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REVIEW

Development of a next-generation closed-loop precision system: multiscale-engineered nanocomposite hydrogel microneedles

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Abstract

Microneedle technology has undergone a paradigm shift from basic transdermal drug delivery to intelligent, closed-loop theranostic systems. Hydrogel materials have emerged as core carriers due to their excellent biocompatibility, efficient drug-loading capacity, and improved patient compliance. Moreover, critical bottlenecks in hydrogel microneedles, including poor mechanical strength, burst release of drugs, and delayed response to treatment, can be addressed via cross-scale integration of nanomaterials. This review systematically outlines several multiscale engineering strategies to overcome these limitations. The construction of nanotopological networks coupled with dynamic crosslinking modulation synergistically enhances the mechanical properties, stability of drug loading, and conductivity of hydrogel microneedles. Furthermore, responsive nanocarriers equipped with biosensors help establish a closed-loop linkage between monitoring and therapeutic functions. We highlight their synergistic theranostic advantages in scenarios such as wound regulation and tumor-immune microenvironments, while revealing the role in integrating flexible electronics with wearable systems in intelligent medicine. We also summarize the research advances on the biosafety and scalable manufacturing processes of nanocomposite hydrogel microneedles (NHMNs), providing examples of clinical translation to elucidate the path from fundamental research to industrial implementation. As a convergence of nanotechnology, biomaterials, and flexible electronics, NHMNs provide new standards for transdermal theranostics as well as a roadmap for iterative advancement of intelligent theranostic devices in personalized medicine. Their cross-scale collaborative design, which spans from the properties of materials to the functional integration of macroscopic devices, can facilitate potential breakthroughs in next-generation closed-loop theranostic systems.

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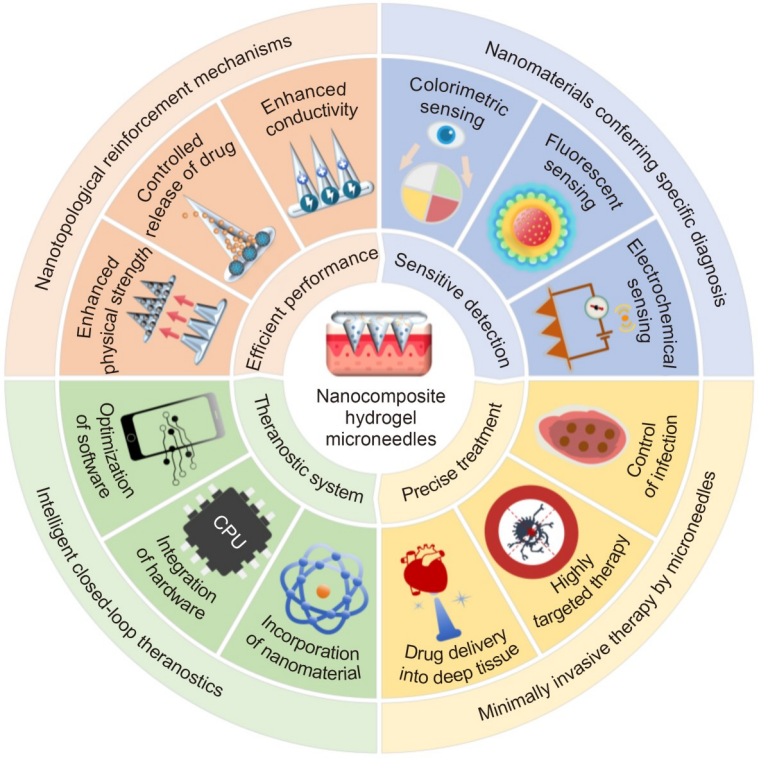
Graphical abstract



Keywords Microneedles · Hydrogel · Nanomaterials · Transdermal drug delivery · Closed-loop theranostic system

1 Introduction

Precision medicine focuses on personalized therapy through spatiotemporal diagnostics and therapeutic interventions [1]. However, clinical implementation in this field is limited due to significant patient burdens and constraints on therapeutic efficacy resulting from multiple technological bottlenecks. Specifically, there are three key technical limitations. First, insufficient precision in drug delivery due to a lack of spatiotemporal control in conventional delivery systems results in inefficient local distribution and off-target toxicity of the drug [2]. This severely restricts the therapeutic efficacy and impairs the patient's quality of life [3]. Oral and intravenous modes of administration enable systemic drug distribution [4], but are associated with low targeting efficiency and risk of toxic accumulation [5–7]. Localized drug delivery systems encounter equally severe challenges. In ophthalmic therapy, conventional eye drops have extremely low bioavailability (less than 5% drug absorption) owing to the corneal barrier and tear clearance mechanism [8, 9]. Over 90% of the administered drug is drained through the nasolacrimal duct, causing systemic side effects [10]. Meanwhile, transdermal patches fail to deliver sufficient therapeutic doses due to the stratum corneum barrier. Second, significant invasive risks—current invasive diagnostic and therapeutic devices often cause pain and tissue damage due to their high penetration depth or material rigidity [11, 12]. This substantially compromises patient compliance and usability, restricting long-term monitoring and clinical applications. Third, lack of dynamic responsiveness—open-loop therapeutic systems exhibit regulatory delays (e.g., prolonged response time in diabetes management) due to the discordance between the "monitoring–decision–execution" phases, failing to address acute pathological fluctuations. This potentially results in suboptimal therapeutic outcomes or even critical adverse events, necessitating the development of minimally invasive precision delivery platforms. Minimally invasive and non-invasive transdermal technologies, with their targeted delivery, low invasiveness, high patient compliance, and controlled-release capabilities [13, 14], are evolving from "passive carriers" to "active theranostic platforms." For example, microneedles can penetrate the stratum corneum barrier while avoiding neural damage, seamlessly integrating diagnostics and therapeutics by mimicking the microarchitecture of the skin [15–17]. Microneedle technology significantly enhances clinical

therapeutic efficacy through its unique targeting capabilities. In addition to improving drug delivery precision, its minimally or non-invasive nature, due to its compact structure, boosts patient compliance [18, 19]. Its dynamic regulation and responsiveness, enabled by integrating electronic devices, amalgamate clinical diagnosis with treatment. Consequently, it has emerged as an ideal platform for constructing closed-loop "monitoring–feedback–treatment" systems.

However, the incompatibility between material properties and the functional needs of clinical applications limits the development of microneedle technology. Since the first patent on microneedles was published in the 1970s [20] and validated for transdermal drug delivery in 1998 [21], first-generation rigid microneedles have been used to penetrate the stratum corneum barrier at the cost of compromised biocompatibility. Despite subsequent advancements, including glucose sensing for diagnostic purposes in 2000 [22] and the systematic exploration of morphological architectures, including solid, coated, and hollow configurations in 2004 [23], the issue of patient non-compliance persisted due to the material's rigidity. While the targeting specificity of microneedles for cancer detection improved in 2015 [24], researchers failed to achieve closed-loop therapeutic drug delivery. By 2019, microneedles became capable of detecting disease-specific biomarkers [25, 26], but due to their rigidity, the functional integration could not be achieved, constraining the development of closed-loop theranostic systems and their wider adoption in precision medicine. Hydrogel materials have emerged as a transformative platform in microneedle technology to address these challenges due to their unique biocompatibility, swelling-controlled drug-loading capacity, and compatibility with flexible electronics [27–29]. This breakthrough has led to the advent of hydrogel microneedles, which utilize physical or chemical crosslinking to construct topological networks that synergistically optimize their mechanical strength and drug-loading efficiency [30]. Their tunable crosslinking density ensures adjustable mechanical properties [31] and facilitates the precise fabrication of complex geometries through solution processability [32]. Due to their exceptional swelling behavior, minimally invasive penetration, and residue-free detachment, hydrogel microneedles integrate a high drug-loading capacity with patient compliance and biocompatibility [33–35]. However, their clinical translation continues to be impeded by unresolved issues, such as the imbalance between their mechanical strength and flexibility, delayed bio-signal responsiveness, and challenges in achieving personalized drug delivery [36–38]. These limitations stem from the inability of conventional homogeneous material systems to couple performance at multiple scales. To overcome these issues, nanoengineering-based strategies integrate interfacial topological reinforcement with material reconfiguration to enable the construction of next-generation, intelligent clinical platforms.

To build these state-of-the-art platforms, the mechanical strength, efficiency of drug loading, and response kinetics of hydrogel needles can be synergistically optimized by precisely balancing the nanomaterials and hydrogel matrices [39–41]. This also helps realize the transformative potential of nanomaterials and hydrogel microneedles in intelligent medical systems. However, fabricating nanocomposite hydrogel microneedles (NHMNs) requires multiscale engineering strategies rather than simple material blending to overcome the performance-related bottlenecks of traditional hydrogel microneedles. The core innovation lies in the topological synergy between the nanoscale components and the hydrogel network, implemented through physical self-assembly or chemical crosslinking methodologies. In physical approaches, nanomaterials are dispersed into hydrogel precursor solutions through mechanical stirring or ultrasonication to ensure uniform distribution. As a result, these nanomaterials form reinforced architectures analogous to steel and concrete. These physical approaches primarily rely on non-covalent interactions involving van der Waals forces, hydrogen bonding, electrostatic interactions, and host–guest interactions for stabilizing the nanomaterials within the hydrogel structure. The absence of complex chemical reactions from this process makes it conducive to large-scale production [42]. Chemical approaches mainly involve functionalizing nanomaterials and polymer backbones and establishing covalent bonds between these components using various crosslinking agents. They include crosslinking induced by either small molecules or macromolecules, photo-crosslinking, and enzyme-catalyzed crosslinking, each of which offers unique advantages in terms of control and specificity. Chemical crosslinking enables the precise tuning of the network architecture, which, in turn, helps develop reconfigurable "smart" hydrogels with tailored properties, such as controlled porosity, swelling behavior, and stimuli-responsive characteristics. Chemically synthesized NHMNs have a more stable and denser structure than those produced via physical methods [43]. Furthermore, customizable NHMNs equipped with drug-loaded microneedle arrays that are tailored to clinical requirements can be constructed using advanced fabrication techniques. Advances in solution-casting technology have revolutionized the fabrication of hydrogel microneedles, which have transitioned from conventional material blending to interfacial nanomaterial-matrix engineering. This advancement interconnects microstructural features with macroscopic functionality through the precise regulation of nanomaterials and hydrogel matrices. Following physical or chemical crosslinking strategies to embed nanomaterials into hydrogel matrices, NHMNs can be synthesized using standardized fabrication protocols, including ultrasonication,

polydimethylsiloxane (PDMS) mold casting, vacuum degassing, and thermal drying [44, 45]. These NHMNs can maintain their mechanical integrity while achieving the ordered spatial distribution of functional nanounits through interfacial interactions, providing an innovative personalized therapeutic platform.

In terms of clinical application, the use of nanocomposite microneedles has expanded to critical fields including targeted ocular drug delivery [46], diabetic wound repair [47], tumor immunotherapy [48], and psoriasis management [49]. Notably, the integration of intelligent stimuli-responsive nanocarriers, including photo-responsive, thermo-responsive, and magneto-responsive systems, has overcome limitations of "passive release" of traditional microneedles. Photo-responsive microneedle-based release systems [50] achieve faster response than conventional pH-responsive or enzyme-responsive systems, transforming transdermal drug delivery from "open-loop control" to "light-controlled release." This photo-responsive nanocarrier can trigger drug release in a pathological microenvironment [51], achieving "sensing–decision–execution" functionalities with a single microneedle device. Furthermore, the convergence of biosensing and therapeutic delivery within closed-loop NHMN systems has a transformative potential for precision medicine, which helps bridge the gap between diagnosis and therapy [52]. The integration of nanomaterial interfacial engineering with functional macroscopic devices heralds a new era of "intelligent closed-loop theranostics" in transdermal technology. At the same time, recent technological innovations are driving microneedle systems toward intelligent, integrated, and portable devices, such as wearable intelligent microneedle systems. These systems combine flexible electronics with microneedles to realize real-time monitoring and adaptive therapy for chronic wounds, providing an interdisciplinary design paradigm for personalized and portable medical devices as well as a critical reference for the design of next-generation therapeutic devices.

In present-day precision medicine, microneedles have overcome three major technological limitations, but their clinical implementation remains limited. Specifically, the conflict between clinical requirements and microneedle performance, which is due to the imbalance between mechanical strength and flexibility, delayed responsiveness to biological signals, and challenges in personalized drug delivery, hinders existing systems from simultaneously achieving high therapeutic precision and optimal patient compliance. This creates a void between single-drug delivery and closed-loop theranostics, inherently resulting from deficient dynamic responsiveness, which disrupts the "sensing–decision–execution" process and impedes true individualized closed-loop therapy management. This creates a disconnect between experimental innovation and clinical translation, where long-term biosafety validation, unified regulatory frameworks, and medical translation pathways remain critical hurdles toward clinical adoption. In this review, we systematically discuss the multiscale interfacial engineering of NHMNs and elucidate solutions addressing three fundamental challenges in this area, from material reconfiguration to functional integration. Initially, we explain how NHMNs overcome conventional microneedle limitations via cross-scale materials engineering, which enhances the clinical performance of microneedles. Subsequently, we investigate their closed-loop integration capability spanning biosensing, feedback, and responsive drug delivery, showcasing the integration of single-drug delivery and closed-loop theranostics. Finally, we evaluate the recent advances in biosafety validation, scalable manufacturing techniques, and preliminary clinical translation cases to mitigate the experimental innovation and clinical translation incompatibility. We explore the generational leap from fundamental research to intelligent "closed-loop" theranostic systems that combine biosensing, real-time feedback, and on-demand therapy. Finally, we examine the extant challenges and propose synergistic development strategies for advanced manufacturing protocols, biointerfacial optimization, and pathways for clinical translation to propel this technology from laboratory research to clinical implementation.

2 Design principles of NHMNs

2.1 Conventional hydrogel microneedles

Hydrogel microneedles have revolutionized transdermal theranostics, surpassing solid microneedles in terms of drug-loading capacity and patient compliance owing to their controllable swelling-related properties and exceptional biocompatibility. These hydrogel microneedles are primarily fabricated using mold replication and three-dimensional (3D) additive manufacturing technologies, both of which are well-established industrial processes. In PDMS mold casting, a precursor hydrogel solution is poured into a PDMS mold, which is then centrifuged or vacuum-degassed to ensure complete mold-filling. Subsequently, the molds are dried and demolded, yielding the final hydrogel microneedle [53]. In additive manufacturing, photocurable resins are used to construct microneedles in a layer-by-layer manner under ultraviolet (UV) irradiation. This requires predefined technical parameters, such as the dimensions and architecture of the microneedle [54]. Traditional hydrogel microneedles are fabricated using a combination of natural polymers (e.g., gelatin, hyaluronic acid, and silk fibroin) and synthetic polymers (e.g., sodium polyacrylate, polyvinyl alcohol, and polymethacrylic acid) [55]. Despite their low toxicity and excellent biocompatibility, these materials have a low mechanical strength that significantly limits

their clinical applicability. Polymer crosslinking strategies can be broadly categorized into chemical and physical crosslinking methods. Chemical crosslinking involves the formation of a covalent bond via photoinitiation, thermal initiation, or crosslinkers (e.g., citric anhydride and glutaraldehyde) to yield stable polymer networks. Physical crosslinking, by contrast, relies on molecular self-assembly via ionic interactions, van der Waals forces, or hydrogen bonding. The resulting reversible crosslinked networks enable rapid gel formation or dissolution under external stimuli, such as changes in temperature or pH [56]. Chemically crosslinked polymers are denser, possess superior swelling capacity, and are inexpensive, but their synthesis faces challenges in terms of controllability, unlike physical methods.

The inherent limitations in the material properties have necessitated the meticulous geometric design of microneedles to ensure a balance between their mechanical performance and patient compliance. The height of microneedles typically ranges from 100 to 1500 μm, with their base diameter spanning from 150 to 300 μm [57]. The length of the needle has been shown to be highly correlated with the intensity of the pain felt by the patient. When its length is increased from 480 to 1450 μm, the reported pain levels escalate from 5% to 37%, whereas standard hypodermic needles have a 100% pain index [58]. Furthermore, the base diameter of the microneedle is a critical parameter as it directly influences its structural stability. The geometric configuration of microneedles also significantly impacts their functional performance. Conical microneedles are the most commonly used due to their reduced resistance to penetration, while the expanded surface area of quadrangular pyramidal configurations enhances their drug-loading capacity. Although various other shapes have been extensively explored, their complex fabrication processes, low mechanical strength, and compromised patient compliance make them unsuitable for mainstream hydrogel microneedle systems [59].

While conventional hydrogel microneedles based on the aforementioned materials and fabrication strategies have been studied extensively, they still exhibit performance-related limitations, including inadequate mechanical strength, limited control over drug release capabilities, and poor electrical conductivity [60–62]. Consequently, optimizing their performance is the main research focus in this area. Nanomaterials exhibit unique advantages due to their high specific surface area and interfacial interactions, which enable a significant enhancement in the mechanical strength and flexibility of hydrogels, thereby improving the mechanical performance of microneedles. Nanomaterials can optimize the drug-loading capacity and control the rate of release of hydrogel microneedles through physical or chemical crosslinking, facilitating precise drug delivery. Furthermore, the surface functionalization and biomimetic structural engineering of nanomaterials mitigate cytotoxicity and enhance the biocompatibility of hydrogels by ensuring the complete dissolution of the polymer after skin penetration and avoiding the deposition of residual polymer. These distinctive advantages of nanomaterials enable the transition of hydrogel microneedles toward nanocomposite strategies. Such systems are anticipated to surpass the intrinsic performance-related thresholds of conventional hydrogels through nanotopological reinforcement, thereby establishing next-generation intelligent transdermal theranostic systems.

2.2 Nanotopological reinforcement mechanisms of hydrogel microneedles

The construction of NHMNs requires multiscale engineering strategies, spanning from microscopic to macroscopic design principles, instead of simple material blending, to surpass the physical and chemical thresholds of traditional hydrogel microneedles. The core mechanism is the topological amalgamation of nanofillers and hydrogel networks, where the precise introduction and strategic distribution of nanomaterials optimize the density of crosslinking and interfacial interactions. This significantly enhances their mechanical robustness, spatiotemporal control of drug release, and electrical conductivity. During the crosslinking process, the incorporation of nanomaterials reinforces the crosslinking within conventional hydrogel polymer networks. The abundant functional groups on the nanomaterials form covalent bonds with the polymer chains in a directional manner, bridging adjacent polymer chains and constructing densely crosslinked networks [63]. The unique topological features of nanomaterials promote a tighter polymer chain through weak intermolecular interactions, thereby increasing the opportunities for frictional contact among polymer chains and enhancing the toughness of the hydrogels [64]. The nanocomposite effects enhance the mechanical performance of the microneedles, providing a critical material-related basis for their structural optimization. By precisely regulating the geometric parameters of microneedles, their efficiency of penetration and drug-loading capacity can be maximized while ensuring their structural integrity, thereby satisfying the clinical requirements. The covalent embedding of nanomaterials into hydrogel networks enhances their topological structure and mitigates the bottlenecks associated with network dilution. This approach also enables hydrogels to maintain a high strength after swelling, improving their mechanical performance and overcoming the abrupt reduction in mechanical strength observed during the swelling of traditional hydrogels [65]. Notably, topological reinforcement exhibits significant material specificity, and the selection of nanofillers determines the effectiveness of the reinforcement. Nanomaterials with varying chemical compositions, morphologies, and dimensions can enhance the mechanical properties of hydrogel microneedles through mechanisms

such as rigid support, crosslinking bridging, or interfacial bonding reinforcement [66, 67]. This mechanical improvement is closely related to the characteristics of the nanofillers, provided the amount of nanomaterials added is not excessive. Wang et al. [40] investigated the effect of varying concentrations of cellulose nanofiber and metal ions on the mechanical properties of the material. They found that cellulose nanofibers possessed a high aspect ratio and exhibited entanglement between molecular chains. However, their excessive addition can lead to aggregate formation, resulting in uneven stress distribution within the hydrogel and diminished mechanical strength. Therefore, in addition to size, morphology, and chemical composition, the amount of nanomaterials added should be optimized according to experimental requirements to clarify the impact of different nanofillers on enhancing mechanical strength within the hydrogel network.

Ding et al. [68] developed drug-loaded NHMNs for treating androgenetic alopecia by embedding polyhydroxyalkanoate nanoparticles into a hydrogel matrix via ultrasonication-assisted dispersion. The rigid network-constructing effect of nanoparticles significantly enhanced the mechanical performance of the microneedles. Under a load of 200 g, the fracture rate of the modified microneedles decreased to 3.5%, achieving a 3.4-fold mechanical improvement compared to the 12% fracture rate of unmodified microneedles. This effectively ensured the mechanical strength required for penetration of the stratum corneum. By employing an interfacial bonding reinforcement mechanism, Tang et al. [69] engineered a hydrogel microneedle integrated with a poly(chondroitin sulfate-acrylamide-2-methylpropane sulfonic acid)–gold nanoparticle composite (Fig. 1a). Gold nanoparticles were incorporated into the hydrogel microneedle system via in situ UV

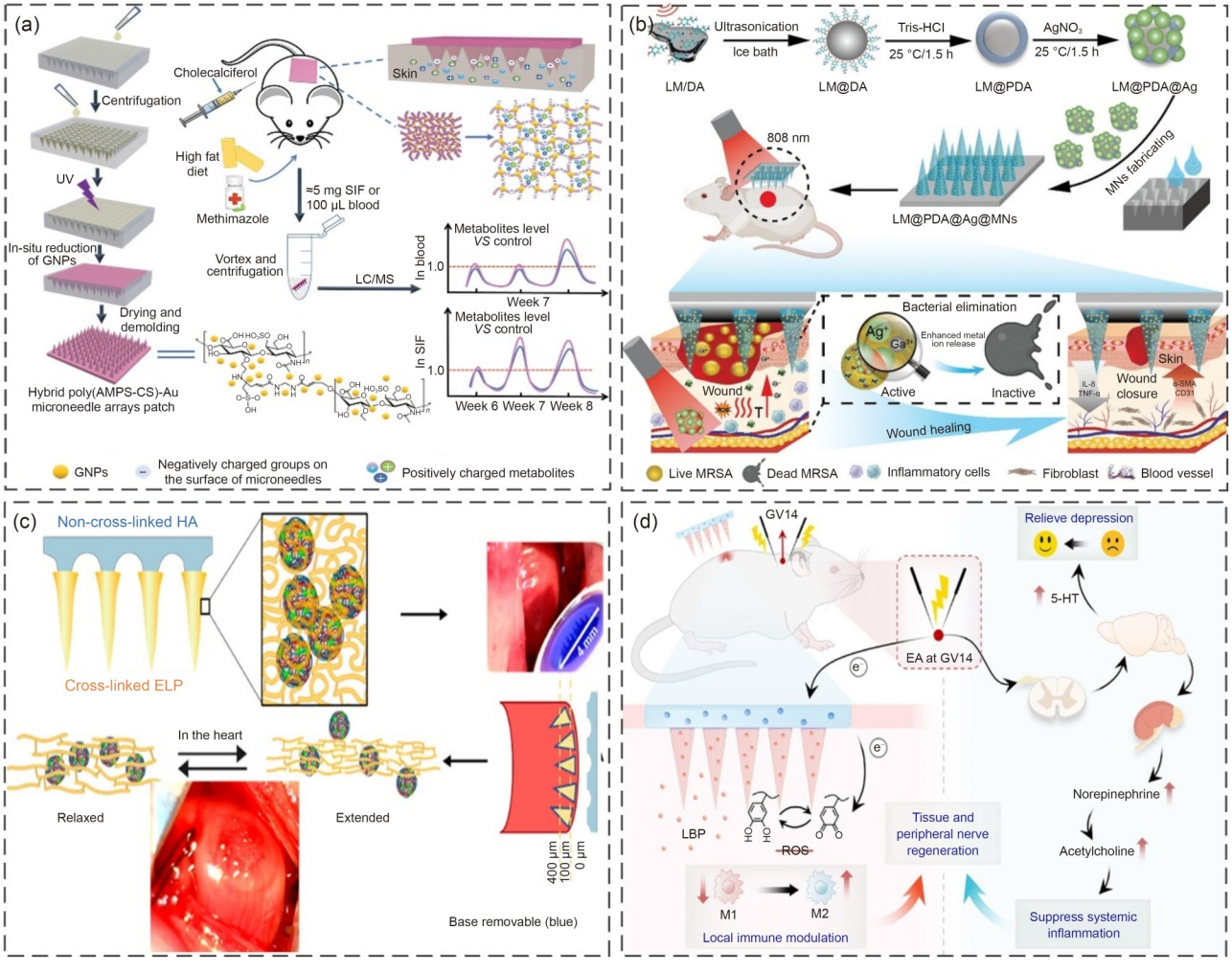


Fig. 1 The incorporation of nanomaterials enhances the performance of hydrogel microneedles. (a) Enhancing the mechanical strength of microneedles and their enrichment efficiency. Reproduced from [69], with permission from Wiley-VCH GmbH. (b) Enhancement of the mechanical properties of microneedles by nanomaterials. Reproduced from [70], with permission from Wiley-VCH GmbH. (c) The addition of nanomaterials enables microneedles to achieve sustained drug release. Reproduced from [72], with permission from the American Chemical Society. (d) The addition of nanomaterials enhances the conductivity of microneedles. Reproduced from [74], licensed under CC BY-NC-ND

polymerization. Serving as physical crosslinking sites and stress-transfer units, the nanoparticles significantly enhanced the load-bearing capacity and structural stability of the microneedles. The maximum compressive force sustained by a single microneedle reached 0.4 N, substantially higher than the 0.12 N observed for pure hydrogel microneedles, making them suitable for skin barrier penetration and interstitial fluid sampling. Furthermore, Wang et al. [70] developed a core–satellite antibacterial gallium nanostructured hydrogel microneedle system (Fig. 1b), which incorporates microneedles containing in situ reduced silver nanoparticles (AgNPs). The introduction of AgNPs enhances the interfacial bonding strength and improves the overall mechanical properties of the composite material, enabling it to meet the force requirement of 0.045 N for stratum corneum penetration while simultaneously conferring excellent antibacterial functionality. These studies demonstrate that incorporating nanofillers with high rigidity or strong interfacial bonding capacity can synergistically enhance the strength, modulus, or toughness of hydrogel microneedles through mechanisms such as physical crosslinking reinforcement, rigid skeleton support, or interfacial toughening. This multiscale synergistic design mitigates the mechanical performance limitations of conventional hydrogels while equipping microneedle arrays with multifunctional adaptability for emerging biomedical applications, including transdermal drug delivery and tissue engineering. These advances provide a foundation for next-generation, intelligent microneedle systems by establishing critical mechanical safeguards for realizing integrated diagnostic and therapeutic systems. Notably, given the material-specific nature of nanomaterial-induced mechanical enhancement, the rational selection of nanofillers is critical to achieving the intended mechanical objectives. To improve interpretability, the core screening strategies should be clearly outlined. First, an objective-oriented selection approach should be applied. When high penetration strength and fracture resistance are required, high-modulus rigid nanoparticles, such as metal oxides or bioinert metals, should be prioritized, as their rigid skeleton effect can significantly enhance load-bearing capacity. In contrast, flexible nanounits such as cellulose nanocrystals or carbon nanotubes, or active fillers with excellent interfacial adhesion, like nanoclays, are more suitable for applications that require high toughness and fatigue resistance. Second, the fundamental material compatibility must be considered to ensure that the fillers and polymer matrix, which exhibit physical or chemical compatibility such as similar polarity or reactive functional groups, can achieve topological synergy within the hydrogel network through surface modification or selection of intrinsically compatible fillers. Next, functional integration should be taken into account; if specific biological functions, such as antibacterial activity or wound-healing promotion, are simultaneously desired, fillers with intrinsic functionalities, such as antibacterial and pro-healing AgNPs, should be prioritized. Finally, cost efficiency and process feasibility must be addressed, including considerations of dispersion methods, stability, and compatibility with existing processing techniques. By employing these strategies, functionalized nanofillers can be effectively selected to meet the specific demands of various microneedle applications.

In addition to substantially enhancing the mechanical properties of hydrogel microneedles, the incorporation of nanomaterials enables the precise modulation of drug release kinetics. This mainly occurs through the optimization of their topological networks, which suppresses the initial burst release of the drug at the intrinsic level of the material, thus achieving controllability and stability in drug release. Chi et al. [71] developed a microneedle system for the anti-tumor drug tetrakis(1-methyl-4-pyridinio)porphyrin (TMPyP) by utilizing topologically integrated poly(lactic-co-glycolic acid) (PLGA) nanoparticles to modulate the crosslinking density of the hydrogel network. The controllable degradation of PLGA and the hydrogel matrix effectively suppressed the burst release of drugs. Compared with nanocomposite-free systems, the burst release rate of TMPyP within 12 h was significantly reduced, from 99.0% to 79.0%, achieving a sustained release gradient. This study presents a novel transdermal therapeutic approach with controllable, prolonged, and low-rate drug release for clinical applications that require long-term administration, such as the treatment of tumors. Similarly, Hu et al. [72] achieved sustained release of vascular endothelial growth factors by incorporating PLGA nanoparticles with the bone marrow-derived mesenchymal stromal cell secretome (Fig. 1c). The NHMNs demonstrated a cumulative release rate of 160% over 30 d, representing a 20% reduction compared to the 200% release observed in the non-encapsulated group. Furthermore, the initial burst release within the first 10 d was effectively mitigated through the nanoparticle-mediated gradual release mechanism. The two aforementioned studies demonstrate that, in the realm of drug-controlled release, the synergistic interaction between nanoscale components and the hydrogel network enables precise modulation of the crosslinking density. This strategy effectively suppresses the initial burst release, facilitates either a gradient or sustained drug release profile, and expands microneedles' therapeutic potential. This in turn provides a critical enabling technology for performance-related breakthroughs in hydrogel microneedles for transdermal drug delivery, spatiotemporally controlled drug release, and tissue engineering.

By combining nanomaterials with the hydrogel matrix through different mechanisms, not only can the mechanical strength of hydrogel microneedles be enhanced and their sustained drug release optimized, but excellent conductive properties can also be endowed to them. Commonly used

methods to this end include physical blending, in situ polymerization, chemical modification, nanocomposite fabrication, electrochemical deposition, and self-assembly. Ghosh et al. [73] engineered a conductive hydrogel microneedle system comprising carbon nanotubes (CNTs) and gelatin methacryloyl (GelMA) hydrogel. In their study, CNTs were incorporated into GelMA hydrogel microneedles, forming a highly efficient conductive network. The addition of CNTs significantly reduced the electrical resistance of the microneedles. At a CNT concentration of 10.0 mg/mL, the impedance decreased from 24 to 10 kΩ, demonstrating excellent electrical conductivity and current stability. This performance advantage stems from the low-impedance interface established by the CNT percolation network, making the system suitable for applications such as electrical stimulation therapy and neural repair. Hou et al. [74] developed a GelMA microneedle system incorporating polydopamine-modified poly(3,4-ethylenedioxythiophene) nanoparticles (PPEDOT). The incorporation of PPEDOT endowed the microneedles with exceptional electrical conductivity and electrochemical activity (Fig. 1d). The electrical conductivity increased with higher PPEDOT content, reaching a maximum of 14 S/m at a concentration of 0.1% (mass fraction). This system demonstrates potential for applications in the synergistic treatment of inflammation and depression, in addition to offering a new clinical perspective for managing diabetic wounds. By embedding conductive nanomaterials within the matrix to construct a percolation network, hydrogel microneedles gain exceptional electrical conductivity and electrochemical activity, significantly broadening their application prospects. This approach exemplifies the functional integration advantages of multiscale interface engineering. The optimization of strength, precise control of drug release, and improvement in conductivity, enabled by the nanomaterials, liberated the hydrogel microneedles from the constraints imposed by the material's intrinsic properties. Their performance-related parameters are now governed by the freedom in design offered by multiscale synergistic engineering, and propel their evolution into "active biointerfaces" through mechanical adaptability, intelligent drug-loading capabilities, and rapid response to stimuli. This paradigm shift marks the official transition of transdermal theranostics to an intelligent era characterized by tunable performance [75].

3 The discrete modules for monitoring and treatment in microneedle systems

3.1 Classification of microneedle sensing mechanisms and comparison of performance

The advancements in the performance of hydrogel microneedles, driven by innovations in nanomaterials, have facilitated the clinical translation of transdermal therapeutic technologies. However, the conventional and unidirectional paradigm of drug delivery by microneedles, characterized by passive release mechanisms, faces a critical limitation in precision medicine for monitoring dynamic pathological biomarkers (e.g., dynamic fluctuations in glucose levels and inflammatory cytokine levels). To surmount this technological barrier, researchers have developed nanocomposite microneedle systems by integrating three sensing modalities: colorimetric detection, fluorescent sensing, and electrochemical analysis. These three technical paths have led to a breakthrough in the dynamic monitoring of pathological biomarkers through real-time visual feedback from chromogenic reactions, the accurate identification of fluorescent molecules, and the highly sensitive detection of electrochemical signals. This, in turn, has helped overcome the technical limitations of the traditional microneedle system, which is often referred to as "therapy without diagnosis."

3.1.1 Colorimetric sensing mechanism

Biosensing is shifting from the lab to the clinic (point-of-care testing). This shift focuses on turning complex molecular recognition into simple, readable signals. In this technological transformation, theranostic systems based on hydrogel microneedles have emerged as a unique interfacial platform for in situ biomarker capture and signal transduction, owing to their minimally invasive transdermal properties. Colorimetric sensing capitalizes on its "naked-eye readable" nature to directly convert biomolecular interactions into signals of the color gradient, thus establishing the most streamlined diagnostic pathway for clinical applications. This feature eliminates the reliance on sophisticated instrumentation characteristic of conventional laboratory assays. Furthermore, when coupled with NHMNs, the colorimetric mechanism enables real-time chromogenic reactions that generate visual criteria for therapeutic decisions. Wang et al. [76] demonstrated a groundbreaking approach by combining synthesized Zr-metal-organic frameworks and Pt (Zr-MOFs@Pt) nanocomposites with hydrogel microneedle systems to establish a high-performance colorimetric sensing platform. The incorporation of Pt nanoparticles triples the peroxidase-like catalytic activity, yielding a highly efficient sensor for detection. Upon the penetration of the skin by the microneedle, glucose oxidase (GOx) immobilizes on its tip to catalyze the conversion of glucose in H_2O_2, which is subsequently decomposed by the Zr-MOFs@Pt nanocomposites into hydroxyl radicals. These radicals induce the oxidation of 3,3′,5,5′-tetramethylbenzidine (TMB) to produce blue oxTMB, which exhibits chromatic intensity proportional to the glucose concentration. The results of the experiments demonstrate the precise

quantification of glucose in human serum samples, providing a clinically translatable technical solution for developing portable, non-invasive devices to monitor blood glucose. Lu et al. [77] developed color-coded microneedle patches by assembling silicon dioxide nanoparticles to construct photonic crystals. Combined with hydrogel, these patches form an intelligent sensing interface that employs a spatially zoned strategy to simultaneously monitor several biomarkers, including pH, glucose, and histamine in wound microenvironments. pH sensing utilizes interactions between carboxyl and hydrogen ions in polyacrylamide to induce structural changes in color. The glucose-sensing component employs glucose-responsive fluorophenylboronic acid to identify specific molecules, while the histamine-sensing unit relies on aptamers and target molecules to generate optical signals. Upon exposure to the target molecules, volumetric variations in each functional module cause visually distinguishable differences in color and characteristic spectral shifts within the photonic crystal architecture, which in turn enables the instrument-free measurement of physiological parameters (Fig. 2a). This integrated system provides efficient real-time monitoring of infected wounds, enabling precise medical intervention. Amourizi et al. [78] developed a hydrogel microneedle sensor using $Fe_3[Fe(CN)_6]_3$/$Mn_3[Fe(CN)_6]_2$ nanozymes, where bimetallic cyanide nanozymes were embedded into an agarose matrix to facilitate colorimetric detection of oxalate. The oxidase-like activity of these nanozymes catalyzes the chromogenic reaction of 3,3′,5,5′-TMB to produce color transitions from green (no oxalate) through light-blue to dark-blue based on the oxalate concentration. Integrated into a wearable wristband device, the microneedle extracts interstitial fluid from the skin via capillary action upon penetration, which subsequently interacts with the nanozyme

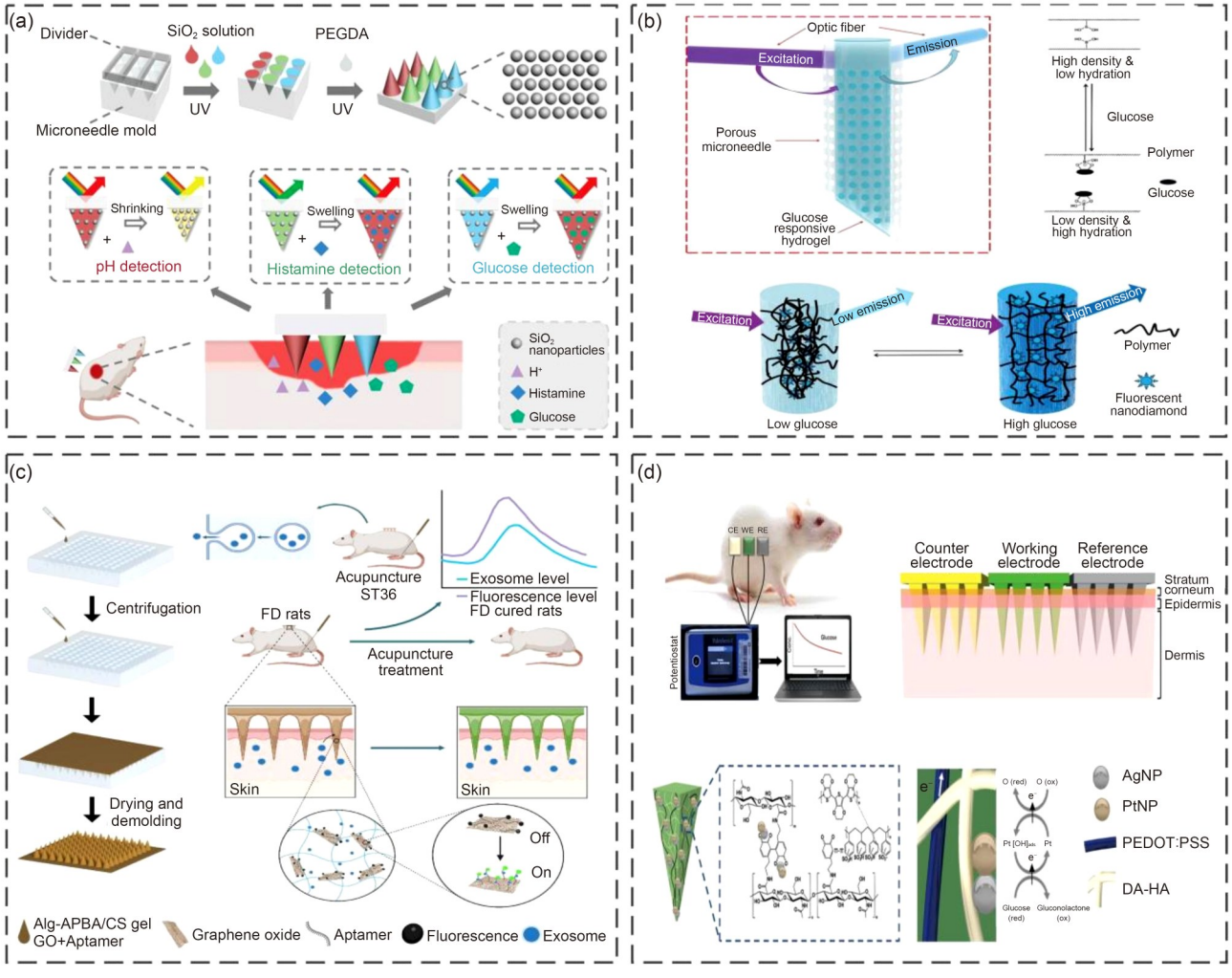


Fig. 2 Detected applications of NHMNs. (a) Zoned microneedles were used to achieve colorimetric sensing. Reproduced from [77], with permission from Wiley-VCH GmbH. (b) NHMNs enable fluorescent detection. Reproduced from [80], licensed under CC BY 4.0. (c) Graphene oxide nanosheets endow the microneedle with fluorescent detection capabilities. Reproduced from [81], with permission from Elsevier B.V. (d) NHMNs achieve electrochemical detection of glucose. Reproduced from [83], with permission from Wiley-VCH GmbH

system, generating optical signals. This minimally invasive sensing platform enables the real-time monitoring of hyperoxaluria in patients with nephropathy, thereby facilitating advancements in personalized disease management. Furthermore, to push the boundaries of colorimetric methods in multiplexed detection, He et al. [79] developed a hydrogel microneedle patch that enabled simultaneous colorimetric monitoring of four key biomarkers in the wound microenvironment: pH, uric acid, glucose, and temperature. This study highlights the potential of colorimetric approaches in addressing the challenges of multi-target detection and offers valuable insights for the future development of NHMNs. These investigations demonstrate how nanomaterial-enhanced colorimetric sensing mechanisms have led to the evolution of hydrogel microneedles from passive vehicles of drug delivery into intelligent diagnostic interfaces. The system's chromogenic responses, which are visually perceivable, enable the immediate visual interpretation of pathological biomarkers, representing a transformative approach in real-time diagnostic technologies.

3.1.2 Fluorescent sensing mechanism

Colorimetric sensing has revolutionized point-of-care diagnostics due to its visual interpretability. However, it is prone to interference from environmental light and has limited multiplexing detection capability. By contrast, fluorescence detection technology leverages specific binding-induced interactions between fluorescent probes and target molecules into quantifiable optical signals. Upon excitation at specific wavelengths, fluorescent molecules emit characteristic fluorescence with variations in intensity or shifts in wavelength that exhibit quantitative correlations with analyte concentrations. By translating molecular recognition into photon emission, this approach provides a groundbreaking pathway for developing highly sensitive and intelligent microneedle systems. Zhang et al. [80] addressed the challenges of signal instability and susceptibility to interference in continuous glucose monitoring (CGM) systems by developing a porous sensing microneedle platform using fluorescent nanodiamond boronic hydrogel composites. The system integrates fluorescent nanodiamonds with high photostability and biocompatibility into a phenylboronic acid-functionalized hydrogel network through covalent bonding, creating glucose-responsive fluorescent probes. Changes in glucose concentration alter the density and hydration state of the hydrogel microneedle, followed by reorganization of its boronic polymer network (Fig. 2b). These effects enhance optical transparency and amplify fluorescent emission under hyperglycemic conditions. The results demonstrate an approximately linear correlation between the fluorescent emission of nanodiamonds and in vitro glucose concentrations, thereby establishing the nanodiamond boronic hydrogel composite as a biosafe and reliable biosensor for long-term CGM applications. Shen et al. [81] engineered a graphene oxide (GO)–aptamer hydrogel microneedle sensor by conjugating GO nanosheets with a fluorophore-modified nucleic acid aptamer. This system enables the on-site detection of exosomes during acupuncture treatment. In the absence of targets, the fluorophore-modified nucleic acid aptamer binds to GO through π–π stacking, hydrogen bonding, or electrostatic interactions to establish a fluorescence-quenched state. In the presence of the targeted exosomes, the aptamers specifically recognize and bind to the biomarkers, subsequently undergoing conformational changes that lead to the detachment of the fluorophores from the GO nanosheets. This results in fluorescence recovery proportional to the gradient of exosomal concentration in interstitial fluid (Fig. 2c). This NHMN system is an innovative method for evaluating the efficacy of acupuncture through the monitoring of exosomal biomarkers, enabling the objective clinical assessment of therapeutic outcomes. These studies demonstrate the nanomaterial-enabled transformation of hydrogel microneedles from unidirectional drug delivery tools into multi-modal diagnostic interfaces through innovative fluorescence-sensing mechanisms. The transduction of the photon signal triggered by molecular recognition enables the ultrasensitive detection of pathological biomarkers via a fluorescent response, thereby overcoming the limitations of colorimetric sensing under environmental interference.

3.1.3 Electrochemical sensing mechanism

Fluorescent detection significantly enhances the sensitivity of detection through the specificity of molecular recognition and the conversion of optical signals. However, it often relies on specialized fluorescent environments and is susceptible to interference due to the autofluorescence of tissues, which substantially hinders the clinical application of point-of-care diagnostics. In this context, electrochemical sensing provides new pathways for theranostic systems based on hydrogel microneedles, owing to its inherent advantages, including the direct conversion of electronic signals and immunity to optical interference. The conductive nanomaterial-modified electrode interface of the microneedle triggers charge transfer through biomarker-induced redox reactions, thereby establishing quantitative correlations between signals of the current or the potential and the concentrations of the target analyte. This, in turn, significantly enhances the sensitivity and accuracy of detection. Jin et al. [82] fabricated an electrochemical sensing system integrated with hydrogel microneedles by doping Au nanoparticles into a Cu_2O substrate for real-time glucose monitoring in the interstitial fluid of live mice. The results showed that the interfacial impedance of the Au

nanocomposite microneedles decreased from 7090.4 Ω in bare electrodes and 4889.0 Ω in Cu_2O electrodes to 3335.1 Ω, with reductions of 53.0% and 31.8%, respectively. This optimized profile of impedance substantially improves the sensitivity of electrochemical glucose detection. This minimally invasive intelligent platform enables the precise monitoring of blood glucose levels, providing a nanomaterial-based strategy for managing clinical diabetes. GhavamiNejad et al. [83] proposed a three-electrode NHMN sensor based on dopamine-hyaluronic acid hydrogel to overcome the limitations of conventional CGMs, including their enzyme dependency and signal instability. By leveraging the redox properties of catechol moieties in dopamine, this system enables the in situ redox conversion of Pt/Ag metal ions into solid Pt/Ag nanoparticles within the hydrogel network, eliminating the need for external reducing agents. This system also embeds a poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) conductive framework to construct a detection interface with enhanced catalytic activity and sensitivity (Fig. 2d). The ex vivo experiments reveal that the system has a high specific response to glucose, with in vivo studies further validating its capability of real-time monitoring of glycemic fluctuations in diabetic rats. By combining a self-reductive strategy with the conductive network, this system enables dynamic monitoring of glucose and establishes scalable technological pathways for the non-invasive detection of other clinical metabolic biomarkers. This nanomaterial-enabled electrochemical sensing system enables the precise quantification and dynamic tracking of pathological biomarkers, and the redox-triggered signals of charge transfer from the target molecules generate quantifiable electrical responses. This innovation surpasses the inherent constraints of conventional fluorescence detection, providing an intelligent diagnostic methodology with integrated robustness to interference and long-term stability for clinically precise therapeutic management.

3.1.4 Comparative analysis of microneedle sensing mechanisms

Colorimetric, fluorescent, and electrochemical methods offer distinct technical pathways for integrating sensing capabilities into NHMNs. Their performance characteristics directly determine their suitability for specific application scenarios (Table 1). As colorimetric sensing provides instrument-free visual detection, it is ideal for resource-limited settings or rapid on-site assessment. However, it generally has lower sensitivity, is susceptible to interference from ambient light, and faces challenges in achieving multiplex detection. The high sensitivity and specificity of fluorescent sensing, which operates by converting biological recognition events into optical signals, make it an ideal method for detecting low-concentration biomarkers. However, its performance typically depends on specialized optical equipment for signal excitation and collection, and may be affected by background autofluorescence from biological tissues. Electrochemical sensing functions by transforming chemical reactions into quantifiable electrical signals such as current or voltage, providing high sensitivity, precision, and strong resistance to optical interference. It is well-suited for continuous, long-term monitoring of dynamic processes. However, it encounters difficulties in electrode design and modification, and may experience stability issues during prolonged operation.

In summary, selecting a sensing mechanism involves balancing its advantages and limitations according to the specific application needs. For example, colorimetry may be the preferred choice for point-of-care testing that demands minimal equipment and low cost. Fluorescence is often selected for detecting trace biomarkers that require extreme sensitivity. Meanwhile, electrochemical methods prove particularly advantageous in environments with complex optical conditions or those that require sustained, stable monitoring. Furthermore, the incorporation of nanomaterials has

Table 1 Comparative analysis of performance in microneedle sensing mechanisms

Mechanism	Principle	Advantage	Limitation	Application	Ref.
Colorimetric	Visible color change induced by biorecognition	Visual readability, operational simplicity, and minimal instrument dependence	Low sensitivity, susceptibility to interference from light	Preliminary blood glucose screening and rapid wound infection assessment	[76–79]
Fluorescent	Target binding induces changes in fluorescence intensity	High sensitivity, strong specificity, and multiplex detection capability	Requiring light sources and detectors, susceptibility to autofluorescence	Glucose monitoring and high-sensitivity biomarker detection	[80, 81]
Electrochemical	Redox reactions generate electrical signals	High sensitivity, superior interference resistance, and real-time monitoring	Complex electrode design, long-term instability, and susceptibility to electroactive substances	Dynamic monitoring of glucose or other metabolite biomarkers	[82, 83]

substantially improved the performance of these sensing mechanisms to address clinical requirements. In the future, multiple sensing modalities can be combined within a unified microneedle platform. Such integration would synergistically enhance the strengths of each method while minimizing their limitations, ultimately enabling comprehensive, accurate, and dynamic monitoring of human physiological and pathological states.

3.2 Transdermal drug delivery of microneedles

While microneedles have achieved transformative advances in clinical biosensing, their foundational role as transdermal drug delivery systems has also undergone rapid development. Conventional invasive methods of drug delivery, such as injection through hypodermic needles, frequently induce pain and compromise patient compliance, whereas widely adopted non-invasive routes like oral administration, while offering convenience, are often plagued by systemic side effects. Microneedles address the challenges of painful and invasive injections, as well as the limitations of non-invasive methods of delivery, including first-pass metabolism and low bioavailability. Through the minimally invasive array-based penetration of the stratum corneum, microneedles create microchannels that facilitate the painless and efficient transport of transdermal drugs across skin barriers. Particularly, NHMNs exhibit high drug-loading efficiency and customizable drug compatibility due to their crosslinked network architecture. Based on the underlying principles of their intelligent design, these systems can be classified into three main categories: pathological microenvironment-responsive drug release, tissue-specific targeted drug delivery, and combinatory therapy employing synergistic mechanisms.

3.2.1 Microenvironment-responsive drug delivery systems

NHMNs designed for pathological microenvironment-responsive drug release aim to utilize biological signals specific to the lesion site for the controlled release of drugs or the activation of nanomaterial functions. This approach enables precise on-demand therapy while minimizing off-target effects on healthy tissues. Complex wound management represents a typical application scenario for such systems. Xuan et al. [84] synthesized cerium dioxide nanozymes and integrated them into a hydrogel microneedle system for treating diabetic wounds. The functionalized cerium dioxide nanozymes, which are the key components, specifically respond to the high levels of reactive oxygen species (ROS) present in the wound microenvironment. By exhibiting catalase-like activity, these nanozymes effectively scavenge ROS and alleviate oxidative stress, thereby suppressing inflammation and promoting angiogenesis (Fig. 3a). In vivo experiments demonstrate that these NHMNs significantly accelerate wound healing. Yu et al. [85] developed a hydrogel microneedle patch fabricated from a poly(γ-glutamic acid) (γ-PGA) hydrogel that contained silver ions, mesoporous silica nanoparticles, and CeO_2 nanoparticles (Ag@MSN@CeO_2). This microneedle system penetrates biofilms and delivers therapeutics deep into wound sites. Under the acidic microenvironment of infected wounds in diabetics, nanoparticles enable the controlled release of Ag^+ to disrupt biofilms and inhibit bacterial proliferation, while CeO_2 continuously neutralizes ROS to mitigate oxidative damage. These actions synergistically induce macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. These findings demonstrate that the integration of multiple regenerative effects of microneedles optimizes the wound microenvironment, enhances collagen production and deposition, and ultimately improves therapeutic outcomes for healing infected wounds. This hydrogel microneedle technology enables the dynamic regulation of drug release tailored to the specific microenvironments of wounds, achieving antibacterial and antioxidant behavior, as well as tissue regeneration. Compared with conventional single-modality therapies, this system operates through coordinated multi-mechanistic interactions that provide a highly integrated solution for complex pathological scenarios, such as diabetic wound management.

3.2.2 Targeted drug delivery systems

Targeted drug delivery systems focus on the precise design of nanocarriers to enable the accumulation of drugs, specifically in target tissues or cells. This approach significantly enhances local therapeutic efficacy while preventing the systemic toxicity and side effects associated with conventional administration routes. Such targeted strategies have demonstrated promising applications in treating obesity. Microneedles enable the localized targeting of adipose tissue for the sustained accumulation and release of drugs, thereby regulating adipocyte lipolytic metabolic pathways and adipose browning processes. Through multiple modulations, the microneedle-targeted obesity treatment technology promotes lipolysis and enhances energy expenditure, offering a minimally invasive therapeutic strategy with high targeting specificity and low systemic side effects for obesity management. Chen et al. [86] developed an NHMN system loaded with oleanolic acid and rosiglitazone. Upon penetration into the skin, the nanocomposite particles within the microneedles are internalized and degraded by macrophages and white adipocytes. The released oleanolic acid subsequently targets and suppresses adipose tissue inflammation, while rosiglitazone induces browning of white

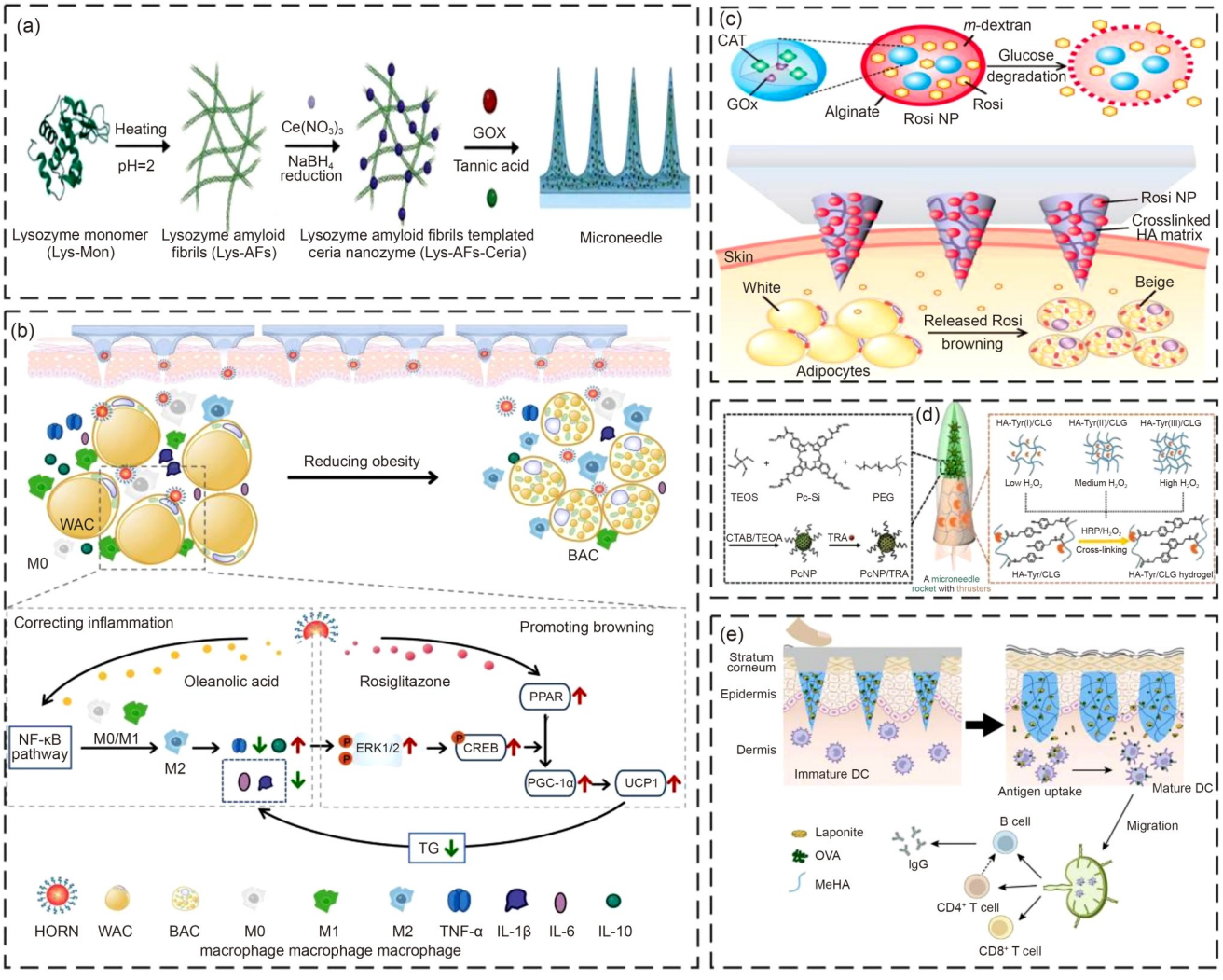


Fig. 3 Therapeutic applications of NHMNs. (a) NHMNs can be used to treat diabetic wounds. Reproduced from [84], licensed under CC BY 4.0. (b) The nanocomposite particles within the microneedles are internalized and degraded by macrophages and white adipocytes to treat obesity. Reproduced from [86], with permission from Elsevier Ltd. (c) Rosiglitazone nanoparticles combined with microneedles can help alleviate obesity. Reproduced from [87], with permission from the American Chemical Society. (d) Mesoporous silica nanoparticles coupled with microneedles can be used to treat solid melanoma. Reproduced from [88], with permission from Wiley-VCH GmbH. (e) Laponite nanoparticle-based microneedles can stimulate adaptive immune responses. Reproduced from [89], with permission from Acta Materialia Inc.

adipocytes to enhance energy metabolism (Fig. 3b). Experimental results demonstrate that this transdermal patch effectively alleviates obesity without compromising skin barrier function. Zhang et al. [87] developed an NHMN system to achieve localized browning of the white adipose tissue. They encapsulated rosiglitazone into nanoparticle suspensions, which were subsequently blended with a hydrogel matrix to fabricate the microneedles. Following transdermal delivery, the sustained-release rosiglitazone nanoparticles selectively accumulated in the subcutaneous fat layer, inducing local browning of white adipose tissue (Fig. 3c). These studies focus on the core strategy of "targeted delivery." By integrating nanomaterials with hydrogel microneedles, these approaches realize the precise accumulation and controlled release of the drug in adipose tissues. These systems overcome the challenges of conventional oral or intravenous drug delivery systems, such as low targeting efficiency and high systemic exposure when treating localized diseases such as obesity, leading to suboptimal therapeutic outcomes and systemic toxicity. By leveraging NHMN platforms functionalized with targeted nanocarriers, both approaches successfully confine drug delivery to local adipose tissues, offering a promising clinical strategy for obesity treatment.

3.2.3 Combinatorial therapy delivery systems

Combinatorial therapy represents an advanced form of intelligent drug delivery, which integrates multiple therapeutic agents or functional modules within a single platform to

achieve synergistic effects across different treatment mechanisms. This approach addresses the challenges posed by complex diseases such as cancer. The incorporation of nanomaterials into hydrogel microneedle systems facilitates sustained drug release. Such a platform enables the coordination of multiple mechanisms, such as combining chemotherapeutic agents with immunomodulators, to simultaneously inhibit tumor proliferation and activate systemic antitumor immune responses. This strategy presents a novel technological approach for targeted interventional therapy in oncology. Pan et al. [88] developed a biomimetic hierarchical "microneedle rocket" drug delivery system, featuring a layered structure. The upper layer utilizes mesoporous silica nanoparticles to co-deliver the MEK pathway inhibitor trametinib and a photosensitizer, combining molecular targeted therapy with photodynamic therapy. The lower layer consists of an enzyme-responsive hydrogel combined with collagenase, forming an intelligent propulsion module that promotes the deep penetration of nanoparticles by remodeling the tumor extracellular matrix (Fig. 3d). In addition to enhancing the depth of drug infiltration, this approach improves therapeutic efficacy through combined treatment mechanisms. Zheng et al. [89] designed a separable NHMN system for sustained delivery of the model antigen ovalbumin to enhance adaptive immune responses (Fig. 3e). The system incorporates laponite nanoparticles into the hydrogel matrix. Upon dissolution, the microneedles not only release the antigen but, more critically, also enable the laponite nanoparticles to synergistically enhance the capture of the antigen by dendritic cells and activate a stronger, more durable adaptive immune response. This approach addresses the limited efficacy of any single therapy in tumor treatment due to the multifaceted physiological barriers. The former work achieves spatiotemporal synergy between drug penetration and photodynamic therapy through an elaborately designed hierarchical structure. The latter leverages the intrinsic immunoadjuvant properties of nanomaterials, combining antigen delivery and immune activation. Together, they signify a transition of nanohydrogel microneedles from mere drug delivery vehicles toward multifunctional combinatorial therapy platforms, offering a highly promising solution for advanced combination treatments.

In summary, the development of intelligent drug delivery systems based on NHMNs has progressed from simple drug loading to microenvironment-responsive release, and subsequently to active targeting and multi-mechanism synergy. These advancements are driven by the ability of nanomaterials to sense and intervene in disease-related physiological processes. Current research has demonstrated their significant potential across diverse clinical scenarios.

4 Closed-loop integration of microneedle-based sensing and therapeutic intervention

While microneedle technology has successfully combined biosensing and transdermal therapeutic functions through nanocomposite strategies, these two components remain functionally segregated in independent operational systems. Biosensors cannot drive therapeutic decisions in real time, while therapeutic actions lack feedback regulation based on pathological dynamics. This separation creates two main problems. First, because detection and treatment are out of sync, treatment often lags behind the disease and cannot stop it from exacerbating. Second, due to fixed-dose static administration, accommodating individual metabolic variations is challenging, potentially inducing fluctuations in therapeutic efficacy or risks of drug resistance. Establishing an integrated closed-loop theranostic system can help address these problems. By enabling real-time bidirectional feedback between sensing signals and therapeutic execution, microneedles can autonomously adjust the drug release parameters according to changes in the dynamic pathophysiological microenvironment, thereby transitioning from "passive release" to "active intervention." This closed-loop regulatory mechanism facilitates precise intervention in complex pathological scenarios by reducing delays in human decision-making and errors in dosage, while establishing a predictable and low-risk therapeutic pathway for clinical precision medicine. Based on the number of integrated signaling modalities, existing closed-loop smart microneedle systems can be categorized into single- and multi-signal response systems. The former features a relatively simple structure focused on responding to a specific pathological signal, while the latter integrates multiple sensing and actuation modules to address more complex pathological environments.

4.1 Single-signal response systems

Single-signal response systems achieve integrated diagnosis and treatment by sensing and responding to a single pathological chemical signal within a closed-loop framework. With a clear design objective, they serve as fundamental building blocks for more complex systems. Among these, pH-responsive and ROS-responsive closed-loop therapeutic microneedle systems have emerged as implementable approaches. For example, Xiao et al. [90] developed a typical single-signal pH-responsive closed-loop microneedle system that employed a nanocatalytic antibacterial module based on metal-organic frameworks (Bi–PCN–222), achieving efficient sterilization through electron transfer effects against pathogenic bacteria. The inflammation regulation module utilizes the antioxidant and anti-inflammatory properties of curcumin to precisely eliminate excess ROS and remodel the wound healing microenvironment. An

integrated sensing module dynamically monitors wound status via smartphone-captured pH-dependent fluorescence signals, enabling real-time adjustment of treatment strategies. This work demonstrates how nanomaterials can be coupled with a single pH signal to implement a fundamental closed-loop logic for targeted therapy. Ruan et al. [91] developed a single pH-responsive microneedle system incorporating glycyrrhizic acid (GA) and zinc, which enables closed-loop precision therapy for alopecia areata through synergistic microenvironment-triggered drug release and real-time zinc ion monitoring. Constructed with dual-crosslinked hydrogel substrates, the microneedle rapidly swells upon penetrating the skin. Under excitation of 365 nm, the varying intensities of the red fluorescence signals provide real-time feedback on the local concentrations of the zinc ions. Concurrently, nanocarriers of the zeolitic imidazolate framework-8 loaded with GA undergo pH-specific degradation in acidic pathological regions, inducing the release of GA and zinc ions. These factors influence the Wnt/β-catenin protein signaling pathway, enabling the regeneration of hair follicles (Fig. 4a), as evidenced by the regrowth of dense black hair in murine models by Day 16. The system ingeniously leverages the acidic microenvironment of the lesion as a triggering signal, enabling simultaneous fluorescence diagnosis and controlled drug release, thereby achieving integrated diagnostics and therapy. Che et al. [92] designed an NHMN that utilized a ROS-responsive hydrogel matrix to detect elevated ROS levels in bacterial microenvironments as a single input signal (Fig. 4b). This detection triggers the rapid release of polydopamine-PtCuTe nanoparticle (PDA-PtCuTe) nanozymes and subsequent efficient ROS scavenging. Following treatment, the local immune response shifts from a pro-inflammatory state to a pro-regenerative state, achieving nearly complete re-epithelialization by Day 3. This work exemplifies the directness of single-signal response systems: elevated ROS levels serve both as the pathological cause requiring treatment and as the signal triggering therapeutic intervention.

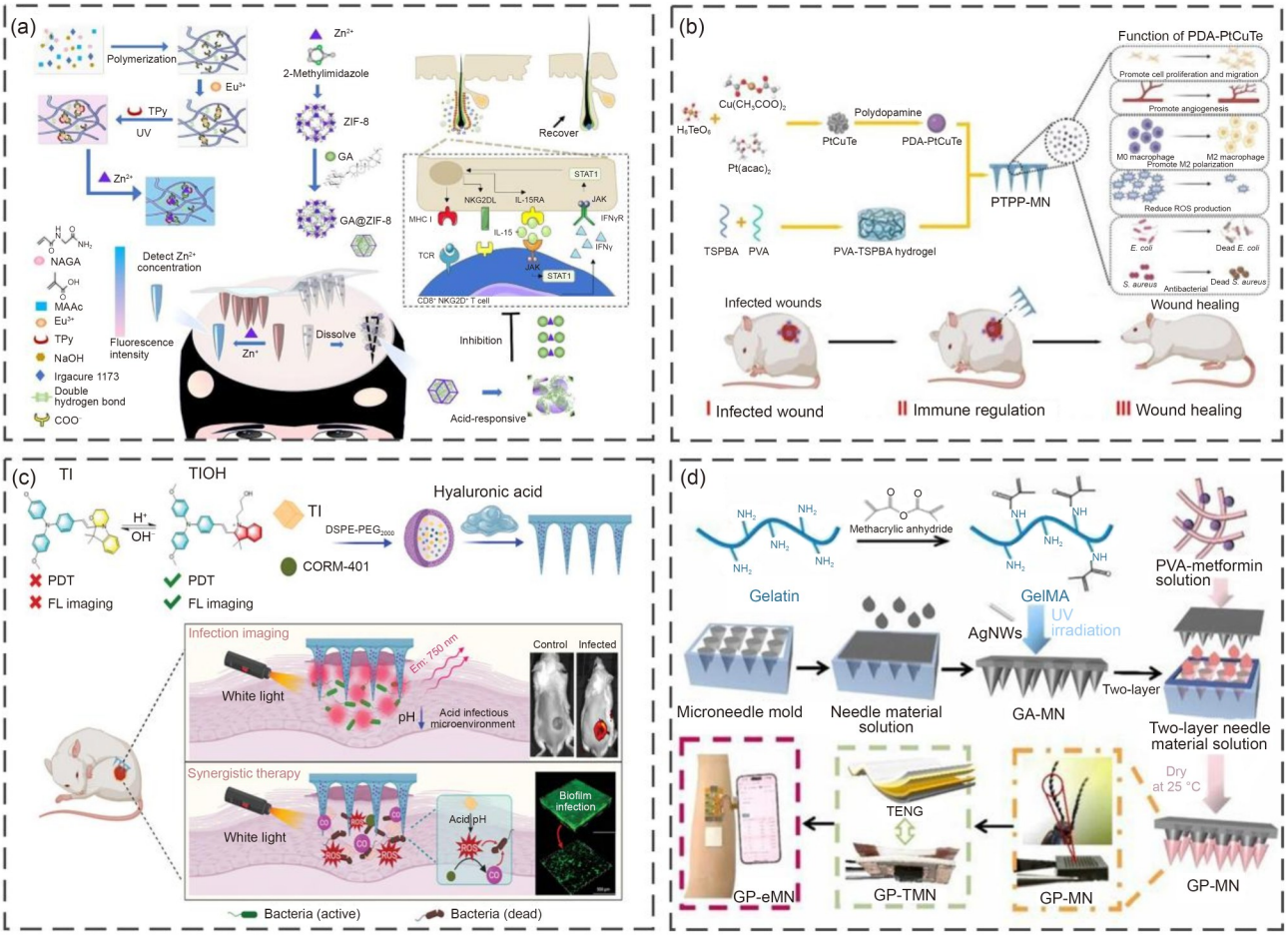


Fig. 4 Closed-loop theranostics systems based on NHMNs. (a) A pH-responsive microneedle system can realize closed-loop precision therapy for alopecia areata. Reproduced from [91], with permission from Elsevier B.V. (b) The NHMN system can promote the healing of infected wounds. Reproduced from [92], licensed under CC BY-NC-ND. (c) The NHMN can achieve theranostics of infected microenvironments. Reproduced from [93], with permission from Wiley-VCH GmbH. (d) The NHMN system enables closed-loop clinical management for chronic diabetic wounds. Reproduced from [95], with permission from Elsevier Ltd.

4.2 Multi-signal response systems

Multi-signal response systems represent the forefront of closed-loop technological development. They integrate multiple sensing and therapeutic modules to address more complex pathological environments, achieving improved precision and synergistic treatment. In these systems, nanomaterials serve as functional carriers and as bridges that enable the integration of multiple modalities. Taking the combination of pH responsiveness and photo-driven activation as an example, Xu et al. [93] constructed a multimodal response system by integrating pH-responsive TI nanoprobes with carbon monoxide (CO) donors (Fig. 4c). The acidic pathological microenvironment triggers a conformational change in the TI nanoprobes, activating near-infrared fluorescence signals for sensitive infection detection. Simultaneously, the photodynamic effect drives the TI probes to generate ROS, which directly kill pathogens while triggering controlled CO release. The system achieves antibacterial effects in conjunction with photodynamic and gas therapies, demonstrating how sophisticated nanomaterial design can integrate chemical signal sensing with physically energy-driven processes to achieve a coordinated multimodal therapeutic outcome. Taking the combination of glucose responsiveness and photo-driven activation as an example, Ge et al. [94] developed a hierarchically structured smart microneedle system. Its base layer incorporates Cu-TCPP(Fe)/GOx nanocomposites to form a glucose-responsive colorimetric sensing module. The tips contain a photothermal-responsive melanin-based nanodrug delivery system that enables precise release of metformin under near-infrared light irradiation. This system represents a typical multi-signal closed-loop architecture, featuring a chemical signal input and a physical energy output. The enzyme-based nanocomposites and melanin nanodrug carriers serve as key components enabling the functional integration of these two modalities. Finally, taking the combination of multi-chemical signal responsiveness and electrical stimulation as an example, the NHMN system developed by Liu et al. [95] represents a highly integrated multimodal responsive system. The microneedles incorporate built-in modules for pH, glucose, and uric acid monitoring, enabling real-time tracking of dynamic changes in the wound microenvironment (Fig. 4d). Simultaneously, the silver nanowire network coupled with a triboelectric nanogenerator generates self-powered electrical signals to accelerate tissue repair. This system represents one of the most sophisticated closed-loop microneedle platforms to date, utilizing nanomaterials to achieve parallel sensing of multiple endogenous chemical signals and synergistic output of exogenous physical therapy. It provides a comprehensive approach to managing chronic diseases.

The aforementioned studies demonstrate that dynamically integrated closed-loop theranostic microneedle systems can overcome the inherent limitations of conventional clinical practices, where diagnosis and treatment are spatially and temporally separated. The single- and multi-signal closed-loop systems highlight a core innovation: the use of nanomaterials to deeply integrate the sensing of pathological signals with the execution of therapeutic actions. Single-signal systems facilitate the execution of closed-loop logic, whereas multi-signal systems represent the future direction of development. Beyond the studies discussed, numerous researchers have contributed to advancing closed-loop microneedle platforms [96–99]. Although significant progress has been made in applications such as wound infection management and diabetes care, the full potential of this technology remains largely untapped. Current applications in areas such as wound and diabetes management mainly focus on two main factors: technical accessibility and clinical urgency. First, these conditions offer technical advantages: key biomarkers (e.g., pH, glucose, and uric acid) are well-defined and easily measurable, while their microenvironments are situated at or near the body surface, facilitating minimally invasive access by microneedles. Second, there should be a pressing clinical need: both wound healing and diabetes require frequent monitoring and immediate intervention, making closed-loop management not only highly desirable but also clinically impactful. Nevertheless, the potential of closed-loop microneedle technology also holds significant promise for broader applications, such as in gout management and cardiovascular disease monitoring, where continuous biomarker sensing and adaptive therapy could transform current treatment paradigms. In gout management [100], microneedles capable of real-time monitoring of subcutaneous uric acid levels can be developed to automatically release therapeutic agents, such as colchicine, when concentrations exceed thresholds, enabling preventive treatment and avoiding acute episodes. For cardiovascular diseases [101], microneedle systems can continuously track markers of heart failure or electrolyte levels in interstitial fluid. Upon detecting abnormal levels, the system may autonomously administer drugs transdermally, achieving unprecedented personalized regulation and preventing acute exacerbations. Certainly, expanding into these new domains presents clear challenges, including difficulties in accessing biomarkers, the need for higher precision in material responsiveness, and ensuring the long-term stability and safety of nanomaterials. In summary, closed-loop NHMN technology is transitioning from a novel concept to a practical medical tool. Its successful applications in wound and diabetes management demonstrate its significant potential. Future research must focus on overcoming the aforementioned challenges to extend this precise and convenient treatment paradigm to a wider range of disease management areas, ultimately benefiting a broader patient population.

5 Clinical translation and application

5.1 Limitations and unresolved issues in clinical translation

Despite their significant potential in interdisciplinary diagnostic and therapeutic applications, the transition of NHMNs into clinical practice and widespread commercialization faces several critical challenges, creating bottlenecks in current development and translation. The primary challenge lies in biological safety, requiring comprehensive evaluation through long-term in vivo retention studies, quantification of metabolic kinetics, and immunogenicity research to fully understand the long-term effects of complex nanomaterial components. The potential for long-term retention of nanomaterials raises significant concerns regarding potential chronic toxicity and bioaccumulation in off-target organs or tissues over extended periods, necessitating rigorous biodistribution and clearance studies that extend beyond standard timeframes. Immunogenicity presents another major hurdle. Nanomaterials or their metabolic byproducts possess the intrinsic capability to trigger complex immune cascades, potentially provoking localized inflammation, systemic hypersensitivity reactions, or unintended autoimmune responses that could compromise their safety and efficacy. Another major hurdle is establishing a robust evaluation framework for NHMNs to address the divergent global regulatory standards. This is particularly pronounced for closed-loop theranostic systems. The integrated systems must comply with and span multiple regulatory pathways, including those for medical devices, pharmaceuticals, and digital systems. As a medical device, NHMNs must demonstrate structural safety of the microneedles, biocompatibility in terms of invasiveness, and the accuracy and reliability of their sensing units. If the system involves loaded drugs or therapeutically responsive agents, their pharmaceutical properties require rigorous evaluation, including drug release kinetics, bioavailability, and toxicological characteristics. Digital systems must address the challenge of coordinating software and hardware. As integral components of medical device software, the accuracy of clinical decisions, robustness against interference, and mechanisms for protecting patient data privacy must be thoroughly validated based on specific digital health regulations. Furthermore, NHMNs face challenges in scaling up production. PDMS mold replication technology significantly constrains the mass production of microneedles with complex structures during large-scale manufacturing. Clinical and scientific uncertainties encompass open challenges, such as the robustness of closed-loop algorithms in real-world scenarios, the long-term functional stability of wearable systems, and the optimization of individualized therapeutic dosing. Furthermore, individual variability in human populations, including differences in skin barrier integrity, immune status, and disease pathophysiology, affects the biosensing accuracy and the precision required for adaptive, closed-loop therapeutic algorithms. Addressing these bottlenecks requires in-depth collaboration among all stakeholders to overcome barriers in safety research and regulatory compliance, establish standardized scaling processes, and ultimately achieve successful translation into clinical practice.

5.2 Evaluating the safety of NHMNs

Nanomaterials have played a pivotal role in diagnostic and therapeutic applications due to their unique functional mechanisms [102, 103]. However, before the nanomaterials and hydrogel microneedles advance to the clinical stage, it is imperative to establish frameworks to confirm their safety and systematically address critical challenges. These include an evaluation of their biocompatibility, toxicity profiling, and compliance with global regulations. Studies have shown that the biocompatibility of hydrogel substrates is integral for their safety. Li et al. [104] conducted histopathological analysis via hematoxylin-eosin staining on rat models. The results revealed that the applied hydrogel matrix significantly mitigated inflammatory responses, confirming the biocompatibility of the fabricated Zn-V-Si-Ca glass nanoparticle-incorporated hydrogel microneedles. Furthermore, Bian et al. [105] assessed the long-term risks of accumulation of nanomaterial components in microneedles (Fig. 5a). They showed that the carrier-free nanoassemblies of a chlorin e6-integrated fast-dissolving microneedle patch demonstrated no significant loss in body weight, negligibly low toxicity, and minimal nanoparticle accumulation in mice. Therefore, it is expected to exhibit reduced toxicity to healthy organs. Variations in the degradation-related behaviors of different materials further complicate the safety validation process, necessitating the analysis of the kinetic profiles of degradation and the thresholds of metabolite toxicity [106]. The comprehensive validation of the in vivo pathways of retention and clearance of non-degradable materials is required to mitigate the risk of their long-term accumulation. During the application process, it is crucial to quantify nanoparticle release from microneedles using advanced characterization techniques, such as transmission electron microscopy and scanning electron microscopy, to monitor release-related behavior dynamically. Moreover, the mechanical stability of microneedles during penetration must be evaluated using biomimetic models [107] to ensure that there is no risk of residual damage. Furthermore, thresholds of the fracture force need to be set to prevent potential hazards from fragments induced by penetration. Adaptive evaluation frameworks for nanomaterials must also be constructed to address global regulatory discrepancies. Building upon these requirements, promoting consensus and

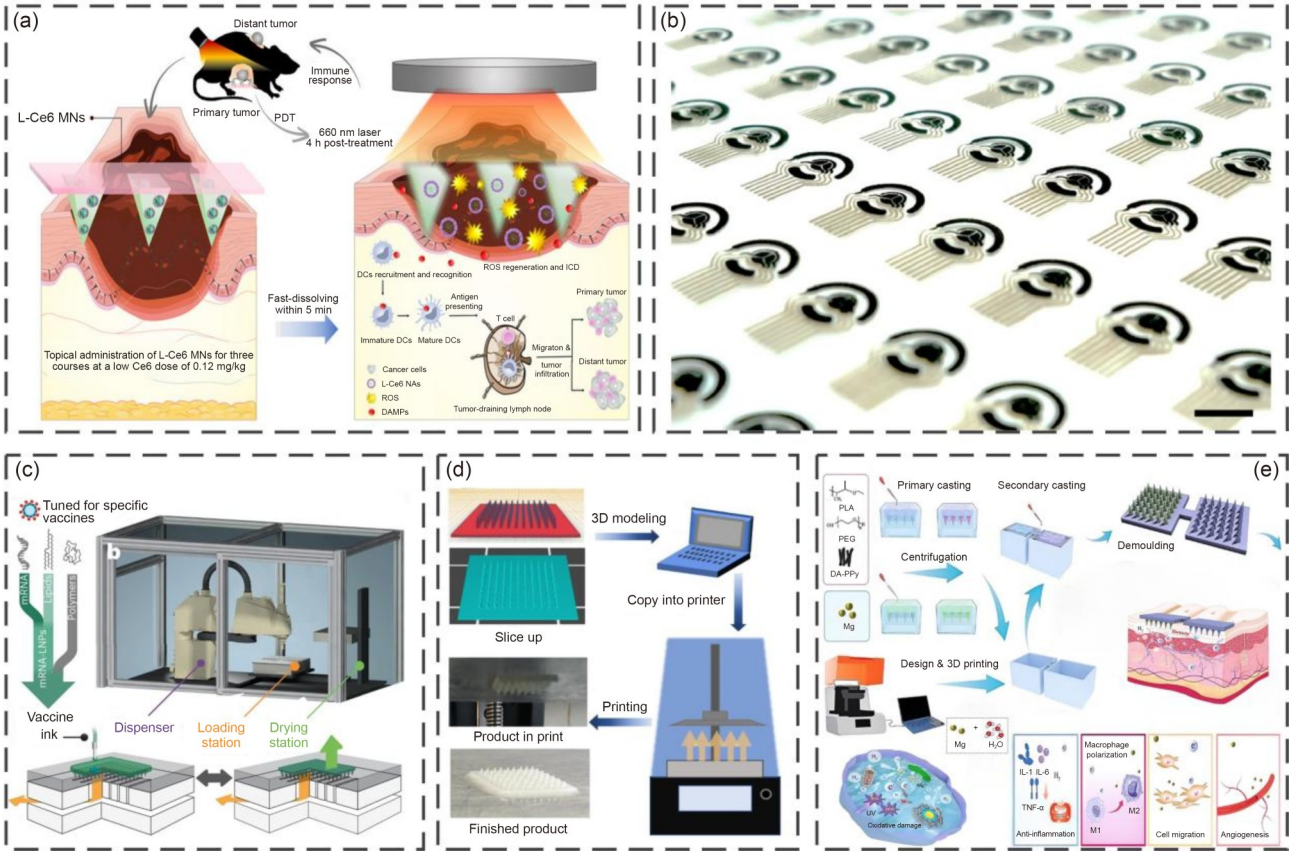


Fig. 5 Clinical translation and commercialization of NHMNs. (a) Assessment of the accumulation of nanomaterial components in microneedles. Reproduced from [105], with permission from the American Chemical Society. (b) Core–shell nanoparticle technology can realize the high-throughput preparation of biosensors. Reproduced from [109], under exclusive licence to Springer Nature Limited. (c) A microneedle vaccine printer with a higher specificity. Reproduced from [110], under exclusive licence to Springer Nature America, Inc. (d) 3D printing of high-precision microneedle patches with triple-responsive functionalities. Reproduced from [111], with permission from Elsevier Inc. (e) Microneedles enable medical cosmetology. Reproduced from [115], with permission from Wiley-VCH GmbH

standardizing key metrics are critical. For instance, the USA Food and Drug Administration (FDA) mandates the submission of biocompatibility data, long-term toxicological profiles, and assessments of the risk of migration of nanomaterials [108]. The European Union Medical Device Regulation (MDR) emphasizes the validation of the degradation kinetics and the verification of the biological persistence of non-degradable materials. In China, the National Medical Products Administration (NMPA) prioritizes the traceability of nanomaterials and the integrity of preclinical experimental data on animals. These systematic studies will propel NHMNs from laboratory research to clinical use, providing the theoretical foundations needed to resolve controversies over biosafety and address challenges to regulatory harmonization. This will ultimately enable the robust clinical translation of closed-loop precision theranostics.

5.3 Standardization of manufacturing

Following evaluations of their biocompatibility, the manufacturing process of NHMNs still requires standardization to ensure successful clinical translation. While traditional laboratory PDMS mold replication technology preserves the activity of the nanomaterial functional group under mild conditions, its single-structure patterns of molding and small-scale production severely limit the scalable manufacture of complex microneedle architectures. To solve this problem, researchers have standardized its manufacture through innovative production processes. In the context of scalable manufacture, Wang et al. [109] developed printable core–shell nanoparticle technology that combined a molecularly imprinted polymer shell for customizable target recognition with a nickel hexacyanoferrate core for stable electrochemical transduction. When integrated with inkjet printing processes, it enables the high-throughput preparation of biosensors (Fig. 5b), providing a new means of controlling the batch consistency of nanomaterials in microneedle sensing electrodes. However, its process parameters remain unoptimized for the specific requirements of microneedle manufacture. By contrast, vander Straeten et al. [110] developed a microneedle vaccine printer with a higher specificity.

Their thermostable printing technology utilizes nanoparticle-polyvinyl alcohol hydrogel composite inks (Fig. 5c). It can produce hundreds of microneedle patch doses daily, with room-temperature storage stability extending up to six months. However, an elevated operational complexity limits its widespread applicability. The method based on digital light processing technology, developed by Zhou et al. [111], exhibits substantial potential for clinical translation. By applying nanocomposite hydrogel precursor solutions and UV light-mediated layer-by-layer curing, this method enables the direct 3D printing of high-precision microneedle patches with triple-responsive functionalities (Fig. 5d). Digital modeling capabilities allow for the flexible customization of microneedle geometries and patch dimensions to meet personalized clinical requirements. Furthermore, 3D printing technology enables the design of gradient distributions of nanomaterials within microneedles, allowing for the localized enrichment of antibacterial nanoparticles at the tips while retaining nanonetworks at the base, thereby achieving enhanced sensing capabilities. Photocurable additive manufacturing technology combines rapid prototyping with the fabrication of complex structures, enabling the multi-functional integration of smart diagnostic and therapeutic microneedles. This innovative 3D printing process has transformed microneedle manufacturing, transitioning from laboratory experience-driven approaches to clinically oriented, digital precision manufacturing. It overcomes the technical barriers of forming complex microneedle architectures while establishing a fundamental criterion for clinical quality control, including the homogeneity of nanomaterial distribution and inter-batch consistency in terms of mechanical strength. This can expedite the industrialization of next-generation intelligent diagnostic and therapeutic microneedle systems. However, transitioning from precision manufacturing to systematic industrial production still requires overcoming two core challenges: cost evaluation and quality control. First, high-performance nanomaterials and high-precision processing equipment, such as 3D printers, significantly increase production costs. Future efforts should focus on developing low-cost, high-performance alternative nanomaterials and optimizing printing processes to reduce energy consumption and material waste. Second, batch-to-batch consistency in mass production is fundamental to ensuring clinical efficacy and safety. This necessitates the implementation of online monitoring systems throughout the entire production process, such as using machine vision to automatically inspect microneedle morphology for integrity and uniformity, or employing spectroscopic techniques to monitor the dispersion homogeneity of nanomaterials within the hydrogel matrix in real time. This ensures that each microneedle product meets stringent medical standards in terms of mechanical strength, drug loading capacity, and functional stability, thereby guaranteeing rigorous quality control. These aspects directly determine the economic viability of the technology and the robustness of its clinical translation.

5.4 Commercialization and technology transfer

Following its biosafety evaluation and the establishment of a standardized manufacturing system, the clinical translation of microneedle technology still requires market-oriented commercialization strategies. Its industrial potential has received authoritative recognition: In 2020, Scientific American and the World Economic Forum ranked it as the top emerging technology worldwide, with its core value validated in medical aesthetics. Its market feasibility was initially demonstrated by the dermatologists Rodan and Fields, who launched the first medical aesthetic microneedle product containing hydrolyzed hyaluronic acid in 2014 [112]. However, the limited clinical evidence since the early products prompted subsequent mechanistic investigations: A 2017 randomized controlled trial involving 84 subjects revealed that after 12 weeks of treatment with adenosine wrinkle cream administered via hyaluronic acid microneedles, the wrinkle grade index significantly decreased from 2.833 to 2.111 ($p<0.05$) [113], resulting in improved skin vitality compared to that with adenosine wrinkle cream. Furthermore, pharmacokinetic studies conducted in 2023 elucidated the commercial advantages of microneedles in medical aesthetics, showing that collagen-loaded microneedles achieved a nicotinamide release of 52% within 8 h, significantly exceeding the rate of 25.6% achieved by traditional creams [114]. With the clarification of these mechanistic advantages, technological innovation is now focusing on multi-functional integration and the optimization of user experience. To this end, nanofibers and hydrogel microneedles that utilize galvanic cell effects to release hydrogen and magnesium ions (Fig. 5e) are being explored, combined with microcurrent stimulation, antioxidant activity, and pro-angiogenic mechanisms [115].

Industrial implementation also requires resolving the user experience issues. Intelligent systems that integrate painlessness, breathability, and flexible electronics will dominate the market share. Flexible substrate materials can reduce the pressure of skin contact and ensure the natural adhesion of patches during body movement [116]. Optimizing the penetration depth demands the interdisciplinary integration of materials science and microfabrication technologies. Tapered needle tips with low-friction coatings keep penetrative forces below the pain threshold, while the viscoelastic properties of hydrogels mitigate mechanical impact. The porous biomimetic architectures, used to construct 3D breathable networks through nanofiber composite membranes, prevent microenvironmental moisture and heat

accumulation, enhancing the breathability. Ultimately, technological integration can enable the development of wearable integrated systems [117], potentially boosting the commercial success of NHMNs. Building upon the established advantages of transdermal delivery regarding medical aesthetics, the design of a senseless wearing experience and all-weather reliability significantly enhances user compliance. The systematic development of a comprehensive pathway for commercialization, from proof-of-concept validation to market penetration for NHMNs, can facilitate the technological transition from laboratory-scale prototypes to industrial-scale commercial applications.

6 Conclusions and perspectives

In this review, we have systematically elucidated the role of a multiscale interfacial engineering framework of NHMNs in addressing three critical issues: resolving conflicts between clinical demands and microneedle performance by linking single-modality-based delivery with closed-loop theranostics. This helps combine experimental innovation with clinical implementation. By revealing the potential for commercialization through innovative manufacturing processes, biointerfacial adaptation, and pathways for clinical translation, this framework offers a feasible solution for advancing precision medicine. Previous reviews on hydrogel microneedles have predominantly focused on optimizing the properties of intrinsic hydrogels without examining the mechanisms by which the integration of nanomaterials across scales expands their functional boundaries. Conversely, studies on nanocomposite hydrogels have emphasized nanomaterial-enhanced effects, but have rarely associated them with the integrated design of microneedle devices. Moreover, systematic analyses of key industrialization-related issues, such as standardizing the manufacturing process, assessing biosafety, and the pathway to clinical translation, are lacking. To address these gaps, we have comprehensively summarized recent advances in synergistic strategies for multiscale microneedles (Table 2), ranging from the co-optimization of nanomaterials to the integration of functional modules [118, 119]. This provides a technical roadmap for NHMNs, from fundamental research to clinical translation, elucidating the interdisciplinary design of intelligent theranostic devices. In addition to providing theoretical support for generational upgrades in microneedle technology, this synergistic design establishes innovative paradigms for multidisciplinary fields, such as flexible electronics and wearable devices. However, the studies discussed here still have several limitations. First, static laboratory testing environments often fail to adequately simulate the dynamic loading of devices in the human body, which can lead to localized nanofiller detachment or fatigue fracture of the hydrogel network. Thus, dynamic models of evaluation are required to closely simulate physiological conditions. Second, multi-component interference and non-specific adsorption in biofluids severely constrain the accuracy of detection, necessitating an enhanced signal-to-noise ratio in the monitoring data. Future efforts should explore strategies for data optimization that combine the functionalization of the nanomaterial surface with artificial intelligence algorithms. Finally, achieving closed-loop theranostics requires overcoming challenges to multi-source data fusion and remote interaction, which can be achieved by developing low-power wireless transmission modules and deep interactive interfaces with cloud-based medical platforms.

Based on the multiscale interface engineering framework established in this review, NHMNs have demonstrated potential in addressing major clinical challenges and show broad application prospects. To enable the successful translation of NHMNs from laboratory research to clinical use, it is essential to address the following key issues: conflicts between clinical demands and the performance of microneedles, bridging the gap between single-modality-based delivery and closed-loop theranostics, and eliminating the mutual exclusivity of experimental innovation and clinical implementation. Here, we propose several potential future solutions to these challenges. First, the integration of nanoscale topological networks and dynamic crosslinking regulation can synergistically enhance the multifunctionality of microneedles. By combining multi-physics simulations to model skin deformation and load distribution under dynamic conditions, reliable design guidelines for real physiological environments can be established [120], addressing fundamental issues such as filler detachment and hydrogel fatigue fracture. Second, leveraging stimuli-responsive nanocarriers and bioinspired molecularly imprinted interfaces, along with a deep learning-driven signal processing architecture, enables real-time Kalman filtering to correct bio-signal baseline drift, convolutional neural networks to extract target molecular features in noisy environments, and AI-based data augmentation to push detection limits. Through the coordination of nanomaterials with stimuli-responsive drug release systems, a precise closed-loop diagnostic and therapeutic process can be achieved. Finally, a systematic plan for the full-chain industrial translation pathway should be established. Low-power wireless microneedle patches should be developed, utilizing encrypted communication modules to securely transmit diagnostic and therapeutic data to smart base stations. Data should be encoded during transmission and decoded at the receiving end to ensure privacy management of diagnostic and therapeutic information. Digital models should be utilized to optimize personalized treatment strategies dynamically. Simultaneously, key industrial milestones must be

Table 2 The applications of nanomaterials in nanocomposite hydrogel microneedles

Function	Nanomaterial	Hydrogel material	Shape	Height (μm)	Fabrication	Effect	Ref.
Enhancement	Polyhydroxyalkanoates nanoparticles	Hyaluronic acid	Conical shape	500	Mold casting	Mechanical enhancement	[68]
	Gold nanoparticles	Poly(chondroitin sulfate-acrylamido-2-methylpropane sulfonic acid)	Pyramidal shape	800	Mold casting	Enhancing the mechanical strength and enrichment efficiency for positively charged metabolites	[69]
	Silver nanoparticles	Polydopamine	Conical shape	1000	Mold casting	Mechanical enhancement	[70]
	Poly(lactic-co-glycolic acid)	Hyaluronic acid-tyramine	Pyramidal shape	1000	Mold casting	Sustained release	[71]
	Poly(lactic-co-glycolic acid)	Hyaluronic acid	Conical shape	600	Mold casting	Sustained release	[72]
	Carbon nanotube	Gelatin methacrylate	Pyramidal shape	700	Mold casting	Enhancing electrical conductivity	[73]
	Polydopamine-modified poly(3,4-ethylenedioxythiophene) nanoparticles	Gelatin-methacryloyl	Conical shape	1100	Mold casting	Enhancing electrical conductivity	[74]
	Dopamine-modified polypyrrole	Polylactic acid	Conical shape	600	Mold casting	Enhancing electrical conductivity	[115]
Detection	Metal-organic framework-based nanozymes with platinum nanoparticles	Polyvinyl alcohol	Conical shape	1200	Mold casting	Sensitive colorimetric sensing	[76]
	MnFeCN/FeFeCN nanozyme	Polyvinyl alcohol and polyvinyl pyrrolidone	Conical shape	300	Mold casting	Sensitive colorimetric sensing	[78]
	Graphene oxide nanosheets	Aminophenylboronic acid-modified sodium alginate with chondroitin sulfate	Pyramidal shape	800	Mold casting	Sensitive fluorescent detection	[81]
	Gold nanoparticles	Polyvinyl alcohol and chitosan	Pyramidal shape	900	Mold casting	Sensitive electrochemical detection	[82]
	Platinum and silver nanoparticles	Dopamine-hyaluronic acid	Conical shape	800	Mold casting	Sensitive electrochemical detection	[83]
	Cu-TCPP(Fe)/GOx hybrid nanosheets	GelMA	Pyramidal shape	1000	Mold casting	Sensitive colorimetric sensing	[94]
Treatment	Cerium dioxide nanozymes	Tannic acid	Conical shape	600	Mold casting	Suppressing inflammation	[84]
	Cerium dioxide and mesoporous silica nanoparticles	Poly(γ-glutamic acid)	Pyramidal shape	600	Mold casting	Reducing inflammation	[85]
	Rosiglitazone nanoparticles	Hyaluronic acid	Conical shape	840	Mold casting	Alleviating obesity	[86]
	Mesoporous silica nanoparticles	Enzyme-mediated hyaluronic acid-tyramine hydrogel	Pyramidal shape	900	Mold casting	Treating solid melanoma	[88]
	Laponite nanoparticles	Methacrylated hyaluronic acid	Conical shape	1200	Mold casting	Boosting immune response	[89]
	MOF (Bi–PCN–222)	Silk fibroin methacryloyl and polyvinyl alcohol	Four-pronged shape	800	Mold casting	Enabling efficient sterilization	[90]

achieved, including the standardization of manufacturing processes, long-term biosafety evaluation, and medical-device regulatory approval, to ensure the practical and interdisciplinary translation of closed-loop theranostic devices. The transition of NHMN technology from disease diagnosis and treatment toward life-enabling applications represents a pioneering step. In the rapidly advancing field of brain–computer interfaces, NHMNs can offer unique contributions. Traditional metal electrodes often cause patient discomfort during long-term implantation in the brain, which limits their use for chronic applications and significantly compromises signal continuity [121, 122]. In contrast, embedding conductive nanomaterials within a biocompatible hydrogel matrix enables the formation of microneedles that can capture electrophysiological signals with high sensitivity and adapt flexibly to neural tissues. The exceptional biocompatibility of NHMNs enables the microneedle structure to conform closely to the morphology of brain tissue, requiring only a minimal cranial opening for implantation. These ultra-fine microneedles not only enable real-time data monitoring but also amplify weak action potentials from motor neurons into clear electrical signals. These signals can then be transmitted via Bluetooth or other wireless devices to interact with bionic exoskeletons or speech synthesizers. By interpreting movement intentions and language signals, this system helps patients suffering from paralysis regain mobility and communication abilities. The integration of brain–computer interfaces and rehabilitation robotics redefines the mission of medical technology, shifting from passive disease treatment toward active life empowerment, ultimately fulfilling the people-centered vision of healthcare. Further enhancing this vision, integrating artificial intelligence and machine learning with NHMN to acquire data can help decipher complex physiological signals and enable truly adaptive closed-loop therapies. Further synergy with the Internet of Things will facilitate robust, real-time wireless data transmission and remote monitoring, propelling these systems toward higher levels of intelligent precision. Such integrated systems could evolve into pioneering intelligent neural interfaces capable of predictive diagnostics or adaptive neurostimulation, proactively maintaining neurological health and optimizing cognitive function, opening transformative avenues for augmenting human capabilities.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study does not contain any studies with human or animal subjects performed by any of the authors.

Use of generative AI tools During the preparation of this work, the authors used ChatGPT to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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