Journal of Nanobiotechnology

REVIEW

Open Access

Advances in microneedle-based drug delivery system for metabolic diseases: structural considerations, design strategies, and future perspectives

Yao Li[1,2†], Qiu Chen[7†], Tingting Wang[2,6], Zengkai Ji[2,3], Sagar Regmi[4], Haibin Tong[1*], Jian Ju[2*] and Aifang Wang[5*]

Abstract

As the prevalence of metabolic diseases such as diabetes and obesity continue to rise, the search for more effective and convenient treatments has become a crucial issue in medical research. Microneedles (MNs), as an innovative drug delivery system, have shown advantages in the treatment of metabolic diseases in recent years. MNs-based drug delivery system, which use MNs to deliver drugs directly to the subcutaneous tissue, improve drug bioavailability and reduce systemic side effects. This review aims to summarize the latest concepts, designs, and types of MNs, and to investigate the materials and manufacturing methods used in their construction. Subsequently, the mechanisms of drug delivery and graded release of MNs and recent research progress are further summarized. This article focuses on the application of MNs in the treatment of common metabolic diseases, with a special emphasis on the progress and optimization of diabetic and anti-obesity MNs. The main challenges and future perspectives in the production and evaluation of MNs, as well as in enhancing treatment efficacy and improving safety, are elucidated.

Keywords Microneedles, Transdermal drug delivery, Metabolic syndrome, Drug carrier, Metabolic disease treatment, Controlled release

†Yao Li and Qiu Chen contributed equally to this work.

*Correspondence:
Haibin Tong
tonghaibin@gmail.com
Jian Ju
jujian@ucas.ac.cn
Aifang Wang
wangaifang19832024@163.com
[1]Zhejiang Provincial Key Laboratory for Water Environment and Marine Biological Resources Protection, College of Life and Environmental Science, Wenzhou University, Wenzhou 325035, China
[2]Wenzhou Institute, University of Chinese Academy of Sciences, Wenzhou 325001, China
[3]College of Materials Science and Engineering, Nanjing Forestry University, Nanjing 210037, China
[4]Department of Radiation Oncology, University Hospital Seidman Cancer Center Cleveland, Cleveland, OH 44106, USA
[5]The People's Hospital of Yuhuan (Yuhuan People's Hospital Health Community Group), Taizhou 317600, China
[6]Zhejiang Provincial Key Laboratory of Medical Genetics, College of Laboratory Medicine and Life Sciences, Wenzhou Medical University, Wenzhou 325035, China
[7]Department of Endocrinology, The Third Affiliated Hospital of Wenzhou Medical University, Wenzhou 325200, China

Introduction

The incidence of metabolic diseases has increased globally over the past two decades, resulting in a significant economic burden and premature deaths [1, 2]. Metabolic diseases, including obesity, hypertension, high triglycerides, type 2 diabetes mellitus, non-alcoholic fatty liver disease, and Polycystic ovary syndrome, are the main culprits [3–5]. According to statistics from the World Health Organization (WHO), the prevalence of diabetes and obesity continues to rise, especially in the context of accelerated urbanization, unhealthy dietary patterns, and irregular lifestyles, making this trend even more pronounced. As patients require lifelong management and treatment, this often leads to long-term health issues and severely reduces their quality of life. The financial and emotional burden placed on individuals, families, and society is significant even in middle and high-income countries [6]. While current treatments may provide relief for certain symptoms, they encounter challenges including suboptimal patient adherence and restricted efficacy. This underscores the pressing necessity for the development of more innovative therapeutic interventions.

With the advent of modern medical technology, the treatment of chronic diseases has become increasingly diverse. This is most striking in the treatment of metabolic disorders, where emerging transdermal drug delivery technologies are transforming traditional therapies such as injections and oral administration [7]. The transdermal drug delivery system (TDDS) represents a technique for the gradual and continuous administration of pharmaceuticals through the dermal layer into the systemic circulation. This approach facilitates the maintenance of stable drug concentrations within the bloodstream, minimizes fluctuations in drug levels, and circumvents the gastrointestinal and hepatic metabolic processes. Furthermore, the absorption of the drug is not influenced by variables such as gastrointestinal pH, dietary intake, or transit time, thereby enhancing bioavailability.

Microneedles (MNs) are the next generation of transdermal drug delivery system [8–10] that provide a physical shortcut for drugs to bypass the epidermal barrier [11, 12]. Since their development in the 1990s, MNs have been applied in various fields [13, 14], including biosensor [15], immunizations [16], treatment of chronic diseases such as diabetes [17], and the skincare and beauty industry [18, 19]. MNs represent a micro-scale drug delivery system that enables effective and painless drug administration in the body and are used to deliver a wide range of drugs, including vaccines [20], insulin [21], and pain medications et al. [22]. MNs typically range from tens to hundreds of microns in depth, allowing them to penetrate the stratum corneum without reaching deeper skin areas where nerve endings are located [23]. MNs-based transdermal drug delivery technology is known for its minimally invasive, high availability, rapid onset, good patient compliance, ease of self-administration, and potential for controlled release [24]. Recently, MNs delivery systems are expected to provide more effective and safer methods of drug administration, improving the therapeutic experience for patients, ongoing research and an increase in clinical trials support this anticipation [25] (see Table 1). Currently, the MNs delivery technology is poised to target the $32 billion transdermal drug delivery market and $25 billion global vaccine market [26]. Furthermore, it is also anticipated that this technology will enter the biologics market, which is valued at over $120 billion [27]. While numerous reviews have been conducted on the use of MNs in transdermal drug delivery for diabetes management and vaccination [24, 28, 29], however, there are very few reviews that address the treatment of metabolic diseases in broader areas other than diabetes.

In this review, we focus on advanced concepts, designs and materials related to the fabrication of MNs. It also discusses in detail the contributions of various types of MNs, nano-engineering and electronic teams to improve the drug delivery capability of MNs. The release modes of MNs are highlighted based on the materials used for their preparation and the delivery mechanisms. In particular, some research advances in combining nanotechnology to intelligently control the drug release rate according to specific environmental variables. This review aims to summarize the latest developments in MNs therapy for the treatment of metabolic diseases, expanding beyond previous work includes not only diabetes mellitus, obesity and hyperlipidemia, but also other metabolic disorders such as fatty liver, polycystic ovary syndrome, and hyperuricemia, etc. The summarized sites of delivery are not only limited to dermal transdermal delivery, but also in vivo transdermal drug delivery systems that act in the gastrointestinal tract. Finally, we address the challenges, prospects, and innovative strategies for employing MNs in the treatment of metabolic diseases, with the intention of providing insights into the design of more effective transdermal systems for future applications in the daily management and treatment of metabolic diseases.

Overview of MNs patch technology

Materials and types

Over the years, scientists have tried to improve MNs design by using different materials, adjusting properties, changing shape and size [30]. To date, a wide range materials have been used to fabricate the MNs, including silicon [31], metals (such as stainless steel and titanium) [32, 33], polymers [34], glass [35], ceramics [36], sugars [37], and others [38]. Degradable or soluble MNs

Table 1 MNs for disease treatment clinical trial description and status

MNs type	NCT No.	Study title	Conditions	Treatment	Phase	Study completion date
Dissolving MN (50 μg)	NCT05377905	Microneedle Array Plus Doxorubicin in Cutaneous Squamous Cell Cancer (cSCC)	Cutaneous Squamous Cell Carcinoma	Drug: MNs Array Doxorubicin (MNA-D)	Phase1 Phase 2	December 2025 (estimated)
Hollow MN (900 μm)	NCT00837512	Insulin Delivery Using Microneedles in Type 1 Diabetes	Type 1 Diabetes Mellitus	Device: MNs Subcutaneous insulin catheter (9000 μm)	Phase 2 Phase 3	July 2013
Solid MN (650 μm)	NCT03203174	The Use of Microneedles With Topical Botulinum Toxin for Treatment of Palmar Hyperhidrosis	Hyperhidrosis	Drug: Botulinum Toxin Type A	Phase 1	August 2016
Coated MNs	NCT02745392	Safety and Efficacy of ZP-Zolmitriptan Intracutaneous Microneedle Systems for the Acute Treatment of Migraine (Zotrip)	Acute Migraine	Drug: ZP-Zolmitriptan Drug: Placebo	Phase 2 Phase 3	January 2017
Dissolving MN (MicronJet600)	NCT05108714	Intradermal Lidocaine Via MicronJet600 Microneedle Device	Local Anesthesia	Intravenous cannulation after intradermal injection of lidocaine via MicronJet600 MNs device	Not Applicable	March 2019
Dissolving MN	NCT03646188	Dose Escalation Trial to Evaluate Dose Limiting Toxicity/Maximum Tolerated Dose of Microneedle Arrays Containing Doxorubicin (D-MNA) in Basal Cell Carcinoma (BCC)	Basal Cell Carcinoma	Drug: Placebo-containing MNA 25 μg, 50 μg, 100 μg, 200 μg doxorubicin-containing MNA	Phase 1	May 2021
Dissolving MN (VX-103)	NCT06125717	Phase 1 Evaluation of H1 Influenza Vaccine Delivered by MIMIX MAP	Influenza	Biological: H1 influenza antigen	Phase 1	March 2023
Solid MN	NCT03380845	Comparison of 1,550-nm Laser and Fractional Radiofrequency Microneedle for the Treatment of Acne Scars in Ethnic Skin	Acne Scars	Erbium-doped 1,550-nm non-ablative fractional laser (Fraxel) Fractional radiofrequency MNs (Fractora)	Not Applicable	October 2018
Dissolving MN	NCT04394689	Measles and Rubella Vaccine Microneedle Patch Phase 1–2 Age De-escalation Trial	Measles	Measles Rubella Vaccine (MRV-SC) MRV-MNP	Phase 1 Phase 2	December 2022

are mainly made of polymethyl methacrylate (PMMA), hyaluronic acid (HA), polyvinyl alcohol (PVA), sodium carboxymethyl cellulose (CMC), polyvinylpyrrolidone (PVP), polylactic acid (PLA), and chitosan [24, 39, 40]. Currently, researchers have developed various types of MNs to enhance drug delivery, which can be broadly categorized into six main types: solid MNs, hollow MNs, porous MNs, coated MNs, dissolvable MNs, and swellable MNs. MNs can perform various biomedical functions, for example, solid MNs can enhance skin permeability through skin puncture, while dissolvable and swellable MNs can control drug release and extract skin interstitial fluid (ISF) [8, 41]. The functions of MNs in biomedicine are influenced by the properties of the materials used (refer to Table 2) and their structural design (refer to Fig. 1).

Solid MNs

Solid MNs, usually fabricated of hard materials like silicon, metals, or certain hard polymers, possess a robust structure that is ideal for skin puncture [54, 55]. The main purpose of solid MNs is to create microchannels in the skin, thereby enhances the permeability of ointment drugs or vaccines. Guo et al. [34] employed thermal micromolding technology to fabricate solid MNs arrays from PLA with varying numbers, densities, heights, and evaluated their effect on drug delivery. The study revealed that MNs with a height of 800 μm and a density of 256 MNs/cm^2 are optimal for enhancing drug penetration. Longer MNs provide better mechanical strength and create deeper microchannels for improved drug delivery through the skin. Furthermore, Hu et al. [56] introduced a method for fabricating metal MNs arrays using thermoplastic drawing technology. They were able to fabricate both solid and hollow MNs with adjustable lengths and tip sharpness by manipulating the rheological properties and fracture behavior of metallic glass (MG). However, solid MNs present risks such as tip bending and needle tip retention in the skin.

Hollow MNs

Hollow MNs are created by drilling solid MNs, resulting in an internal cavity [57]. This unique structure allows for the direct delivery of drugs or other therapeutic agents into the subcutaneous layers of the skin. The use of syringes or micro-pumps enables precise control over drug dosage and delivery rate, making it particularly beneficial for treatments that require accurate dose management, such as insulin injections [58, 59]. In a study by Detamornrat et al. [60], iontophoresis was integrated with hollow MNs for the delivery of various small or large molecules. The results demonstrated a notable enhancement in skin permeability for the model drug over a six-hour period when a 1 mA cm^{-2} electrical current was applied. It is important to note that manufacturing hollow MNs is a complex process that requires a meticulous methodology for the fabrication of hollow structures. Moreover, users are advised to accept the diminished mechanical strength inherent to hollow MNs, resulting from the absence of an internal support framework due to the high aspect ratio of these structures. Furthermore, the presence of drug residues or skin fragments may obstruct the hollow channels, thereby hindering or compromising the effective delivery of the drug [61].

Porous MNs

The introduction of porous MNs with a finely turned pore structure is expected to address the previously mentioned limitations of hollow MNs. This porous structure facilitated the storage and delivery of drugs across the entire surface or within the internal structure of the MNs [62]. It is evident that the porous structure significantly enhances the drug loading capacity and allows for the simultaneous carriage of different drugs on the same MNs. Porous MNs are typically constructed from biocompatible and biodegradable materials, allowing them to safely degrade within the body after drug release without the need for removal. This type of MNs is particularly well-suited for long-term or sustained drug delivery applications, such as those related to the management of chronic diseases and the vaccine administration. Li et al. [33] utilized metal injection molding (MIM) technology to create a titanium porous MNs array (TPMA), with a porosity of approximately 30.1% and an average pore size of about 1.3 μm. Experiments demonstrated successful penetration through rabbit skin, where the cumulative permeation flux of calcein loaded on the TPMA was 27 times higher than that through intact skin, significantly enhancing drug delivery efficiency. Nazia et al. [63] fabricated porous silicon MNs with adjustable porosity and high loading capacity through a combination of dry and wet etching. The thickness of the porous layer can be adjusted from 1.5 μm to 4.0 μm. The Sonkusale group has reported the development of a novel polymer porous MNs with both small and large area porous structures, accompanied by a flexible backing, for the management of pain [64]. The solid formulation employs to enhance the drug loading capacity of the novel porous MNs, enabling the loading and subsequent release of anesthetic and non-steroidal anti-inflammatory drug (NSAID) solid formulations, including lidocaine and ibuprofen in the same MNs. The porous MNs can be delivered at high strengths, which represents a significant advantage over conventional MNs. The porous MNs offers a novel avenue for combination drug therapy [65, 66].

Table 2 List of MNs with their Preparation material, types, fabrication techniques, advantages, limitations and applications

Materials	MN types	Fabrication techniques	Characteristic		Applications	Refs.
			Advantages	Limitations		
Metals: titanium, stainless steel, nickel, Silicon, Ceramics: silicon carbide, zirconia, alumina. Glass: borosilicate glass, quartz glass. Non-degradable polymers: PMMA, PDMS, nylon, PC, PS, photoresist	Solid MNs	Lithography; etching; laser cutting	Strong mechanical strength; chemical and thermal stability	Prone to breaking; low biocompatibility	Used for skin pre-treatment to enhance permeability	[31, 39, 42]
	Hollow MNs	LIGA deep X-ray lithography; drawing lithography; 3D printing (TPP)	Strong mechanical strength	Easy to break; complex to manufacture; channel blocked	Used for precise metered drug delivery and ISF extraction	[43, 44]
	Porous MNs	Micro molding (hot embossing, draw molding)	Increases drug payload; tunable porosity	Complex to manufacture; blocked pores	Suitable for the treatment of chronic diseases requiring long-term or continuous drug delivery	[33, 45]
	Coated MNs	Dipping method; spray coating method	Wide adaptability	Drug load limit; penetration limit	Suitable for the delivery of small doses of drugs	[46–48]
Biodegradable polymers: PLA, PGA, PCL, PVP, PVA, HA, PEG, Gelatin, Alginate Chitosan	Dissolvable MNs	Micro milling; 3D printing (SLA, SLS); droplet-born air blowing	Excellent biocompatibility; adjustable	relatively complex production; Relatively low mechanical strength	Used for controlled release of drugs and vaccines	[49–51]
	Swellable MNs	Micro molding; 3D printing (SLA, DLP)	dissolution curve		Sampling of ISF and controlled release of drugs	[52, 53]

Coated MNs

To address clinical requirements for rapid drug release upon skin penetration of the skin, the researchers have developed coated MNs with a thin layer of drug coating on their surface. The methods used to load the drugs include application by immersion, spraying, spin coating and other technologies [46]. The drug layer dissolves upon contact with the skin, rapidly delivering the drug into the body. Coated MNs serve as an ideal drug delivery system for small doses due to their low load capacity. Zhou et al. [67] developed a gel encapsulated coated MNs (GEC-MNs). The drug is encapsulated with sodium alginate (SA) both internally and externally, preventing the coating from dissolving rapidly during insertion. Moreover, the swelling of the gel induces coating detachment, thereby minimizing drug residues on the PLA substrate. This study highlights the potential of GEC-MNs as a promising drug delivery system. Delivery of rhIFNα-1b via GEC-MNs is more efficient and stable, allowing for sustained release of water-soluble drugs. Future research on coated MNs should focus on improving the stability of the drug coating and reducing the rate of drug loss while ensuring efficient drug release [68].

Dissolvable MNs

Dissolvable MNs made of biodegradable materials have been the focus of extensive research due to their ability to provide precise and controlled drug release over a duration ranging from minutes to hours. The polymer's biocompatibility and solubility ensure its long-term stability within the skin, eliminating the need for removal as is required with traditional injections [69]. Wang et al. [70] successfully fabricated soluble, layered MNs using a three-step casting method. The drug was put in the HA layer, which served as the "shell," and the PVA layer acted as the core and base. Upon insertion of the MNs device into the skin, the HA layer rapidly dissolves, allowing for the efficient release of the drug. Testing results demonstrated that an impressive 90% of the drug was delivered into the skin within a mere 10 s. Zhu et al. [71] developed an ultrafast dissolution MNs using water-soluble cyclodextrin. The proposed MN system has the potential to be utilized to deliver high doses of a hydrophobic model drug (ibuprofen) into the skin of mice. Although DMNs enable rapid dissolution and subcutaneous release of therapeutic drugs upon contact with skin interstitial fluid, the "bed of needles" effect and skin deformation limit their efficient [72] and rapid delivery over large skin areas. Guo et al. [73] introduced a dissolvable MNs Roller device based on PVA. The dissolvable MNs break easily under shear force and pressure, with the drug-laden tip penetrating the skin first, followed by dissolution and drug release. This design minimizes the risk of

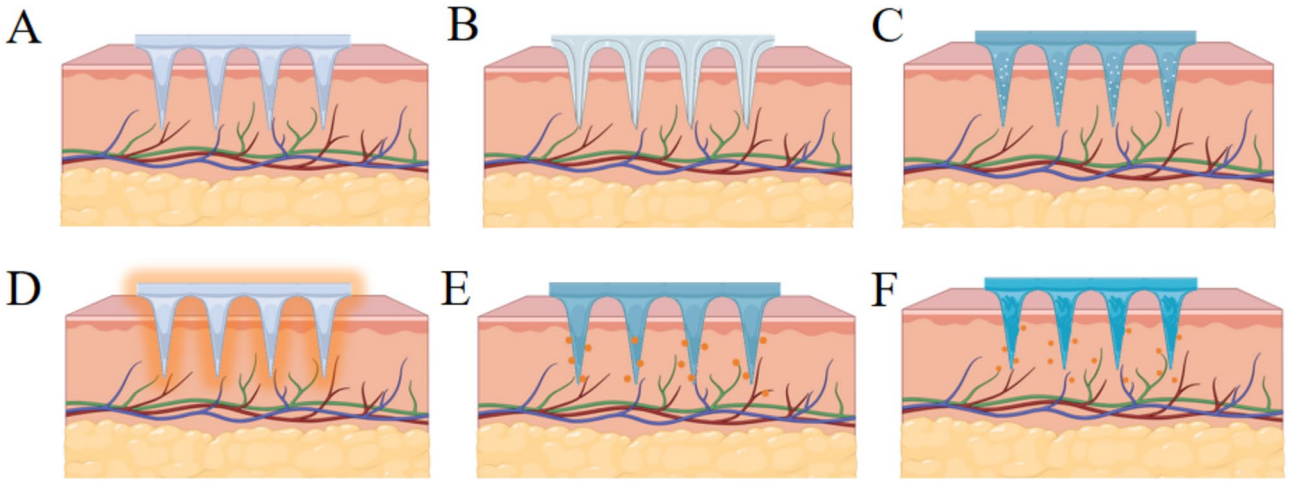

Fig. 1 Schematic diagram of the structure of different types of MNs. (**A**) Solid MNs. (**B**) Hollow MNs. (**C**) Porous MNs. (**D**) Coated MNs. (**E**) Dissolvable MNs. (F) Swellable MNs. Created with BioRender.com

prolonged patch application, which can lead to infection or erythema.

Swellable MNs

Swellable MNs function differently from other types of MNs. Swellable MNs are manufactured using a hydrogel three-dimensional network structure in an aqueous medium [74]. This cross-linked network enhances the utility of hydrogel MNs, allowing them to retain significant amounts of water, are soft and elastic. Swellable MNs function differently from other types of MNs [51]. As first reported in 2012, hydrogel MNs undergo a swelling phenomenon upon contact with the moist environment of the skin, this process is attributed to the absorption of water by the polymer network within the hydrogel. The drug release mechanism involves hydrogel swelling, gradual release, drug diffusion, and complete degradation [75]. Peng et al. [76] explored an implantable MNs with poly(lactic-co-glycolic acid) (PLGA) tips and a hydrogel base, which can embed drugs into the skin with up to 80% within one minute. Notably, the hydrogel base can be completely removed after delivery, thereby eliminating sharp biohazardous residues. Moreover, the application of swellable MNs is not limited to drug delivery, as they can also extract ISF for subsequent analysis [53].

Design and manufacturing technology

Recently, advancements of micro-nano fabrication technology, researchers to design and manufacture MNs with varying sizes, morphologies, materials, and costs to satisfy the functional requirements of MNs applications. Precision numerical control techniques, such as photolithography [77], laser cutting [78], and mechanical milling [50], enable the creation of complex and precise MNs designs. Furthermore, micro-molding [45] and droplet-jetting [49] methods offer flexible solutions for fabricating polymer MNs, particularly suitable for rapid production of MNs templates. Electrochemical etching, dry, and wet etching techniques are mainly used to manufacture of silicon and metal MNs [31, 42]. Advanced additive manufacturing techniques, such as 3D printing technologies [52, 58], including stereolithography (SLA) [79], digital light processing (DLP) [80], selective laser sintering (SLS) [81], continuous liquid interface production (CLIP) [82], fused deposition modeling (FDM) [83], and two-photon polymerization (TPP) [44], can rapidly produce high-precision, customized three-dimensional MNs prototypes. These technological advancements have optimized these methods, enhancing manufacturing precision, efficiency, and customization.

Graded release for drug delivery

Understanding drug release patterns is crucial for designing and optimizing drug delivery systems to achieve more effective therapeutic outcomes. The functionality of controllable drug release MNs systems is currently governed mainly by the physicochemical properties of the matrix materials, the design of the MNs, drug interactions, and in vivo environment [9]. Drug release from MNs is typically controlled by diffusion, swelling, and degradation mechanisms in the absence of external stimuli [84]. Many researchers have also explored the interaction between stimulus-responsive materials and MNs systems, introducing a concept of intelligent and automated drug delivery that can respond to specific biological signals or target locations [85, 86]. Inspired by the successful cases of transdermal controlled drug delivery achieved through MNs, various innovative designs have emerged, revealing the immense potential for precise targeting of specific cells and local tissues. These innovative strategies are expected to significantly enhance therapeutic outcomes while greatly reducing systemic side effects [87].

Direct release via matrix swelling/degradation

In general, matrix swelling controlled release systems can absorb surrounding biological fluids after implantation into the human body, promoting the therapeutic agents into the microcirculation [9, 75]. In degradable MNs systems, the drugs are loaded into biodegradable materials and encapsulated within the MNs, creating a long-lasting dermal reservoir for precise and controlled drug release within the skin [88]. These delivery systems are simple, effective and controllable, making them suitable for applications such as vaccination and drug therapy.

Recently, Zhao et al. [89] used 3D printing technology to develop therapeutic exosome-encapsulated bionic adaptive MNs for diabetic wound healing. These MNs consist of an adjustable PVA hydrogel tip that encapsulates mesenchymal stem cell (MSC) exosomes and a detachable 3 M medical tape base. PVA hydrogel is ion-responsive due to the Hofmeister effect [90]. Sulfate ions contribute to the formation of a harder surface on the MNs tips, thus enhancing their ability to penetrate the skin more efficiently. Conversely, nitrate ions soften the MNs tips, facilitating the release of exosomes upon detachment from the base (Fig. 2A). The study revealed

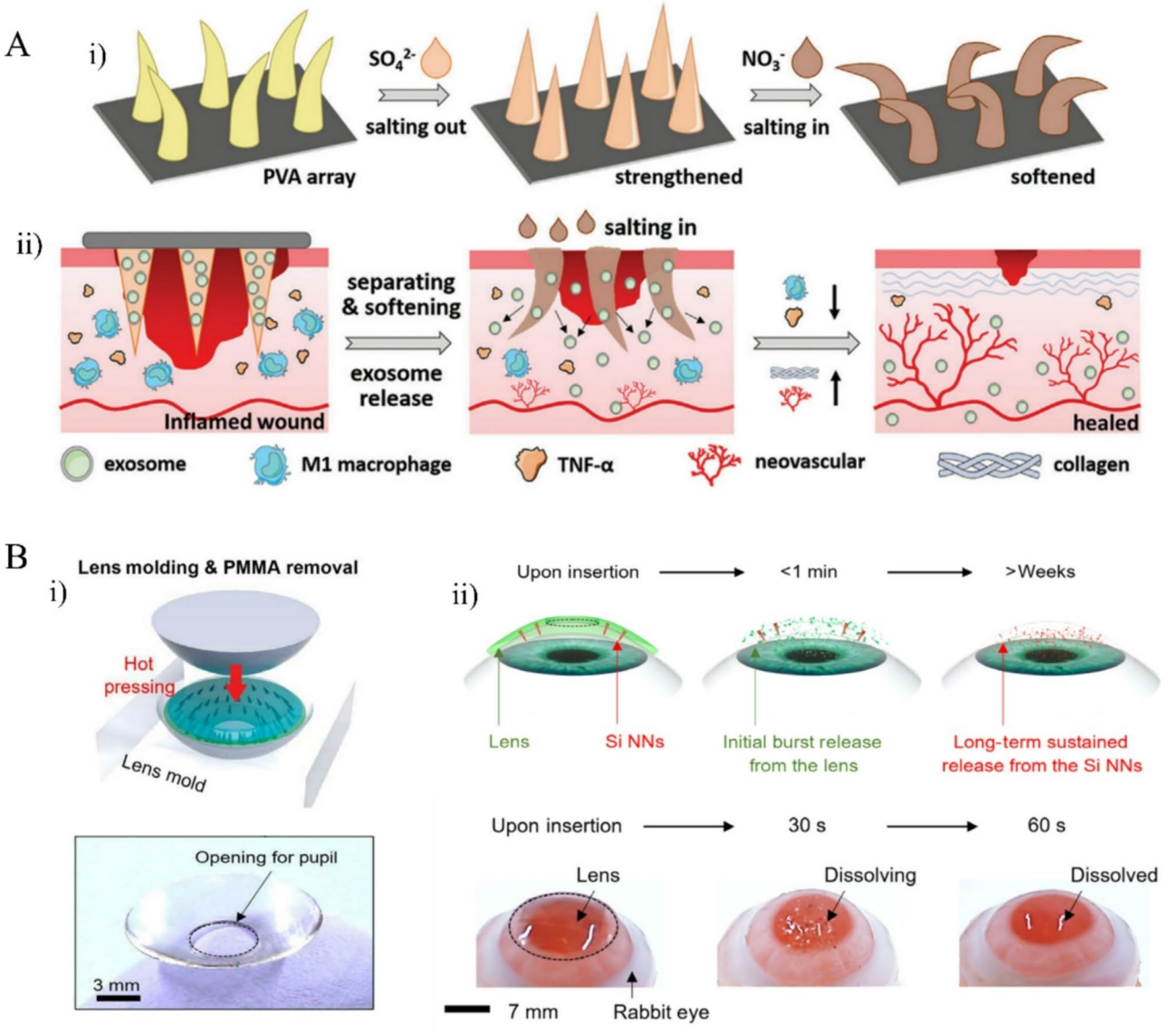

Fig. 2 MNs released directly via matrix swelling/degradation. (**A**) Exosome-encapsulated MNs for diabetic wound healing: (i) The strength of the PVA hydrogel array is modulated by various ions; (ii) Exosome-loaded MNs promote wound healing mechanism. Reprinted with permission from Ref [89]. 2023, Wiley. (**B**) Silicon nanoneedles and tear-soluble contact lenses for ocular drug delivery: (i) Preparation diagram of soluble contact lenses; (ii) Time-lapse of drug delivery and photos of a rabbit eye with a dissolving contact lens. Reprinted with permission from Ref [91]. 2022, The American Association for the Advancement of Science

that MSC-derived exosomes effectively promote the generation of new tissues and accelerate wound healing in diabetic rats. As illustrated in Fig. 2B, Lee et al. [91] combined PMMA and PVA-coated silicon nanoneedles with tear-soluble contact lens to propose a unique ocular drug delivery platform. These contact lenses are soluble in tears and can fit corneas of different sizes. MNs dissolve quickly in tear fluid, releasing anti-inflammatory medication within one minute. The silicon nanoneedles, designed for minimally invasive penetration into the cornea, degrade gradually over several months, enabling biphasic drug release.

Environmental stimulus-responsive release

Stimulus-responsive MNs are the intelligent drug delivery platform that can sensitively respond to specific external or internal stimuli [92]. These MNs are capable of autonomously regulating drug release upon detection of particular physiological conditions or stimuli, making them suitable for therapeutic scenarios requiring fine-tuned control over the timing and dosage of drug release, thereby achieving precise and controlled drug delivery.

External physical stimulation regulation

Exogenous trigger MNs systems facilitate drug release by sensing specific external signals, such as temperature, light, ultrasound, and electrical fields [92, 93]. This provides an unprecedented opportunity for patients to tailor the timing and dosage to their specific needs. Among other external conditions, the use of light (such as ultraviolet, visible, or near-infrared light) as a stimulus to control drug release enables precise drug delivery to specific sites in the body by adjusting the light's intensity, duration, and wavelength [94, 95], which represents a gentler and more flexible method of drug delivery.

Pioneering work on a light-responsive hydrogel MNs was reported by John et al. [96]. As shown in Fig. 3A, the array is composed of 2-hydroxyethyl methacrylate (HEMA) and ethylene glycol dimethacrylate (EGDMA), is light-responsive, and can load up to 5% ibuprofen. Raman spectroscopy analysis confirmed the delivery of up to three doses of 50 mg ibuprofen over a period of 160 h. This demonstrates significant potential for prolonged and controlled drug release. In addition, Yu et al. [97] embedded photothermal converter Prussian blue nanoparticles and metformin into polycaprolactone (PCL) to fabricate near-infrared (NIR) light-triggered MNs. These MNs tips are capped on a soluble PVA/PVP base. As the substrate dissolves and absorbs tissue fluid, the detachable tips penetrate to the skin. The photothermal effect of PBNPs is activated by exposing the embedded MNs tips to NIR radiation. This causes the MNs tips to melt, releasing the encapsulated metformin. This mechanism enables patients to control the timing and dosage of drug release based on their individual needs.

In recognition of the limitations of single-stimulus responses in achieving desired results and to enhance patient self-management, Luo et al. [98] developed a magnetothermal responsive dual-layer MNs system (Fig. 3B), composed of HA, ferro-ferric oxide (Fe_3O_4), and selenium nanoparticles encapsulated in micelles. A disk-shaped electromagnetic field device (Disk-ZVS) that generates an electromagnetic field with minimal attenuation in living tissues. By utilizing magnetic penetration, the magnetothermal conversion therein achieves deep sterilization effects through the tough epidermis. When applied to diabetic wounds, excess hyaluronidase gradually degrades HA, releasing SeNPs. This process reduces reactive oxygen species (ROS) production and helps regulate the wound's redox balance. Furthermore, SeNPs promote angiogenesis, accelerating wound healing. Consequently, this MNs system integrates multiple functions including magnetothermal sterilization, deep tissue penetration, anti-inflammatory action, and promotion of angiogenesis, demonstrating significant potential as an adjunct therapy for diabetic wound infections. Simultaneously, sonodynamic therapy (SDT) has gained attention in recent years due to its non-invasive treatment approach and high penetration capabilities [99]. In their investigation into the sonocatalytic properties of TiO_2 nanoparticles across varying crystal phases, Wu et al. [100] discovered that anatase-brookite TiO_2 exhibited exceptional antibacterial activity against Staphylococcus aureus following a 15-minutes ultrasound (US) treatment, attributing this effect to enhanced O_2 adsorption and reduced O_2 activation energy, leading to an increased production of ROS and a disinfection rate of 99.94%. Based on this discovery, the authors proposed an innovative AB-based dissolvable MNs approach. As shown in Fig. 3C, these MNs, designed to rapidly dissolve the cavitation effect of US, efficiently delivering anatase-brookite TiO_2 into biofilms, offering a potent solution for deep biofilm infections. Ultrasound-assisted MNs therapy represents a novel approach for treating wound biofilm infections.

Internal physiological molecular regulation

Endogenous physiological stimulus-responsive MNs are created by integrating functional materials that respond to endogenous stimuli such as pH changes, fluctuations in glucose concentration, and increased enzyme activity [94, 101, 102]. In recent years, researchers have explored the potential application of these smart MNs patches, including innovations in materials, optimization of drug loading, and customization of drug release profiles in a spatiotemporally controllable manner [103].

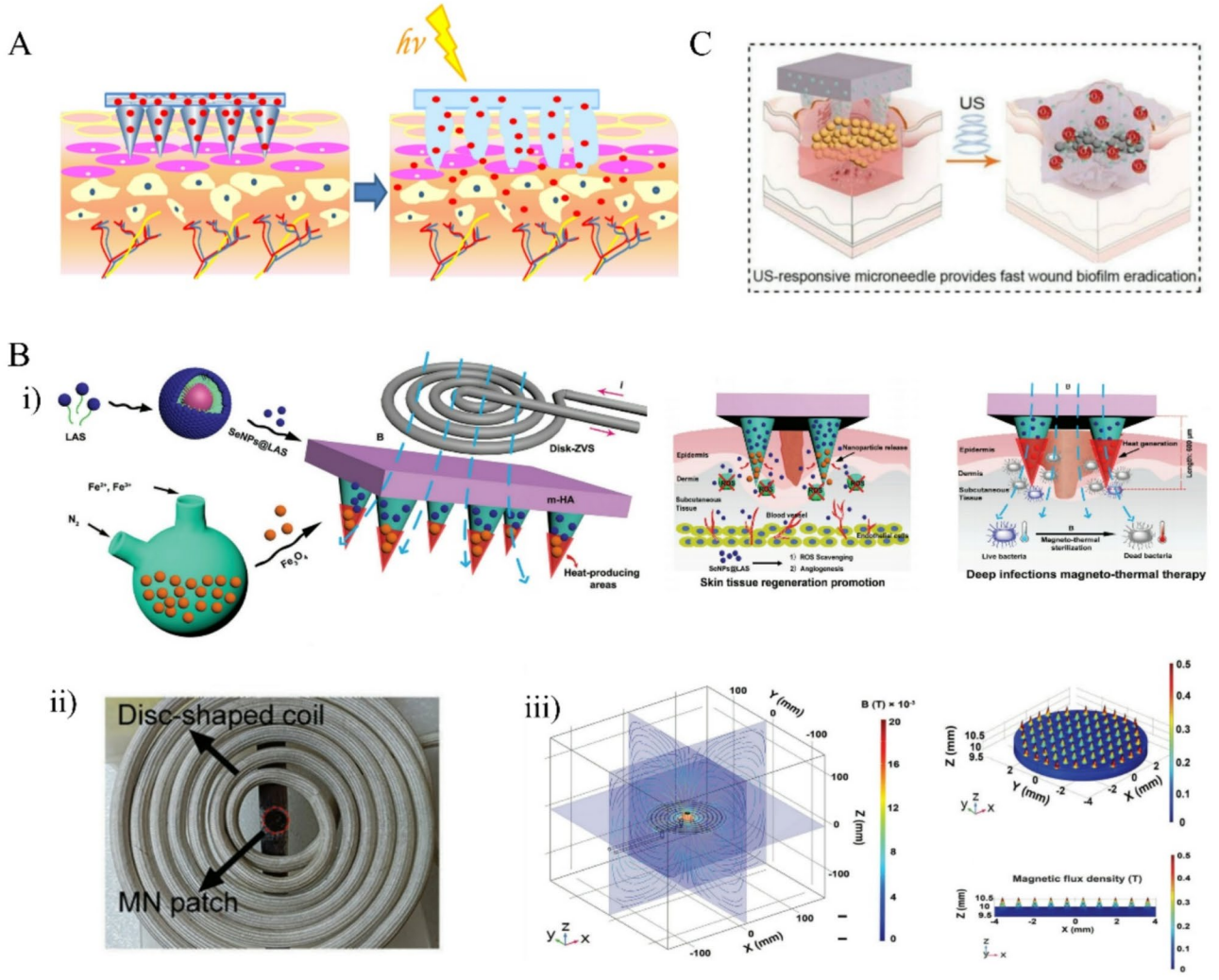

Fig. 3 The MNs system responds to external environmental stimuli. (**A**) Release mechanism of light-responsive hydrogel MNs loaded with a model drug (ibuprofen). Reprinted with permission from Ref [96]. 2016, American Chemical Society. (**B**) A magnetothermal-responsive dual-layer MNs for diabetic wound treatment assistance: (i) MNs relies on the electromagnetic field generated by Disk-ZVS for magnetocaloric conversion to achieve deep sterilization, while releasing SeNPs to reduce ROS and promote angiogenesis; (ii) Schematic diagram of the disk-shaped coil and MNs position simulation; (iii) The total magnetic field distribution of the vortex coil and MNs, along with the overall view and side view. Reprinted with permission from Ref [98]. 2023, Wiley. (**C**) Working mode of AB-MN + US for wound biofilm treatment. Reprinted with permission from Ref [100]. 2022, Wiley

The solubility, stability, and absorption rate of drugs are deeply affected by pH values, and some modern wound dressings and therapeutic strategies consider pH modulation as a mechanism to promote wound healing. Ullah et al. [104] designed and manufactured a porous polymer coating on MNs that automatically releases therapeutic drugs in response to wound pH conditions (Fig. 4A). To ensure that there is no drug leakage, the porous layer was effectively covered the porous layer with a film coating of Eudragit S100. Under the healthy skin pH conditions (pH 4.5), drug the release of the medication from the MNs in the test medium was found to be negligible. However, when the MNs were exposed to chronic wound pH conditions (pH 7–9), a significant increase in drug release was observed.

Glucose is another important internally responsive physiological molecule [105, 106]. As shown in Fig. 4B, Gu et al. [107] designed a glucose-responsive insulin patch that releases insulin and GOx-loaded vesicles based on blood glucose levels. These vesicles are composed of hypoxia-sensitive hyaluronic acid (HS-HA) combined with hydrophobic 2-nitroimidazole (NI). GOx catalyzes the breakdown of glucose in the presence of oxygen, which reduces HS-HA and accelerates insulin release. This mechanism has been shown to effectively regulate blood glucose levels in a mouse model of type 1 diabetes. Glucose is a vital substance in cell metabolism that supports cell survival, growth, and the construction of the tumor microenvironment. Singh et al. [108] fabricated a dissolvable polymer MNs containing GOx and copper

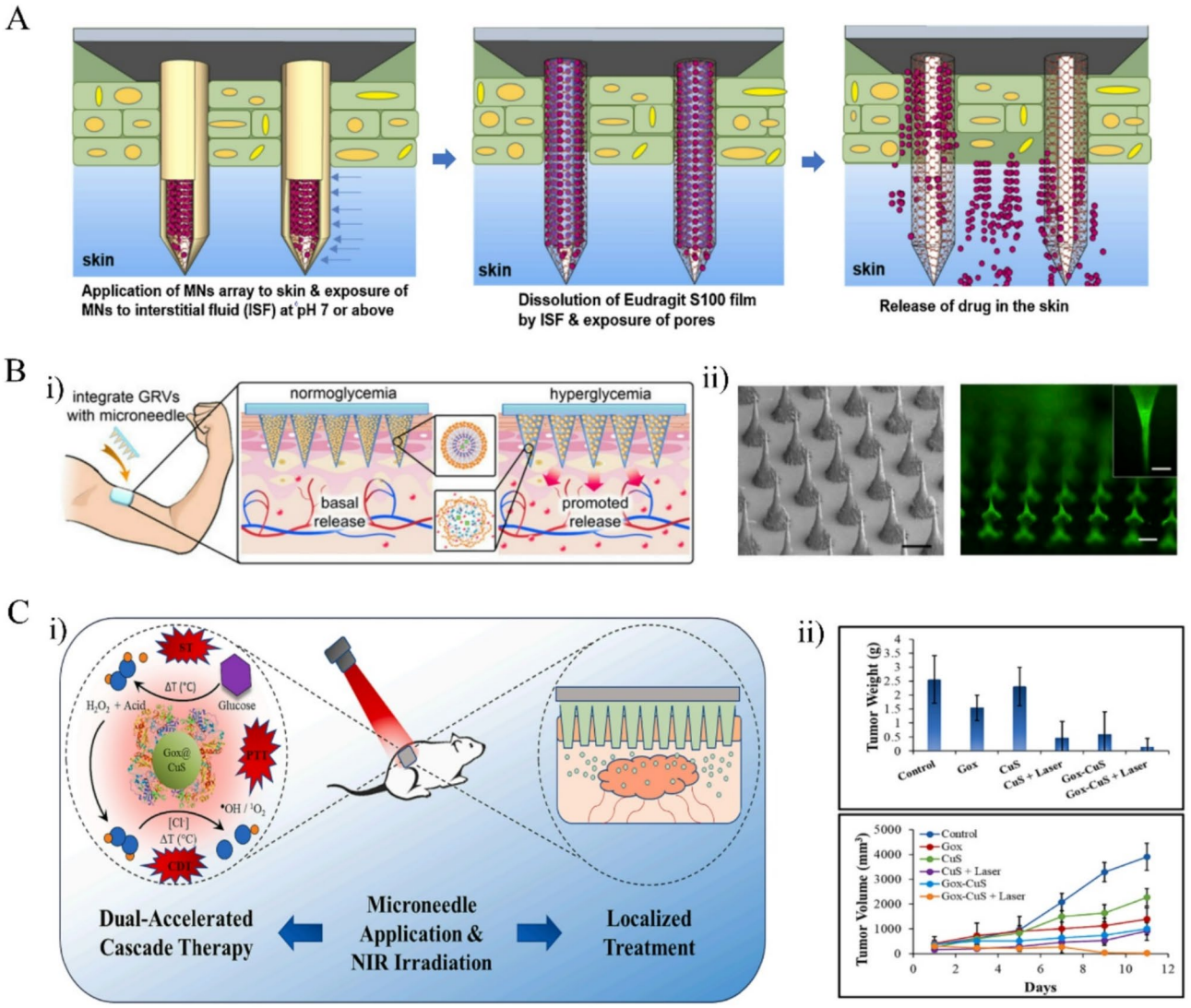

Fig. 4 The MNs system responds to internal environmental stimuli. (**A**) Wound pH-dependent release system schematic illustration. Reprinted with permission from Ref [104]. 2021, Elsevier. (**B**) Glucose-responsive insulin MNs: (i) A schematic of the MNs, containing vesicles that trigger insulin delivery in vivo in response to hyperglycemic conditions; (ii) SEM images of the MNs array and fluorescence images of MNs labeled with FITC-insulin. Reprinted with permission from Ref [107]. 2015, PNAS. (**C**) GOx and CuS nanozyme composite dissolvable MNs: (i) Schematic representation of melanoma treatment using GOx-CuS in MNs; (ii) Final tumor weight and changes in tumor volume during treatment in each group. Reprinted with permission from Ref [108]. 2024, Elsevier

sulfide (CuS) nanozymes with NIR chloroperoxidase-like activity (Fig. 4C). The GOx enzyme initiates starvation therapy and activates the CuS nanozyme to generate ROS using endogenous glucose and Cl^-. The combination of CuS-based chemodynamic therapy (CDT) and photothermal therapy (PTT) is further enhanced by near-infrared radiation. The GOx-CuS nanosystems exhibited promising therapeutic efficacy in a mouse melanoma model.

Targeted release in localized areas

MNs systems could be used to achieve localized therapeutic effects by targeting molecular modifications, modulating the local physiological environment and employing specific delivery strategies. These advanced systems aim to release drugs precisely to specific local tissues or lesions, optimizing drug uptake and maximizing therapeutic effects while circumventing the obstacles associated with systemic administration [9]. Localized targeting of MNs has shown promise in the treatment of diseases such as diabetes, obesity, and cancer [23, 109], and their application has subsequently expanded to include ocular, oral, cardiac, gastrointestinal delivery, and other areas [110–112].

Nanomaterial encapsulation targeted regulation

Nanomaterials can facilitate the targeted delivery of MNs through the conjugation of targeting ligands or antibodies [113]. Moreover, the incorporation of nanomaterials into MNs allows for the enhancement of drug delivery characteristics, including an increase in the drug loading capacity and the implementation of prolonged, controlled drug release [114, 115]. Figure 5 shows the innovative nanomedicine developed by Bao et al. [116], they partially hydrolyzed α-lactalbumin (α-lac) nanomicelles with Bacillus licheniformis protease (BLP) and encapsulated the known anti-obesity agent capsaicin (Cap) within them, the fabricated nanomedicine was then directly delivery to adipose tissue via MNs. Furthermore, Maryam et al. [117] aimed to enhance the solubility of the third-generation antidiabetic drug glimepiride (GM) by incorporated GM-encapsulated nanomicelles into MNs. The nanomicelles were uniformly distributed within PVP and PVA polymer matrices, with each array achieving a drug load of 80.3 μg. The solubility was significantly increased by 250 times, demonstrating higher availability and lower dosages compared to oral administration. As a result, the use of nano-micelle dissolvable MNs provides a more effective and regulated drug release methodology, which may facilitate the enhancement of transdermal delivery and drug absorption.

Microelectronic programmable control regulation

In recent years, Micro electromechanical systems (MEMS) have emerged as a powerful suite of new technologies designed to achieve precise localization and programmable control over drug release via microelectronic

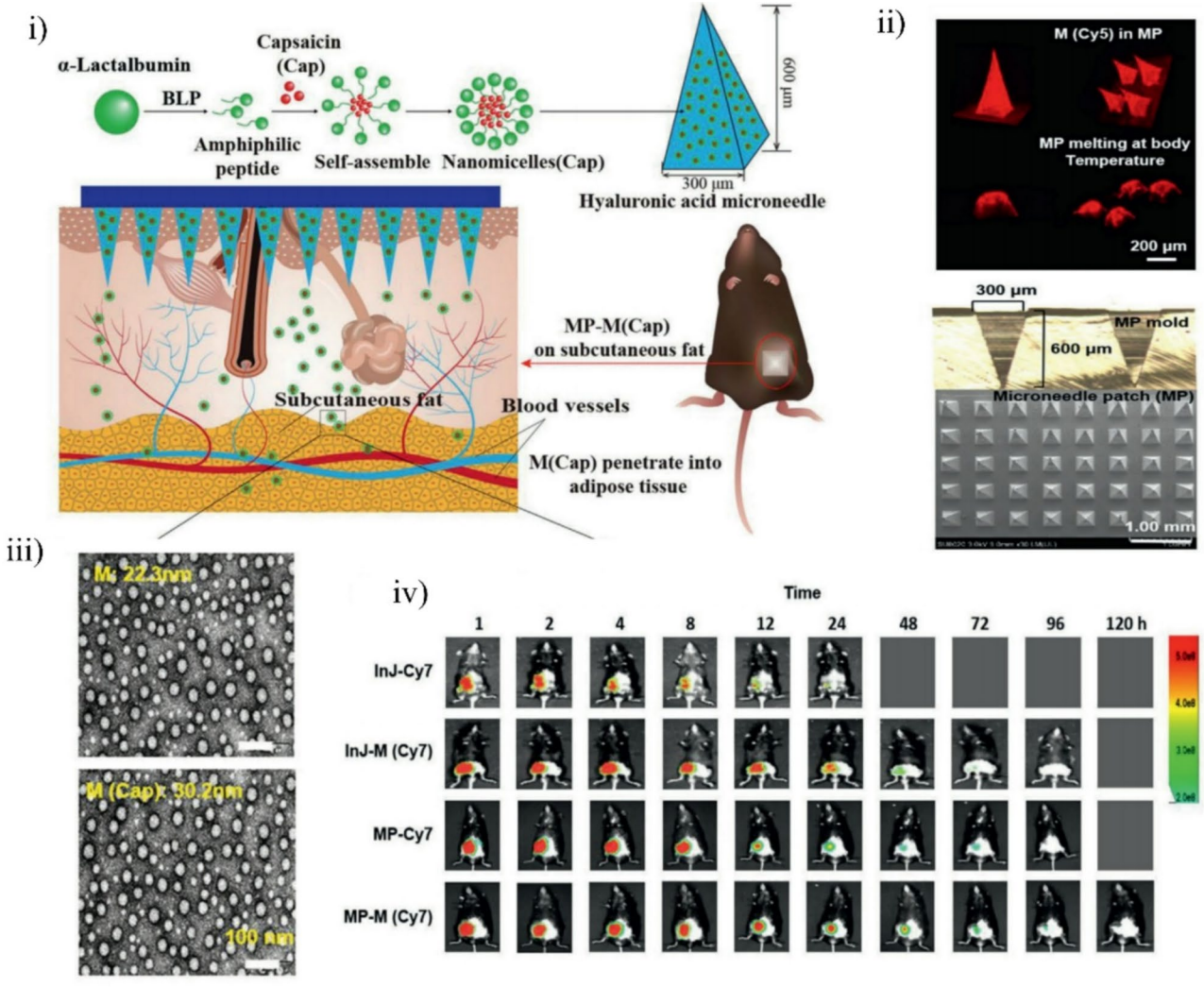

Fig. 5 Targeted release of MNs via local area. MNs for localized targeting of adipose tissue: (**i**) Schematic illustration of a multifunctional MNs loaded with capsaicin-loaded micelles; (**ii**) SEM images of the MNs and CLSM images before and after loading M (Cy5) on the depilated skin of the left inguinal adipose tissue; (**iii**) TEM images of α-lac nanomicelles and Cap-loaded nanomicelles; (**iv**) In vivo fluorescence imaging display. Reprinted with permission from Ref [116]. 2021, Wiley

techniques [118, 119]. Rao et al. [120] proposed a design for an integrated MNs piezoelectric micro pump. This micro pump utilizes a rectangular piezoelectric actuator, with four main components: electrodes, a piezoelectric plate, a polydimethylsiloxane (PDMS) membrane, and inlet and outlet channels arranged from bottom to top. The flow rate of the micro pump at an input voltage of 10 V and frequency of 300 Hz is 4.1 mL/min, while the flow rate integrated with MNs is 4.67 mL/min. In terms of safety, the high pumping rate at low applied voltages is crucial for transdermal controlled drug delivery applications. Zhang et al. [121] investigated an alternating current electrothermal (ACET) micro pump with high working pressure and rapid flow rate, utilizing a MNs array for liquid transport. This micro pump is capable of achieving rapid pumping rates (10^2–10^3 nl/s) and high working pressures (1–12 kPa), which are important for the continuous fluid delivery applications of biomedical devices such as MNs arrays.

Combination drug therapy

MNs combined with drug therapies are the most effective approach for synergistic target disease treatment [122, 123]. This method allows for the simultaneous delivery of multiple drugs within a single MNs, and it is particularly applicable to diseases that require multi-step treatment processes, such as combination chemotherapy in cancer treatment and antibacterial and anti-inflammatory in wound healing [124]. Li et al. [123] developed individually coated MNs for loading and co-delivery of various drugs, with each MNs is independently coated with different drugs. Research has demonstrated that coated MNs are capable of delivering various drugs or particles, providing a method for simultaneous delivery of multiple drug formulations to the skin.

Subsequently, as shown in Fig. 6A, Wang et al. [125] designed a trilayer MNs for the controlled release of three different molecules. The first layer was made of CMC, the second layer of ethyl cellulose (EC), and the third layer was made of PVP. Experimental results showed that the MNs exhibited multiphasic release curves for each molecule: the outermost layer of CMC released fluorescein

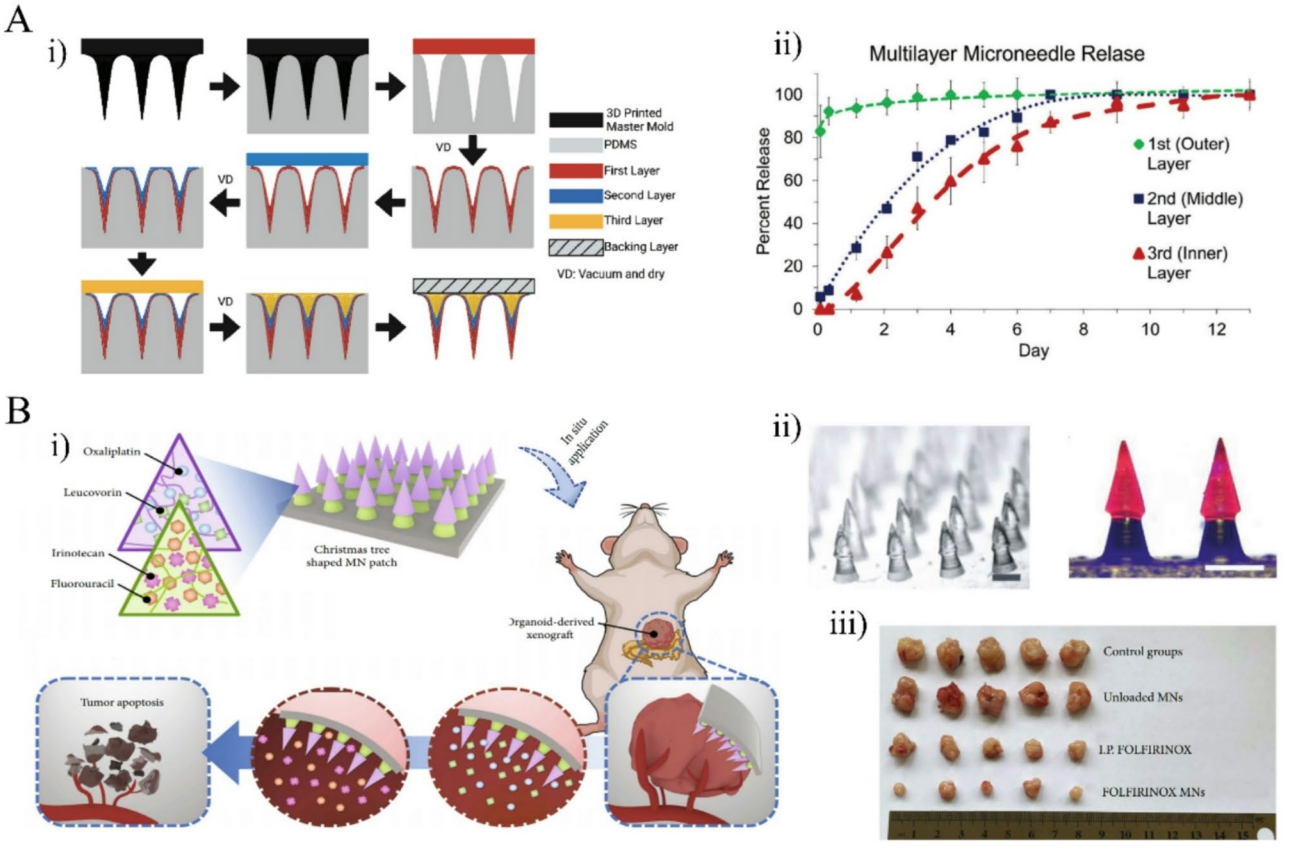

Fig. 6 Multidrug combination therapy MNs. (**A**) Triple-layered MNs for controlled release of three different molecules: (i) Stepwise fabrication method of multilayered MNs; (ii) Changes over time in the release curves of different layers in triple-layered MNs. Reprinted with permission from Ref [125]. 2023, Wiley. (**B**) MNs scheme for combined chemotherapy treatment of PC: (i) Design and application of the Christmas tree-shaped MNs; (ii) Optical microscopy image of a Christmas tree-shaped MNs; (iii) Digital images of pancreatic tumor samples. Reprinted with permission from Ref [126]. 2022, The American Association for the Advancement of Science

immediately, while the middle layer, containing methylene blue, exhibited controlled release over several days. Additionally, the middle layer delayed the release of tetramethylrhodamine (TRITC)-labeled antibodies in the innermost layer, achieving a sustained release effect over the course of a week. Additionally, by varying the manufacturing parameters, it was possible to regulate the thickness of the layers, thereby controlling the timing of drug release. The proposed technique is promising as it enables multimodal therapy to be provided within a single treatment session. As depicted in Fig. 6B, Huang et al. [126] developed a novel Christmas tree-shaped adhesive MNs that concurrently loads fluorouracil, folinic acid, irinotecan, and oxaliplatin, with the aim to implementing a spatiotemporal FOLFIRINOX regimen for the orthotopic treatment of pancreatic cancer (PC). This MNs was made using a layer-by-layer molding method. Oxaliplatin and folinic acid were placed in the top MNs, while irinotecan and fluorouracil were set in the bottom MNs. The multilayer structure enhances the adhesion capabilities of the MNs and provides spatiotemporal control over drug release, thereby facilitating the release of the drugs and offering an effective strategy for combined chemotherapy in the treatment of PC.

Application of MNs in the treatment of metabolic diseases

MNs is a highly anticipated therapeutic approach for the treatment of metabolic diseases. This method enables the targeted delivery and controlled release of medications, provides a promising avenue for the management of metabolic diseases [127]. For the treatment of diabetes, MNs can facilitate the rapid and precise delivery of insulin or other medications, thereby maintaining stable blood glucose levels [128]. MNs can also be utilized to treat obesity, hypertension, and other diseases related to metabolic disorders by regulating hormone levels or through other therapeutic pathways to improve the metabolic state of patients [129, 130]. An overview of the latest research on MNs for the treatment of metabolic diseases is presented in Table 3.

Diabetes

Diabetes, a globally prevalent metabolic disease, is commonly associated with elevated blood glucose levels (BGL) [127]. There are two main types of diabetes: type 1 and type 2. Type 1 diabetes is also called juvenile or childhood-onset diabetes. It is caused by the body attacking the pancreas, which leads to a lack of insulin. Type 2 diabetes is usually caused by the body not using insulin properly. It can be managed through medication, lifestyle changes, and diet [137, 138]. For patients with type 1 and advanced type 2 diabetes, traditional care requires continuous monitoring of blood glucose levels and insulin injections or pumps to maintain normal glucose levels. However, injecting insulin is painful, inconvenient, and sometimes not enough to control blood sugar. Oral insulin appears to be an alternative to subcutaneous injections, however, the efficacy of this approach has been limited by the degradation of the insulin prior to absorption, resulting in low utilization efficiency and poor membrane permeability [139].

Over the past two decades, numerous studies have demonstrated the efficacy of MNs in delivering insulin for glycemic control [28, 140]. Insulin-containing MNs, which bypass the gastrointestinal tract and increase efficiency while reducing pain, have become a highly sought-after method of drug delivery. In the initial design stages the insulin, O_2 and H_2O_2 were frequently selected as the response molecules for insulin release [106, 107]. Nevertheless, the presence of H_2O_2 in this system has led to concerns regarding its long-term biocompatibility. In 2018, Gu et al. [141] proposed a glucose-responsive smart insulin delivery system. As can be seen from Fig. 7A, GOx encapsulated in the core is used to generate H_2O_2 and then release insulin. Importantly, the outer shell contains catalase, which filters and scavenges excess H_2O_2, thereby reducing the risk of H_2O_2-induced inflammation. Liu et al. reported a glucose and H_2O_2 -responsive polymeric vesicles MNs for insulin sensitive transcutaneous delivery [142]. In Fig. 7B, GOx catalyzes the production of gluconic acid and H_2O_2 from glucose, the generated H_2O_2 can then stimulate the hydrolysis of phenylboronic acid pinacol ester (PBEM) to achieve dual-response release of insulin. Yu et al. [132] proposed a detachable transdermal patch equipped with MNs loaded with insulin and a glucose-responsive polymer matrix, capable of regulating glucose levels for over 20 h. Under hyperglycemic conditions, phenylboronic acid within the polymer matrix reversibly forms glucose-borate complexes, utilizing its increased negative charge to cause the polymer matrix to swell and weaken the bonds between the negative insulin and the polymer, so the insulin is released more quickly. Despite the ability to regulate insulin release in response to fluctuations in blood glucose, in practice, human blood glucose fluctuates in a complex manner and may be influenced by numerous factors, including diet, exercise, and emotional states. Therefore, the patch's ability to respond accurately to these complexities requires further optimization to achieve more precise blood glucose control.

Although transdermal techniques have achieved rapid release of the insulin-MNs, it is still difficult to maintain therapeutic levels of insulin for the patients remains challenging. Recent studies have focused on releasing insulin-MNs in the oral cavity and even to deliver assembled insulin-MNs into the gastrointestinal tract, utilizing gastrointestinal peristalsis to facilitate MNs puncture

Table 3 MNs-based pharmaceutical formulations for metabolic syndrome management

Types	Medications	Application	Materials	Morphology	Dose	Results	Refs.
Dissolving MN	Caffeine	Obesity	HA	7 × 7 array, height is 500 ± 50 μm, tip diameter is 30 ± 2 μm	15% w/w	Weight loss, decreased leptin, and increased adiponectin levels	[130]
Dissolving MN	BTX-A	Obesity	PVP, PVA, HA	10 × 10 conical needles, aspect ratio of 2, heights of 300, 600, and 1000 μm	6.7 IU	Slow down gastric emptying speed, improve fatty liver degeneration, and improve glucose tolerance.	[131]
Glucose responsive MN	Insulin	Diabetes	N-vinylpyrrolidone (NVP), DMAEA, 3APBA, EGDMA	A 20 × 20 array, with a base width of 400 μm and a height of 900 μm	7 mg	Quickly regulates glucose levels in the blood	[132]
Theranostic MN	Insulin	Diabetes	Sodium alginate, chondroitin sulfate	10 × 10 array with base width 400 μm, height 600 μm and tip diameter 35 μm	5 mg	Real-time blood glucose sensing and self-regulated insulin release	[17]
Dissolving MN	SNP, ST	Hypertension	Sodium carboxymethylcellulose (SCMC, Mw: 90 000, 8% w/v)	9 × 9 array with 250 μm base and 600 μm height	SNP: 150 mg/mL ST: 500 mg/mL	Reduces high blood pressure and is used in hypertensive emergency management	[129]
Targeted MN	Capsaicin	Obesity	HA, PVA	10 × 10 array with 700 μm pitch, 300 μm base length on each side, 600 μm height	115.26 mg/g per α-lac protein	Promotes the browning of white fat, inhibits PPAR-γ, CEBPα levels, and increases TRPV1, UCP-1, CytC levels	[116]
pH responsive MN	Rosi	Obesity	HA, dextran	11 × 11 array with 600 μm center-to-center spacing, 300 μm base diameter, and 800 μm height	10 mg/ kg	Upregulates brown adipocyte markers *Elovl3* and *Cidea*, and represses white adipocyte genes *Resistin* and *Adipsin*	[133]
Hydrogel MN	PFD	Liver fibrosis	Gelatin, methacrylic anhydride (MA)	15 × 15 array, 800 μm in height, 300 μm in diameter, and 600 μm in pitch	10 mg/mL	Downregulate TGF-β1, inhibit the expression of Col1a and α-SMA, and enhance the anti-apoptotic effect	[134]
Dissolving MN	DYD	PCOS	TCS, PVA	15 × 15 array with base dimensions of 200 μm diameter and 575 μm height	5 mg	Treatment of gynecological diseases and enhanced drug delivery efficiency	[135]
Dissolving MN	AP	Hyperuricemia	CMC, PVP	20 × 20 array with base width 200 μm and height 800 μm	2 mg/mL	Reduce serum uric acid levels and inhibit ADA and XOD activities	[136]

and absorption. Compared to the skin, the buccal cavity offers an effective route for drug delivery due to its ease and speed. Caffarel-Salvador et al. [110] have demonstrated that MNs can be used to deliver macromolecules, including human insulin and human growth hormone (hGH), and delivered 1-mg payload of swine within 30s. One hundred human volunteers described the potential discomfort of MNs punctures in different parts of the oral cavity.

MNs robots represent an innovative approach to oral drug delivery system. A thicker stomach wall (4–6 nm) provides enhanced protection and space for insulin. Inspired by the self-orienting leopard tortoise, Langger and Traverso et al. [143] developed an ingestible self-orienting millimeter-scale applicator (SOMA). The SOMA is constructed from low-density PCL and high-density 316 L stainless steel, which makes it easy to self-orient. The exterior of the insulin capsule is composed of a material that can be safely degraded, while the interior contains a needle compressed from freeze-dried insulin. Upon reaching the stomach, the gradual degradation of the outer shell allows allow the spring inside to insert the tip of the insulin needleinto the stomach wall, resulting in a gradual release of insulin. In this study, 0.3 mg of insulin was successfully delivered into a swine model, and 10 to 70 pM of the active pharmaceutical ingredients was observed within 3.5 h. Although the current rate of drug release from the tip of the MNs robot exhibits a discernible pattern, it has not yet reached the level of precise control. In view of the individual differences

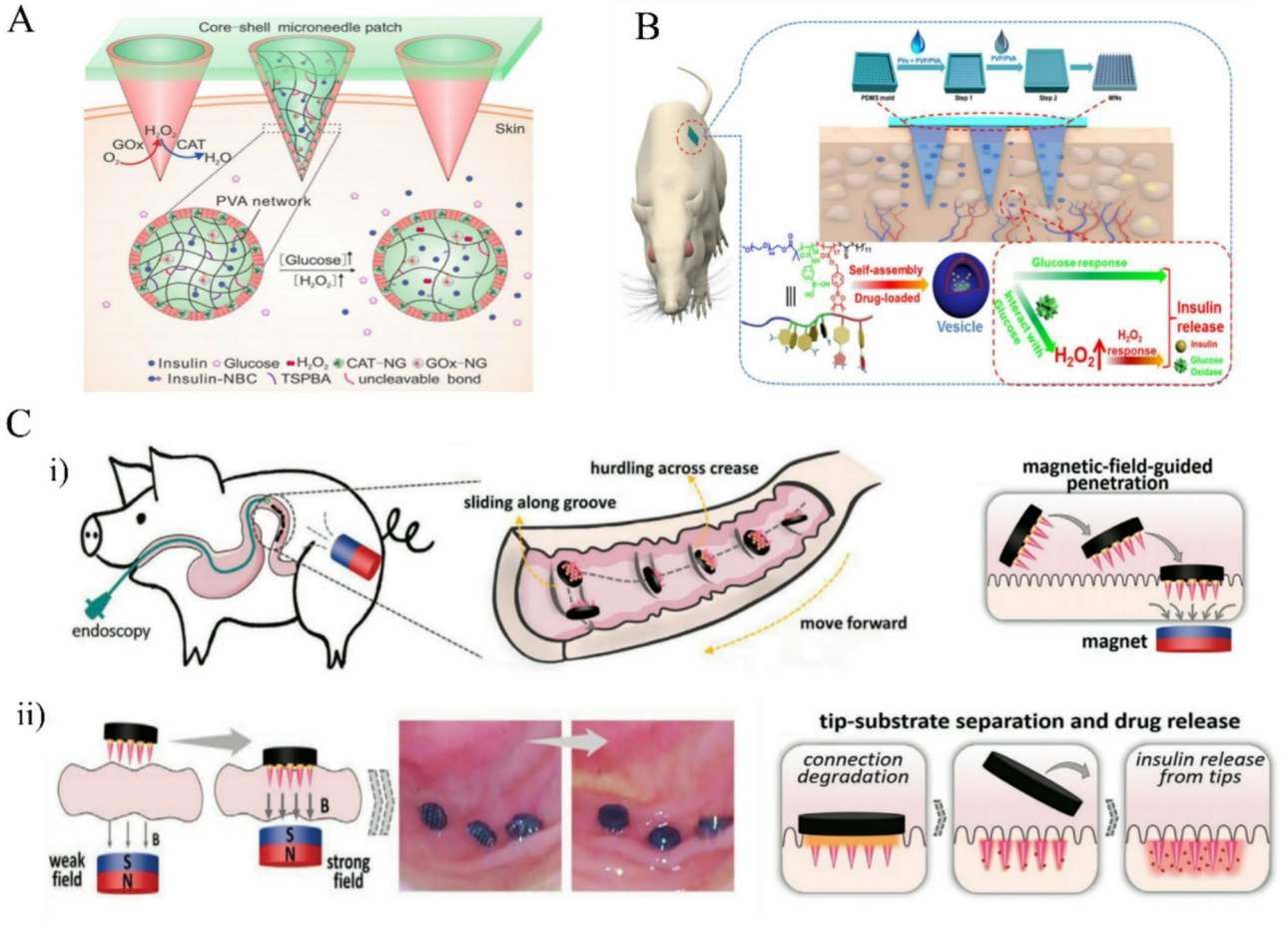

Fig. 7 Application of MNs in the treatment of diabetes. (**A**) Schematic diagram of the H_2O_2-glucose responsive MNs insulin delivery system. Reprinted with permission from Ref [141]. 2018, American Chemical Society. (**B**) Schematic diagram of MNs used for transdermal drug delivery in diabetic rats. Reprinted with permission from Ref [142]. 2018, American Chemical Society. (**C**) Oral magnetically responsive MNs robot for insulin delivery: (i) The MNs robot penetrates the wall of the small intestine under the guidance of a magnetic field, separates the tip from the matrix and releases the drug; (ii) Scheme and digital images of MNs robotic penetration of small intestinal tissue. Reprinted with permission from Ref [144]. 2021, Wiley

among patients and the dynamic changes in disease states, achieving precise control of drug release to optimize therapeutic effects remains a challenge that must be addressed in the next stage of this technology. Furthermore, the potential risks associated with long-term use have not been fully elucidated.

In addition, the intestinal wall can be considered as a potential site for drug delivery via MNs. Abramson et al. [72] reported a luminal unfolding MNs injector (LUMI) for insulin delivery. The LUMI is encased in a capsule with a diameter of 9 mm and a length of 30 mm, and the capsule is coated with poly(methacrylic acid-co-ethyl acrylate). When the pH exceeds 5.5, the capsule dissolves and the propelled the LUMI out of the capsule. The study revealed a 10% increase in systemic absorption over a 4-hour period compared to subcutaneous injections. To overcome the technical challenge of whether drugs and drug carriers can efficiently diffuse through viscous digestive fluids to the targeting site. From Fig. 7C, Zhao et al. developed novel magnetically responsive MNs robots [144], that consists of three parts: a magnetic substrate, separable connection and needle tips. By encapsulating these MNs robots in a commercially available enteric capsule, they can be stabilized in gastric fluid and released at the small intestine. A magnetic belt is wrapped around the abdomen for at least 4 h to guide the release of the MNs into the small intestine wall. Recently, Xu et al. [145] proposed an intestinal MN robot that uses rhythmic peristaltic contractions to penetrate the mucosa and rapidly expands after absorbing intestinal fluid. In vivo experiments confirmed that the intestinal peristaltic microrobot has an insulin delivery effect comparable to subcutaneous injection. For patients with diabetes, oral drug delivery is a highly acceptable, convenient, and economically feasible approach [146]. The integration of a physical device consisting of insulin MNs with mechanical force has demonstrated the ability to overcome physiological barriers and facilitate the delivery of insulin

to the gastrointestinal tract. This innovative approach eliminates the need for daily puncture injections and is expected to facilitate the rapid clinical introduction of oral insulin. However, in practical applications, the intricate physiological structure and environment of the human body may disrupt the distribution of the magnetic field, thereby impacting the precise manipulation of the MNs robot. Furthermore, the effective operational range of the magnetic field is constrained and may not cover the entirety of the gastrointestinal tract, leading to suboptimal drug delivery in specific areas.

Obesity

Obesity is a chronic metabolic disease characterized primarily by an excessive accumulation of body fat, leading to a body weight that exceeds the normal range [147]. According to the World Health Organization (WHO) standards, an adult with a Body Mass Index (BMI) of 30 kg/m² or higher is diagnosed as obese [148]. Common treatments for obesity include diet, exercise, drugs, and surgery, but these are often associated with weight regain or complications [131]. MNs-based treatments for obesity have been shown to improve efficacy and reduce side effects [149, 150]. Gu et al. [133] first proposed a transdermal browning agent patch to locally induce adipose tissue transformation for the treatment of obesity. This MN-based patch delivers browning agents consistently and efficiently to subcutaneous adipocytes and initiates WAT "browning" in the target area. As depicted in Fig. 8A, the MNs is made from a crosslinked HA matrix, loaded with pH-responsive dextran nanoparticles encapsulating the browning agent rosiglitazone (Rosi), GOx and catalase (CAT). GOx converts glucose into gluconic acid, thereby lowering the local pH, while CAT consumes the H_2O_2 produced in the reaction. In vivo experiments showed that the tip of the MNs effectively penetrated the skin in the inguinal region of mice, resulting in an approximately 15% reduction in the body weight of obese mice by the end of a 4-week treatment period.

Improving the therapeutic efficacy of poorly water-soluble drugs with low oral availability remains a significant clinical challenge. The integration of MNs technology with nanomaterials offers a novel approach to address these issues. Li et al. [151] utilized the flavonol glycoside plant chemical rutin, loaded into liposomes self-assembled from lecithin and cholesterol. Rutin-loaded liposomes were added to a patch made of PVP and PVA (Fig. 8B). The results demonstrated that liposomes increased both the water solubility and cellular uptake of rutin in adipocytes. In the pH 6.5 adipose tissue microenvironment, the MNs released more rutin, and achieved localized delivery to adipocytes. It showed significant anti-obesity effects by downregulating proteins involved in lipid synthesis (PPARγ and C/EBPα) in adipocytes and promoting the expression of proteins involved in beige fat formation (UCP-1 and Cyt C) in a high-fat diet (HFD)-induced obese mouse model. Liposomes as drug carriers present certain advantages, including low immunogenicity and a low of risk associated with viral gene integration, in contrast to viral carriers. This paper examines rutin liposomes; while they did not demonstrate significant toxicity in cellular experiments, the potential toxicity and side effects that may result from prolonged circulation and accumulation within the body remain inadequately understood.

To reduce the effects of oxidative stress and chronic inflammation on fat browning, Zan et al. [152] made a dense core-shell dry powder nanoparticle with a loading capacity 200 times higher than traditional nanoparticles (8 μg/MN). The shell is composed of manganese dioxide nanoparticles (MnO_2-NPs), which possess nanocatalytic activity (superoxide dismutase and catalase) and directly react with H_2O_2 to produce O_2 (Fig. 8C). The MNs core is a combination of resveratrol and MnO_2-NPs. Local treatment showed that subcutaneous WAT (sWAT) significantly reduced its mass and also improved systemic metabolism, with significant reductions in liver fat, hyperlipidemia, and systemic inflammation. However, Inflammation-related signaling pathways are complex, and the body may utilize adaptive regulatory mechanisms that facilitate the development of resistance or compensatory responses during prolonged interventions, potentially resulting in the re-exacerbation of inflammation. Furthermore, the long-term accumulation of manganese may disrupt normal physiological functions, thereby inducing complications within the nervous and endocrine systems.

MNs have also been used to construct gene delivery systems. In Fig. 8D, Choi et al. [153] designed a dissolvable HA-based self-locking MNs (LMN) that encapsulates and delivers plasmid DNA to adipocytes by incorporating self-assembling oligopeptoplex (SA-OP) encoding shRNA. The geometric shape of the MNs gradually expands from a 2 μm tip to a 340 μm mid-section, then tapers down to a 250 μm base, providing precise skin penetration and adhesion characteristics. Treatment over six weeks resulted in a 21.92% ± 2.51%reduction in body weight, improved insulin sensitivity, and decreased inflammation and liver fat. This study advances the stability and efficacy of targeted anti-obesity gene therapy, and holds potential for the treatment of obesity and related metabolic diseases. Although the article mentions the use of lyophilization and other methods to increase the concentration, the specific large-scale production process and quality control methods need to be further optimized, which is crucial for the translation of this technology into practical clinical applications.

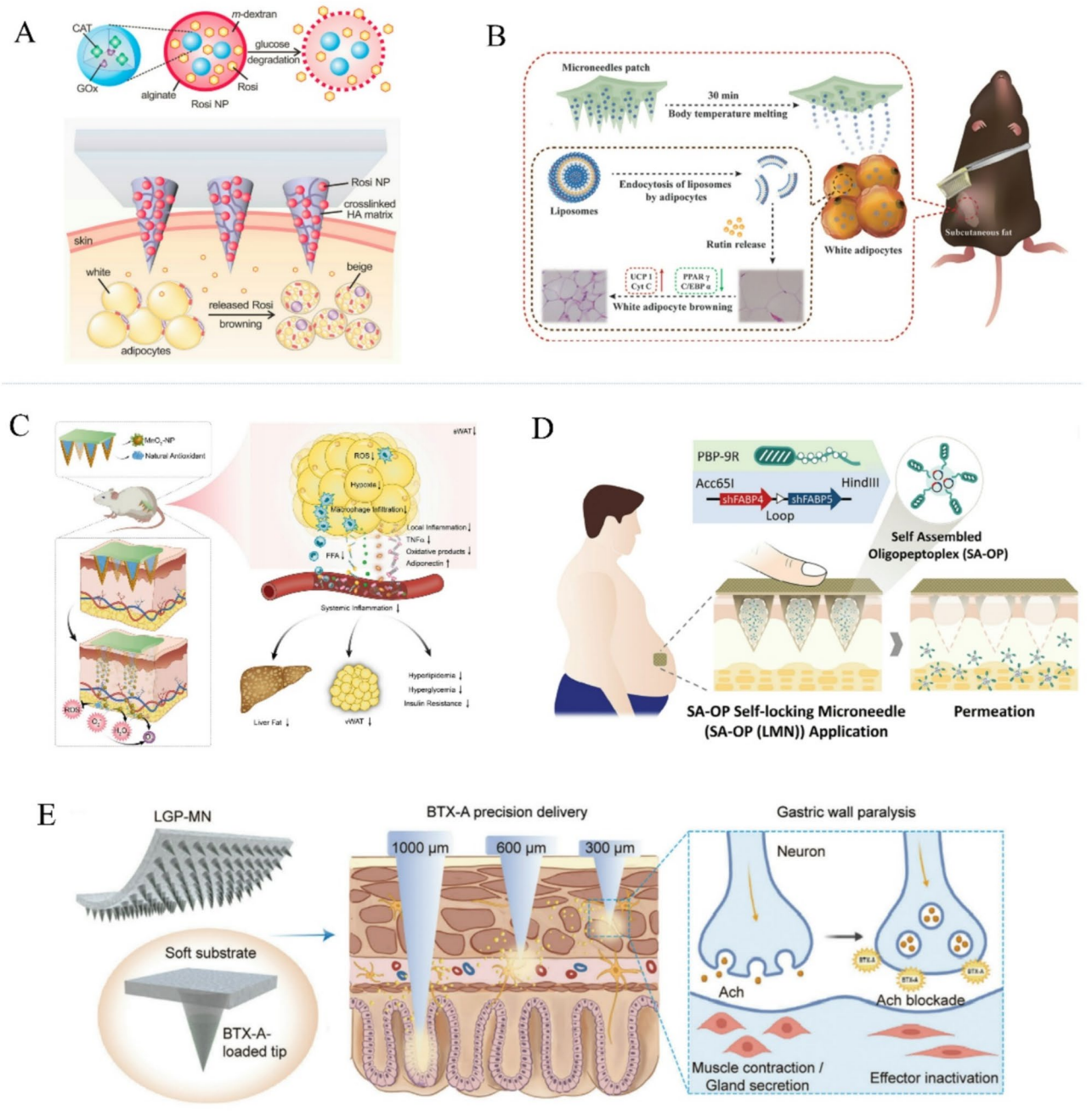

Fig. 8 Application of MNs in the treatment of obesity. (**A**) Schematic illustration of the browning reagents-loaded transcutaneous MNs. Reprinted with permission from Ref [133]. 2017, American Chemical Society. (**B**) Mechanism of loaded rutin liposome MNs array promoting white fat browning. Reprinted with permission from Ref [151]. 2023, American Chemical Society. (**C**) Dry powder MNs relieves oxidative stress, hypoxia and inflammation to reshape subcutaneous fat and improve body metabolism. Reprinted with permission from Ref [152]. 2024, Elsevier. (**D**) Schematic illustration of SA-OP (LMN) application. Reprinted with permission from Ref [153]. 2024, Wiley. (**E**) Schematic diagram of the manufacturing and mechanism of LGP-MNs. Reprinted with permission from Ref [131]. 2023, Wiley

Direct drug delivery to internal organs can also be achieved with MNs, Wang et al. [131] employed dissolvable MNs to implement a specific layered drug delivery strategy to study the site of action and therapeutic effects of Botulinum toxin A (BTX-A, a muscle contraction inhibitor) in gastric intramural. The tips of Layered Gastric Paresis MNs (LGP-MN) loaded with the drug could rapidly release BTX-A, achieving uniform distribution within designated gastric wall layers. As shown in Fig. 8E, MNs of 300 μm, 600 μm, and 1000 μm were fabricated corresponding to the thickness of different gastric wall layers and were able to dissolve completely within

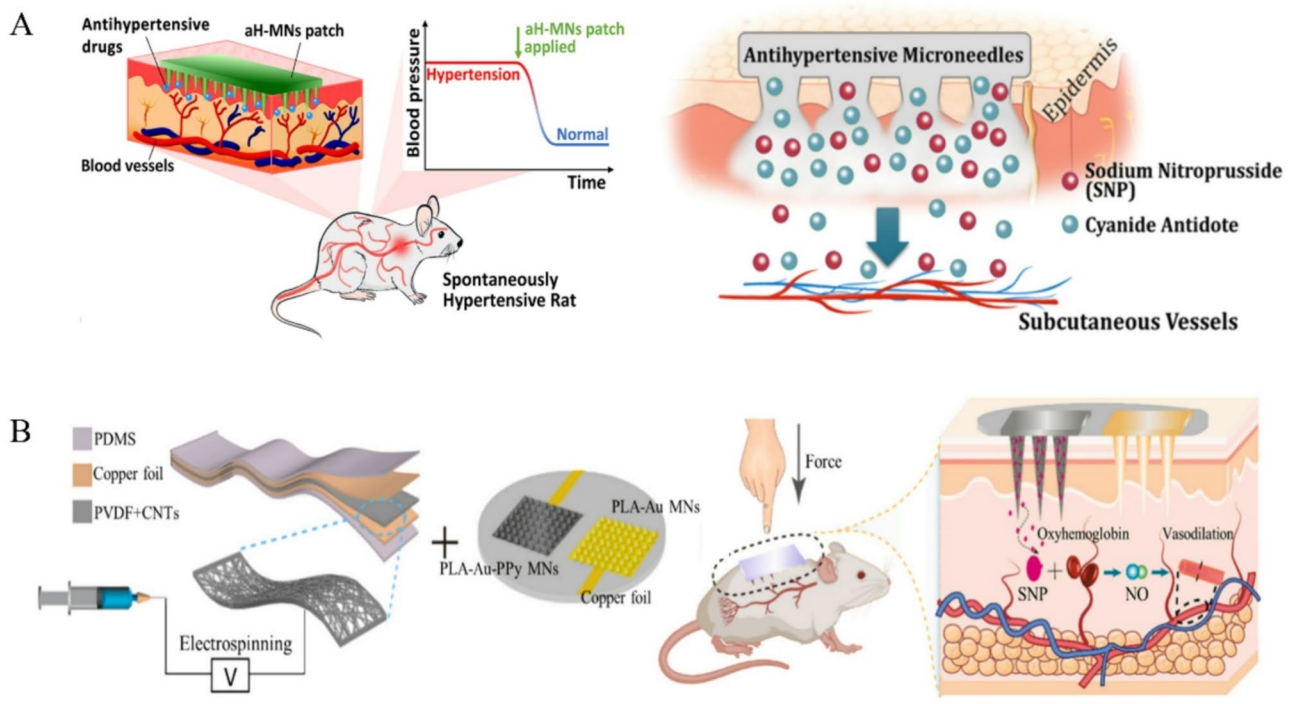

Fig. 9 Applications of MNs for the treatment of hypertension. (**A**) Developing antihypertensive drug delivery strategies using MNs. Reprinted with permission from Ref [129]. 2019, American Chemical Society. (**B**) Self-powered controllable MNs system for rapid blood pressure reduction and its underlying mechanism. Reprinted with permission from Ref [156]. 2024, Elsevier

120 s, with all drug-loaded tips dissolving within 30 s. In an obese rat model, LGP-MNs showed safer characteristics and demonstrated more significant therapeutic effects in drug delivery to the muscular layer compared to traditional injection methods. Specifically, the weight loss rate in the LGP-MNs treatment group reached 16.23%, which was 3.06 times higher than that of the traditional injection method. Additionally, the gastric emptying rate was reduced by 55.20%, liver steatosis was improved, lipid levels were lowered, and the intestinal microbiota shifted towards a healthier composition. The preparation and application techniques associated with this method are innovative, however, the implementation of invasive surgical procedures remains necessary in actual clinical practice.

Hypertension

Hypertension is a common, long-lasting disease by sustained elevation of arterial blood pressure beyond the normal range. Normal blood pressure for adults (ages 20 and older) is less than 120/80 mmHg [154]. Long-term hypertension increases the risk of cardiovascular diseases, cerebrovascular accidents, kidney diseases, and other complications. MNs show potential in treating hypertension, especially since oral medications are often ineffective and sublingual doses are limited.

Permana et al. [155] developed a thermosensitive hydrogel combined with solid MNs for the continuous transdermal delivery of valsartan. The combination with the highest permeability was produced by a 1.55 mm MNs, with a drug penetration of 2.27 ± 0.01 mg. Compared to oral administration, this combined method enhanced the availability of valsartan. Li et al. [129] developed an antihypertensive MNs (aH-MN) for the transdermal delivery of sodium nitroprusside (SNP) combined with sodium thiosulfate (ST) as a cyanide antidote (Fig. 9A). SNP binds with oxyhemoglobin, releasing cyanide and nitric oxide, which relaxes blood vessels and lowers blood pressure. After skin penetration of the skin by aH-MNs, SNPs are immediately released into the systemic circulation via subcutaneous capillaries. Co-administration with ST effectively inhibited skin irritation and target organ damage caused by continuous SNP intake. Rapid and effective blood pressure reduction was achieved in a spontaneously hypertensive rat model, meeting the requirements clinical blood pressure control in hypertensive emergencies. In this paper, the stability of SNPs in MNs was investigated over a 7-day period, and the stability over longer periods of time needs to be explored in order to advance the process of clinical application.

To provide a user-friendly system for reducing blood pressure quickly in emergencies, Chen et al. [156]

developed a self-powered MNs drug delivery system. As depicted in Fig. 9B, it mainly consists of two parts: a piezoelectric film self-powered module made of polyvinylidene fluoride (PVDF) and carbon nanotubes (CNT), and a drug delivery module composed of PLA-gold MNs and PLA-gold-polypyrrole MNs. Different voltages are generated by applying different pressures on the self-powered module to control the drug release efficiency of the MNs. It demonstrates a higher drug release rate and greater effectiveness compared to traditional active devices. In this work indicates that the doping of CNT has positively influenced the piezoelectric properties of PVDF, it is anticipated that further optimization of other nanomaterial combination will enhance the performance of the system.

Moreover, combination antihypertensive therapy is crucial for minimizing the need for high-dose monotherapy and reducing associated side effects, such as pretibial edema and gastrointestinal bleeding. Shende et al. [157] combined nifedipine (a cardiac inhibitor) and diltiazem (a vasodilator), to prepare a bioresponsive MNs. pH-responsive diltiazem PLGA nanospheres prepared by a double emulsion method were added to a nifedipine-PVP mixture to develop MNs. The skin's acidity causes CO_2 bubbles to form, which increase the internal pressure and lead to the formation and rupture of pores in the PLGA shell, thereby releasing the drug. The release of nifedipine was nearly 96.93 ± 2.31% within 24 h. Compared to the disease control group (109.9 ± 1.825 mmHg), the average blood pressure after MNs treatment dropped to 84.11 ± 2.98 mmHg, demonstrating significant antihypertensive effects.

Other metabolic diseases

In addition to obesity, diabetes, and hypertension, there are a number of other common metabolic diseases, such as polycystic ovary syndrome, non-alcoholic fatty liver disease, and hyperuricemia. Currently, these diseases have seen limited integration with MNs transdermal delivery systems, and represent potential areas of focus for future research by investigators.

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is a hepatic manifestation of metabolic syndrome, characterized by the accumulation of fat in the liver in the absence of alcohol consumption [158]. It is marked by hypertriglyceridemia, reduced high-density lipoprotein, increased waist circumference, hypertension, and fasting hyperglycemia [114]. Due to the lack of treatment and the increasing prevalence of diabetes and obesity worldwide, the prevalence of NAFLD is likely to increase and represent a serious health crisis in the coming decades. Currently, there are no specific treatments for NAFLD patients; the European and American Association for the Study of the Liver only recommends vitamin E and the PPARγ ligand pioglitazone for certain patients [159].

In addition, MNs has been applied in the treatment liver fibrosis. Gu et al. [134] developed a hydrogel MNs based on gelatin and MA materials for the sustained release of pirfenidone (PFD). Studies have demonstrated that PFD can slow down liver fibrosis by inhibiting the activation of hepatic stellate cells (HSCs), thereby reducing the accumulation of extracellular matrix (ECM) produced by HSCs around liver cells. However, it has not yet been approved for actual clinical use [160]. Experiments have demonstrated that Gel-PFD outperforms oral PFD by reducing dosing frequency and improving anti-fibrosis efficacy.

Polycystic ovary syndrome

Polycystic Ovary Syndrome (PCOS) is an endocrine disorder, a common condition affecting the physical and emotional health of many women worldwide. It arises from a combination of reproductive and metabolic dysfunctions, with symptoms including infertility, insulin resistance, obesity, depression, an increased risk of Type 2 diabetes, hypertriglyceridemia, gestational diabetes, and metabolic syndrome [161]. Hirsutism is often a prominent sign of PCOS, meaning that women may have experience excessive body hair on the face, chest, back, or other areas, which is associated with abnormal androgen levels. Eflornithine, approved by the United States Food and Drug Administration (FDA) in 2000, is used to reduce facial hair growth for the treatment of hirsutism [162]. Cui et al. [163] proposed a method to enhance the local efficacy of eflornithine. Ornithine decarboxylase is an enzyme that catalyzes the conversion of ornithine to putrescine, which is crucial for the growth and proliferation of hair follicles. Thus, the mechanism of action of eflornithine primarily involves inhibiting the production of putrescine to affect hair follicle growth. Pre-treating the skin with MNs prior to applying ethiofluvium cream may improve its effectiveness in inhibiting hair regrowth. Furthermore, Ahmad et al. [135] made a patch with thiolated chitosan (TCS) and PVA to deliver dydrogesterone (DYD) throughout the body. Dydrogesterone can be used for various conditions caused by progesterone deficiency, such as those associated with PCOS. Experimental results showed that the MNs-loaded DYD continuously released 81.45 ± 2.768% over 48 h, promising way to deliver DYD. This work still needs to take into account the effects of drug-polymer interactions, skin microenvironment, and other relevant factors on drug release in order to provide theoretical support for the optimization of formulation and design.

Hyperuricemia

Hyperuricemia and gout are pathological conditions resulting from an imbalance in uric acid metabolism, caused by either excessive production or inadequate excretion of uric acid, a byproduct of purine breakdown that is normally eliminated through urine [164]. Prolonged hyperuricemia (serum uric acid concentration saturation point of 7 mg/dL) leads to the deposition of monosodium urate (MSU) crystals, becoming the most severe risk factor for gout [165, 166]. Oral colchicine (Col) is widely used as a first-line option for both the treatment and prevention of gout. Since the therapeutic index of Col is narrow and the dosage needs to be strictly controlled, the effectiveness of oral Col is limited. Here, Yang et al. [165] reported a sustained-release MNs system containing chitosan and a dual-loaded formulation of collagen (Col) and uricase (UAO) liposomes was fabricated. Under the action of uricase decomposing uric acid, MSU crystals are reduced, supplemented by the powerful anti-inflammatory effect of colchicine, which has a strong effect on long-term urate-lowering therapy.

Over the past decades, allopurinol (AP) has been used as the most effective anti-hyperuricemic medication to control hyperuricemia and gout, reducing gout complications [167]. Here, Jiang et al. [136] developed a core-shell MNs featuring programmable drug release, specifically designed to regulate serum uric acid (SUA) levels. AP is encapsulated within a CMC layer. Its core contains polyvinylpyrrolidone loaded with urate oxidase-calcium peroxide nanoparticles (UOx-CaO_2 NPs). Upon insertion into the skin, the loaded AP is immediately released, effectively inhibiting the production of SUA due to the solubility of CMC. Subsequently, the sustained release of UOx aids in the metabolism and breakdown of SUA and CaO_2 NPs. Notably, CaO_2 exhibits strong oxidative properties that can effectively reduce uric acid levels. In vivo experiments demonstrated that MNs were able to lower SUA levels to normal within 3 h and maintain normouricemia for up to 12 h. Additionally, serum creatinine (Cr) and blood urea nitrogen (BUN) levels remain within the normal range, with effective inhibition of liver adenosine deaminase (ADA) and xanthine oxidase (XOD) activity to achieve long-term hyperuricemia management.

Limitations and future perspective

Despite much of the research has moved into clinical trials (refer to Table 1), there remains a considerable gap in moving MNs from laboratory settings to mass production in factory environment. (i) Current manufacturing techniques, such as microinjection molding, photolithography, and 3D printing, have limitations in precision and are affected by variations in equipment and environmental factors. These issues can lead to MNs with suboptimal dimensions, which could adversely affect their clinical efficacy [168]. In addition, standardization of material selection, biosafety, quality control and sterilization are key factors in obtaining medical device approval and are challenges that must be addressed for clinical applications [58]. (ii) The clinical evaluation of MNs drug delivery necessitates comprehensive assessments of pharmacokinetics, pharmacodynamics, and safety, with the complexity and variety of these factors complicating standardization difficult. (iii) Another challenge is how to reduce the biological risk associated with the fabrication of MNs materials (such as metals, silicon, glass, and polymeric materials) [32, 169]. Repetitive skin injury or immunologic site involvement from frequent use of MNs may cause an immunologic response. Regulatory authorities may require certain immunologic safety assurances during regulatory submissions. (iv) How to improve the drug-carrying capacity is the key technical issue of whether to promote the industrialization of such products. The size and structure of MNs can limit the ability to load and release drugs, resulting in suboptimal therapeutic efficacy [68, 170]. For example, uniform coating of the tip with the drug formulation is a common technical problem for hollow MNs, solid MNs, and solid-coated MNs. In addition, hollow MNs may have a risk of leakage at the "weakest bridge" [171]. (v) For MNs delivery systems, the diffusion of hydrophilic drugs from the tip to the substrate site is also another factor that affects the effectiveness of drug delivery [172]. (vi) While MNs prepared with crosslinked hydrophilic polymers are superior in drug delivery, the chemical reaction process under high temperature or ultraviolet irradiation may affect the output of heat-sensitive drugs [76, 173]. This is another technical issue that must be considered when developing a method for encapsulating drugs into MNs.

While transdermal MNs delivery has shown advantages for use in the treatment of metabolic diseases, it has also been noted that the dermis of the skin is rich in antigen-reactive cells that may trigger an immune response when a foreign MNs enters the skin. As an alternative strategy, gastrointestinal drug delivery will become a further and more prominent focus for the release site. Oral drug delivery is analogous to dermal drug delivery in that it is a simple matter of identifying suitable release sites that are acceptable to the patient. Conversely, drug delivery to the gastric and small intestinal mucosa requires the use of more complex physical devices. However, this technology is not infallible, and its limitations include the following: (i) The materials used to encapsulate MNs and injectors must have properties that remain stable in gastric fluids to avoid drug leakage and denaturation [143, 174]. (ii) Potentially biohazardous materials used to manufacture the physical devices (ejection, angle control, magnetic guidance) may pose a risk of human injury and metabolic burden [72]. (iii) The intelligent MNs release

system must be able to withstand and utilize sufficient peristaltic force to penetrate the mucosa, while the length of the MNs must be precisely controlled to avoid puncturing the mucosa [144]. These integrated systems are expected to become multifunctional and efficient medical tools, offering new opportunities for the diagnosis and treatment of metabolic diseases.

Future research should focus more on the following areas, (i) Novel fully biodegradable biosafety materials for MNs array should be elucidated for drug loading. In chronic disease management, even small polymer deposits can interfere with drug absorption and accumulate in body tissues such as the liver. (ii) More innovations or approaches should be carried out on controlled release rates of the MNs drug delivery system. Including, in the treatment of obesity and other chronic metabolic diseases, it is necessary to design slow-release MNs that can remain in the skin for a longer period of time and ensure patient compliance. (iii) The safe delivery of gene drugs represents the most promising research direction of MNs technology for the treatment of metabolic diseases. Nevertheless, various environmental factors (e.g., temperature, humidity, pH) and interactions with MNs materials may adversely affect the stability of gene therapies. Consequently, it is imperative to develop suitable encapsulation materials (such as liposomes, polymers, nanomaterials, and cell membranes) and techniques to enhance the stability of gene drugs within MNs. Additionally, the interactions among MNs fabrication materials, gene therapies, and their carriers significantly affect their release kinetics, highlighting the necessity for the development of specific enzymes or environmentally responsive conditions to facilitate the release process. (iv) To enhance the use of MNs for drug delivery in the gastrointestinal tract, it is essential to design MNs with specific sizes and shapes that align with the physiological features of various gastrointestinal regions. Additionally, the materials used for MNs fabrication must be resistant to degradation from gastric acid and enzymes, which may involve modifying the surface of polymer MNs with hydrophobic alkyl groups. Another challenge is effectively targeting MNs within the gastrointestinal tract, which can be improved through biorecognition mechanisms like ligand-receptor targeting and utilizing intestinal microflora to facilitate the targeted release of drugs. Furthermore, employing external magnetic fields and ultrasound guidance can significantly enhance the precision of MNs delivery.

Conclusions

The advanced design with unique properties of MNs drug delivery system for the treatment of metabolic diseases is summarized. Novel and significant studies on preparation materials, structure, controlled drug release mechanisms and treatment of various types of metabolic diseases have been reviewed. This review pays special attention on the unique attributes of MNs when integrated with other physical devices, highlighting their applications that range from the epidermis of the skin to the gastrointestinal tract for the management of metabolic diseases. Finally, the paper discusses the future prospects for the clinical application of MNs, such as the expansion of drug libraries, biosafety considerations, and the establishment of standards for scaling up production. We envisage that painless, inexpensive and patient-friendly MNs will become ideal medical devices for managing metabolic diseases in the future.

Acknowledgements
Not applicable.

Author contributions
Yao Li: Writing - original draft, Conceptualization, Validation, Investigation, Formal analysis. Qiu Chen: Writing - original draft, Conceptualization, Validation, Investigation, Formal analysis. Tingting Wang: Investigation. Zengkai Ji: Investigation. Sagar Regmi: Writing - original draft, Formal analysis. Haibin Tong: Conceptualization, Supervision. Jian Ju: Formal analysis, Writing - original draft, Conceptualization, Validation, Supervision, Writing - review & editing. Aifang Wang: Conceptualization, Supervision.

Funding
This work was financially supported by Zhejiang Provincial Natural Science Foundation of China under grant No. LTGY23B050002; the Wenzhou Public Welfare Basic Research Program (grant No. S20220021) and start-up grant from the Wenzhou Institute, University of Chinese Academy of Sciences, China (WIUCASQD2021027).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors consent to publish.

Competing interests
The authors declare no competing interests.

Received: 12 November 2024 / Accepted: 1 May 2025
Published online: 16 May 2025

References

1. Chew N, Ng C, Tan D, Kong G, Lin C, Chin Y, Foo R, Chan M, Muthiah M. Global burden of metabolic diseases: data from global burden of disease 2000–2019. A cosortium of metabolic disease. J Eur Heart J. 2023;44:ehac779.
2. Chew NW, Ng CH, Tan DJH, Kong G, Lin C, Chin YH, Lim WH, Huang DQ, Quek J, Fu CE. The global burden of metabolic disease: data from 2000 to 2019. J Cell Metabolism. 2023;35(3):414–28. e413.
3. Saklayen MG. The global epidemic of the metabolic syndrome. Curr Hypertens Rep. 2018;20:12.
4. Tsigos C, Kyrou I, Chala E, Tsapogas P, Stavridis JC, Raptis SA, Katsilambros N. Circulating tumor necrosis factor alpha concentrations are higher in abdominal versus peripheral obesity. Metabolism. 1999;48(10):1332–5.
5. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, Nakayama O, Makishima M, Matsuda M, Shimomura I. Increased oxidative

stress in obesity and its impact on metabolic syndrome. J Clin Invest. 2004;114(12):1752–61.
6. Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome. Pathophysiology, management, and modulation by natural compounds. Ther Adv Cardiovasc Dis. 2017;11(8):215–25.
7. Shi S, Kong N, Feng C, Shajii A, Bejgrowicz C, Tao W, Farokhzad OC. Drug delivery strategies for the treatment of metabolic diseases. Adv Healthc Mater. 2019;8:e1801655.
8. Zheng M, Sheng T, Yu J, Gu Z, Xu C. Microneedle biomedical devices. Nat Reviews Bioeng. 2024;2:324–42.
9. Chen BZ, He YT, Zhao ZQ, Feng YH, Liang L, Peng J, Yang CY, Uyama H, Shahbazi M-A, Guo XD. Strategies to develop polymeric microneedles for controlled drug release. Adv Drug Deliv Rev. 2023;203:115109.
10. Escobar-Chavez JJ, Bonilla-Martinez D, Villegas-Gonzalez MA, Molina-Trinidad E, Casas-Alancaster N, Revilla-Vazquez AL. Microneedles: a valuable physical enhancer to increase transdermal drug delivery. J Clin Pharmacol. 2011;51(7):964–77.
11. Bouwstra JA, Ponec M. The skin barrier in healthy and diseased state. Biochim Et Biophys Acta (BBA)– Biomembr. 2006;1758(12):2080–95.
12. Donnelly RF, Garland MJ, Morrow DIJ, Migalska K, Singh TRR, Majithiya R, Woolfson AD. Optical coherence tomography is a valuable tool in the study of the effects of microneedle geometry on skin penetration characteristics and in-skin dissolution. J Control Release. 2010;147(3):333–41.
13. Shakoor A, Gao W, Zhao L, Jiang Z, Sun D. Advanced tools and methods for single-cell surgery. Microsystems Nanoengineering. 2022;8:47.
14. Li W, Tang J, Terry RN, Li S, Brunie A, Callahan RL, Noel RK, Rodríguez CA, Schwendeman SP, Prausnitz MR. Long-acting reversible contraception by effervescent microneedle patch. Sci Adv. 2019;5:eaaw8145.
15. Teymourian H, Tehrani F, Mahato K, Wang J. Lab under the skin: microneedle based wearable devices. Adv Healthc Mater. 2021;10:2002255.
16. DeMuth PC, Min Y, Irvine DJ, Hammond PT. Implantable silk composite microneedles for programmable vaccine release kinetics and enhanced immunogenicity in transcutaneous immunization. Adv Healthc Mater. 2014;3(1):47–58.
17. Sun X, Ji W, Zhang B, Ma L, Fu W, Qian W, Zhang X, Li J, Sheng E, Tao Y, Zhu D. A theranostic microneedle array patch for integrated glycemia sensing and self-regulated release of insulin. Biomater Sci. 2022;10(5):1209–16.
18. Yang G, Chen Q, Wen D, Chen Z, Wang J, Chen G, Wang Z, Zhang X, Zhang Y, Hu Q, Zhang L, Gu Z. A therapeutic microneedle patch made from hair-Derived keratin for promoting hair regrowth. ACS Nano. 2019;13(4):4354–60.
19. Zhang JN, Chen BZ, Ashfaq M, Zhang XP, Guo XD. Development of a BDDE-crosslinked hyaluronic acid based microneedles patch as a dermal filler for anti-ageing treatment. J Ind Eng Chem. 2018;65:363–9.
20. Tran KT, Gavitt TD, Farrell NJ, Curry EJ, Mara AB, Patel A, Brown L, Kilpatrick S, Piotrowska R, Mishra N. Transdermal microneedles for the programmable burst release of multiple vaccine payloads. Nat Biomedical Eng. 2021;5(9):998–1007.
21. Zong Q, Guo R, Dong N, Ling G, Zhang P. Design and development of insulin microneedles for diabetes treatment. Drug Delivery Translational Res. 2021;12:1–8.
22. Xie X, Pascual C, Lieu C, Oh S, Wang J, Zou B, Xie J, Li Z, Xie J, Yeomans DC. Analgesic microneedle patch for neuropathic pain therapy. ACS Nano. 2017;11(1):395–406.
23. Rzhevskiy AS, Singh TRR, Donnelly RF, Anissimov YG. Microneedles as the technique of drug delivery enhancement in diverse organs and tissues. J Control Release. 2018;270:184–202.
24. Waghule T, Singhvi G, Dubey SK, Pandey MM, Gupta G, Singh M, Dua K. Microneedles: A smart approach and increasing potential for transdermal drug delivery system. Biomed Pharmacother. 2019;109:1249–58.
25. Chen BZ, Liu JL, Li QY, Wang ZN, Zhang XP, Shen CB, Cui Y, Guo XD. Safety evaluation of solid polymer microneedles in human volunteers at different application sites. ACS Appl Bio Mater. 2019;2(12):5616–25.
26. Ma G, Wu C. Microneedle, bio-microneedle and bio-inspired microneedle: A review. J Controlled Release. 2017;251:11–23.
27. Donnelly R, Douroumis DJDD, Research T. Microneedles for drug and vaccine delivery and patient monitoring. Springer. 2015;5:311–2.
28. Chen X, Wang L, Yu H, Li C, Feng J, Haq F, Khan A, Khan RU. Preparation, properties and challenges of the microneedles-based insulin delivery system. J Controlled Release. 2018;288:173–88.
29. Wang R, Jiang G, Aharodnikau UE, Yunusov K, Sun Y, Liu T, Solomevich SO. Recent advances in polymer microneedles for drug transdermal delivery: design strategies and applications. Macromol Rapid Commun. 2022;43(8):2200037.
30. Zhang X, Lu M, Cao X, Zhao Y. Functional microneedles for wearable electronics. Smart Med. 2023;2(1):e20220023.
31. Li WZ, Huo MR, Zhou JP, Zhou YQ, Hao BH, Liu T, Zhang Y. Super-short solid silicon microneedles for transdermal drug delivery applications. Int J Pharm. 2010;389:122–9.
32. Yuen C, Liu Q. Towards in vivo intradermal surface enhanced Raman scattering (SERS) measurements: silver coated microneedle based SERS probe. Wiley Online Libr. 2014;7:683–9.
33. Li J, Liu B, Zhou Y, Chen Z, Jiang L, Yuan W, Liang L. Fabrication of a Ti porous microneedle array by metal injection molding for transdermal drug delivery. PLoS ONE. 2017;12(2):e0172043.
34. Li QY, Zhang JN, Chen BZ, Wang QL, Guo XD. A solid polymer microneedle patch pretreatment enhances the permeation of drug molecules into the skin. RSC Adv. 2017;7(25):15408–15.
35. Sartawi Z, Blackshields C, Ariamanesh A, Farag FF, Griffin B, Crean A, Devine K, Elkhashab M, Aldejohann AM, Kurzai O. Glass microneedles: A case study for regulatory approval using a quality by design approach. Adv Mater. 2023;35(52):2305834.
36. Vallhov H, Xia W, Engqvist H, Scheynius A. Bioceramic microneedle arrays are able to deliver OVA to dendritic cells in human skin. J Mater Chem B. 2018;6(42):6808–16.
37. Loizidou EZ, Williams NA, Barrow DA, Eaton MJ, McCrory J, Evans SL, Allender CJ. Structural characterisation and transdermal delivery studies on sugar microneedles: experimental and finite element modelling analyses. Eur J Pharm Biopharm. 2015;89:224–31.
38. Sabbagh F, Kim BS. Recent advances in polymeric transdermal drug delivery systems. J Controlled Release. 2022;341:132–46.
39. Luo X, Yang L, Cui Y. Microneedles: materials, fabrication, and biomedical applications. Biomed Microdevices. 2023;25(3):20.
40. Chi J, Zhang X, Chen C, Shao C, Zhao Y, Wang Y. Antibacterial and angiogenic Chitosan microneedle array patch for promoting wound healing. Bioactive Mater. 2020;5(2):253–9.
41. Zhang X, Chen G, Bian F, Cai L, Zhao Y. Encoded microneedle arrays for detection of skin interstitial fluid biomarkers. Adv Mater. 2019;31(37):1902825.
42. Yan G, Warner KS, Zhang J, Sharma S, Gale BK. Evaluation needle length and density of microneedle arrays in the pretreatment of skin for transdermal drug delivery. Int J Pharm. 2010;391:7–12.
43. Lee K, Lee HC, Lee DS, Jung HJAM. Drawing lithography: three-dimensional fabrication of an ultrahigh-aspect-ratio microneedle. Adv Mater. 2010;22(4):483–6.
44. Moussi K, Bukhamsin A, Hidalgo T, Kosel J. Biocompatible 3D printed microneedles for transdermal, intradermal, and percutaneous applications. Adv Eng Mater. 2020;22(2):1901358.
45. Chen BZ, He MC, Zhang XP, Fei WM, Cui Y, Guo XD. A novel method for fabrication of coated microneedles with homogeneous and controllable drug dosage for transdermal drug delivery. Drug Deliv Transl Res. 2022;12(11):2730–9.
46. Gill HS, Prausnitz MR. Coating formulations for microneedles. Pharm Res. 2007;24(7):1369–80.
47. McGrath MG, Vucen S, Vrdoljak A, Kelly A, O'Mahony C, Crean AM, Moore A. Production of dissolvable microneedles using an atomised spray process: effect of microneedle composition on skin penetration. Eur J Pharm Biopharm. 2014;86(2):200–11.
48. Gill HS, Prausnitz MR. Coated microneedles for transdermal delivery. J Controlled Release. 2007;117(2):227–37.
49. Kim JD, Kim M, Yang H, Lee K, Jung H. Droplet-born air blowing: novel dissolving microneedle fabrication. J Control Release. 2013;170(3):430–6.
50. Bediz B, Korkmaz E, Khilwani R, Donahue C, Erdos G, Falo LDJ, Ozdoganlar OB. Dissolvable microneedle arrays for intradermal delivery of biologics: fabrication and application. Pharm Res. 2014;31(1):117–35.
51. Sartawi Z, Blackshields C, Faisal W. Dissolving microneedles: applications and growing therapeutic potential. J Controlled Release. 2022;348:186–205.
52. Zheng Z, Eglin D, Alini M, Richards GR, Qin L, Lai Y. Visible Light-Induced 3D Bioprinting technologies and corresponding Bioink materials for tissue engineering: A review. Engineering. 2021;7(7):966–78.
53. Chang H, Zheng M, Yu X, Than A, Seeni RZ, Kang R, Tian J, Khanh DP, Liu L, Chen P, Xu C. A swellable microneedle patch to rapidly extract skin interstitial fluid for timely metabolic analysis. Adv Mater. 2017;29(37):e1702243.
54. Tariq N, Ashraf MW, Tayyaba S. A review on solid microneedles for biomedical applications. J Pharm Innov. 2021;17(4):1464–83.

55. Lee K, Goudie MJ, Tebon P, Sun W, Luo Z, Lee J, Zhang S, Fetah K, Kim HJ, Xue Y, Darabi MA, Ahadian S, Sarikhani E, Ryu W, Gu Z, Weiss PS, Dokmeci MR, Ashammakhi N, Khademhosseini A. Non-transdermal microneedles for advanced drug delivery. Adv Drug Deliv Rev. 2020;165–166:41–59.
56. Hu Z, Meduri CS, Ingrole RS, Gill HS, Kumar G. Solid and Hollow metallic glass microneedles for transdermal drug-delivery. Appl Phys Lett. 2020;116(20):203703.
57. Dervisevic M, Alba M, Yan L, Senel M, Gengenbach TR, Prieto-Simon B, Voelcker NH. Transdermal electrochemical monitoring of glucose via high-density silicon microneedle array patch. Adv Funct Mater. 2022;32(3):2009850.
58. Economidou SN, Uddin MJ, Marques MJ, Douroumis D, Sow WT, Li H, Reid A, Windmill JF, Podoleanu A. A novel 3D printed Hollow microneedle microelectromechanical system for controlled, personalized transdermal drug delivery. Additive Manuf. 2021;38:101815.
59. Vora LK, Sabri AH, Naser Y, Himawan A, Hutton AR, Anjani QK, Volpe-Zanutto F, Mishra D, Li M, Rodgers AM. Long-acting microneedle formulations. Adv Drug Deliv Rev. 2023;201:115055.
60. Detamornrat U, Parrilla M, Domínguez-Robles J, Anjani QK, Larrañeta E, De Wael K, Donnelly RF. Transdermal on-demand drug delivery based on an iontophoretic Hollow microneedle array system. Lab Chip. 2023;23(9):2304–15.
61. Larrañeta E, Lutton REM, Woolfson AD, Donnelly RF. Microneedle arrays as transdermal and intradermal drug delivery systems: materials science, manufacture and commercial development. Mater Sci Engineering: R: Rep. 2016;104:1–32.
62. Bao L, Park J, Bonfante G, Kim B. Recent advances in porous microneedles: materials, fabrication, and transdermal applications. Drug Delivery Translational Res. 2021;12(2):395–414.
63. Tabassum N, Alba M, Yan L, Voelcker NH. Porous silicon microneedles for enhanced transdermal drug delivery. Adv Ther. 2023;6(1):2200156.
64. Sadeqi A, Kiaee G, Zeng W, Rezaei Nejad H, Sonkusale S. Hard polymeric porous microneedles on stretchable substrate for transdermal drug delivery. Sci Rep. 2022;12(1):1853.
65. Kusama S, Sato K, Matsui Y, Kimura N, Abe H, Yoshida S, Nishizawa M. Transdermal electroosmotic flow generated by a porous microneedle array patch. Nat Commun. 2021;12(1):658.
66. Liu L, Kai H, Nagamine K, Ogawa Y, Nishizawa M. Porous polymer microneedles with interconnecting microchannels for rapid fluid transport. RSC Adv. 2016;6(54):48630–5.
67. Zhou Z, Zhang S, Yang G, Gao Y. Enhanced delivery efficiency and sustained release of biopharmaceuticals by complexation-based gel encapsulated coated microneedles: rhIFNalpha-1b example. Asian J Pharm Sci. 2021;16(5):612–22.
68. Zhang W, Zhang W, Li C, Zhang J, Qin L, Lai Y. Recent advances of microneedles and their application in disease treatment. Int J Mol Sci. 2022;23(5):2401.
69. Demuth PC, Garcia-Beltran WF, Ai-Ling ML, Hammond PT, Irvine DJ. Composite dissolving microneedles for coordinated control of antigen and adjuvant delivery kinetics in transcutaneous vaccination. Adv Funct Mater. 2013;23(2):161–72.
70. Wang QL, Zhang XP, Chen BZ, Guo XD. Dissolvable layered microneedles with core-shell structures for transdermal drug delivery. Mater Sci Engineering: C. 2018;83:143–7.
71. Wang H, Fu Y, Mao J, Jiang H, Du S, Liu P, Tao J, Zhang L, Zhu J. Strong and tough supramolecular microneedle patches with ultrafast dissolution and Rapid-Onset capabilities. Adv Mater. 2022;34(51):2207832.
72. Abramson A, Caffarel-Salvador E, Soares V, Minahan D, Tian RY, Lu X, Dellal D, Gao Y, Kim S, Wainer J. A luminal unfolding microneedle injector for oral delivery of macromolecules. Nat Med. 2019;25(10):1512–8.
73. Zhang XP, Zhang BL, Chen BZ, Zhao ZQ, Guo XD. Dissolving microneedle rollers for rapid transdermal drug delivery. Drug Delivery Translational Res. 2022;12:459–71.
74. Liu Y, Huang T, Qian Z, Chen W. Extensible and swellable hydrogel-forming microneedles for deep point-of-care sampling and drug deployment. Chin Chem Lett. 2023;34(6):108103.
75. Donnelly RF, Singh TRR, Garland MJ, Migalska K, Majithiya R, McCrudden CM, Kole PL, Mahmood TMT, McCarthy HO, Woolfson AD. Hydrogel-Forming microneedle arrays for enhanced transdermal drug delivery. Adv Funct Mater. 2012;22(23):4879–90.
76. Peng K, Vora LK, Domínguez-Robles J, Naser YA, Li M, Larrañeta E, Donnelly RF. Hydrogel-forming microneedles for rapid and efficient skin deposition of controlled release tip-implants. Mater Sci Engineering: C. 2021;127:112226.
77. Sullivan SP, Murthy N, Prausnitz MR. Minimally invasive protein delivery with rapidly dissolving polymer microneedles. Adv Mater. 2008;20(5):933–8.
78. Nejad HR, Sadeqi A, Kiaee G, Sonkusale S. Low-cost and cleanroom-free fabrication of microneedles. Microsystems Nanoengineering. 2018;4(1):17073.
79. Pere CPP, Economidou SN, Lall G, Ziraud C, Boateng JS, Alexander BD, Lamprou DA, Douroumis D. 3D printed microneedles for insulin skin delivery. Int J Pharm. 2018;544(2):425–32.
80. Bagde A, Dev S, Sriram LMK, Spencer SD, Kalvala A, Nathani A, Salau O, Mosley-Kellum K, Dalvaigari H, Rajaraman S. Biphasic burst and sustained transdermal delivery in vivo using an AI-optimized 3D-printed MN patch. Int J Pharm. 2023;636:122647.
81. Li R, Zhang L, Jiang X, Li L, Wu S, Yuan X, Cheng H, Jiang X, Gou M. 3D-printed microneedle arrays for drug delivery. J Controlled Release. 2022;350:933–48.
82. Johnson AR, Caudill CL, Tumbleston JR, Bloomquist CJ, Moga KA, Ermoshkin A, Shirvanyants D, Mecham SJ, Luft JC, DeSimone JM. Single-step fabrication of computationally designed microneedles by continuous liquid interface production. PLoS ONE. 2016;11(9):e0162518.
83. Luzuriaga MA, Berry DR, Reagan JC, Smaldone RA, Gassensmith JJ. Biodegradable 3D printed polymer microneedles for transdermal drug delivery. Lab Chip. 2018;18(8):1223–30.
84. Singh P, Carrier A, Chen Y, Lin S, Wang J, Cui S, Zhang X. Polymeric microneedles for controlled transdermal drug delivery. J Controlled Release. 2019;315:97–113.
85. Ye Y, Yu J, Wang C, Nguyen N-Y, Walker GM, Buse JB, Gu Z. Microneedles integrated with pancreatic cells and synthetic Glucose-Signal amplifiers for smart insulin delivery. Adv Mater. 2016;28(16):3115–21.
86. Veiseh O, Langer R, Diabetes. A smart insulin patch. Nature. 2015;524(7563):39–40.
87. Prausnitz MR, Gomaa Y, Li W. Microneedle patch drug delivery in the gut. Nat Med. 2019;25(10):1471–2.
88. Park JH, Allen MG, Prausnitz MR. Biodegradable polymer microneedles: fabrication, mechanics and transdermal drug delivery. J Controlled Release. 2005;104(1):51–66.
89. Zhang X, Gan J, Fan L, Luo Z, Zhao Y. Bioinspired adaptable indwelling microneedles for treatment of diabetic ulcers. Adv Mater. 2023;35(23):e2210903.
90. Wu S, Hua M, Alsaid Y, Du Y, Ma Y, Zhao Y, Lo CY, Wang C, Wu D, Yao B. Poly (vinyl alcohol) hydrogels with broad-range tunable mechanical properties via the hofmeister effect. Adv Mater. 2021;33(11):2007829.
91. Park W, Nguyen VP, Jeon Y, Kim B, Li Y, Yi J, Kim H, Leem JW, Kim YL, Kim DR. Biodegradable silicon nanoneedles for ocular drug delivery. Sci Adv. 2022;8(13):eabn1772.
92. Mi P. Stimuli-responsive nanocarriers for drug delivery, tumor imaging, therapy and theranostics. Theranostics. 2020;10(10):4557–88.
93. Giulbudagian M, Yealland G, Honzke S, Edlich A, Geisendorfer B, Kleuser B, Hedtrich S, Calderon M. Breaking the Barrier-Potent Anti-Inflammatory activity following efficient topical delivery of etanercept using thermoresponsive nanogels. Theranostics. 2018;8(2):450–63.
94. Makvandi P, Jamaledin R, Chen G, Baghbantaraghdari Z, Zare EN, Di Natale C, Onesto V, Vecchione R, Lee J, Tay FR, Netti P, Mattoli V, Jaklenec A, Gu Z, Langer R. Stimuli-responsive transdermal microneedle patches. Mater Today. 2021;47:206–22.
95. Fan L, Zhang X, Nie M, Xu Y, Wang Y, Shang L, Zhao Y, Zhao Y. Photothermal responsive microspheres-triggered separable microneedles for versatile drug delivery. Adv Funct Mater. 2022;32(13):2110746.
96. Hardy JG, Larrañeta E, Donnelly RF, McGoldrick N, Migalska K, McCrudden MT, Irwin NJ, Donnelly L, McCoy CP. Hydrogel-forming microneedle arrays made from light-responsive materials for on-demand transdermal drug delivery. Mol Pharm. 2016;13(3):907–14.
97. Yu W, Jiang G, Zhang Y, Liu D, Xu B, Zhou J. Near-infrared light triggered and separable microneedles for transdermal delivery of Metformin in diabetic rats. J Mater Chem B. 2017;5(48):9507–13.
98. He D, Liu X, Jia J, Peng B, Xu N, Zhang Q, Wang S, Li L, Liu M, Huang Y, Zhang X, Yu Y, Luo G. Magnetic Field-Directed deep thermal therapy via Double-Layered microneedle patch for promoting tissue regeneration in infected diabetic skin wounds. Adv Funct Mater. 2023;34(2):2306357.
99. Feng X, Ma L, Lei J, Ouyang Q, Zeng Y, Luo Y, Zhang X, Song Y, Li G, Tan L, Liu X, Yang C. Piezo-Augmented sonosensitizer with strong Ultrasound-Propelling ability for efficient treatment of osteomyelitis. ACS Nano. 2022;16(2):2546–57.
100. Ouyang Q, Zeng Y, Yu Y, Tan L, Liu X, Zheng Y, Wu S. Ultrasound-Responsive microneedles eradicate Deep-Layered wound biofilm based on TiO(2) crystal phase engineering. Small. 2023;19(3):e2205292.

101. Molina M, Asadian-Birjand M, Balach J, Bergueiro J, Miceli E, Calderon M. Stimuli-responsive nanogel composites and their application in nanomedicine. Chem Soc Rev. 2015;44(17):6161–86.
102. Zhang X, Chen G, Liu Y, Sun L, Sun L, Zhao Y. Black phosphorus-loaded separable microneedles as responsive oxygen delivery carriers for wound healing. ACS Nano. 2020;14(5):5901–8.
103. Li J, Ma YJ, Wang Y, Chen BZ, Guo XD, Zhang CY. Dual redox/pH-responsive hybrid polymer-lipid composites: synthesis, preparation, characterization and application in drug delivery with enhanced therapeutic efficacy. Chem Eng J. 2018;341:450–61.
104. Ullah A, Jang M, Khan H, Choi HJ, An S, Kim D, Kim YR, Kim UK, Kim GM. Microneedle array with a pH-responsive polymer coating and its application in smart drug delivery for wound healing. Sens Actuators B. 2021;345:130441.
105. Hu X, Yu J, Qian C, Lu Y, Kahkoska AR, Xie Z, Jing X, Buse JB, Gu Z. H_2O_2-Responsive vesicles integrated with transcutaneous patches for Glucose-Mediated insulin delivery. ACS Nano. 2017;11(1):613–20.
106. Yu J, Qian C, Zhang Y, Cui Z, Zhu Y, Shen Q, Ligler FS, Buse JB, Gu Z. Hypoxia and H_2O_2 Dual-Sensitive vesicles for enhanced Glucose-Responsive insulin delivery. Nano Lett. 2017;17(2):733–9.
107. Yu J, Zhang Y, Ye Y, DiSanto R, Sun W, Ranson D, Ligler FS, Buse JB, Gu Z. Microneedle-array patches loaded with hypoxia-sensitive vesicles provide fast glucose-responsive insulin delivery. Proceedings of the National Academy of Sciences. 2015; 112(27): 8260–8265.
108. Singh P, Chen Y, Youden B, Oakley D, Carrier A, Oakes K, Servos M, Jiang R, Zhang X. Accelerated cascade melanoma therapy using enzyme-nanozyme-integrated dissolvable polymeric microneedles. Int J Pharm. 2024;652:123814.
109. Lee JW, Prausnitz MR. Drug delivery using microneedle patches: not just for skin. Expert Opin Drug Deliv. 2018;15(6):541–3.
110. Caffarel-Salvador E, Kim S, Soares V, Tian RY, Stern SR, Minahan D, Yona R, Lu X, Zakaria FR, Collins J. A microneedle platform for buccal macromolecule delivery. Sci Adv. 2021;7(4):eabe2620.
111. Lim S, Park TY, Jeon EY, Joo KI, Cha HJ. Double-layered adhesive microneedle bandage based on biofunctionalized mussel protein for cardiac tissue regeneration. Biomaterials. 2021;278:121171.
112. Chen W, Wainer J, Ryoo SW, Qi X, Chang R, Li J, Lee SH, Min S, Wentworth A, Collins JE. Dynamic omnidirectional adhesive microneedle system for oral macromolecular drug delivery. Sci Adv. 2022;8(1):eabk1792.
113. Liu R, Luo C, Pang Z, Zhang J, Ruan S, Wu M, Wang L, Sun T, Li N, Han L. Advances of nanoparticles as drug delivery systems for disease diagnosis and treatment. Chin Chem Lett. 2023;34(2):107518.
114. Adetunji CO, Michael OS, Rathee S, Singh KRB, Ajayi OO, Adetunji JB, Ojha A, Singh J, Singh RP. Potentialities of nanomaterials for the management and treatment of metabolic syndrome: A new insight. Mater Today Adv. 2022;13:100198.
115. Shi S, Zhou M, Li X, Hu M, Li C, Li M, Sheng F, Li Z, Wu G, Luo M, Cui H, Li Z, Fu R, Xiang M, Xu J, Zhang Q, Lu L. Synergistic active targeting of dually integrin alphavbeta3/CD44-targeted nanoparticles to B16F10 tumors located at different sites of mouse bodies. J Control Release. 2016;235:1–13.
116. Bao C, Li Z, Liang S, Hu Y, Wang X, Fang B, Wang P, Chen S, Li Y. Microneedle patch delivery of Capsaicin - Containing α - Lactalbumin nanomicelles to adipocytes achieves potent Anti-Obesity effects. Adv Funct Mater. 2021;31(20):2011130.
117. Pervez S, Nasir F, Hidayatullah T, Khattak MA, Alasmari F, Zainab SR, Gohar S, Tahir A. Maryam Ge. Transdermal Delivery of Glimepiride: A Novel Approach Using Nanomicelle-Embedded Microneedles. Pharmaceutics. 2023; 15(8): 2019.
118. Villarruel Mendoza LA, Scilletta NA, Bellino MG, Desimone MF, Catalano PN. Recent advances in Micro-Electro-Mechanical devices for controlled drug release applications. Front Bioeng Biotechnol. 2020;8:827.
119. Caldorera-Moore M, Peppas NA. Micro- and nanotechnologies for intelligent and responsive biomaterial-based medical systems. Adv Drug Deliv Rev. 2009;61(15):1391–401.
120. Rao KS, Sateesh J, Guha K, Baishnab KL, Ashok P, Sravani KG. Design and analysis of MEMS based piezoelectric micro pump integrated with micro needle. Microsyst Technol. 2018;26(10):3153–9.
121. Zhang R, Jullien GA, Dalton C. Study on an alternating current electrothermal micropump for microneedle-based fluid delivery systems. J Appl Phys. 2013;114(2):024701.
122. Rejinold NS, Shin JH, Seok HY, Kim YC. Biomedical applications of microneedles in therapeutics: recent advancements and implications in drug delivery. Expert Opin Drug Deliv. 2016;13(1):109–31.
123. Li S, Li W, Prausnitz M. Individually coated microneedles for co-delivery of multiple compounds with different properties. Drug Deliv Transl Res. 2018;8(5):1043–52.
124. Jin Y, Liu S, Wang X, Wang C, Ruan Q, Li W. Multifunctional microneedle patches loaded with engineered nitric Oxide-Releasing nanocarriers for targeted and synergistic chronic wound therapy. Adv Mater. 2025; 37 (5): 2413108.
125. Wright N, Wu T, Wang Y. Multilayered microneedles for triphasic controlled delivery of small molecules and proteins. Macromol Biosci. 2024;24(4):e2300431.
126. Huang D, Fu X, Zhang X, Zhao Y. Christmas Tree-Shaped Microneedles as FOLFIRINOX Spatiotemporal Delivery System for Pancreatic Cancer Treatment. Research (Wash D C). 2022; 2022: 9809417.
127. Hu X, Zhang H, Wang Z, Shiu CYA, Gu Z. Microneedle array patches integrated with nanoparticles for therapy and diagnosis. Small Struct. 2021;2(4):2000097.
128. Jin X, Zhu DD, Chen BZ, Ashfaq M, Guo XD. Insulin delivery systems combined with microneedle technology. Adv Drug Deliv Rev. 2018;127:119–37.
129. Li Y, Liu F, Su C, Yu B, Liu D, Chen HJ, Lin DA, Yang C, Zhou L, Wu Q, Xia W, Xie X, Tao J. Biodegradable therapeutic microneedle patch for rapid antihypertensive treatment. ACS Appl Mater Interfaces. 2019;11(34):30575–84.
130. Dangol M, Kim S, Li CG, Fakhraei Lahiji S, Jang M, Ma Y, Huh I, Jung H. Anti-obesity effect of a novel caffeine-loaded dissolving microneedle patch in high-fat diet-induced obese C57BL/6J mice. J Control Release. 2017;265:41–7.
131. Wang S, Wang Y, Lin L, Li Z, Liu F, Zhu L, Chen J, Zhang N, Cao X, Ran S, Liu G, Gao P, Sun W, Peng L, Zhuang J, Meng H. Layer-Specific BTX-A delivery to the gastric muscularis achieves effective weight control and metabolic improvement. Adv Sci. 2023;10(28):e2300822.
132. Yu J, Wang J, Zhang Y, Chen G, Mao W, Ye Y, Kahkoska AR, Buse JB, Langer R, Gu Z. Glucose-responsive insulin patch for the regulation of blood glucose in mice and minipigs. Nat Biomedical Eng. 2020;4(5):499–506.
133. Zhang Y, Liu Q, Yu J, Yu S, Wang J, Qiang L, Gu Z. Locally induced adipose tissue Browning by microneedle patch for obesity treatment. ACS Nano. 2017;11(9):9223–30.
134. Gu X, Wu Z, Wu D, Hou B, Bian L, Zhou T, Hou Y, Wang H, Zheng Z. Hydrogel microneedle patch for treatment of liver fibrosis. Mater Today Adv. 2023;20:100417.
135. Khalid A, Shoaib Sarwar H, Sarfraz M, Farhan Sohail M, Jalil A, Bin Jardan YA, Arshad R, Tahir I, Ahmad Z. Formulation and characterization of thiolated Chitosan/polyvinyl acetate based microneedle patch for transdermal delivery of dydrogesterone. Saudi Pharm J. 2023;31(5):669–77.
136. Wang R, Sun Y, Wang H, Liu T, Shavandi A, Nie L, Yunusov KE, Jiang G. Core-shell structured microneedles with programmed drug release functions for prolonged hyperuricemia management. J Mater Chem B. 2024;12(4):1064–76.
137. McAlister E, Kirkby M, Domínguez-Robles J, Paredes AJ, Anjani QK, Moffatt K, Vora LK, Hutton ARJ, McKenna PE, Larrañeta E, Donnelly RF. The role of microneedle arrays in drug delivery and patient monitoring to prevent diabetes induced fibrosis. Adv Drug Deliv Rev. 2021;175:113825.
138. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Reviews Endocrinol. 2017;14(2):88–98.
139. Chen BZ, Zhang LQ, Xia YY, Zhang XP, Guo XD. A basal-bolus insulin regimen integrated microneedle patch for intraday postprandial glucose control. Sci Adv. 2020;6(28):eaba7260.
140. Kim S, Yang H, Eum J, Ma Y, Fakhraei Lahiji S, Jung H. Implantable powder-carrying microneedles for transdermal delivery of high-dose insulin with enhanced activity. Biomaterials. 2020;232:119733.
141. Wang J, Ye Y, Yu J, Kahkoska AR, Zhang X, Wang C, Sun W, Corder RD, Chen Z, Khan SAJAn. Core-shell microneedle gel for self-regulated insulin delivery. ACS Nano. 2018;12(3):2466–73.
142. Tong Z, Zhou J, Zhong J, Tang Q, Lei Z, Luo H, Ma P, Liu X. Glucose-and H_2O_2-responsive polymeric vesicles integrated with microneedle patches for glucose-sensitive transcutaneous delivery of insulin in diabetic rats. ACS Appl Mater Interfaces. 2018;10(23):20014–24.
143. Abramson A, Caffarel-Salvador E, Khang M, Dellal D, Silverstein D, Gao Y, Frederiksen MR, Vegge A, Hubálek F, Water JJ. An ingestible self-orienting system for oral delivery of macromolecules. Science. 2019;363(6427):611–5.
144. Zhang X, Chen G, Fu X, Wang Y, Zhao Y. Magneto-Responsive microneedle robots for intestinal macromolecule delivery. Adv Mater. 2021;33(44):2104932.
145. Gao X, Li J, Li J, Zhang M, Xu J. Pain-free oral delivery of biologic drugs using intestinal peristalsis–actuated microneedle robots. Sci Adv. 2024;10(1):eadj7067.

146. Levy JA, Straker MA, Stine JM, Beardslee LA, Ghodssi R. Magnetically triggered ingestible capsule for localized microneedle drug delivery. Device. 2024;2(10):100438.
147. Vishvanath L, Gupta RK. Contribution of adipogenesis to healthy adipose tissue expansion in obesity. J Clin Invest. 2019;129(10):4022–31.
148. Bouchard C. Defining the genetic architecture of the predisposition to obesity: a challenging but not insurmountable task. Am J Clin Nutr. 2010;91(1):5–6.
149. Gao Z, Liu Y, Lin W, Lian H, Meng Z. A microneedle patch realizes weight loss through photothermal induction of fat Browning. Biomaterials Sci. 2024;12:1726–37.
150. Chen S, Wang J, Sun L, Xia F, Li W, Yuan L, Liu C, Li P, Bao C, Wang M. A quick paster type of soluble nanoparticle microneedle patch for the treatment of obesity. Biomaterials. 2024;311:122687.
151. Li Z, Liang S, Sun H, Bao C, Li Y. Antilipogenesis effect of Rutin-Loaded liposomes using a microneedle delivery system. ACS Appl Mater Interfaces. 2023;15(47):54294–303.
152. Zan P, Than A, Leow MKS, Cai HX, Wen H, Zhang Z, Chen P. Dry powder microneedle-enabled transdermal anti-inflammatory therapy for obesity, diabetes, hyperlipidemia, and fatty liver. Chem Eng J. 2024;484:149395.
153. Choi H, Hong J, Seo Y, Joo SH, Lim H, Lahiji SF, Kim YH. Self-Assembled Oligopeptoplex-Loaded dissolving microneedles for Adipocyte-Targeted Anti-Obesity gene therapy. Adv Mater. 2024;36:e2309920.
154. Khalid R, Mahmood S, Mohamed Sofian Z, Hilles AR, Hashim NM, Ge Y. Microneedles and Their Application in Transdermal Delivery of Antihypertensive Drugs - A Review. Pharmaceutics. 2023; 15(8): 2029.
155. Nirmayanti N, Alhidayah A, Usman JT, Nur JF, Amir MN, Permana AD. Combinatorial approach of thermosensitive hydrogels and solid microneedles to improve transdermal delivery of Valsartan: an in vivo proof of concept study. AAPS PharmSciTech. 2022;24(1):5.
156. Chen Z, Lai Y, Xu S, Zhu M, Sun Y, Cheng Y, Zhao G. A self-powered controllable microneedle drug delivery system for rapid blood pressure reduction. Nano Energy. 2024;123:109344.
157. Sardesai M, Shende P. Engineering of nanospheres dispersed microneedle system for antihypertensive action. Curr Drug Deliv. 2020;17(9):776–86.
158. Younossi Z, Tacke F, Arrese M, Chander Sharma B, Mostafa I, Bugianesi E, Wai-Sun Wong V, Yilmaz Y, George J, Fan J, Vos MB. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology. 2019;69(6):2672–82.
159. Paternostro R, Trauner M. Current treatment of non-alcoholic fatty liver disease. J Intern Med. 2022;292(2):190–204.
160. Salah MM, Ashour AA, Abdelghany TM, Abdel-Aziz A-AH, Salama SA. Pirfenidone alleviates Concanavalin A-induced liver fibrosis in mice. Life Sci. 2019;239:116982.
161. Stener-Victorin E, Deng Q. Epigenetic inheritance of polycystic ovary syndrome-challenges and opportunities for treatment. Nat Reviews Endocrinol. 2021;17(9):521–33.
162. Jackson J, Caro JJ, Caro G, Garfield F, Huber F, Zhou W, Lin CS, Shander D, Schrode K, Group EHS. The effect of Eflornithine 13.9% cream on the bother and discomfort due to hirsutism. Int J Dermatol. 2007;46(9):976–81.
163. Kumar A, Naguib YW, Shi YC, Cui Z. A method to improve the efficacy of topical Eflornithine hydrochloride cream. Drug Deliv. 2016;23(5):1495–501.
164. Gliozzi M, Malara N, Muscoli S, Mollace V. The treatment of hyperuricemia. Int J Cardiol. 2016;213:23–7.
165. Yang Y, Li Z, Huang P, Lin J, Li J, Shi K, Lin J, Hu J, Zhao Z, Yu Y, Chen H, Zeng X, Mei L. Rapidly separating dissolving microneedles with sustained-release Colchicine and stabilized uricase for simplified long-term gout management. Acta Pharm Sin B. 2023;13(8):3454–70.
166. Hao Y, Li H, Cao Y, Chen Y, Lei M, Zhang T, Xiao Y, Chu B, Qian Z. Uricase and horseradish peroxidase hybrid $CaHPO_4$ Nanoflower integrated with transcutaneous patches for treatment of hyperuricemia. J Biomed Nanotechnol. 2019;15(5):951–65.
167. Wang R, Wang H, Jiang G, Sun Y, Liu T, Nie L, Shavandi A, Yunusov KE, Aharodnikau UE, Solomevich SO. Transdermal delivery of allopurinol to acute hyperuricemic mice via polymer microneedles for the regulation of serum uric acid levels. Biomater Sci. 2023;11(5):1704–13.
168. Wang X, Wang Z, Xiao M, Li Z, Zhu Z. Advances in biomedical systems based on microneedles: design, fabrication, and application. Biomater Sci. 2024;12(3):530–63.
169. Ju J, Hsieh CM, Tian Y, Kang J, Chia R, Chang H, Bai Y, Xu C, Wang X, Liu Q. Surface enhanced Raman spectroscopy based biosensor with a microneedle array for minimally invasive in vivo glucose measurements. ACS Sens. 2020;5(6):1777–85.
170. Farzan M, Roth R, Schoelkopf J, Huwyler J, Puchkov M. The processes behind drug loading and release in porous drug delivery systems. Eur J Pharm Biopharm. 2023;189:133–51.
171. Alshammari MK, Ghazwani JA, Alsharari FO, Alotaibi SS, Alotaibi RM, Alsayahani AA, Alosaimi RB, Alotaibi AN, Imran M, Arshad MF. An update on microneedle in insulin delivery: quality attributes, clinical status and challenges for clinical translation. J Drug Deliv Sci Technol. 2022;75:103668.
172. Zhang LQ, Zhang XP, Hao YY, Zhang BL, Guo XD. Codelivery of hydrophilic and hydrophobic drugs in a microneedle patch for the treatment of skin pigmentation. J Ind Eng Chem. 2020;88:241–50.
173. Chen MC, Lin ZW, Ling MH. Near-infrared light-activatable microneedle system for treating superficial tumors by combination of chemotherapy and photothermal therapy. ACS Nano. 2016;10(1):93–101.
174. Abramson A, Frederiksen MR, Vegge A, Jensen B, Poulsen M, Mouridsen B, Jespersen MO, Kirk RK, Windum J, Hubálek F. Oral delivery of systemic monoclonal antibodies, peptides and small molecules using gastric auto-injectors. Nat Biotechnol. 2022;40(1):103–9.

Publisher's note