious wounds. *Adv Healthc Mater.* 2024;13(29):e2401788.
doi: 10.1002/adhm.202401788
56. Kim SJ, Shin JH, Noh JY, Song CS, Kim YC. Development of the novel coating formulations for skin vaccination using stainless steel microneedle. *Drug Deliv Transl Res.* 2016;6(5):486-497.
doi: 10.1007/s13346-016-0321-z
57. Choi IJ, Cha HR, Hwang SJ, Baek SK, Lee JM, Choi SO. Live vaccinia virus-coated microneedle array patches for smallpox vaccination and stockpiling. *Pharmaceutics.* 2021;13(2):209.
doi: 10.3390/pharmaceutics13020209
58. Baek SH, Shin JH, Kim YC. Drug-coated microneedles for rapid and painless local anesthesia. *Biomed Microdevices.* 2017;19(1):2.
doi: 10.1007/s10544-016-0144-1
59. Zhu Q, Zarnitsyn VG, Ye L, *et al.* Immunization by vaccine-coated microneedle arrays protects against lethal influenza virus challenge. *Proc Natl Acad Sci U S A.* 2009;106(19):7968-7973.
doi: 10.1073/pnas.0812652106
60. Shin Y, Kim J, Seok JH, *et al.* Development of the H3N2 influenza microneedle vaccine for cross-protection against antigenic variants. *Sci Rep.* 2022;12(1):12189.
doi: 10.1038/s41598-022-16365-2
61. Liang L, Zhao ZQ, Chen Y, Ren GY, Li JY, Guo XD. Some attempts to increase the amount of drug coated onto the microneedles. *J Drug Deliv Sci Technol.* 2022;67:102986.
doi: 10.1016/j.jddst.2021.102986
62. Matadh AV, Jakka D, Pragathi SG, *et al.* Polymer-coated polymeric (PCP) microneedles for controlled dermal delivery of 5-fluorouracil. *AAPS PharmSciTech.* 2022;24(1):9.
doi: 10.1208/s12249-022-02471-x
63. Lu Z, Du S, Li J, *et al.* Langmuir-blodgett-mediated formation of antibacterial microneedles for long-term transdermal drug delivery. *Adv Mater.* 2023;35(38):e2303388.
doi: 10.1002/adma.202303388
64. Mutlu ME, Ulag S, Sengor M, Daglılar S, Narayan R, Gunduz O. Electrosprayed collagen/gentamicin nanoparticles coated microneedle patches for skin treatment. *Mater Lett.* 2021;305:130844.
doi: 10.1016/j.matlet.2021.130844
65. Diao N, Qu H, Wang W, *et al.* Preparation and evaluation of a soluble microneedle loaded with resveratrol nanocrystals. *J Drug Deliv Sci Technol.* 2024;94:105463.
doi: 10.1016/j.jddst.2024.105463
66. Chen HJ, Lin DA, Liu F, *et al.* Transdermal delivery of living and biofunctional probiotics through dissolvable microneedle patches. *ACS Appl Bio Mater.* 2018;1(2):374-381.
doi: 10.1021/acsabm.8b00102
67. Cseh M, Katona G, Berkó S, Budai-Szűcs M, Csóka I. A stereolithography-based modified spin-casting method for faster laboratory-scale production of dexamethasone-containing dissolving microneedle arrays. *Pharmaceutics.* 2024;16(8):1005.
doi: 10.3390/pharmaceutics16081005
68. Kim NW, Kim SY, Lee JE, *et al.* Enhanced cancer vaccination by *in situ* nanomicelle-generating dissolving microneedles. *ACS Nano.* 2018;12(10):9702-9713.
doi: 10.1021/acsnano.8b04146
69. Lee IC, Lin WM, Shu JC, Tsai SW, Chen CH, Tsai MT. Formulation of two-layer dissolving polymeric microneedle patches for insulin transdermal delivery in diabetic mice. *J Biomed Mater Res A.* 2017;105(1):84-93.
doi: 10.1002/jbm.a.35869
70. Li Y, Gong JY, Wang P, *et al.* Dissolving microneedle system containing Ag nanoparticle-decorated silk fibroin microspheres and antibiotics for synergistic therapy of bacterial biofilm infection. *J Colloid Interface Sci.* 2024;661:123-138.
doi: 10.1016/j.jcis.2024.01.147
71. Sabri AHB, Anjani QK, Gurnani P, *et al.* Fabrication and characterisation of poly(sulfonated) and poly(sulfonic acid) dissolving microneedles for delivery of antibiotic and antifungal agents. *Int J Pharm.* 2023;644:123292.
doi: 10.1016/j.ijpharm.2023.123292
72. Bauleth-Ramos T, El-Sayed N, Fontana F, Lobita M, Shahbazi MA, Santos HA. Recent approaches for enhancing the performance of dissolving microneedles in drug delivery applications. *Mater Today.* 2023;63:239-287.
doi: 10.1016/j.mattod.2022.12.007
73. Meng Y, Li XJ, Li Y, *et al.* Novel double-layer dissolving microneedles for transmucosal sequential delivery of multiple drugs in the treatment of oral mucosa diseases. *ACS Appl Mater Interfaces.* 2023;15(11):13892-13906.
doi: 10.1021/acsami.2c19913
74. Gu X, Wu Z, Wu D, *et al.* Hydrogel microneedle patch for treatment of liver fibrosis. *Mater Today Adv.* 2023;20:100417.
doi: 10.1016/j.mtadv.2023.100417
75. Dawud H, Edelstein-Pardo N, Mulamukkil K, Amir RJ, Abu Ammar A. Hydrogel microneedles with programmed mesophase transitions for controlled drug delivery. *ACS Appl Bio Mater.* 2024;7(3):1682-1693.
doi: 10.1021/acsabm.3c01133
76. Zhang Q, Na J, Liu X, He J. Exploration of the delivery of oncolytic newcastle disease virus by gelatin methacryloyl microneedles. *Int J Mol Sci.* 2024;25(4):2353.
doi: 10.3390/ijms25042353
77. Darmau B, Sacchi M, Texier I, Gross AJ. Self-extracting dextran-based hydrogel microneedle arrays with an interpenetrating bioelectroenzymatic sensor for transdermal monitoring with matrix

protection. *Adv Healthc Mater.* 2025;14(2):e2403209. doi: 10.1002/adhm.202403209
78. Baek S, Lee KP, Han CS, Kwon SH, Lee SJ. Hyaluronic acid-based biodegradable microneedles loaded with epidermal growth factor for treatment of diabetic foot. *Macromol Res.* 2024;32(1):13-22. doi: 10.1007/s13233-023-00206-w
79. Chandran R, Mohd Tohit ER, Stanslas J, Salim N, Tuan Mahmood TM. Drug-loaded hydrogel microneedles for sustainable transdermal delivery of macromolecular proteins. *Curr Drug Deliv.* 2025. doi: 10.2174/0115672018346286241121052105
80. Chi Y, Zheng Y, Pan X, *et al.* Enzyme-mediated fabrication of nanocomposite hydrogel microneedles for tunable mechanical strength and controllable transdermal efficiency. *Acta Biomater.* 2024;174:127-140. doi: 10.1016/j.actbio.2023.11.038
81. Shriky B, Babenko M, Whiteside BR. Dissolving and swelling hydrogel-based microneedles: An overview of their materials, fabrication, characterization methods, and challenges. *Gels.* 2023;9(10):806. doi: 10.3390/gels9100806
82. Chen S, Matsumoto H, Moro-Oka Y, *et al.* Smart microneedle fabricated with silk fibroin combined semi-interpenetrating network hydrogel for glucose-responsive insulin delivery. *ACS Biomater Sci Eng.* 2019;5(11):5781-5789. doi: 10.1021/acsbiomaterials.9b00532
83. Bhadale RS, Londhe VY. Solid microneedle assisted transepidermal delivery of iloperidone loaded film: Characterization and skin deposition studies. *J Drug Deliv Sci Technol.* 2023;79:104028. doi: 10.1016/j.jddst.2022.104028
84. Omolu A, Bailly M, Day RM. Assessment of solid microneedle rollers to enhance transmembrane delivery of doxycycline and inhibition of MMP activity. *Drug Deliv.* 2017;24(1):942-951. doi: 10.1080/10717544.2017.1337826
85. Gholami S, Mohebi MM, Hajizadeh-Saffar E, Ghanian MH, Zarkesh I, Baharvand H. Fabrication of microporous inorganic microneedles by centrifugal casting method for transdermal extraction and delivery. *Int J Pharm.* 2019;558:299-310. doi: 10.1016/j.ijpharm.2018.12.089
86. Li Y, Zhang H, Yang R, *et al.* Fabrication of sharp silicon hollow microneedles by deep-reactive ion etching towards minimally invasive diagnostics. *Microsyst Nanoeng.* 2019;5:41. doi: 10.1038/s41378-019-0077-y
87. Chong RH, Gonzalez-Gonzalez E, Lara MF, *et al.* Gene silencing following siRNA delivery to skin via coated steel microneedles: *In vitro* and *in vivo* proof-of-concept. *J Control Release.* 2013;166(3):211-219. doi: 10.1016/j.jconrel.2012.12.030
88. Mansouri Majd S. Hydrogel-coated microneedle biosensor for selective and low-potential glucose detection in skin-mimicking interstitial fluid phantoms. *Talanta.* 2025;297:128555. doi: 10.1016/j.talanta.2025.128555
89. Liu Y, Zhao ZQ, Liang L, *et al.* Toward a solid microneedle patch for rapid and enhanced local analgesic action. *Drug Deliv Transl Res.* 2024;14(7):1810-1819. doi: 10.1007/s13346-023-01486-6
90. Joy D, Jose J, Bibi S, *et al.* Development of microneedle patch loaded with *bacopa monnieri* solid lipid nanoparticles for the effective management of Parkinson's disease [retracted in: *Bioinorg Chem Appl.* 2024;2024:9852582. doi: 10.1155/2024/9852582.]. *Bioinorg Chem Appl.* 2022;2022:9150205. doi: 10.1155/2022/9150205
91. Liu J, Zhang Z, Lin X, *et al.* Magnesium metal-organic framework microneedles loaded with curcumin for accelerating oral ulcer healing. *J Nanobiotechnology.* 2024;22(1):594. doi: 10.1186/s12951-024-02873-y
92. Zhang Y, Zhao G, Zheng M, Hu T, Yang C, Xu C. A nanometallic conductive composite-hydrogel core-shell microneedle skin patch for real-time monitoring of interstitial glucose levels. *Nanoscale.* 2023;15(40):16493-16500. doi: 10.1039/d3nr01245j
93. Zhang R, Rana MS, Huang L, Qian K. An antibacterial sensitive wearable biosensor enabled by engineered metal-boride-based organic electrochemical transistors and hydrogel microneedles. *J Mater Chem A.* 2025;13(24):18590-18599. doi: 10.1039/d5ta01335f
94. Gautier L, Wiart-Letort S, Massé A, *et al.* Design of hydrogel microneedle arrays for physiology monitoring of farm animals. *Micromachines (Basel).* 2024;16(9):1015. doi: 10.3390/mi16091015
95. Mohan AMV, Windmiller JR, Mishra RK, Wang J. Continuous minimally-invasive alcohol monitoring using microneedle sensor arrays. *Biosens Bioelectron.* 2017;91:574-579. doi: 10.1016/j.bios.2017.01.016
96. Jin D, Xu Z, Zhao H, *et al.* A minimally invasive sensing system based on hydrogel microneedle patches and Au/Cu_2O nanospheres modified screen-printed carbon electrode for glucose monitoring in interstitial skin fluid. *Microchem J.* 2024;205:111367. doi: 10.1016/j.microc.2024.111367
97. Dahis D, Dion MZ, Cryer AM, *et al.* Monitoring melanoma responses to sting agonism and focused ultrasound thermal ablation using microneedles and ultrasensitive single molecule arrays. *Adv Funct Mater.* 2023;33(50):2301659. doi: 10.1002/adfm.202301659
98. Huang H, Qu M, Zhou Y, *et al.* A microneedle patch for breast cancer screening via minimally invasive interstitial fluid sampling. *Chem Eng J.* 2023;472:145036. doi: 10.1016/j.cej.2023.145036
99. Li X, Zheng S, He M, *et al.* Self-calibrating multiplexed microneedle electrode array for continuous mapping of subcutaneous multi-analytes in diabetes. *Innovation (Camb).* 2025;6(2):100781. doi: 10.1016/j.xinn.2024.100781
100. Liu Y, Yang L, Cui Y. A wearable, rapidly manufacturable, stability-enhancing microneedle patch for closed-loop diabetes management. *Microsyst Nanoeng.* 2024;10(1):112. doi: 10.1038/s41378-024-00663-y
101. Yang Y, Sheng C, Dong F, Liu S. An integrated wearable differential microneedle array for continuous glucose monitoring in interstitial fluids. *Biosens Bioelectron.* 2024;256:116280. doi: 10.1016/j.bios.2024.116280
102. Xu J, Yang B, Kong J, Zhang Y, Fang X. Real-time monitoring and early warning of a cytokine storm *in vivo* using a wearable noninvasive skin microneedle patch. *Adv Healthc Mater.* 2023;12(18):e2203133. doi: 10.1002/adhm.202203133
103. Gao Z, Lu Z, Zhao S, *et al.* Microneedle sensor for real-time monitoring of inflammatory cytokine signature. *Nano Today.* 2025;64:102777. doi: 10.1016/j.nantod.2025.102777
104. Yang J, Zhao X, Yan LX, Chen LJ, Yan XP. Dual-Indicator loaded porous polymer microneedle patches for rapid and colorimetric detection of water-injected meat. *Food Chem.* 2025;467:142218. doi: 10.1016/j.foodchem.2024.142218
105. Xu W, Hu J, Liang H, Liu N, Zhou Y, Zhao Z. Construction of an effective colorimetric and fluorescent dual-mode microneedle patch for non-destructive detection of nitrite in pickling foods. *Biosens Bioelectron.* 2025;287:117744. doi: 10.1016/j.bios.2025.117744
106. Huang S, Liu J, Liu Y, *et al.* Inhibit diffusion of the small molecule drug lidocaine hydrochloride in dissolving microneedles based on a phase separation approach. *J Drug Deliv Sci Technol.* 2024;100:106030. doi: 10.1016/j.jddst.2024.106030
107. Wright N, Wu T, Wang Y. Multilayered microneedles for triphasic controlled delivery of small molecules and proteins. *Macromol Biosci.* 2024;24(4):e2300431. doi: 10.1002/mabi.202300431
108. Bhatnagar S, Kumari P, Pattarabhiran SP, Venuganti VVK. Zein microneedles for localized delivery of chemotherapeutic agents to treat breast cancer: Drug loading, release behavior, and skin permeation studies. *AAPS PharmSciTech.* 2018;19(4):1818-1826. doi: 10.1208/s12249-018-1004-5
109. He Y, Zang M, Zhang J, *et al.* A universal powder-laden crosslinked chitosan microneedle patch for high-dose controllable drug delivery. *Int J Biol Macromol.* 2024;255:127988. doi: 10.1016/j.ijbiomac.2023.127988
110. Yang J, Chen Z, Ye R, *et al.* Touch-actuated microneedle array patch for closed-loop transdermal drug delivery. *Drug Deliv.* 2018;25(1):1728-1739.

doi: 10.1080/10717544.2018.1507060
111. Pires LR, Amado IR, Gaspar J. Dissolving microneedles for the delivery of peptides-Towards tolerance-inducing vaccines. *Int J Pharm.* 2020;586:119590. doi: 10.1016/j.ijpharm.2020.119590
112. D'Amico C, Fusciello M, Hamdan F, *et al.* Transdermal delivery of PeptiCRAd cancer vaccine using microneedle patches. *Bioact Mater.* 2024;45:115-127. doi: 10.1016/j.bioactmat.2024.11.006
113. Lee J, Neustrup MA, Slütter B, O'Mahony C, Bouwstra JA, van der Maaden K. Intradermal vaccination with PLGA nanoparticles via dissolving microneedles and classical injection needles. *Pharm Res.* 2024;41(2):305-319. doi: 10.1007/s11095-024-03665-7
114. Pukfukdee P, Banlunara W, Rutwaree T, *et al.* Solid composite material for delivering viable cells into skin tissues *via* detachable dissolvable microneedles. *ACS Appl Bio Mater.* 2020;3(7):4581-4589. doi: 10.1021/acsabm.0c00498
115. Hao T, Guo H, Wang C, *et al.* Mitochondria-targeted microneedles reverse doxorubicin resistance via apoptosis-ferroptosis synergy. *ACS Nano.* 2025;19(25):23315-23333. doi: 10.1021/acsnano.5c06302
116. Li X, Xiao X, Zhang Y, *et al.* Microneedles based on hyaluronic acid-polyvinyl alcohol with antibacterial, anti-inflammatory, and antioxidant effects promote diabetic wound healing. *Int J Biol Macromol.* 2024;282(Pt 5):137185. doi: 10.1016/j.ijbiomac.2024.137185
117. Liu S, Jin MN, Quan YS, *et al.* The development and characteristics of novel microneedle arrays fabricated from hyaluronic acid, and their application in the transdermal delivery of insulin. *J Control Release.* 2012;161(3):933-941. doi: 10.1016/j.jconrel.2012.05.030
118. Chen X, Yu H, Wang L, Shen D, Li C, Zhou W. Cross-linking-density-changeable microneedle patch prepared from a glucose-responsive hydrogel for insulin delivery. *ACS Biomater Sci Eng.* 2021;7(10):4870-4882. doi: 10.1021/acsbiomaterials.1c01073
119. Zhao J, Wu Y, Chen J, *et al. In vivo* monitoring of microneedle-based transdermal drug delivery of insulin. *J Innov Opt Health Sci.* 2018;11(5):1850032. doi: 10.1142/S1793545818500323
120. Kim Y, Min HS, Shin J, *et al.* Film-trigger applicator (FTA) for improved skin penetration of microneedle using punching force of carboxymethyl cellulose film acting as a microneedle applicator. *Biomater Res.* 2022;26(1):53. doi: 10.1186/s40824-022-00302-5
121. Wang S, Yang C, Zhang W, *et al.* Glucose-responsive microneedle patch with high insulin loading capacity for prolonged glycemic control in mice and minipigs. *ACS Nano.* 2024;18(38):26056-26065. doi: 10.1021/acsnano.4c05562
122. Xiu X, Fu H, Zhang R, *et al.* Novel antigen-presenting cell-targeted nanoparticles enhance split vaccine immunity through microneedles inoculation. *Int J Nanomedicine.* 2025;20:5529-5549. doi: 10.2147/IJN.S502724
123. Kim YC, Lee JW, Esser ES, *et al.* Fabrication of microneedle patches with lyophilized influenza vaccine suspended in organic solvent. *Drug Deliv Transl Res.* 2021;11(2):692-701. doi: 10.1007/s13346-021-00927-4
124. Choi Y, Lee GS, Li S, *et al.* Hepatitis B vaccine delivered by microneedle patch: Immunogenicity in mice and rhesus macaques. *Vaccine.* 2023;41(24):3663-3672. doi: 10.1016/j.vaccine.2023.05.005
125. Zheng Y, Ling Z, Li Z, *et al.* A rapidly dissolvable microneedle patch with tip-accumulated antigens for efficient transdermal vaccination. *Macromol Biosci.* 2023;23(12):e2300253. doi: 10.1002/mabi.202300253
126. Zheng Y, Li Z, Li S, *et al.* Separable nanocomposite hydrogel microneedles for intradermal and sustained delivery of antigens to enhance adaptive immune responses. *Acta Biomater.* 2024;185:203-214. doi: 10.1016/j.actbio.2024.07.031
127. Zhang L, Xiu X, Li Z, *et al.* Coated porous microneedles for effective intradermal immunization with split influenza vaccine. *ACS Biomater Sci Eng.* 2023;9(12):6880-6890. doi: 10.1021/acsbiomaterials.3c01212
128. Liu T, Sun Y, Jiang G, *et al.* Porcupine-inspired microneedles coupled with an adhesive back patching as dressing for accelerating diabetic wound healing. *Acta Biomater.* 2023;160:32-44. doi: 10.1016/j.actbio.2023.01.059
129. Guo M, Wang Y, Gao B, He B. Shark tooth-inspired microneedle dressing for intelligent wound management. *ACS Nano.* 2021;15(9):15316-15327. doi: 10.1021/acsnano.1c06279
130. Choi J, Shim S, Shin J, *et al.* Suprachoroidal space-inducing hydrogel-forming microneedles (SI-HFMN): An innovative platform for drug delivery to the posterior segment of the eye. *Bioact Mater.* 2025;50:47-60. doi: 10.1016/j.bioactmat.2025.03.024
131. Liu J, Hu J, Li Y, *et al.* Microneedle-mediated biomimetic nanoparticles for targeted antioxidant and anti-inflammatory therapy in age-related macular degeneration. *J Control Release.* 2025;384:113908. doi: 10.1016/j.jconrel.2025.113908
132. Ma J, Tai Z, Li Y, *et al.* Dissolving microneedle-based cascade-activation nanoplatform for enhanced photodynamic therapy of skin cancer. *Int J Nanomedicine.* 2024;19:2057-2070. doi: 10.2147/IJN.S443835
133. Chen Y, Liu N, Feng S, Xu W, Mao C, Wan M. Microneedle-based nanomotor cancer vaccine combined with chemotherapy for synergistic melanoma therapy. *Nanoscale.* 2025;17(20):12716-12726. doi: 10.1039/d5nr01240f
134. Xue H, Jin J, Huang X, *et al.* Wearable flexible ultrasound microneedle patch for cancer immunotherapy. *Nat Commun.* 2025;16(1):2650. doi: 10.1038/s41467-025-58075-z
135. Huang S, Wen T, Wang J, *et al.* Nanoparticle-integrated dissolving microneedles for the co-delivery of R848/aPD-1 to synergistically reverse the immunosuppressive microenvironment of triple-negative breast cancer. *Acta Biomater.* 2024;176:344-355. doi: 10.1016/j.actbio.2024.01.009
136. Lan X, Zhu W, Huang X, *et al.* Microneedles loaded with anti-PD-1-cisplatin nanoparticles for synergistic cancer immuno-chemotherapy. *Nanoscale.* 2020;12(36):18885-18898. doi: 10.1039/d0nr04213g
137. Huang J, Yao Z, Li B, Ping Y. Targeted delivery of PROTAC-based prodrug activated by bond-cleavage bioorthogonal chemistry for microneedle-assisted cancer therapy. *J Control Release.* 2023;361:270-279. doi: 10.1016/j.jconrel.2023.07.062
138. He Y, Chen N, Zang M, *et al.* Glucose-responsive insulin microneedle patches for long-acting delivery and release visualization. *J Control Release.* 2024;368:430-443. doi: 10.1016/j.jconrel.2024.03.001
139. Tang N, Zheng Y, Jiang X, *et al.* Wearable sensors and systems for wound healing-related pH and temperature detection. *Micromachines (Basel).* 2021;12(4):430. doi: 10.3390/mi12040430
140. Ullah A, Jang M, Khan H, *et al.* Microneedle array with a pH-responsive polymer coating and its application in smart drug delivery for wound healing. *Sens Actuat B Chem.* 2021;345:130441. doi: 10.1016/j.snb.2021.130441
141. Deng S, Tai Y, Liu C, *et al.* Multifunctional microneedle-mediated photothermo-gas-ion synergic therapy accelerates MRSA infacted diabetic wound healing. *Mater Today Bio.* 2025;32:101903. doi: 10.1016/j.mtbio.2025.101903
142. Zheng Z, Ye H, Wang J, *et al.* Visible-light-controllable drug release from multilayer-coated microneedles. *J Mater Chem B.* 2017;5(34):7014-7017. doi: 10.1039/c7tb01546a
143. Liao Y, Liu C, Guo L, *et al.* Temperature-responsive detachable microneedles integrated with minoxidil nanoparticle for effectively promoting hair regrowth. *Chem Eng J.* 2024;495:153666. doi: 10.1016/j.cej.2024.153666
144. Yang J, Gong X, Zheng Y, *et al.* Microneedle-based integrated pharmacokinetic and pharmacodynamic evaluation platform for personalized medicine. *Nat Commun.* 2025;16(1):6260. doi: 10.1038/s41467-025-61549-9
145. Economidou SN, Pere CPP, Reid A, *et al.* 3D printed microneedle patches

using stereolithography (SLA) for intradermal insulin delivery. *Mater Sci Eng C Mater Biol Appl.* 2019;102:743-755. doi: 10.1016/j.msec.2019.04.063

146. Dul M, Alali M, Ameri M, *et al.* Assessing the risk of a clinically significant infection from a Microneedle Array Patch (MAP) product. *J Control Release.* 2023;361:236-245. doi: 10.1016/j.jconrel.2023.07.001
147. Du G, Zhang Z, He P, Zhang Z, Sun X. Determination of the mechanical properties of polymeric microneedles by micromanipulation. *J Mech Behav Biomed Mater.* 2021;117:104384. doi: 10.1016/j.jmbbm.2021.104384
148. Merzougui C, Yang X, Meng D, Huang Y, Zhao X. Microneedle array-based dermal interstitial fluid biopsy for cancer diagnosis: Advances and challenges. *Adv Healthc Mater.* 2025;14(7):e2404420. doi: 10.1002/adhm.202404420

Received: July 30, 2025
Revised: September 18, 2025
Accepted: September 23, 2025
Available online: November 5, 2025