Microneedles for Non-transdermal Drug Delivery: Design Strategies and Current Applications

Jinhong Xu [a], Xiangyi Liao [b], Danli Chen [b], Xiuzhuo Jia [c, *], Xufeng Niu [b, *]

[a]*Department of Pharmacy, The Fourth Central Hospital of Baoding City, Baoding 072350, China;*

[b]*Key Laboratory of Biomechanics and Mechanobiology (Beihang University), Ministry of Education, Beijing Advanced Innovation Center for Biomedical Engineering, School of Biological Science and Medical Engineering, Beihang University, Beijing 100083, China;*

[c]*Department of Medical Business, The Fourth Central Hospital of Baoding City, Baoding 072350, China*

* Corresponding author.
E-mail address: neilneilniu@hotmail.com. (X.J.).
E-mail address: nxf@buaa.edu.cn. (X.N.).

Abstract

Microneedles (MNs), as an innovative and viable option for drug delivery, has distinct advantages of non-invasive, painless, stable drug loading, efficient drug permeation, and ideal biocompatibility. Microneedles are initially used to penetrate the skin surface and obtain transcutaneous drug delivery, and have achieved a great success in the field. In recent years, the application of MNs has been introduced into non-transdermal drug delivery, extending to a variety of tissues and organs. This review captures the fabrication methods for MNs, provides advanced designing strategies of MNs for achieving controlled drug release mechanism and summarizes current MNs applications delivering multiple therapeutic agents to the cardiovascular system, oscular tissue, digestive system, oral cavity, central nervous system and reproductive system. We hope that this article would better guide readers to design their MNs system according to different situations, including material selection, structure design, choice of fabrication methods and tissue considerations, so as to determine the optimal therapeutic regimen towards the target treatment area.

Keywords: Microneedles · Biocompatible Materials · Non-transdermal drug delivery · Controlled release

Article Highlights

1. Microneedles (MNs) are advanced drug delivery devices with high efficiency and minimal invasiveness;
2. Advanced MNs fabrication strategies for achieving close tissue adhesion and controlled release properties are summarized;
3. Current applications of MNs-based devices for non-transdermal drug delivery are reviewed.

1. Introduction

Conventional transdermal drug delivery methods including hypodermic, intradermal, and intravenous injections, can easily break through human stratum corneum barrier with rigid needles, known as cheap and convenient ways to achieve drug injection and body fluid collection[1]. Though current ways of transdermal drug delivery could solve the problems of drug efficacy decline after gastrointestinal (GI) action during oral administration and overcome poor drug permeation restriction during topical drug delivery, traditional needles may cause pain as well as tissue damage[2, 3]. In the meantime, there are a certain quantity of people are extremely afraid of needles, who declare themselves as blood-injury-injection (BII) phobia[4]. Microneedles (MNs) is a kind of micron-scaled needle, and was initially explored for delivery of therapeutic agents across skin, of which the concept was first proposed by Prausnitz in 1998 to deal with all these questions brought by standard needles[5, 6]. As one of the third-generation enhancement strategies of transdermal drug delivery, it has become a major tool for macromolecules and vaccines delivery. Compared to other means of drug delivery mentioned above, currently MNs-based drug delivery has a series of advantages, such as less invasive and lower risk of infection. By physically penetrating the stratum corneum barrier and increase skin permeability, MNs serves as can an efficient method to transport target drug molecule without stimulating the nerves, which can overcome the delivery efficiency issue with minimum tissue damage[7, 8].

With the development of material science and equipment upgrade of microfabrication, MNs patch with an array of micron scale needles can be manufactured into various forms. Typically, MNs can be sorted into four main categories: solid, coated, hollow and dissolvable or biodegradable. Solid MNs are made of silicon and biocompatible metal which could be coated with drug or loaded with drug; hollow MNs with chamber inside can be used for liquid drug infusion or body fluid sampling; dissolvable MNs fabricated through biodegradable polymer can release drug with the supporting hydrophilic material dissolve into interstitial fluid in a short time[9]. Additionally, a novel form of MNs, hydrogel needles, are being extensively explored most recently. These MNs comprise cross-linked hydrogels loaded with drugs, once applied onto the tissue surface and in contact with the aqueous media, they tend to swell and then facilitate the influx of drug into the tissues[10-12]. A variety of materials including silicon, metals, ceramic, natural polymers as well as synthetic polymers have been

used in MNs fabrication, and with different strategies, the needle part can be shaped into pyramidal, conical, bullet-shaped, arrowhead or other complicated geometries to perform specific applications[13, 14]. With the micron needles array piercing the skin barrier, macro molecule and micro molecule can be delivered to the dermis of specific skin region, to achieve vaccine delivery, cancer therapy, hormone therapy, wound healing and tissue regeneration.

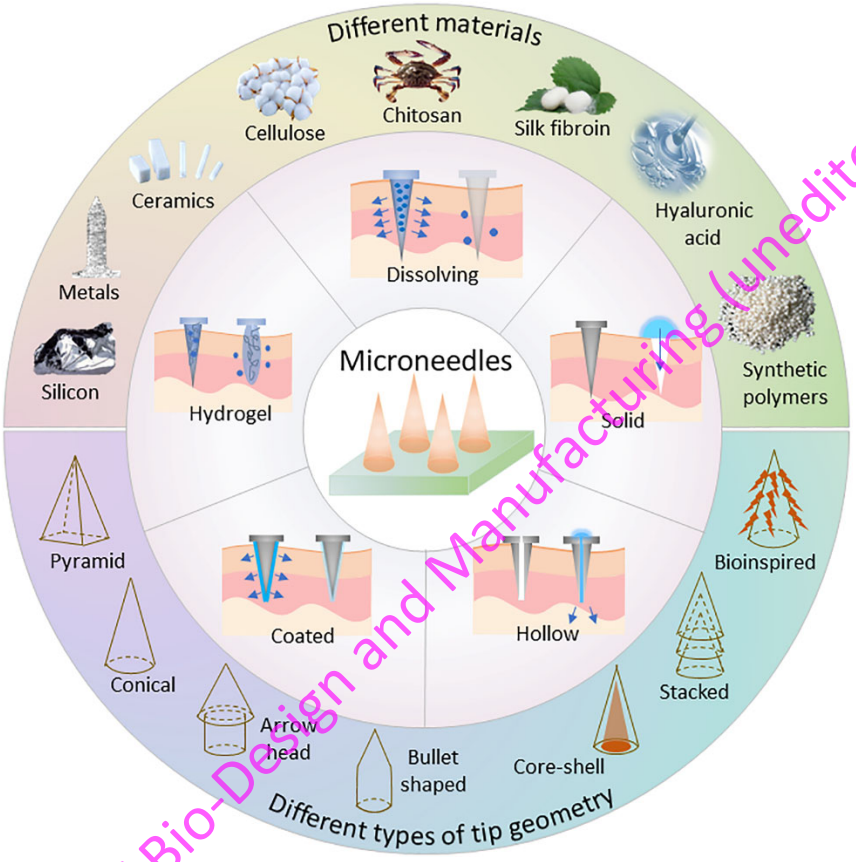

Fig 1. Classification of microneedles (MNs) under different criteria.

Over the past decades, though extensive developments of MNs drug delivery still centered around transdermal implementations, investigations were in progress to deploy the technology for delivering drug to other tissues and organs, suggesting that the field of non-transdermal drug delivery using MNs have been preliminarily explored. Recently, more cutting-edge researches are employing the utilization of MNs in these areas and studies focusing on the extension of structure and function of the MNs are being carried out actively. In this Review, we focus on MNs for internal use in soft tissues. Applications for scalp, nail and bone drug delivery are out of the scope, as some of their design criteria are different from those of soft tissue, either have extremely high mechanical requirements or lack the need for biodegradation. Furthermore, by discussing fabrication techniques, design strategies selection, and

leading-edge achievements of MNs for the delivery of therapeutic drugs across different biological barriers, we also provide concise discussion of design principles of non-transdermal MNs for specific tissues applications, that might minimize the gap between applied researches and clinical translation, putting forward prospects on future research directions at the same time.

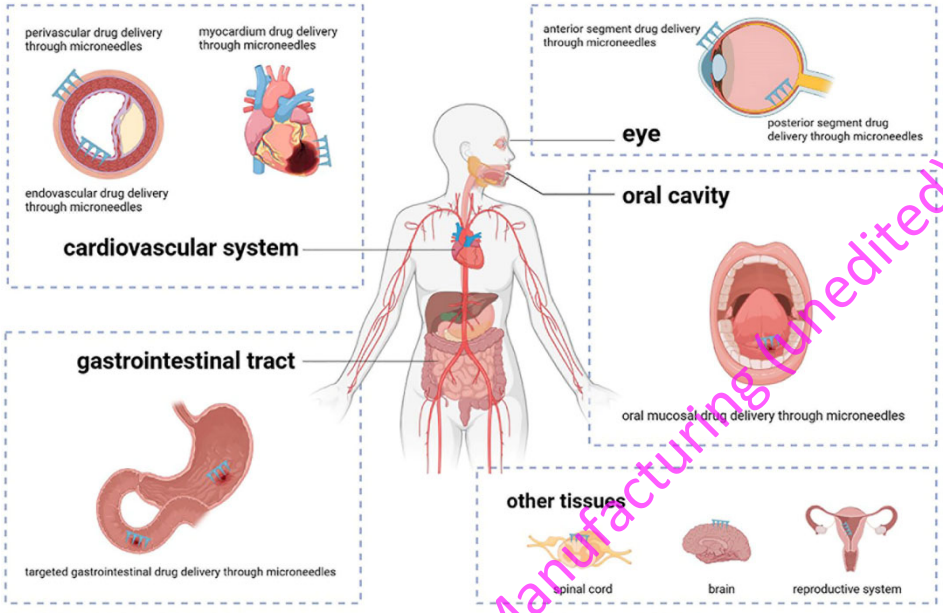

Fig 2. Tissues of non-transdermal drug delivery MNs.

2. Advanced fabrication strategies and characterization for MNs

Specific material selection together with novel manufacturing technologies provide the premise for the diversified morphology of MNs-related devices. In order to overcome the complicated anatomy and diverse physical properties of organs and tissues, more sophisticated fabrication methods are often used during the preparation of MNs, thus provide optimal properties such as mechanical strength, biodegradability and biocompatibility for the applications, with significant advantages in bypassing drug resistance and minimizing detrimental side effects.

2.1. Materials

Different types of materials have been used for MNs manufacturing according to the corresponding requirement of different application. It is critical to choose appropriate material when constructing non-transdermal MNs. Silicon[5, 15], silicon dioxide[16], ceramics[17], metals such as titanium[18] and stainless steel[19] were initially used to fabricate solid MNs which simply open pores on skin for promoting drug permeation due to their high stiffness. Hollow MNs and coated MNs also consider

these non-degradable materials as preference. Compared with metal, polymers have controllable drug release characteristic and biodegradable nature, MNs made from these materials can be designed to dissolve after insertion into the body[20, 21]. Carbohydrate-based materials including trehalose, chitosan, maltodextrin, cellulose, glucose, hyaluronic acid (HA) and carboxymethylcellulose (CMC) have been widely applied in dissolving MNs fabrication, among which CMC and HA are the most frequently used. CMC is a biocompatible, biodegradable structural polymer that is often added to the matrix solution to increase viscosity. HA is a crucial element of the extracellular matrix and cartilage, which is endowed with high biocompatibility and ideal mucoadhesive properties. Additionally, high molecular weight HA (>50 kDa) has been reported to be immunosuppressive in vivo while low molecular weight HA (<50 kDa) might be pro-inflammatory but with no side effects indicated [22, 23]. Synthetic polymers such as polycarbonate (PC), polymethyl methacrylate (PMMA) polylactic acid (PLA), polyglycolide acid (PGA), poly(lactic-co-glycolic acid) (PLGA), Polyvinyl acetate (PVA), Polyvinylpyrrolidone (PVP) have also been extensively used in MN-based drug delivery productions[24-26]. Because both PVA and PVP have the advantages of rapid dissolution when in contact with interstitial fluid and are both mechanically robust enough to bear the insertion force required for tissue penetration, they meet all the criteria for obtaining advanced dissolving MNs, thus have been most commonly used as fabrication matrix. Controlled release of drug over time can be realized via manipulating the degradation of polyesters, for example, through varying the ratio between PLA and PGA in the copolymer of PLGA[27]. These polymers are expediently available and without the requirement of complex preparation for use, so they are likely to be introduced into industrial production lines and may enable a large-scale manufacturing in the near future. Silk fibroin is another novel material used for fabricating dissolving MNs, which is obtained from the natural source of Bombyx mori silkworm cocoons. The inclusion of fibroin can enhance the mechanical strength and robustness of the MNs and its controllable properties enables a sustained drug release profile[24]. Also, by adjusting crosslinking methods and chemical modification techniques, polymers can be formed into certain hydrogels, then mixed with different types of drugs including small molecules, macromolecules, nanoparticles and nucleic acids to fabricate swellable MNs. Hydrogels like Poly(ethylene glycol) diacrylate (PEGDA), Gantrez S-97, Gantrez AN-139, gelatin methacryloyl (GelMA) and methacrylated hyaluronic acid (MeHA), are typically biocompatible and often own relatively low mechanical property and faster degradation which can be used for rapid drug release. Hydrogels could

also be designed accordingly for controlled drug release corresponding to the drug size. By adjusting the weight percentage of crosslinker or the MW of the crosslinker itself to alter the crosslinking density, may lead to the changes of swelling ability. More rapid swelling of the hydrogel results in a more rapid drug release[28, 29].

2.2. Fabrication Techniques

With the extension of material using as well as continuous development of micro-processing technology, the manufacturing of MNs array has also been expanded from the conventional microfabrication technique to other advanced technologies like 3D printing, drawing lithography, multistep micromolding and so on. These strategies enable the morphology of the needle tips to be flexibly adjust during fabrication process.

2.2.1. Microfabrication

Since the first report of the MNs application in drug delivery was developed from silicon using deep reactive ion etching (DRIE)[5], traditional silicon manufacturing technology including photolithography, dry etching and wet etching, were subsequently led into the fabrication process then. Currently, these microfabrication methods based on micro-electro-mechanical (MEM) system technology have been wildly used in the fabrication of both in-plane and out-of-plane MNs arrays, which serve as ideal gateways for achieving high production efficiency with low costs[30].

In general, dry etching techniques can be divided into plasma etching, reactive ion etching and ion milling, based on the differentiator of process pressure during fabrication. The most common dry etching process is deep reactive ion etching (DRIE), commonly known as the Bosch process[31]. DRIE enables highly anisotropic silicon etching with high-selectivity, and by controlling parameters including gas flow rates, etch pressure, temperature, power and bias, and type of masking layer, desired MN applications with especially high aspect-ratio features and smooth vertical sidewall geometries can be feasibly achieved. Wet etching can be classified into different types according to the aqueous etchants used respectively, involving Tetra-methyl-ammonium-hydroxide (TMAH), Ethylenediamine pyrocatechol (EDP), potassium hydroxide (KOH), HF, and HNO_3. For either isotropic etch (the etch rate is the same in all directions) or anisotropic etch (the etch rate differs for different crystal planes), the etch rate of the etchant material chosen should be greater than the etch mask material so that the

exposed position can be dissolved and then removed[32, 33].Wet etching can be used to demonstrate different aspect ratio MNs which enable targeted drug delivery depths [15, 34]. Hamzah's team proved that the high aspect ratio can be accessed under optimal production parameters by aligning the surface of the sample perpendicular to the etchant flow direction[35]. Though wet etching is generally faster and requires less cost than dry etching, it cannot be effectively applied to produce high aspect ratio boreholes for hollow MNs. Indeed, hollow structured MNs with flow channels can be defined using combined wet and dry etching steps, during which front and rear DRIE firstly form the pillar structure while wet etch progress then sharpen the pillars to needles[31, 36, 37]. Photolithographic approach is usually used in the fabrication of polymeric MNs. By covering the target substrate with particular photoresist and then expose to ultraviolet radiation, template etching can be actualized (Fig. 3a)[38]. Combining single step photolithography and etching, solid MNs with high aspect ratio can be manufactured. Pradeep Narayanan's work demonstrated tapered MNs with sharper tips. During the process, single step lithography and anisotropic TMAH wet etching techniques are incorporated for the realization of high aspect ratio, successfully increase the insertion length of the MNs with sharper tips and unique geometry[39]. Roh et al. proposed a single step photolithography plus two subsequent deep reactive ion etching (DRIE) steps fabrication method, by using dumbbell well photomask patterns, the study successfully obtained high density out-of-plane MNs with various heights and diverse cross-sectional shapes, which can reach adequate penetration depths of the skin or the brain to promote more effective utilization in drug delivery as well as neurophysiological researches[40].

2.2.2. Photopolymerization-based 3D printing

Three-dimensional (3D) printing is a rapid additive manufacturing method, and mainly include two streams: photopolymerization-based 3D printing and extrusion-based 3D printing[41, 42]. Among all 3D printing methods, photopolymerization based techniques lately attracted extensive attention due to its advantages of simple preparation process, short preparation period, high preparation precision, and large freedom of structure design. During fabrication, the introduction of photocrosslinkable biomaterials with enhanced physical and chemical properties enables fast gelation upon exposure to light irradiation with the presence of photoinitiators. Photopolymerization based 3D printing can be further divided into point-by-point printing including streolithography (SLA) and two-photon polymerization (TPP), and layer-by-layer printing such as Digital Light Processing (DLP) (Fig. 3b).

In SLA, the computer-controlled ultraviolet light beam is utilized to induce the polymerization reaction of photosensitive resins point by point, and then deposit on the material surface. By adjusting the irradiation area, illumination time and intensity of the UV light, MNs arrays with different shapes can be prepared[43]. Compared to SLA, TPP is a method with higher resolution and better printing accuracy, during which 3D structures are formed through the simultaneous absorption of two or more photons and photosensitive materials can achieve point-by-point solidification. TPP enables the production with complex structures in a relatively simple way[44]. Cordeiro et al. highlighted that TPP served as a flexible and reliable approach in the manufacture of MNs with the shapes of full conical, full pyramidal, cuboidal base/pyramidal tips and cross-shaped, showed high drug delivery rate in both ex vivo and in vitro experiments[45]. Also, hollow MNs with various hole structure and MNs with open microfluid channels can be easily fabricated using TPP[46, 47]. During DLP, the geometry of a needle is constructed by solidifying photosensitive resin layer by layer using digital micro mirror device (DMD). Parallel printing can be achieved by projecting the entire plane of optical pattern onto the photopolymer solution, which can achieve high-speed preparation with low cost. The resolution of the printer is at micron scale, decided by the focal size of the light beam from each micromirror[48]. Due to these advantages, DLP may serve as a potential possibility to construct finer surface microstructure of needle body as well as fabricating in-plane and out-of-plane hollow MNs with different aspect ratios.

In order to match native tissue dynamics better and meet the shape changes, the concept of four-dimensional(4D) printing has been proposed. By extending 3D space to the fourth dimension of time, the development of biomaterials and bioinks can be continually controlled. Constructed of active/smart materials with the ability to self-assemble, self-heal, remember their shapes, and have self-reproducing, the productions can be pre-programmed and adjusted to achieve more native-like results, which ideally satisfy the functional requirements of MNs applications for non-transdermal drug delivery[49]. At present, 4D printing has been successfully applied to the new regenerative therapy of cardiovascular diseases. It has been proved that biomechanical adaptive heart patch manufactured by this technology successfully attached to physiological surface of the tissue, and repair the injured myocardium[50, 51].

2.2.3. Drawing-based technologies

Novel dissolving MN fabrication techniques basic on drawing are providing different choices for the manufacture of non-transdermal drug delivery MNs. Thermal drawing, as a drawing lithography

method allowing 3D structure directly formed from 2D materials, is commonly used in the construction of polymer MNs with high aspect ratio. Heated viscous polymer is vertically drawn by a metal micropillar at a manipulated speed, then goes through a rapid lift after a cooling step to fracture the narrow neck microstructure and form the MNs[52]. During the continuous fabrication procedure, the viscosity of the drawn polymer can be controlled by adjusting the temperature and drawing points in the glass transition history of the polymer materials, which relatively change the extensional deformation, in order to precisely modulate the tip geometry (Fig. 3c)[53]. But this might as well result in the formation of irregular structured MNs with either cylinder shape or bat shape[54]. Therefore, a stepwise controlled thermal drawing method is designed to avoid the unsuitable shapes from developing, through which particular MNs with sharp tip ends can be correspondingly defined. Lee et al. proposed a three-step thermal drawing technique, including contact drawing, body drawing and tip drawing process, which can rapidly manufacture polymer MNs with various shapes on various surfaces[55]. Utilizing temperature-dependent polymeric behavior and controlling the thermal mapping parameters, MNs with different features were manufactured. During drawing process, the final shape of a single needle can be variably determined by temperatures of a micropillar and substrate (temperatures at boundaries of the drawn polymer) and dwell time. The change of temperature could lead to different polymer chain mobility at each local point of the drawn polymer, when it changed from low to high, the aspect ratio increased correspondingly. The aspect ratio also increased with the extension of dwell time. Based on the conventional three-step thermal drawing method, transfer thermal drawing is then proposed to form MNs on different substrates.

Other drawing-based technologies like electro-drawing, droplet-born, air-blowing drawing, magnetorheological drawing can also be applied to MNs fabrication. Electro-drawing (ED) has been proposed as a contact free process without the utilization of UV-light for the manufacturing of polymer MNs, such as PLGA based MNs (Fig. 3d) [56, 57]. Droplet-born air blowing (DAB) is an advanced method with the benefits of simple process, gentle fabrication conditions, low cost and massive productivity. Via air blowing, DAB enables the polymer droplet to solidify and form the MN shape directly within 10 min, allowing the loaded drugs to maintain the biological activity during the quick fabrication (Fig. 3e)[58]. Magnetorheological drawing lithography (MRDL) is rapid and easy fabrication that eliminates the need of mask, light irradiation the drawing temperature adjustment. In

MRDL, droplets of curable magnetorheological fluid (CMRF) can be drawn directly from almost any substrate to produce multiple tip structures of MNs under an external magnetic field. A tilted MN can also be fabricated by altering the direction of magnetic field, by which the tilt angle of the needle tips is adjustably determined[59, 60]. As a 3D additive manufacturing process, MRDL can be used to produce complex bio-inspired microstructures, such as tilted micro barbs, which helps the MNs to achieve easy skin insertion and difficult removal (Fig. 3f)[61].

2.2.4. Molding techniques

In addition to those multifarious and complicated manufacturing techniques for directly constructing MN structures, methods based on micromolding provide other choices (Fig. 3g). In micromolding process, a patterned polydimethylsiloxane (PDMS) is used as a mold for substrates[62]. PDMS mold with different microchannels geometry can be directly formed by laser technology[63-65], or through multistep casting after defining the multiform microfluidic by lithography[66, 67] or 3D printing[68], PDMS is then poured over to obtain the negative mode structure. After filling shaped cavities with certain biomaterial solution and solidification, MNs with specific functions can be customization. Correspondingly, single or composite materials are selected for MNs preparation according to the fabricating requisite mechanical strength and solubility property. Based on micromolding method, solidification of polymeric solution or melt enables MNs to bind stably on a macro-scale structure, which facilitates a wide range of applications such as separable MNs, MN-pen and MN-mesh. Several studies have developed separable MNs constructed with PVA/PVP soluble base and drug-loaded tips with certain biofunctionability via a two-step molding technology. The soluble supporting bases dissolution after absorption of tissue fluid allowed the separable MNs arrowheads to insert and embed into skin[69, 70]. In Leonard's work, the MN arrowheads were firstly formed in micron cavities, then connected to the backing shaft arrays under gentle force which embedded the MN shafts into the base of the arrowheads. After drying/solidification, arrowheads were removed from the mold to yield complete MNs patch (Fig. 3h)[71]. Similarly, the method can be used in the fabrication of a series of MN-pen applications. SU-8 droplets were used as junction of MN tips and pen substrate, which solidified under heating and UV curing (Fig. 3i)[72, 73]. Wrappable MN-mesh applications for perivascular drug delivery using transfer molding method were reported. Drug-embedded material was filled into the PDMS mold, and an adhesion layer was left above MN cavities. Heated micropillar was

then used to melt the adhesion layer after attaching the flexible mesh to the needle tips, thus accomplished the assembly of MN-mesh upon cooling (Fig. 3j)[74, 75].

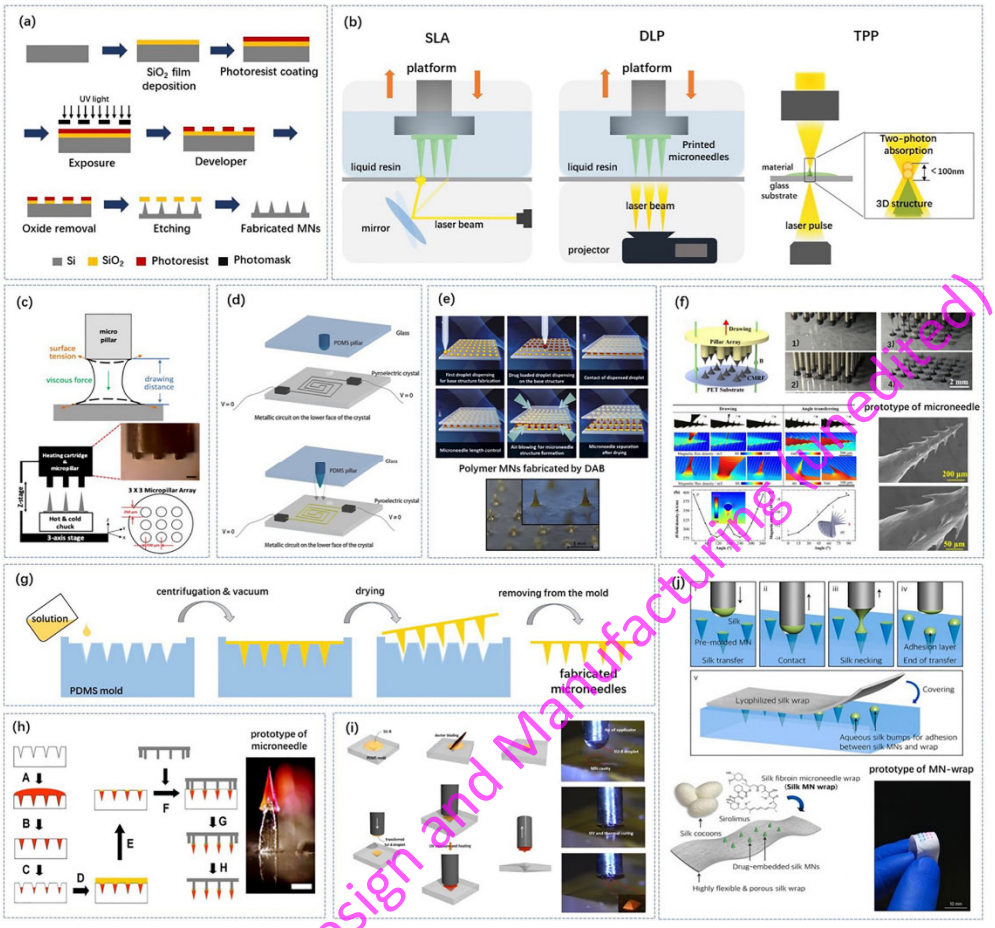

Fig 3. Various fabrication methods of MNs. (a) Typical microfabrication method through etching. (b) Photopolymerization-based 3D printing including SLA, DLP and TPP. (c) Schematic diagrams of thermal drawing process (Copyright © 2019 by Lee, published by MDPI)[55]. (d) Schematic diagrams of electro drawing process (Copyright © 2017 by Elsevier B.V.)[57]. (e) Schematic diagrams of DAB process (Copyright © 2013, Elsevier B.V.)[58]. (f) Fabrication progress of MRDL (Copyright © 2018 by American Chemical Society). Micro barbs on the parent MN can be shaped through this method, of which the tilted angles can be decided by magnetic field (Copyright © 2019 by American Chemical Society)[59, 61]. (g) Fabrication steps of conventional micromolding method. (h) Fabrication progress of MNs manufactured through multistep molding, with prototype of a single needle (scale bar, 300 μm) (Copyright © 2010 by Elsevier B.V.) [71]. (i) Fabrication progress of a MN-pen manufactured through transfer-molding method (Copyright © 2015 by Elsevier B.V.)[76]. (j) Fabrication progress of a wrappable silk MN-mesh manufactured through transfer-molding method (Copyright © 2021 by

Elsevier B.V.)[74]. All the figures are cited with permission.

3. Special design strategies for non-transdermal drug delivery MNs

When administering drugs, lesions at different non-dermal tissues requires corresponding therapeutic criteria as well as specific dosing strategies. MNs for treatment are ought to remain closely attached to the tissue and degrade over time, allowing the loaded drugs to be released safely and sustainably. For some diseases that require long-term administration for treatment, or diseases that require periodic administration, it is necessary to develop smart MNs that can control the release of drugs. By selecting appropriate methods for precise control over the morphology and structure, variable forms of MNs-based drug delivery devices with ideal mechanical properties can be manufactured, and to carry specific biomolecules for curing as well as monitoring the diseases.

3.1. Safety considerations

3.1.1. Biodegradability and biocompatibility

As the MNs will come in contact with interior organs and tissues, it is also critical to consider their fundamentals of biosafety and biosecurity while applying. Owing to the considerations of bioavailability and drug release efficiency, biodegradable and bio-absorbable materials may serve as the essential choice for medical applications including therapeutical used MNs[77]. In vitro degradation evaluation as well as in vivo experiments should be carried out to characterize the MNs' biodegradability. When it comes to describe the biocompatibility of MNs, it not only means the biomaterials would not elicit any adverse local or systemic reaction such as inflammation, edema and other pathological changes when applying, but also refers to the nontoxicity of degradation byproduct that would not cause detrimental side effects while accumulation, and it would be better to achieve sustained release capability with long-term anti-inflammatory effects[78, 79]. In vitro cell experiments are often performed, in which specific cells (depending on the tissues for application) are co-cultured with the MNs then assess the viability and proliferation. Overall evaluation of tissue pathology as well as systematical hematologic and biochemical analyses in vivo are also needed to ensure there's no side effect in response to the implantation of MNs device.

3.1.2. Self-locking for secure fixation

The basic consideration of efficient drug delivery to non-dermal tissues is smartly deciding how to

let the MNs be immobilized to various surface environment in case of falling off and cause injury. Inspired by the natural bio-MNs, structures of needle tips can be manufactured into various novel forms which benefit from the optimal geometry, and can possess excellent tissue fixation performance mainly due to the intelligent combination of microstructures and insertion modes[80]. By fabricating MNs with replicated angled tips, the patch could remain firmly adherent when the attached substrate moved and rotated or even under external forces. Zhang et al. designed a novel serration-like clamping MNs array based on ferrofluid-configured moldings[81]. It was demonstrated that the improved adhesive ability of the tilted MNs could be attributed to the increased grasping force caused by the centrally oriented structures of the serrated clamping array (Fig. 4a). Later, the team then applied the clamp structured MNs to another device for linear wound healing[82]. Another approach of constructing "array in array" needle tips may also increase MNs' tissue adhesion capability. Inspired by natural honeybee stingers that generate higher interlocking strengths at the cross-section area of contact point, a tip structure with an array of barbs localized in the second half of the MNs cone has been proposed[61]. Lu et al. proposed a bio-inspired self-interlocking MNs patches with backward-facing barbs[83]. Patch interlocking and adhesion in tissues was confirmed by optical coherence tomography, mechanical testes and in vivo experiments (Fig. 4b). Also, sufficient tissue adhesion ability can be realized through many other forms of microstructure surfaces. In Liu's work, a porcupine quill-like multilayer MNs patch with an adhesive hydrogel back patching was fabricated by a layer-by-layer stacking using mold technology[84]. The extra area generated at the junction of the two adjacent layers of the MNs ingeniously created barb-like structure， which contributed to the enhancement of MNs' adhesion after piercing (Fig. 4c). In addition, swellable MNs using certain materials which allow an expansion of the polymer network structure after tissue fluid diffuse into the MNs, may serve as a promising alternative to achieve mechanical interlocking with tissue (Fig. 4d)[85-87]. These prepared arrays mentioned above have great potential as exquisite drug release devices with ideal attachment capability, bring more possibilities for the biomedical application of MNs.

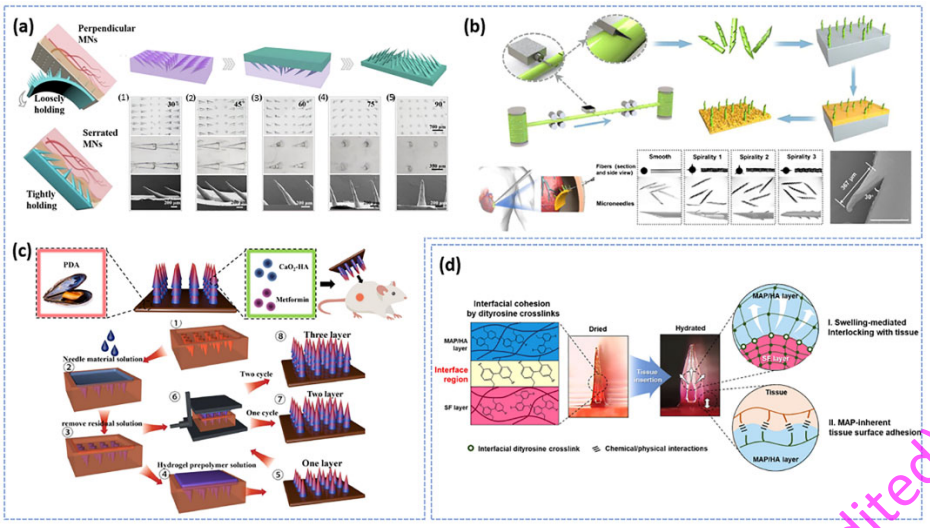

Fig 4. Schematic diagrams of MNs for achieving secure tissue fixation. (a) A clamping MNs array with center-facing tilted needles (Copyright © 2019 by Science China Press)[81]. (b) A MNs patch with backward-facing barbs which help achieve self-interlocking in heart tissue (Copyright © 2022 by Acta Materialia Inc) [83]. (c) A self-locking structure MNs patch fabricated via layer-by-layer stacking (Copyright © 2023 by Acta Materialia Inc)[84]. (d) Swellable hydrogel materials enhance MNs' adhesion (MAP: mussel adhesive protein) (Copyright © 2019 by Elsevier Ltd.) [87]. All the figures are cited with permission.

3.2. Strategies for achieving controlled release

3.2.1. Long-term drug release

Dissolving MNs have mainly been investigated for drug delivery due to their fully water-soluble designs. To achieve long-term release, MNs patches can be designed with multilayer-coated structures, which is remarkably functional due to the distinctive advantages such as various drug loaded possibility and regulation of drug-release behavior. By adjusting the coating composition film by film, the release curve of vaccine components can be flexibly adjusted. Uppu's group generated MNs with polymer multilayer thin films to co-deliver a model combination of three chemically distinct vaccine components[88]. The MNs facilitated sustained and rapid release of individual vaccine components from polymer multilayers by implanted thin films. By modulating layer-by-layer composition and architecture, component in the MNs could be independently controlled release from days up to two weeks. (Fig. 5a).

Detachable MNs are fabricated following the principle of making the backing layer separable from the needle tips, which contribute to the proper insertion or implantation of MNs loaded with drugs into the skin for long-term delivery. Various types of applications can be designed through the utilization of different backing layer separation mechanism. By capping drug-loaded dissolving needle tips onto a solid base without drug via multistep molding fabrication, rapidly separation can be implanted (Fig. 5b)[70]. Or achieve easy separation by using a certain intermediate to connect the tips and the backing that possess disparate mechanical properties. Jung et al. developed a separable micropillar integrated dissolving MN(SPDMN) which was capable to insert and can be detached immediately[89]. The micropillars were fabricated with a diameter of 500 μm and a curved edge, while the base diameter of the MNs was 300 μm, which created a 200 μm safety ring over each micropillar, ensuring that only DMNs penetrated the skin and could then be separated by applying a lateral force (Fig. 5c). Li et al. facilitated rapid separation of MNs after inserting into the skin by constructing an air bubble between the backing layer and MNs with the two-step micromolding method[90]. The air bubbles tolerated sufficient stress, allowed MNs to efficiently penetrate skin under vertical compression while being easy to detach under modest shear force, so that achieved MNs separating from the patch matrix and implanting into the skin. By introducing a porous interface between MNs and backing layer can achieve the same performance. Lee et al. fabricated a MNs patch with a porous interface between needle tips and a patch backing made of PVP/sucrose, which enabled complete separation within one second after skin insertion due to the fragile character of the lyophilized porous interface between tips and backing[91](Fig. 5d). Also, through constructing a synergistically separable system with a multi-layer structure, detachable MNs can be developed. Ning et.al proposed a dual-layer dressing MNs system (DDMNS) by adding a Mg/PVP layer, which would accelerate separation and promote drug release[92]. In the experiment, H_2 was generated by the reaction between Mg and the inflammatory microenvironment and formed air cavities in the Mg/PVP layer, which increased the reaction area, accelerated the dissolution of PVP, and then realized synergistic detachment of MNs and continuous drug release (Fig. 5e).

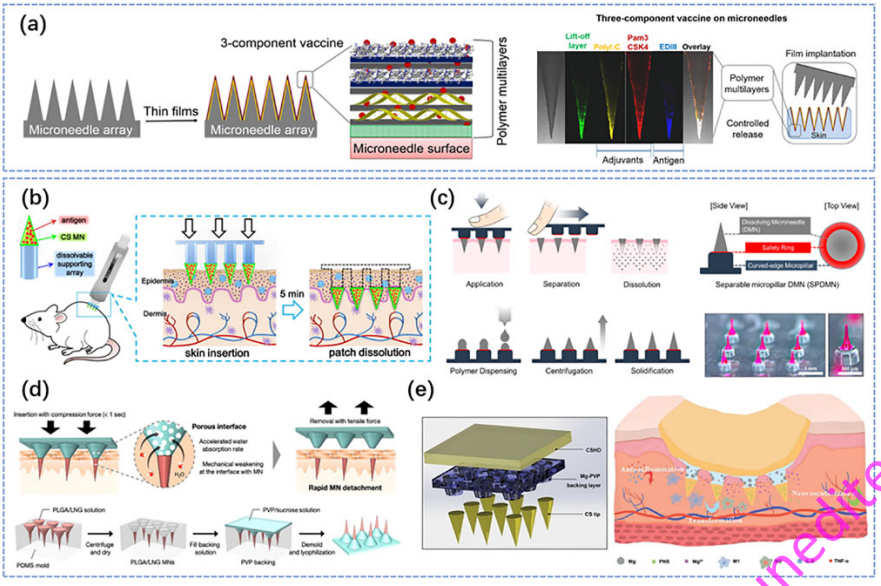

Fig 5. Schematic diagrams of MNs for achieving long-term drug delivery. (a) Multiple films of coating (Copyright © 2020, Elsevier B.V.)[88]. (b) Detachable MNs with supporting array (Copyright © 2017 by Acta Materialia Inc)[70]. (c) Separable MNs with micropillars (Copyright © 2020 by Jung, published by MDPI)[89]. (d) MNs with porous interface for rapid detachment after applying to tissue surface(Copyright © 2021 by Elsevier B.V.)[91]. (e) Detachable microneedle with multiple layers (Copyright © 2022 by Wiley VCH GmbH)[92]. All the figures are cited with permission.

3.2.2. Multistage drug release

By integrating well-characterized controlled release microspheres and microparticles made of hydrophobic biodegradable materials with dissolving MNs, multistage drug release can be achieved [93-96]. To increase vaccination safety and coverage, Mazzara et al. explored controlled release microparticles made of PLGA that could stably encapsulate various antigens via aqueous active self-healing encapsulation (ASE)[97]. The microparticles were then incorporated into rapid-dissolving MNs for vaccination. The study formed a new platform with multiple advantages over traditional vaccine delivery strategies, which could perform controlled antigen release via PLGA microparticles as well as maintaining antigen stability by avoiding antigen exposure to the protein-damaging stresses at the same time. This MNs patch demonstrated bi-phasic release in vitro with initial burst of soluble antigen followed by delayed release over approximately 2 months, and generated more robust immune responses than conventional vaccines in animal models (Fig. 6a).

Owing to the advantages of stable mechanical property and programmed drug delivery, the core-shell structure MNs have become more reliable and satisfied tools for efficient self-administration. Khanh et al. proposed a core-shell micro-structured MN, including a MN shell, a MN cap and a dried drug or vaccine core[98]. The MNs were generated through a 3D manufacturing process that assembled the three components together. The drug or vaccine core is encapsulated by the cap and base layer, which are made from PLGA. By tailoring the degradation of the PLGA shell, precisely controlled drug release could be achieved. In the clinical setting, multiple sets of MNs with different PLGA shells could be inserted into the skin of patients at once to achieve multiple burst release after different periods of time, obtaining an effect that is similar to multiple drug injections. Li et al. provided a more constant release system of levonorgestrel (LNG) for 6 months, also based on core-shell-cap structure, of which the release time was treble longer than MNs just having the monolithic core without a surrounding shell[99]. In this work, LNG was incorporated into a monolithic core made of a biodegradable PLGA which's degradation expected to be less than 6 months. The core was surrounded by a shell and cap layer made of PLA, which has a longer degradation expected to be more than 6 months to minimize initial burst release and provide a slower, more constant delivery of drug (Fig. 6b).

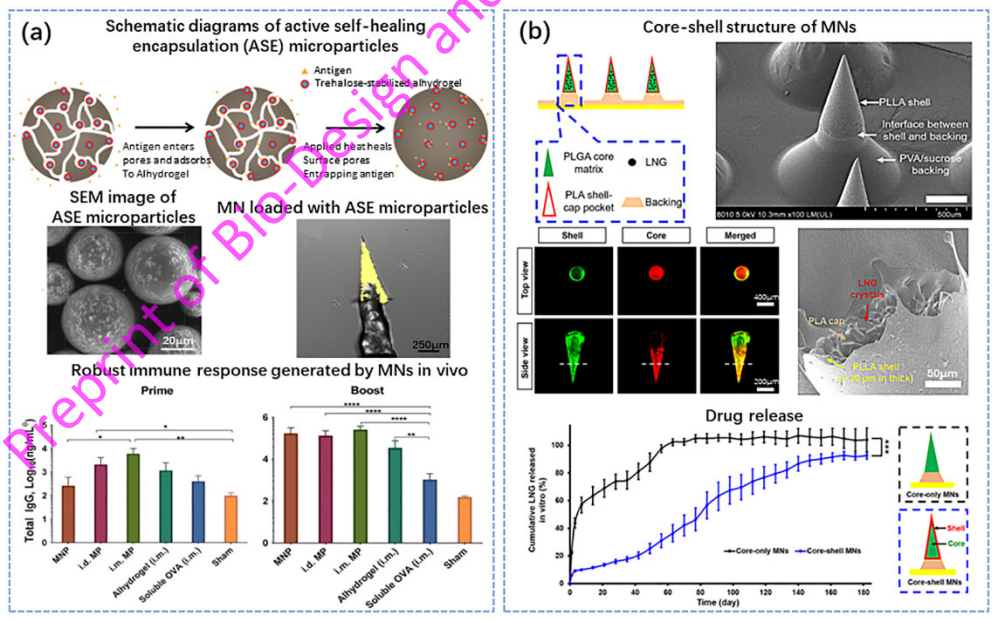

Fig 6. Schematic diagrams and prototypes of MNs for achieving multistage drug delivery. (a) Dissolving MNs loaded with PLGA microparticles containing antigens (MNP: microneedle patch, i.d.MP: intradermal injection microparticle, i.m.MP: intramuscular injection microparticle, OVA: ovalbumin) (Copyright © 2022 by Mazzara, published by Wiley Periodicals Inc.)[97]. (b) A core-shell

structured MNs patch for sustaining LNG release (Copyright © 2022 by Elsevier B.V.)[99]. All the figures are cited with permission.

3.2.3. Responsive drug release

Currently, stimuli-responsive MNs based on specific polymer materials that are capable of responding to changes in their surrounding environment have been introduced to achieve controlled and programmed drug release. Physiological signal like near infrared (NIR), internal stimuli including pH, redox potential, glucose and enzymes may be the trigger which can lead to MNs' responses including matrix degradation and matrix swell[100]. pH-responsive MNs are often made of polymers that possess hydrophilic and ionic functional groups in the polymer segments, and drugs can be released upon matrix's disassembly or deswelling associated with pH changes[101]. Low pH at the area of chronic wounds and inflammation site are most common stimulus for designing pH-sensitive drug delivery systems[102, 103]. For example, a MNs system loaded with micelle formed by the self-assembling of pH-responsive tri-block polymer (DMA-PEI-PLGA, DPP) and Ce6-coupled antimicrobial peptide sequence (AMP-Ce6, AC) was recently reported for the controlled release of antimicrobial drug in the skin[104]. The acidic environment protonated the PLGA block tertiary amine and made it hydrophobic to hydrophilic, which then caused the disintegration of micelle and the subsequent release of the DMA group presenting positive charge, thereby significantly improving the specific targeting ability of the antimicrobial peptide to bacteria (Fig. 7a). Also, because the microenvironment of most tumors has a pH that is lower than non-cancerous tissues, pH-responsive MNs may have significant practical implications in cancer therapy[105]. When exposed to the acidic tumor microenvironment, the pH-responsive polymer underwent charge conversion, the polymeric layers swelled and released the gene cargos, which is efficiently access to targeted delivery of antitumor therapeutic agents could be achieved (Fig. 7b)[106].

Closed-loop systems based on MNs have become a novel method for glucose-responsive insulin delivery, which eliminates the need for diabetes patients to voluntarily inject insulin. Glucose sensing function of these devices can be accomplished via several approaches, including glucose oxidase (GOx) catalyzed environmental changes[107], glucose-binding molecules and glucose-detecting compounds mediated molecular recognition[100]. GOx catalyzed induced pH decrease[108], O_2 consumption (hypoxia) and generation of H_2O_2[109, 110] are most frequently used as the triggers in the glucose-

responsive MNs (Fig. 7c,d). MNs based on some specific glucose-sensitive molecules have also been used in self-regulated insulin delivery. Yu et al. firstly introduced a phenylboronic acid (PBA)-based glucose-responsive MNs system for experimental treatment of diabetes[111]. When exposed to a hyperglycemic state, the formation of the glucose–PBA complexes leaded to the increase of negative charges, and weakened the electrostatic interaction between negatively charged insulin and polymers. That would induce the volume variation of the polymeric matrix and resulted in the quick release of insulin from the MNs. Once the blood glucose level returned to normal condition, the inhibited volume variation and the restore of electrostatic interaction would slow down the insulin release in case of hypoglycemia that might occur.

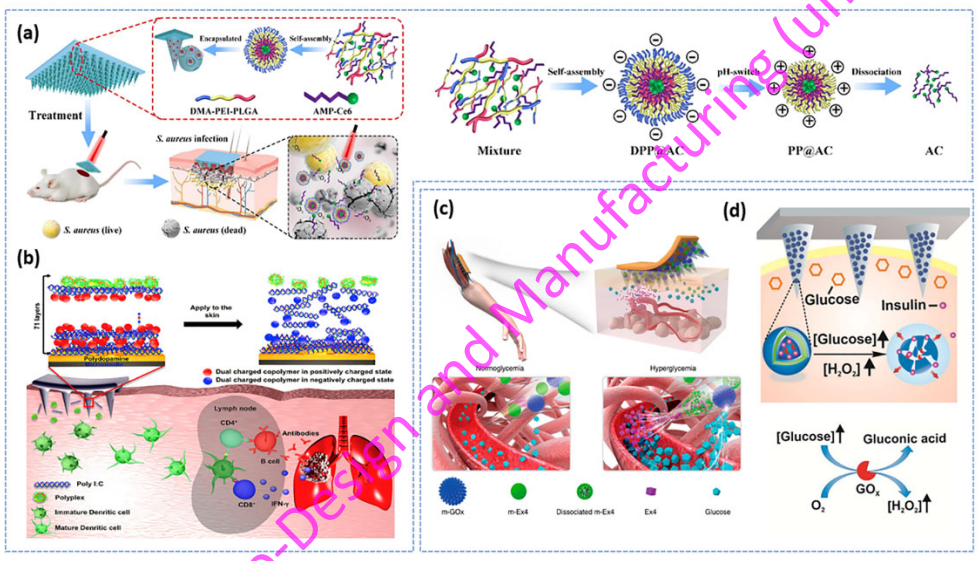

Fig 7. Schematic diagrams MNs for achieving internal stimuli-responsive drug delivery. (a) A pH-responsive MNs patch for wound healing (Copyright © 2023 by Elsevier B.V.)[104]. (b) A pH-responsive MNs patch for vaccine delivery of cancer therapy (Copyright © 2018 by Elsevier Ltd.)[106]. (c) A glucose-responsive MNs patch loaded with dual mineralized particles (Copyright © 2017 by Chen)[108]. (d) Glucose-responsive insulin delivery MNs generated by H_2O_2 sensitive GOx particles (Copyright © 2017 by American Chemical Society)[110].

4. Advanced applications for different tissues

Non-transdermal MNs can deliver drugs to a variety of tissues which own moist, dynamic tissue environments. Differ from flat, dry and easy-to-handle skin surface, these MNs require more consideration to surmount multiple barriers. Various organizational application can be classified

according to the properties of local environment, surface characteristics, organ motion and mechanical properties.

4.1. Cardiovascular system

Cardiovascular diseases (CVD) including myocardial infarction, stroke and peripheral vascular disease are the first leading cause of death in the world[112]. Currently, MNs have been reported to be feasible for the treatment of cardiovascular diseases. However, the cardiovascular system is a wet, dynamic and pressurized system, making it a challenging environment for the application of MNs.

Atherosclerosis is the is one of the high risk factors that may cause CVD[113]. Vascular bypass and insertion drug-eluting stents (DES) are the most common clinical practices for atherosclerosis treatment. However, some of the patients may suffer from neo intimal hyperplasia (IH) at the site of surgery after undergoing these therapies. Current researches on vascular drug delivery mainly aimed at delivering anti-proliferative drugs such as sirolimus or paclitaxel to investigate the prevention of IH[114-116]. Considering that the structure of arteries and veins are all composed of three layers: tunica adventitia, tunica media, tunica intima, perivascular drug delivery through adventitia and endovascular drug delivery through endothelium might be the most viable strategies.

4.1.1. Perivascular

Due to the elastic characteristics of blood vessels and repeated blood pressure changes, the rigid perivascular drug delivery device may cause abnormal proliferation of smooth muscle cells in the blood vessels and exacerbate the problem of secondary stenosis of blood vessels. Thus, devices with curved substrate which could exert their drug delivery effect through wrapping around the vascular were then proposed. Over the past decades, series of meshes, wraps, regels and cuffs have been applicated in perivascular drug delivery, proven safe and feasible[117]. By introducing MNs to these devices' flexible substrate, it may provide closer adhesion between wraps and vascular, resulting in the enhancement of the drug delivery efficiency. Choi et al. proposed a drug-loaded MNs cuff which successfully inserted through adventitia layer, and delivered fluorescent molecule RB as a model compound to tunica media[118]. The curved patch base is made of relatively slow degrading polymer, and the curvature was developed by post-annealed inside a cylindrical stainless tube at the temperature of 72 °C. Works of Lee et al. and Kim et al. further confirmed that the drug delivery efficiency to the

inner layers of vascular tissue increased evidently after installing MN structure onto the cuff surface, and the therapeutic effect was demonstrated by subsequent *in vivo* experiments[119, 120]. In 2017, Lee et al. proposed a biodegradable PLGA80/20 MNs array developed on a flexible woven surgical mesh via a transfer molding method[75]. Enhanced drug delivery efficiency, efficacy for IH reduction, and safety of MN mesh were proved through *ex vivo* and *in vivo* experiments, with suppressed side effects at the same time (Fig. 8a). Later in 2021, the team developed a highly flexible and porous silk fibroin MN-wrap which directly injected antiproliferative drug to the anastomosis sites while ensuring sufficient vascular exchanges[74]. The result of *in vivo* studies on New Zealand white rabbits confirmed that the silk MNs wrap showed superior pharmaceutical efficacy compared to drug loaded silk wrap without use of MNs, with enhanced perivascular drug delivery efficacy for IH reduction, improved vessel patency and the maintenance of healthy tunica media structures. The remarkable flexibility due to the structural characteristics of mesh substrate may allow the MN-based device to be used for complex shapes and various sizes of blood vessels, which shows promising prospect in perivascular drug delivery (Fig. 8b).

Since the MNs are applied to the outer surface of the blood vessel, invasive surgeries are unavoidable during the implantation. Surgical risk may be a major limiting factor for further research. Therefore, considering how to minimize surgical injuries and how to properly monitor the effects of MNs degradation and drug release in real time without repeated operations might become the key for future studies.

4.1.2. Endovascular

Current clinic trails such as DES and drug-eluting balloons (DEB) have been revolutionized the treatment of atherosclerosis in coronary and peripheral vasculature[121]. Various modifications to DEB aimed at improving the efficiency of endovascular drug delivery have been carried out in recent years. Lee's study developed a linear micropattern-based drug eluting balloon with 16 linear micropatterns on the surface which successfully increased the contact force between the drug coated surface and the lumen, thereby result in the enhancement of endovascular drug delivery efficiency[122]. Another way was to set up a micro-infusion system, combining a hollow needle with a balloon catheter[123]. Only when the catheter is opened, the needle extends out of the balloon and is used to inject drugs directly into the surrounding luminal tissue. The Bullfrog micro-infusion devices were correspondingly

designed and facilitated better drug distribution through the tissue. MN structures have also been introduced into DEB by molding MNs array onto the balloon surface to improve drug delivery efficiency. A microneedles DEB (MNDEB) was fabricated via a conformal transfer molding process[124]. During the *in vivo* animal experiment, MNDEB was deployed in the illiac arteries of an atherosclerotic rabbit model. Results showed that compared to conventional DEB, drug coated MNs onto balloon surface enhance the efficiency of endovascular drug delivery, while integrity of the vascular tissue was not impaired by MN insertion (Fig. 8c). Inspired by changeable thorny appearances and inflatable behaviors of globefish, Zhang et al. fabricated an intelligent hierarchical balloon catheters with concealed MNs for cardiovascular disorders remedy[125]. The microneedles balloon catheters (MNBCs) consisted of three coatings outside the bare balloon catheter: two BP-encapsulated gelatin layers and MNs in between. After implantation, the MNBCs expanded and fully contacted to the tunica intima, then the gelatin layers melted under NIR and left MNs in tissue. The bare balloon catheter was later recycled. Through intravascularly delivering rapamycin to abdominal aorta restenosis rat models, drug-loaded MNBCs achieved ideal endovascular drug delivery and disease curing effect, indicating that this application might be a practical novel approach for cardiovascular therapy (Fig. 8d).

When establishing subsequent surgical scheme of endovascular drug delivery MNs, current sophisticated methods of DEBs or intravascular stent implantation can be used for reference. The intervention path should be decided according to the lesion site, diameter, vascular flexibility and tortuosity of target artery, the structural characteristics of DEB-based MNs as well as the complexity of the operation. Future researches are ought to focus on conducting repeated *in vivo* experiments on large animals for the purpose of establishing systematic surgical implantation programs corresponding to specific lesion site. The gradual transition from animal studies to clinical trials as well as the evaluation of the therapeutic effects of endovascular MNs products on human are also urgently need to be addressed.

4.1.3. Cardiac tissue

When it comes to the treatment of myocardial infarction, it is generally believed that the necrosis cannot be regenerated. Stem cell therapy has been proved to be effective in heart regeneration. Intramyocardial injection allows stem or myoblast cells to be directly delivered to the infarct

boundaries, but may cause the squeeze of the drug solution due to the contraction of the myocardium, thus lead to the poor retention[126]. The MN patches which can be tightly attached to the myocardium surface and precisely convey corresponding therapeutic agent to target area, offering a potential solution to these problems. In 2018, Tang et al. firstly applied MNs in the treatment of myocardial infarction (MI) [127]. MN-integrated cardiac stromal cells secreting heart regeneration factors were loaded into the back of a PVA patch and diffused into the scar tissue. Enhancement of angiomyogenesis effect in a rat model and protection of cardiac function in a porcine model were observed in this study (Fig. 8e). Hu et al. developed a detachable MN patch which transported mesenchymal stromal cell-secreted factors-loaded poly(lactic-co-glycolic acid) nanoparticles into myocardium, promoted the proliferation of injured cardiomyocytes, reduced cardiomyocyte apoptosis as well as fibrosis, and restored myocardium volume during the cardiac remodeling process[128]. There are also many researches focusing on MN-mediated gene delivery for myocardial disease treatment. MNs associated with adeno-associated virus encoding vascular endothelial growth factor (VEGF) gene result in heart function improvement by enhancing VEGF expression, promoting functional angiogenesis, and activating the Akt signaling pathway[129]. In Lim's study, a Double-layered adhesive MN delivering biofunctional peptide (BFP) fused bioengineered mussel adhesive protein was developed. BFP from four different sources was genetically fused to the C-terminus of bioengineered foot protein type 1 (fp-1) composed of 12 repeats of decapeptide (AKPSYPPTYK)[130]. Yuan's study proposed a biocompatible MN patch based on gelatin is fabricated to load exosomes containing microRNA-29b (miR-29b) mimics with antifibrotic activity(Fig. 8f)[131]. All the therapies showed distinct effect and provided resultful options for MI treatment.

Indeed, MNs patches have shown its advantages on cardiac tissue regeneration after MI. However, further improvements are still needed. Because the heart is an internal organ, thoracotomy is inevitable for the MNs implantation. During the progress of patch placement, a hand vacuum device is still required. Minimally invasive surgery could be a possible alternative to solve the problems above, which suggests MNs to have a tiny size or a shape memory property accordingly. Further enhancements for advanced treatments may focus on apparatus applied for minimally invasive surgery.

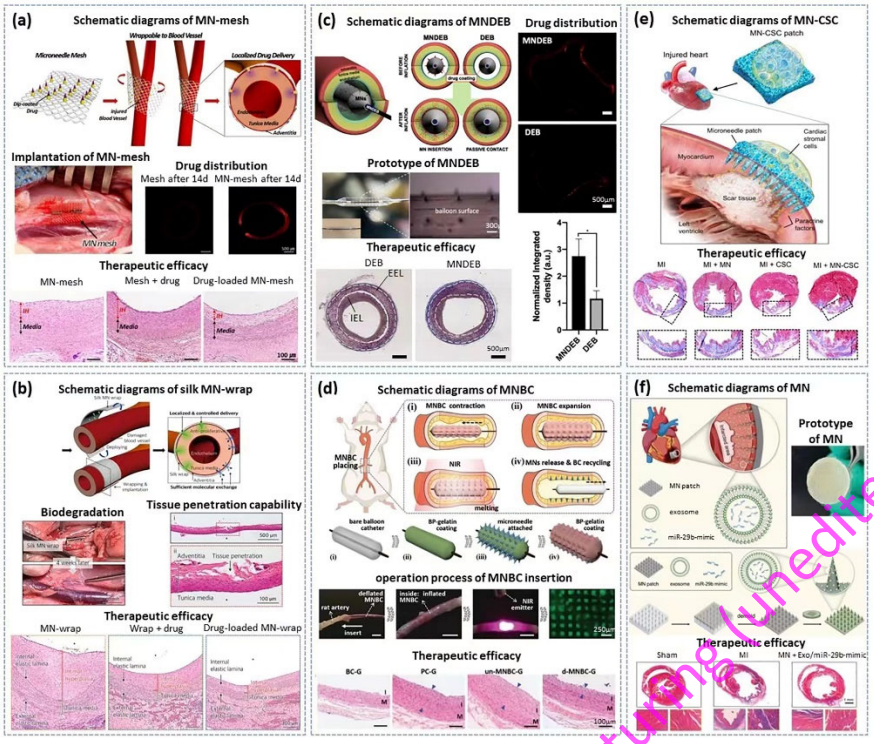

Fig 8. MN-based applications for cardiovascular drug delivery. (a) Biodegradable MNs array developed on a flexible woven surgical mesh for perivascular drug delivery (Copyright © 2017 by Elsevier B.V.)[75]. (b) A highly flexible and porous silk fibroin MN wrap for perivascular drug delivery (Copyright © 2021 by Elsevier B.V.)[74]. (c) An endovascular microneedles DEB (MNDEB) for endovascular drug delivery (EEL: external elastic layer, IEL: internal elastic layer) (Copyright © 2020 by Elsevier B.V.)[124]. (d) NIR triggered intelligent microneedles balloon catheters (MNBCs) for endovascular drug delivery (I: intima, M: media)(Copyright © 2022 by Zhang) [125]. (e) MNs patch loaded with cardiac stromal cells (MN-CSCs) for the treatment of MI (Copyright © 2018 by Tang)[127]. (f) MNs loaded with exosomes containing microRNA-29b (miR-29b) for cardiac tissue regeneration (Copyright © 2023 by Wiley VCH GmbH)[131]. All the figures are cited with permission.

4.2. Ocular tissue

Because of the presence of ocular barriers and clearance mechanisms, it is challenging to administer drugs safely and effectively to the eye. Traditional eye drops, gels and ointments are most often used in clinic. Unfortunately, these ways still face with the problems of low drug permeation, low bioavailability, and fast clearance caused by physiological processes such as blinking and nasolacrimal drainage. Few static barriers such as tear film, mucin layer, cornea also prevent exogenous substances from permeating[132]. The posterior segment of the eye contains sclera, choroid, Bruch's membrane,

and blood-retinal barrier. Conventional posterior drug delivery is achieved by invasive injection, which is directly injected through sclera and into the vitreous humor. In this case, severe side effects including tissue damage, eyeball perforation, optic nerve injury and intraocular infections may be caused[133]. Constant rotations of the eyeball and movements of eyelids also decreased the treatment efficiency. MN-based system, as a non-invasive drug delivery form, have been remarkably developed in ophthalmic treatment during recent years. When applying to ocular drug delivery, the main aim is to improve the bioavailability by increasing the diffusion across cornea, conjunctiva and sclera. Previous reviews have listed a series of hollow, coated and dissolving polymer MNs have been proved to achieve high permeation of the drug[134, 135]. Herein, we mainly summarize the relatively new and reliable intraocular drug delivery MN products that have been validated through *ex vivo* or *in vivo* studies.

4.2.1. Anterior segment

Drug delivery to anterior segment of the eye is actualized by intracorneal ways. The thin, unsupported structure of the cornea makes it difficult for MNs puncture and retention. In order to better fit the spherical structure of the eyeball and insert the needle tips into the cornea, some MN patches have referred to semi sphere design features of contact lens. Datta et al. prepared a polyvinyl pyrrolidone MNs patch with 3.08 cm circumference convex curvature, 3.85 mm sagittal height and array of 25 conical MNs by micromolding technique[136]. MNs were found to completely dissolve in the cornea within 60 s of application. The *ex vivo* corneal permeation studies using porcine eye globe showed a disposition distribution of 45.5, 29.1, 8.3, 5.2, 3.0 and 0.2% of loaded drug within the cornea, aqueous humor, lens, vitreous humor, sclera and choroid-retinal complex respectively. Roy's study also reported a MNs corneal patch with a concave shaped design to mimic the commercially available contact lens, and achieved firm placement on the porcine and rabbit corneas(Fig. 9a)[137]. When it comes to the depth of penetration, clinic settings suggested that the length of MNs should be matched within the maximum injection depth of corneal epithelium correspondingly, which ranges from 43 to 63 μm[135]. However, in Than's study, the team fabricated an eye patch bound to an array of detachable MNs with a length of 600 μm and an insertion depth of approximately 150 μm. The MNs did not cause significant inflammation or angiogenesis in animal tests of mouse cornea[138].

Considering that long presence of the patches on eye surface may lead to the potential risk of hypoxia, drug delivery through single micron scaled needle has been suggested. Better performance of single

MN insertion can be realized by combining it with an injection assisting applicator[72]. In Lee's research, a biodegradable MN tip and the supporting base were assembled to form a hybrid detachable MN-pen (d-MNP) by pressure-assisted transfer molding[73]. When applied to the cornea, the spring-loaded pen platform injected MNs instantaneously by a spring-generated impact, with an optimum dwell time as 10 s and force of 13.74 N. The drug-loaded detachable tip was left within the corneal tissue, and allowed sustained drug release for more than 9 days. The antimicrobial agent-containing tip was delivered to the mouse cornea, though the amount of drug containing was only 2.6 ng, it was large enough to show efficacy of reducing the progression of keratitis (Fig. 9b).

limitations of current researches mainly lie in the lack of uniform regulations on puncture depth. Therefore, more *in vivo* studies are still needed to discuss the requirements of length and insertion depth of ocular MNs. Besides, whether the results of animal experiments on corneal penetration can be applied to human might still need further consideration, confirmatory clinic tests should be carried out if possible.

4.2.2. Posterior segment

For posterior segment diseases which commonly require drugs to reach the macular or peripheral retina, intrascleral administration allows drugs to be closer to the target site, providing efficient drug concentrations for the treatment. Roy et al. demonstrated the effectiveness of a MNs scleral patch in delivering the triamcinolone acetonide as a model molecule to the posterior segment of the eye[137]. Wu et.al proposed to develop a nanoparticle (NP)-loaded bilayer dissolving MNs array which was determined to be biocompatible with retinal cells (ARPE-19)[139]. Ex vivo scleral distribution studies confirmed that NP-loaded MNs arrays were anticipated to exhibit a longer lag-time in the sclera and sustain the release of encapsulated drugs. The group then fabricated a triamcinolone acetonide nanosuspensions loaded microneedles which was demonstrated biocompatible with ocular tissues using the hen's egg chorioallantoic membrane assay and cytotoxicity test[140]. The researches of novel hybrid system mentioned above enable the delivery of drugs to the posterior segment of the eye, though both need further exploring, they indeed provided novel ideas to alleviate relevant diseases in a therapeutically effective and minimally invasive manner.

Beside MNs array, single tip micron needle can also be used for intrascleral drug delivery. Similar

to the previous intracorneal strategies, MN-pens can be adopted to deliver drugs to the posterior segment. Park et al. developed a MN-pen by combining an MNs with a customized applicator consisting of an end tip, stopper, trigger, spring and slot[141]. Through *ex vivo* studies, it was confirmed that the insertion depths of MNs could be finely controlled by insertion speeds. RB drug-loaded MNs was then applied to the beagle eyes *in vivo*. Results showed that strong fluorescent signal was evident along the inner surface of the sclera and the choroid from beneath the insertion site to the adjacent area, indicating the fast diffusion of the model drug to the posterior segment of the eye (Fig. 9c). Lee et al. modified the previously described d-MNP by adding a fast dissolving layer consisted of a porous blend of PVA/PVP fabricated via freeze drying technique, located between the drug-loaded tip and the base [142]. After optimization, the rapidly detachable microneedles pen enabled almost immediate release of the tip upon contact with porcine sclera and embedded it at the appropriate depth (Fig. 9d). In order to avoid needle retraction, Lee et al. developed a self-plugging microneedle (SPM) to perform intraocular drug delivery and to seal the scleral puncture simultaneously[143]. Once the whole SPM was completely inserted into the vitreous body, the scleral plugging component at the bottom of the needle tip would contact the eyeball and swell to plug the scleral hole (Fig. 9e).

Drugs can also be delivered into the space between sclera and choroid through MN insertion. A series of hollowed MNs were shown to deliver sulforhodamine B as well as nanoparticle and microparticle suspensions into the suprachoroidal space of rabbit, pig, and human eyes[144]. From then on, suprachoroidal delivery has become another choice for delivering drugs to the back of the eye, and has been evaluated in animal models of posterior segment diseases and has been tested in clinical trials[134, 145]. In this method, MN can serve as a tool to first target ocular drug delivery within the eye, and by combining it to other therapies such as iontophoresis, precisely controlled drug delivery especially toward the posterior pole can be easily implemented[146].

For posterior ocular drug delivery through MN-pens, the effectiveness of drug penetration has been demonstrated mainly through *in vitro* and *ex vivo* drug delivery experiments, further in vivo studies are still required. On account of the inevitably puncture through vitreous body during MN implantation, invasiveness of the operation may become a major limitation for further application. Thus, how to determine the optimal insertion route of MN into the target area of sclera with minimal invasiveness and injuries may serve as the emphasis of further researches.

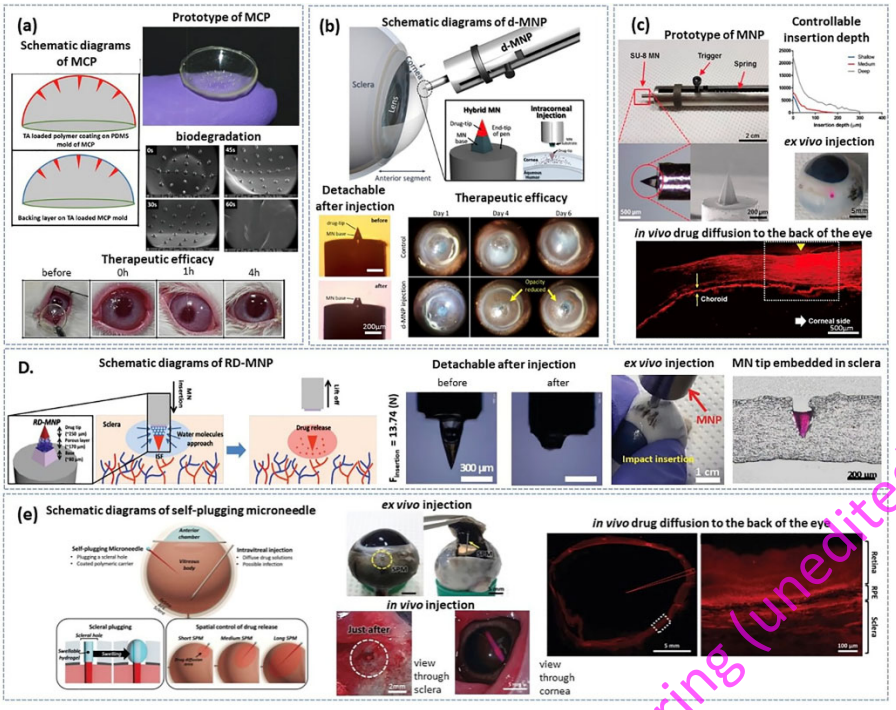

Fig 9. MNs-based applications for ocular drug delivery. (a) A concave-shaped microneedle corneal patch (MCP) inspired by the structure of lens (Copyright © 2021 by Elsevier B.V.)[137]. (b) A hybrid detachable microneedles pen (d-MNP) with a biodegradable MN tip for corneal drug delivery (Copyright © 2018 by Acta Materialia Inc) [73]. (c) A detachable microneedle pen (MNP) with controllable insertion depths for posterior segment drug delivery (Copyright © 2018 by Elsevier B.V.)[141]. (d) A rapidly detachable microneedle pen (RD-MNP) with an additional fast dissolving layer between drug-loaded tip and the base (Copyright © 2021 by Wiley VCH Verlag GmbH & Co.KGaA Weinheim)[142]. (e) A self-plugging MN (Copyright © 2022 by Wiley VCH GmbH) [143]. All the figures are cited with permission.

4.3. GI tract

Oral administration of biopharmaceuticals including peptide and protein drugs can avoid the pain and risk of infection caused by traditional injections. However, due to the barriers of the GI tract such as acidic pH environment and the existence of multiple proteases, therapeutic proteins may lose their specific structures and functions, leading to poor permeation efficacy and low bioavailability[147, 148]. Targeted drug delivery systems with specific shielding structures which can deliver the biomolecule precisely to specified sites without any degradation may serve as a potential remedy to problems above. Various trials have been extensively explored, such as pH-dependent release[149], microrobot

system[150], micromotors[151] and capsule endoscopy[152, 153]. MNs can pierce the alimentary canal wall without causing gastric perforation, which offer promise to the treatment of gastric diseases. However, the peristalsis of gastrointestine and the flow of chyme makes it difficult for the MNs to locate and penetrate the GI mucosa. Therefore, considering how to orient the supplementary component of MNs so that the needles can maintain contact with the tissue surface is the priority principle for designing the drug delivery devices.

Giovanni et al. proposed a hollow MNs roller capsuled in a pH-responsive coating which loaded insulin can be transported to the GI tract [154]. The roller structure guaranteed that the tips of MNs were always vertical to the GI tract. When the capsule reached the target area, the pH-responsive coating dissolved to expose MNs, and the loaded drug could be delivered to the GI tract (Fig. 10a). However, the study still had the problems of low MNs fall off rate and failed to achieve effective targeted drug delivery. Chen's publishment introduced a dynamic omnidirectional adhesive microneedle system (DOAMS) capable of prolonged gastric mucosa fixation, of which was inspired by horny-headed intestinal worm[155]. The smart capsule could either avoid premature exposure of the drug to the harsh pH environment, or act as a self-triggered device to deliver a tablet to the stomach. It ejected the tablets containing biphasic core-shell structured MNs into the gastric cavity, therefore induced appropriate contact with tissue surface. The DOAMS performed a remarkable adhesion onto the tissue, which profit from both the mechanically interlocking hooks and the material dependent adhesion of hydrogel MNs (Fig. 10b). Abramson et al. engineered a luminal unfolding microneedle injector (LUMI) ingested in waterproof enteric capsules which served as a platform to orally deliver therapeutic doses of macromolecule drugs[156]. When reaching the small intestine, a compressed spring would propel the LUMI out of the capsule regardless of orientation. The LUMI was consisted of three degradable arms, each of them was attached with MNs, which created multiple contact points with the tube-like geometry of the small intestine tissue. The rapid unfolding of the support arm provides power for the piercing of the MNs. In the same year, the research team designed an ingestible self-orienting millimeter-scale applicator (SOMA) out of the inspiration from leopard tortoise, which was able to autonomously adjust its positions to engage with GI tissue[157]. Once the SOMA was on the right position, the pH triggered spring would be freed, pushing the single MN into the GI mucosa (Fig. 10c). The capsule equipped with drug-loaded MNs can also be driven to the desired target lesions by the

magnetic force. In 2020, a multilayer MNs patch combined with a neodymium permanent magnet capsule was developed[158]. The motion of the magnetically driven capsule was divided into locomotion state and delivery state according to the relative position between the permanent magnet and the capsule body. By adjusting between two motions under an external magnetic field, the capsule successfully implemented an *ex vivo* localized GI drug delivery.

At present, most orientation tests and drug delivery experiments of the capsuled MNs were still carried out *ex vivo*, there is a lack of *in vivo* animal studies to explore the treatment effect of current devices. Here in, breakthroughs in follow-up studies should be focus on evaluating *in vivo* MNs insertion performance, drug release efficiency and biosafety of capsule systems. It is requisite to put forward more assessments of whether the devices can be taken orally and whether the non-degradable shell of which can be safely discharged from the GI tract.

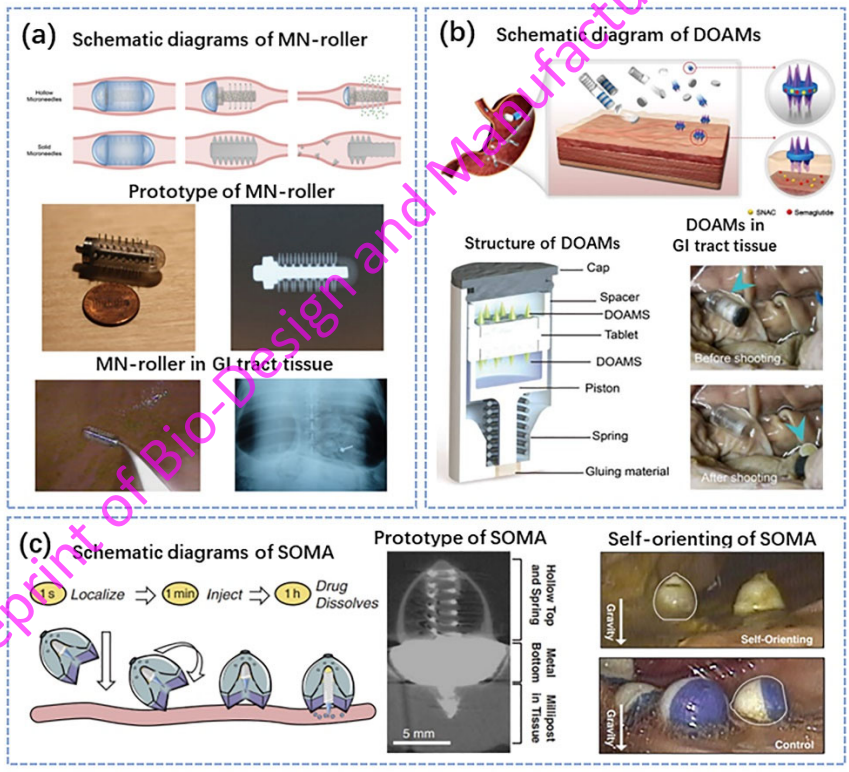

Fig 10. MNs-based applications for GI-tract drug delivery. (a) A hollow MNs roller capsule for drug delivery under harsh pH environment (Copyright © 2014, Wiley Periodicals Inc. and the American Pharmacist Association)[154]. (b) A dynamic omnidirectional adhesive microneedle system (DOAMS) (Copyright © 2022 by Chen)[155]. (c) A self-orienting millimeter-scale applicator (SOMA) (Copyright © 2022 by Abramson)[157]. All the figures are cited with permission.

4.4. Oral cavity

The oral mucosa is considered as a minimally invasive and immunologically rich site which may become an alternative strategy for drug delivery in topical formulations. Transmucosal route has series of advantages such as rapid action, reduced first-pass metabolism, and less drug degradation. MNs enable precise control over drug and vaccine delivery properties including penetration depth, uniformity, and dosing, making it a potential choice for transmucosal drug delivery in oral cavity[159, 160]. The first application on oral mucosal drug delivery through MNs was reported in 2014. Researchers used single row coated MNs to successfully transport drugs to either the inner lip or the dorsal tongue of rabbits. Both experiments showed ideal penetration ability and delivery efficiency with no significant difference, which confirmed that microneedles can be considered as an ideal tool to achieve drug and vaccine delivery through oral mucosa[161].

The oral cavity has a moist environment with saliva flux, which constantly flushes the oral mucosa, dilutes the drug, and can reduce the contact of topical preparations and their bioavailability. This is a phenomenon called "saliva flushing"[162]. Serpe et al. carried out a simulated saliva flow experiment proved that saliva will wash away part of the drug deposited in the oral mucosal tissue of the coated MNs and resulted in a decrease in the efficiency of administration[163]. For the treatment of dental diseases like periodontitis, biodegradable MN patches that can be inserted into the pocket between the tooth and gingival tissue achieve a painless and suture-free placement regardless of saliva secretion[164]. Despite selecting special insertion sites, drug concentration and multiple layers design can also cut down the impact of saliva flushing. Caffarel-Salvador et al. prepared a MNs patch with a large amount of drug-loaded buccal macromolecule delivery by directly embedding solid active pharmaceutical ingredients in sorbitol and PVP[165]. Preferentially settles of drug into the MN tips was realized through centrifuging the mold at 4000rpm for 10min during the molding process, which achieved clinically relevant highly concentrated MNs capable of drug delivery. The deposition of active pharmaceutical ingredients ensures that the medicine can resist the poor therapeutic effect caused by saliva flushing (Fig. 11a). Aiming at achieving efficient and precise drug release, Li et al. prepared a composite microneedles through a two-step casting process to make sure that the drug was concentrated in the tips[166]. By additionally attaching a mucoadhesive PVA layer and a waterproof ethyl cellulose backing, the MNs patch could remain in contact with the lesion for a quite time without

being eroded by saliva. Cheng et.al fabricated a composite MNs patch with double layers to effectively deliver triamcinolone to the lesion site for the treatment of oral submucous fibrosis[167]. The mucoadhesive top-layer was made of an adhesive pyrogallol-rich tannic acid/silk fibroin gel film to achieve wet adhesion, and a non-adhesive silk fibroin handling film to prevent adhesion to surrounding tissues, together exhibited an enhanced wet adhesion performance. The experiment also measured the interfacial adhesion force between two layers (94.54 kPa), indicating the MNs patch would not delaminate during usage (Fig. 11b). Additionally, there are abundant nerves in the oral cavity, which might cause intense pain during injection, resulting in low administration compliance and efficiency [168]. Therefore, strategies to minimize the pain of MNs is crucial. Through clinical trials, Caffarel's study has explored the relationship between pain and the choice of administration site when MNs are used for oral mucosa drug delivery. The results revealed that the palates and cheeks have the lowest pain and is most suitable for MNs administration, meanwhile the sublingual might be the most painful (Fig. 11a)[165]. Further large-scale investigations in clinic are imperative to determine the optimal course of treatment.

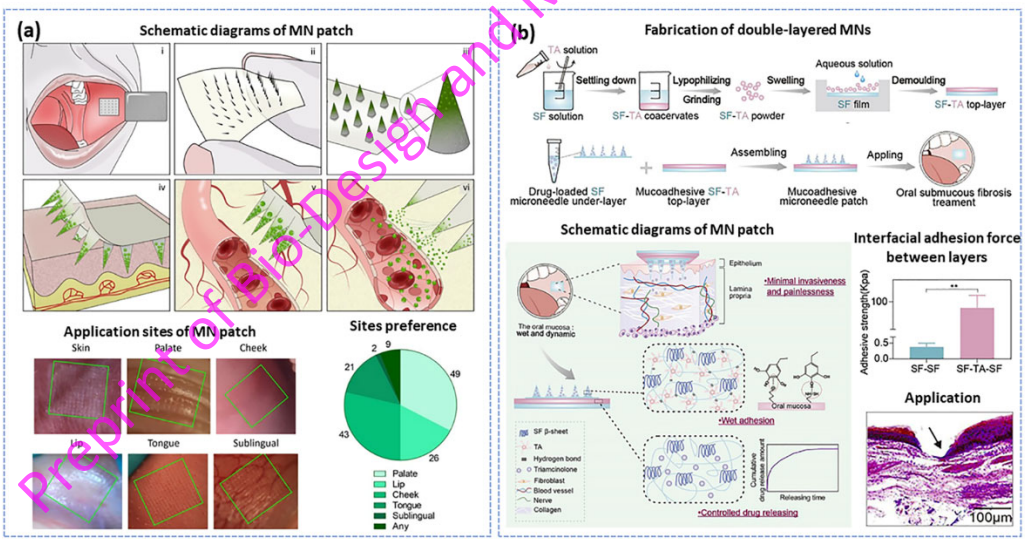

Fig 11. MNs applications for oral mucosa drug delivery. (a) A MNs patch fabricated by two-step casting, with the drug deposited on the tips (Copyright © 2021 by Caffarel-Salvador)[165]. (b) A double-layered MNs patch with enhanced wet adhesion performance (Copyright © 2023 Cheng)[167]. All the figures are cited with permission.

4.5. Applications for other tissues

4.5.1. Central nervous system

In addition to the applications mentioned above, MNs have been exploited for central nervous system including spinal cord and brain. Han et al. proposed a controlled 3D-exohydrogel hybrid MNs array to deliver three-dimensional cultured exosomes derived from mesenchymal stem cells and exhibited great potentials in spinal cord injury therapy (Fig. 12a)[169]. Although MNs effectively regulated the immune response, scar formation and promoted the spinal cord regeneration, the therapy was quite risky. Implantation might require complicated and potentially dangerous surgical procedures involving the opening of the spine, any carelessness may cause severe secondary trauma like paralysis.

When it comes to brain drug delivery, the primary difficulty was to overcome the obstacle of the blood-brain barrier (BBB). Currently, methods for brain drug transportation are mainly focusing on the nose-to-brain pathway, which brings medicines directly and noninvasively into the brain bypassing the BBB[170]. Considering that MNs can overcome the limitations of systemic delivery and achieve targeted transfection, it has become a promising candidate for brain drug delivery in recent years. A heterogenous silk fibroin microneedles (SMNs) patch designed by Wang et al. was reported for circumventing the BBB and releasing multiple drugs directly to the tumor site for drug combination treatment of Glioblastoma[171]. The biocompatible and biodegradable SMNs patch could be triggered by NIR remotely to induce rapid drug delivery at a designated stage after implantation, then dissolved slowly over time, allowing the sustained release of multiple drugs at different doses (Fig. 12b). Liu et al. presented a GelMA MN-based platform for the treatment of ischemic stroke and repairment of other neurologically diseased tissues[172]. The MNs sustained and controlled the local delivery of an adeno-associated virus that expressing human VEGF, and achieved homogenous distribution and high transfection efficiency of the load in ischemic brains. Though invasive, these strategies can be applied to other neurological disorders, such as traumatic brain injury or cerebral hemorrhage.

Given the unavoidable requirement of craniotomy during MNs patch placement, future clinical translation of these MNs products may encounter substantial challenges due to the associated high surgical risk. Solutions for achieve long-term MNs implantation into brain tissue without causing infection as well as other side effects are worthy of further consideration. In comparison to the existing non-invasive nose-to-brain pathway of drug delivery, further explorations to optimize drug release efficiency of MNs and enhance the advantages of long-term drug permeation during MNs application

to counteract its invasiveness may represent an urgent concern which demand more attention.

4.5.2. Reproductive system

In the past years, several works have used MNs for uterine regeneration and intrauterine adhesions (IUAs) therapy. Combing stem-cell-based therapy with MNs tool, Shi et al. developed a MNs patch for in situ intrauterine repair[173]. The flexible MNs are consisted of lactoferrin, which conferred high bioactivity, biocompatibility and antibacterial activity. An array of microwells on MNs enabled the loaded human endometrium-derived adventitial cells (En-ADVs) to form 3D cell spheroids, which performed higher potential for cell proliferation, differentiation, and migration than dissociated cells. The MNs patch was designed to better fit the intrauterine surface and achieve steady settlement in uterine tissue according to its shape. The MN/En-ADV resulted in swell-defined myometrial regeneration, angiogenesis, and an increase of endometrial receptivity in the experiment with an Asherman's syndrome rat model (Fig. 12c). Zhang et al. proposed a basic fibroblast growth factor (b-FGF) encapsulated novel MNs patch with arrowhead structures and anisotropic surface adhesion for the treatment of IUAs[174]. The bioactive N-acryloyl-glycinamide (NAGA) and adhesive PEGMA base materials let the MNs to have anisotropic surface adhesion to adjust to the irregular morphology of the uterus. Manufactured through a multistep micromolding method, the arrowhead structures allowed the MNs to tightly fix on endometrium. Results of *in vivo* studies demonstrated that these biocompatible MNs displayed effective inhibition of the tissue adhesion and showed better tissue regeneration. When discussing the insertion route of MNs aimed at the treatment of intrauterine lesion, the delivery of patches via the vagina can be taken into consideration, or it may be integrated with current gynecological laparoscopic operation.

Besides uterus, vaginal cavity is a suitable for inoculation of mucosal vaccines to prevent sexually transmitted pathogens, has been considered as a newly found a site for MNs drug delivery. Wang et al. developed a dissolving MNs array made of sucrose, PVP, and CMC for stably-loaded proteinbased vaccine agents[175]. Two types of multifunctional lipid liposomes (SLL and MLL) both loaded with a model antigen and NH_4HCO_3 were fabricated together into the needles to forming the proSLL/MLL-constituted MNs array (proSMMA). As a vaginal mucosal vaccine, administration of proSMMAs successfully induced the establishment of humoral as well as cellular immunity in treated mice (Fig. 12d). Since intravaginal drug delivery has become a novel vaccine delivery method with promising

application prospects, there is scope for investigations of combining various vaccines delivery with MNs. However, current research on vaginal drug delivery using MN technology remains constrained, with the potential limitation lie in the moist and curved feature of vaginal wall. To address this challenge, MNs can be designed with bendable, adherable configuration, resembling endovascular drug delivery systems, while a supporting scaffold can be utilized to facilitate MNs implantation.

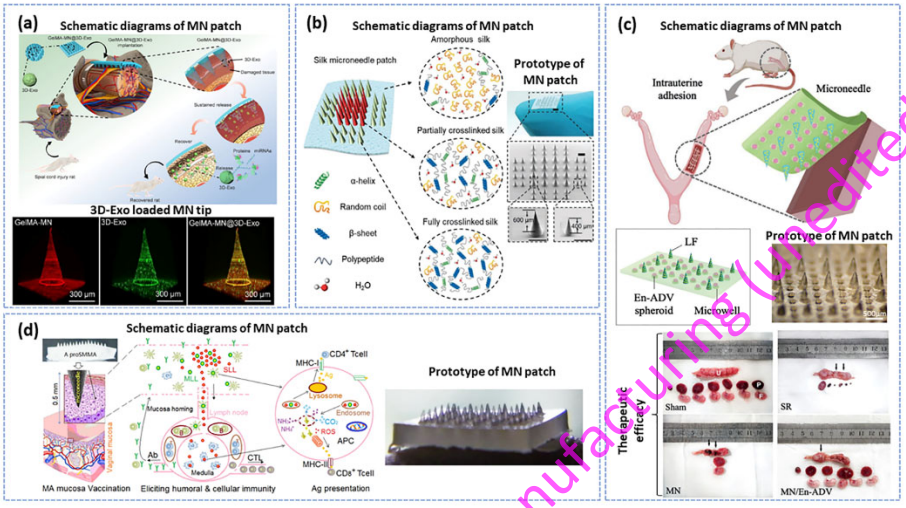

Fig 12. MNs applications for drug delivery to other tissues. (a) A GelMA MNs patch loaded with 3D-exosomes (3D-Exo) derived from mesenchymal stem cells for the treatment of spinal cord injury(Copyright © 2022 by America Chemical Society)[169]. (b) A silk fibroin biodegradable MNs patch which could achieve controlled multiple drug release for brain hemostasis and treatment of glioblastoma(Copyright © 2021 by Wiley VCH GmbH)[171]. (c) A patch for the treatment of intrauterine adhesions, on which MNs loaded with lactoferrin (LF) and microwells for endometrium-derived adventitial cells (En-ADV) culturing are arranged alternately (U: uterus, P: placenta, F: fetus) (Copyright © 2021 by Wiley VCH GmbH)[173]. (d) A multifunctional liposome-loaded MNs patch for virginal vaccine delivery (Copyright © 2017 by Elsevier B.V.)[175]. All the figures are cited with permission.

Table 1. MNs applications for different tissues.

Tissues	Types	Materials	Drugs	Specific considerations	Fabrication methods	Cites
Tunica adventitia	Dissolving	PLGA50/50 (tips) PLGA90/10 (base and cuff)	Rhodamine B (RB)	Cuff shape formed by annealing in a cylinder mold enables better tissue adhesion, fast degradation of MN allows effective drug delivery	Thermal drawing	[118]
	Dissolving, drug coated	PLGA90/10	Paclitaxel	Curving shape formed by annealing in a cylinder mold enables better adhesion to the target region, drug volume is controlled by the dipping depth during dip coating progress	Thermal drawing	[119]
	Dissolving, drug coated	PLGA90/10	Paclitaxel, sirolimus, and sunitinib	Cuff shape formed by annealing in a cylinder mold enables targeted tissue adhesion, dip coating of drug allows sustained drug delivery	Thermal drawing	[120]
	Dissolving, drug coated	PLGA80/20 (MNs) PLGA90/10 (mesh)	Sirolimus	Flexible mesh base enables MNs to wrap around vessels to achieve better tissue adhesion	Transfer-molding	[75]

	Dissolving	Silk	Sirolimus	Flexible and porous wrap base enables better tissue adhesion of MNs and shows ideal biocompatibility under long-term wrapping, degradation of MNs allows sustained drug delivery	Transfer-molding	[74]
Tunica intima	Hollow	Stainless steel (35-gauge)	Dexamethasone	The device has been approved by Food and Drug Administration (FDA) for clinical use		[123]
	Drug coated	208CTH-F, DYMAX (a UV-curable adhesive)	Paclitaxel	Combining MNs with drug eluting balloons (DEB) enables better tissue adhesion and achieves efficient drug delivery	Transfer-molding	[124]
	Hydrogel	NAGA (MNs) Gelatin with BP (layer)	Sirolimus	Combining MNs with balloon catheter enables better tissue adhesion, NIR-triggered MNs exposure allows controllable and targeted drug delivery	Transfer-molding	[125]
Myocardium	Dissolving	PVA	Cardiac stem cells (CSCs)	Porous structure allows the permeation of CSCs through the MNs, slow	Micromolding	[127]

				dissolution of MNs provides sustained CSCs release		
	Hydrogel	Crosslinked ELP (MN tips) Non-crosslinked HA (MN base)	Mesenchymal stromal cell-secreted factors (MSCF)-loaded PLGA nanoparticles	Detachment of MNs after insertion allows close tissue insertion and sustained drug delivery	Multi-step casting	[128]
	Hydrogel	PVA	Adeno-associated virus encoding vascular endothelial growth factor gene (AAV-VEGF)	Swellable MNs enable better tissue adhesion and achieve burst-release of loaded therapeutic agents into precise regions	Micromolding	[129]
	Hydrogel	SH (non-swellable tips) HA (swellable root)	Bio-functional peptide fused bioengineered mussel adhesive protein (MAP-BFP)	Swellable hydrogel films coated on MNs enable better tissue adhesion and effective drug delivery	Multi-step casting	[130]
	Dissolving	Gelatin	Exosomes containing microRNA-29b	Exosomes are loaded via soaking method, fast degradation of MNs allows	Micromolding	[131]

				effective drug delivery		
Cornea	Dissolving	PVP-K90 (MNs) PVP-K90 /PVA/PEG-400 (back layer)	Cyclosporine A (CsA)	Semi sphere feature enables better cornea adhesion	Micromolding	[136]
	Drug coated	SU-8	Sunitinib malate	Microneedle pen with single MN tip and a spring-loaded MN applicator enables impact insertion, dip coating of drug allows effective drug delivery	Transfer-molding	[72]
	Dissolving	PLGA5050/ DMSO (MN tip) SU-8 (MN base)	Polyhexamethylene Biguanide (PHMB)	Microneedle pen with a detachable and MN tip enables localized insertion, dissolving capacity of MN allows long-term drug delivery	Transfer-molding	[73]
Cornea, sclera	Dissolving	PVP-K90 (MNs) Chitosan/PVA/ PVP-K90 (back layer)	Triamcinolone acetonide (TA)	Concave shape enables better adhesion to the eyeball, dissolving capacity of MNs allows effective drug delivery	Micromolding	[137]
Sclera	Drug coated	SU-8	RB	Loaded spring of microneedle pen enables depthwise-controlled impact insertion, dip coating of drug allows effective	Transfer-molding	[141]

				drug delivery		
	Dissolving	PLGA/DMSO (MN tip) PVP/PVA (porous layer) SU-8 (MN base)	RB	Porous PVA/PVP layer of MN allows immediate detachment and insertion of the tip after contacting with sclera, dissolving capacity of MN allows long-term drug delivery	Transfer-molding	[142]
	Drug coated	PLA (needle) PLGA (coating) MeSH (plugging)	RB	The plugging component swells after injection to plug the hole and avoid needle retraction, dip coating of drug allows effective drug delivery	Thermal drawing	[143]
Suprachoroidal space	Hollow	Stainless steel (33-gauge)	Subbroston e, brimonidine	Highly targeted delivery to the supraciliary space	Laser	[144]
GI tract	Hollow	Stainless steel (25-gauge)	Insulin	MN roller with pH-responsive degradable coating enables targeted MN exposure and insertion	Needles are fitted manually into central metallic core	[154]
	Hydrogel	Carbopol (shell) PCL (core)	Semaglutide, sodium N-[8(2hydroxybenzoyl) amino] caprylate (SNAC)	Tube-shaped and self-triggered capsule system enables drug delivery under harsh pH environment, core-shell structured MNs allow	Mutiple-step casting	[155]

				sustained drug delivery		
	Dissolving	PVP	Insulin	Breakable pH-triggered capsule system with a compressed spring enables targeted MNs injection under harsh pH environment, dissolving capacity of MNs allows effective drug delivery	Micromolding, 3D printing	[156]
	Dissolving	PEO/ hydroxypropyl methylcellulose	Insulin	Self-orienting capsule system with a pH-triggered spring allows targeted MN injection under harsh pH environment, dissolving capacity of MNs allows effective drug delivery	Micromolding	[157]
	Dissolving	Gelatin (MN patch) PDMS (layer)	Rhodamine 6G	Capsule system driven by magnet field allow located drug delivery, three-layer MN patches can be sequentially separated then achieve target lesions insertion	Micromolding, 3D printing	[158]
Oral mocusa	Dissolving	PVP	Human insulin (HI), human	Drug-concentrated MN tips overcome saliva flushing, degradation of	Two-step casting	[165]

			growth hormone (hGH)	MNs allows effective drug delivery		
	Dissolving	HA (MN tips) PVP (base) PVP/EC (backing)	BSP	Waterproof backing layer and drug-concentrated MN tips overcome saliva flushing, degradation of MNs allows effective drug delivery	Two-step casting	[166]
	Hydrogel	Silk fibroin (MN tips) Tannic acid/silk fibroin (top layer)	Triamcinolone	Hydrogel film enables wet adhesion onto oral mucosa,	Multi-step casting	[167]
Spinal cord	Hydrogel	GelMA	Three-dimensional cultured MSCs exosomes (3D-Exo)	Hydrogel MNs with great biocompatibility and degradability	Micromolding	[169]
Brain	Dissolving	Silk fibroin	Thrombin, temozolomide	Degradation of MNs allows sustained drug release, which can be controlled by adjusting the crosslinking degree	Micromolding	[171]
	Hydrogel	GelMA	Adeno-associated virus expressing human vascular endothelial growth	Swelling MNs enable better tissue adhesion, degradation of MNs allows effective drug delivery, while both swelling ratio	Micromolding	[172]

			factor (AAV-VEGF)	and degradation rate can be controlled by crosslinking durations		
Uterus	Hydrogel	GelMA	Human endometrium-derived adventitial cells (En-ADVs), lactoferrin (LF)	Alternately arranged MNs and cell culture microwells achieve dual therapeutic agents delivery	Micromolding	[173]
	Dissolving	NAGA/PEGMA	b-FGF	Arrowhead MNs adjusting to the irregular morphology of the uterus enable close adhesion to endometrium, dissolving capacity of MN allows sustained drug delivery	Multi-step casting	[174]
Virginal	Dissolving	Sucrose/PVP/CMC	$NH_4^+HCO_3$ loaded multifunctional liposomes	MNs array is fabricated to fit the vaginal anatomic feature, dissolving capacity of MN allows sustained drug delivery	Micromolding	[175]

5. Conclusions and future perspectives

Recently, MNs have shown tremendous potential not only in the field of transdermal drug delivery, but also in drug administration to many other tissues. In this review, we summarized the current trends of using MNs-based devices for non-transdermal drug delivery. Specific considerations including

materials, fabrication method, design strategies for controlled drug release have been discussed. MNs patches with various tip geometries can be fabricated by technologies based on traditional semiconductor technology, such as wet or dry etching and photolithographic. Novel additive manufacturing like 3D or 4D printing can also be utilized to rapidly create diverse shapes with low cost. Drawing lithography methods makes it easy to develop high aspect ratio polymeric MNs without harsh manufacturing conditions. In addition, multiple step casting as well as transfer molding techniques deriving from conventional micromolding method enables the fabrication of applicator devices for facile and standardized MNs insertion. By selecting specific hydrogels with controllable crosslinking rate as well as flexibly adjusting assembly strategies of layered structure, it is possible to attain various release mechanism of loaded drugs, including long-term diffusion, triggered release or responsive release, which provide MNs with enhanced drug permeability through various biological barriers. We then comprehensively reviewed the situations using MNs applications in various visceral organs and soft tissues, including vascular, cardiac, ocular, GI, oral, spinal, cerebral, uterine and virginal. For vascular MNs drug delivery, in order to achieve close adhesion to the curved structure of blood vessels, flexible and flexional materials are selected to form a primary cuff base, then methods like thermal drawing or transfer molding which would be convenient for additionally fabricating MNs onto the existing substrate can be utilized. When preparing MNs patches for MI treatment, biocompatible materials should be used to ensure that the therapeutic agents for stem cell therapy remain active. Swellable hydrogels are preferred in order to achieve secure fixation with the myocardium. For the manufacturing of ocular drug delivery MNs, in order to fit the sphere surface of eyeball, one possible solution is to prepare curved features of patches by micromolding. Another designing strategy is to fabricate detachable single MN tip with assistant pen structure through transfer molding, which can realize impact insertion with minimal invasiveness and achieve sustained drug release. For MNs aimed at GI administration, the devices should be designed as capsule systems to withstand harsh pH environments. 3D printing is often used during the fabrication of complex shell of the capsule, while MNs can be simply prepared through micromolding. What's more, assistant structures such as triggers are needed to enable the devices to attain controllable MNs exposure without being disturbed by gastrointestinal peristalsis. When it comes to oral MNs drug delivery, it is important to combine drug concentrated tips with water proof back layer to overcome saliva flushing and enhance wet adhesion. Multi-step casting may serve as a possible fabrication method to achieve multi-layer

structure of oral MNs patch. For MNs that deliver therapeutic agents to nervous system, the main consideration is to select applicable polymers for MNs fabrication. Biocompatible materials such as HA and silk fibroin should be prioritized. When considering the fabrication of MNs for drug delivery to the reproductive system, in pursuit of ideal tissue adhesion capacity, swellable hydrogel MNs can be further manufactured with arrowhead tips through multi-step casting. The specific geometry of MNs may as well perform long-term drug release with enhanced permeation efficiency. By designing and manufacturing MNs-based devices suitable for the target tissue, close adhesion, ideal penetration as well as high drug permeation efficiency that outperforms traditional administrations can be subsequently achieved.

Currently, MNs integrated with sensors have already been used in diagnosis and direct monitoring of physiological parameters, medications and biomarkers[176, 177]. By combining with advanced biosensor technology, intelligent non-transdermal drug delivery devices may enable intuitional surveillance of patients' real-time reactions to drug administration[178, 179]. As a promising approach, the array of MNs could be fabricated to consist of two sections, the drug release section and the monitoring section. For the drug release section, specific polymer or hydrogel can be selected to achieve programmed drug delivery, while the MNs in the monitoring section may serve as sensors, fabricated through certain biosensing materials and for transmitting electronic and chemical signal. With the feedback data, the whole MNs system will keep monitoring the condition of target tissue and self-regulate the permeation behavior of drugs until reaching the ideal therapeutic effect. The devices can accurately determine the patient's drug demand and response, and achieve a personalized drug release strategy. Though challenging, this idea may bring more efficient and convenient treatment options to patients and reduce the discomfort during treatment process.

Furthermore, putting MNs into clinical use and commercialization are both urgent goals waiting to be achieved. For skin application, extensive researches have been carried out, clinical conversion as well as primary commercialization of the MNs devices are already on their way[180, 181]. However, when it comes to MNs-based systems for non-transdermal drug delivery, investigations still remain in its early stage. Systematic clinical trials ought to be carried out, only that the risks of applying MNs can be evaluated, and corresponding improvements can be provided. As previously mentioned at the end of each section in the chapter of advanced applications for different tissues, drug delivery strategies to

distinct tissues are faced with corresponding dilemmas. The drug delivery route through MNs was originally intended as a minimally invasive method to address the issue of low administration efficiency. However, when applied in non-transdermal settings, the insertion of MNs onto the surface of the target tissue involves significant surgical risks and may result in adverse effects, which contradicts the original intention of minimal invasiveness. This inherent contradiction needs to be further addressed. For this reason, it is imperative to seek proper strategies for the implantation of non-transdermal MNs to minimize surgical injuries and prevent unnecessary tissue damages. Furthermore, another common limitation of non-transdermal MNs lies in the fact that the experiments are still majored on small animals. It remains uncertain whether the therapeutic effects of these MN-based products will be consistent when applied to humans. Once the solutions to these key problems mentioned above are found, they may as well shed light on further researches and future clinical trials. Subsequently, *in vivo* experiments on large animals can be gradually implemented, eventually leading to the human application in clinic. Designing the structure of MNs to meet different patients' individual needs should then be taken into account, so that customization may further be realized. Leap-forward development of non-transdermal drug delivery through MNs might be accomplished consequently.

Acknowledgements

The authors would like to acknowledge financial support from the Beijing Natural Science Foundation (No. L234020), the National Natural Science Foundation of China (No. 12272032), and the 111 Project (No. B13003).

Author contributions

Conceptualization, XZJ and XFN; Writing-original draft, JHX and XYL; Writing-review & editing, all authors; Supervision, XZJ and XFN.

Compliance with ethics guidelines

The authors declare no competing financial interests.

References

[1] Prausnitz MR, Langer R (2008) Transdermal drug delivery. Nat Biotechnol 26(11):1261-1268. https://doi.org/10.1038/nbt.1504

[2] Kovacik A, Kopecna M, Vavrova K (2020) Permeation enhancers in transdermal drug delivery: benefits and limitations. Expert Opin Drug Deliv 17(2):145-155. https://doi.org/10.1080/17425247.2020.1713087

[3] Al Hanbali OA, Khan HMS, Sarfraz M et al (2019) Transdermal patches: Design and current approaches to painless drug delivery. Acta Pharm 69(2):197-215. https://doi.org/10.2478/acph-2019-0016

[4] Ayala ES, Meuret AE, Ritz T (2009) Treatments for blood-injury-injection phobia: a critical review of current evidence. J Psychiatr Res 43(15):1235-1242. https://doi.org/10.1016/j.jpsychires.2009.04.008

[5] Henry S, McAllister DV, Allen MG et al (1998) Microfabricated Microneedles: A Novel Approach to Transdermal Drug Delivery. J Pharm Sci-Us 87(8):922-925. https://doi.org/https://doi.org/10.1021/js980042+

[6] Ahmed Saeed Al-Japairai K, Mahmood S, Hamed Almurisi S et al (2020) Current trends in polymer microneedle for transdermal drug delivery. Int J Pharm 587:119673. https://doi.org/10.1016/j.ijpharm.2020.119673

[7] Waghule T, Singhvi G, Dubey SK et al (2019) Microneedles: A smart approach and increasing potential for transdermal drug delivery system. Biomed Pharmacother 109:1249-1258. https://doi.org/10.1016/j.biopha.2018.10.078

[8] Wang R, Wang J, Gao H et al (2023) Composite double-layer microneedle loaded with traditional Chinese medicine for the treatment of androgenic alopecia. Medicine in Novel Technology and Devices 18:100216. https://doi.org/https://doi.org/10.1016/j.medntd.2023.100216

[9] Hao Y, Li W, Zhou X et al (2017) Microneedles-Based Transdermal Drug Delivery Systems: A Review. J Biomed Nanotechnol 13(12):1581-1597. https://doi.org/10.1166/jbn.2017.2474

[10] Yadav PR, Dobson LJ, Pattanayek SK et al (2022) Swellable microneedles based transdermal drug delivery: Mathematical model development and numerical experiments. Chem Eng Sci 247:117005. https://doi.org/https://doi.org/10.1016/j.ces.2021.117005

[11] Wang Y, Liu H, Yang X et al (2023) A responsive hydrogel-based microneedle system for

minimally invasive glucose monitoring. Smart Materials in Medicine 4:69-77. https://doi.org/https://doi.org/10.1016/j.smaim.2022.07.006

[12] Chen Z, He J, Qi J et al (2020) Long-acting microneedles: a progress report of the state-of-the-art techniques. Drug Discov Today 25(8):1462-1468. https://doi.org/https://doi.org/10.1016/j.drudis.2020.05.006

[13] Bhatnagar S, Gadeela PR, Thathireddy P et al (2019) Microneedle-based drug delivery: materials of construction. J Chem Sci 131(9):90. https://doi.org/10.1007/s12039-019-1666-x

[14] Aldawood FK, Andar A, Desai S (2021) A Comprehensive Review of Microneedles: Types, Materials, Processes, Characterizations and Applications. Polymers (Basel) 13(16). https://doi.org/10.3390/polym13162815

[15] Li WZ, Huo MR, Zhou JP et al (2010) Super-short solid silicon microneedles for transdermal drug delivery applications. Int J Pharm 389(1-2):122-129. https://doi.org/10.1016/j.ijpharm.2010.01.024

[16] Kim S, Shetty S, Price D et al (2006) Skin penetration of silicon dioxide microneedle arrays. Conf Proc IEEE Eng Med Biol Soc 2006:4088-4091. https://doi.org/10.1109/IEMBS.2006.260142

[17] Gittard SD, Narayan RJ, Jin C et al (2009) Pulsed laser deposition of antimicrobial silver coating on Ormocer microneedles. Biofabrication 1(4):041001. https://doi.org/10.1088/1758-5082/1/4/041001

[18] Choi HJ, Bondy BJ, Yoo DG et al (2013) Stability of whole inactivated influenza virus vaccine during coating onto metal microneedles. J Control Release 166(2):159-171. https://doi.org/10.1016/j.jconrel.2012.12.002

[19] Shirkhanzadeh M (2005) Microneedles coated with porous calcium phosphate ceramics: effective vehicles for transdermal delivery of solid trehalose. J Mater Sci Mater Med 16(1):37-45. https://doi.org/10.1007/s10856-005-6444-2

[20] Wang W, Zhang L, Sun L et al (2018) Biocompatibility and Immunotoxicology of the Preclinical Implantation of a Collagen-based Artificial Dermal Regeneration Matrix. Biomed Environ Sci 31(11):829-842. https://doi.org/https://doi.org/10.3967/bes2018.110

[21] Li Z, Ruan C, Niu X (2023) Collagen-based bioinks for regenerative medicine: Fabrication, application and prospective. Medicine in Novel Technology and Devices 17:100211.

https://doi.org/https://doi.org/10.1016/j.medntd.2023.100211

[22] Bhadale RS, Londhe VY (2021) A systematic review of carbohydrate-based microneedles: current status and future prospects. J Mater Sci Mater Med 32(8):89. https://doi.org/10.1007/s10856-021-06559-x

[23] Yalcintas EP, Ackerman DS, Korkmaz E et al (2020) Analysis of In Vitro Cytotoxicity of Carbohydrate-Based Materials Used for Dissolvable Microneedle Arrays. Pharm Res 37(3):33. https://doi.org/10.1007/s11095-019-2748-7

[24] Moore LE, Vucen S, Moore AC (2022) Trends in drug- and vaccine-based dissolvable microneedle materials and methods of fabrication. Eur J Pharm Biopharm 173:54-72. https://doi.org/10.1016/j.ejpb.2022.02.013

[25] Moronkeji K, Todd S, Dawidowska I et al (2017) The role of subcutaneous tissue stiffness on microneedle performance in a representative in vitro model of skin. J Control Release 265:102-112. https://doi.org/10.1016/j.jconrel.2016.11.004

[26] Naves L, Dhand C, Almeida L et al (2017) Poly(lactic-co-glycolic) acid drug delivery systems through transdermal pathway: an overview. Prog Biomater 6(1-2):1-11. https://doi.org/10.1007/s40204-017-00630

[27] Grayson AC, Voskerician G, Lynn A et al (2004) Differential degradation rates in vivo and in vitro of biocompatible poly(lactic acid) and poly(glycolic acid) homo- and co-polymers for a polymeric drug-delivery microchip. J Biomater Sci Polym Ed 15(10):1281-1304. https://doi.org/10.1163/1568562041959991

[28] Turner JG, White LR, Estrela P et al (2021) Hydrogel-Forming Microneedles: Current Advancements and Future Trends. Macromol Biosci 21(2):e2000307. https://doi.org/10.1002/mabi.202000307

[29] Li J, Mooney DJ (2016) Designing hydrogels for controlled drug delivery. Nat Rev Mater 1(12):16071. https://doi.org/10.1038/natrevmats.2016.71

[30] Huff M (2021) Recent Advances in Reactive Ion Etching and Applications of High-Aspect-Ratio Microfabrication. Micromachines-Basel 12(8). https://doi.org/10.3390/mi12080991

[31] O'Mahony C, Sebastian R, Tjulkins F et al (2023) Hollow silicon microneedles, fabricated using combined wet and dry etching techniques, for transdermal delivery and diagnostics. Int J Pharm 637:122888. https://doi.org/10.1016/j.ijpharm.2023.122888

[32] Mamun AA, Zhao F (2022) In-Plane Si Microneedles: Fabrication, Characterization, Modeling and Applications. Micromachines-Basel 13(5). https://doi.org/10.3390/mi13050657

[33] Faraji Rad Z, Prewett PD, Davies GJ (2021) An overview of microneedle applications, materials, and fabrication methods. Beilstein J Nanotechnol 12:1034-1046. https://doi.org/10.3762/bjnano.12.77

[34] Howells O, Blayney GJ, Gualeni B et al (2022) Design, fabrication, and characterisation of a silicon microneedle array for transdermal therapeutic delivery using a single step wet etch process. Eur J Pharm Biopharm 171:19-28. https://doi.org/10.1016/j.ejpb.2021.06.005

[35] Hamzah AA, Abd Aziz N, Yeop Majlis B et al (2012) Optimization of HNA etching parameters to produce high aspect ratio solid silicon microneedles. J Micromech Microeng 22(9). https://doi.org/10.1088/0960-1317/22/9/095017

[36] Berry CA, Smith ZR, Collins SD et al (2020) Dermal ISF Collection Using a Si Microneedle Array. In: 2020 IEEE 33rd International Conference on Micro Electro Mechanical Systems (MEMS), vol. https://doi.org/10.1109/MEMS46641.2020.9056394. pp 365-368

[37] Li Y, Zhang H, Yang R et al (2019) Fabrication of sharp silicon hollow microneedles by deep-reactive ion etching towards minimally invasive diagnostics. Microsyst Nanoeng 5:41. https://doi.org/10.1038/s41378-019-0077-y

[38] Wang J, Wang H, Lai L et al (2020) Preparation of Microneedle Array Mold Based on MEMS Lithography Technology. Micromachines-Basel 12(1). https://doi.org/10.3390/mi12010023

[39] Pradeep Narayanan S, Raghavan S (2016) Solid silicon microneedles for drug delivery applications. Int J Adv Manuf Tech 93(1-4):407-422. https://doi.org/10.1007/s00170-016-9698-6

[40] Roh H, Yoon YJ, Park JS et al (2021) Fabrication of High-Density Out-of-Plane Microneedle Arrays with Various Heights and Diverse Cross-Sectional Shapes. Nanomicro Lett 14(1):24. https://doi.org/10.1007/s40820-021-00778-1

[41] Yang Q, Zhong W, Xu L et al (2021) Recent progress of 3D-printed microneedles for transdermal drug delivery. Int J Pharmaceut 593:120106. https://doi.org/https://doi.org/10.1016/j.ijpharm.2020.120106

[42] Li R, Zhang L, Jiang X et al (2022) 3D-printed microneedle arrays for drug delivery. J Control Release 350:933-948. https://doi.org/10.1016/j.jconrel.2022.08.022

[43] Kumar H, Kim K (2020) Stereolithography 3D Bioprinting. Methods Mol Biol 2140:93-108. https://doi.org/10.1007/978-1-0716-0520-2_6

[44] Fei P, Ding H, Duan Y et al (2021) Utility of TPP-manufactured biophysical restrictions to probe multiscale cellular dynamics. Bio-Design and Manufacturing 4(4):776-789. https://doi.org/10.1007/s42242-021-00163-2

[45] Cordeiro AS, Tekko IA, Jomaa MH et al (2020) Two-Photon Polymerisation 3D Printing of Microneedle Array Templates with Versatile Designs: Application in the Development of Polymeric Drug Delivery Systems. Pharm Res 37(9):174. https://doi.org/10.1007/s11095-020-02887-9

[46] Liao C, Anderson W, Antaw F et al (2019) Two-Photon Nanolithography of Tailored Hollow three-dimensional Microdevices for Biosystems. Acs Omega 4(1):1401-1409. https://doi.org/10.1021/acsomega.8b03164

[47] Faraji Rad Z, Nordon RE, Anthony CJ et al (2017) High-fidelity replication of thermoplastic microneedles with open microfluidic channels. Microsyst Nanoeng 3:17034. https://doi.org/10.1038/micronano.2017.34

[48] Zhu W, Ma X, Gou M et al (2016) 3D printing of functional biomaterials for tissue engineering. Curr Opin Biotech 40:103-112. https://doi.org/https://doi.org/10.1016/j.copbio.2016.03.014

[49] Willemen NGA, Morsink MAJ, Veerman D et al (2022) From oral formulations to drug-eluting implants: using 3D and 4D printing to develop drug delivery systems and personalized medicine. Bio-Design and Manufacturing 5(1):85-106. https://doi.org/10.1007/s42242-021-00157-0

[50] Miao S, Cui H, Nowicki M et al (2018) Photolithographic-stereolithographic-tandem fabrication of 4D smart scaffolds for improved stem cell cardiomyogenic differentiation. Biofabrication 10(3):035007. https://doi.org/10.1088/1758-5090/aabe0b

[51] Cui H, Liu C, Esworthy T et al (2020) 4D physiologically adaptable cardiac patch: A 4-month in vivo study for the treatment of myocardial infarction. Sci Adv 6(26):eabb5067. https://doi.org/10.1126/sciadv.abb5067

[52] Lee J, Park SH, Seo IH et al (2015) Rapid and repeatable fabrication of high A/R silk fibroin microneedles using thermally-drawn micromolds. Eur J Pharm Biopharm 94:11-19. https://doi.org/10.1016/j.ejpb.2015.04.024

[53] Choi CK, Lee KJ, Youn YN et al (2013) Spatially discrete thermal drawing of biodegradable

microneedles for vascular drug delivery. Eur J Pharm Biopharm 83(2):224-233. https://doi.org/10.1016/j.ejpb.2012.10.020

[54] Lee K, Jung H (2012) Drawing lithography for microneedles: A review of fundamentals and biomedical applications. Biomaterials 33(30):7309-7326. https://doi.org/10.1016/j.biomaterials.2012.06.065

[55] Lee K, Park S, Lee J et al (2019) Three-Step Thermal Drawing for Rapid Prototyping of Highly Customizable Microneedles for Vascular Tissue Insertion. Pharmaceutics 11(3). https://doi.org/10.3390/pharmaceutics11030100

[56] Onesto V, Di Natale C, Profeta M et al (2020) Engineered PLGA-PVP/VA based formulations to produce electro-drawn fast biodegradable microneedles for labile biomolecule delivery. Prog Biomater 9(4):203-217. https://doi.org/10.1007/s40204-020-00143-2

[57] Ruggiero F, Vecchione R, Bhowmick S et al (2018) Electro-drawn polymer microneedle arrays with controlled shape and dimension. Sensors and Actuators B: Chemical 255:1553-1560. https://doi.org/10.1016/j.snb.2017.08.165

[58] Kim JD, Kim M, Yang H et al (2013) Droplet-born air blowing: novel dissolving microneedle fabrication. J Control Release 170(3):430-436. https://doi.org/10.1016/j.jconrel.2013.05.026

[59] Chen Z, Ye R, Yang J et al (2019) Rapidly Fabricated Microneedle Arrays Using Magnetorheological Drawing Lithography for Transdermal Drug Delivery. Acs Biomater Sci Eng 5(10):5506-5513. https://doi.org/10.1021/acsbiomaterials.9b00919

[60] Chen Z, Ren L, Li J et al (2018) Rapid fabrication of microneedles using magnetorheological drawing lithography. Acta Biomater 65:283-291. https://doi.org/10.1016/j.actbio.2017.10.030

[61] Chen Z, Lin Y, Lee W et al (2018) Additive Manufacturing of Honeybee-Inspired Microneedle for Easy Skin Insertion and Difficult Removal. Acs Appl Mater Inter 10(35):29338-29346. https://doi.org/10.1021/acsami.8b09563

[62] Nazary Abrbekoh F, Salimi L, Saghati S et al (2022) Application of microneedle patches for drug delivery; doorstep to novel therapies. J Tissue Eng 13:20417314221085390. https://doi.org/10.1177/20417314221085390

[63] Wang QL, Zhu DD, Chen Y et al (2016) A fabrication method of microneedle molds with controlled microstructures. Materials Science and Engineering: C 65:135-142. https://doi.org/https://doi.org/10.1016/j.msec.2016.03.097

[64] Silvestre SL, Araujo D, Marques AC et al (2020) Microneedle Arrays of Polyhydroxyalkanoate by Laser-Based Micromolding Technique. Acs Appl Bio Mater 3(9):5856-5864. https://doi.org/10.1021/acsabm.0c00570

[65] Anbazhagan G, Suseela SB, Sankararajan R (2023) Design, analysis and fabrication of solid polymer microneedle patch using CO_2 laser and polymer molding. Drug Deliv Transl Res 13(6):1813-1827. https://doi.org/10.1007/s13346-023-01296-w

[66] Lin YH, Lee IC, Hsu WC et al (2016) Rapid fabrication method of a microneedle mold with controllable needle height and width. Biomed Microdevices 18(5):85. https://doi.org/10.1007/s10544-016-0113-8

[67] Hatsuzawa T, Kurosaka M (2018) A cell culture device equipped with a micro-needle electrode array fabricated using backside exposure mold and resin casting. Biomed Microdevices 20(3):58. https://doi.org/10.1007/s10544-018-0303-7

[68] Wang Z, Fu R, Han X et al (2022) Shrinking Fabrication of a Glucose-Responsive Glucagon Microneedle Patch. Adv Sci 9(28):e2203274. https://doi.org/10.1002/advs.202203274

[69] Zhang Y, Wang D, Gao M et al (2018) Separable Microneedles for Near-Infrared Light-Triggered Transdermal Delivery of Metformin in Diabetic Rats. Acs Biomater Sci Eng 4(8):2879-2888. https://doi.org/10.1021/acsbiomaterials.8b00642

[70] Chen MC, Lai KY, Ling MH et al (2018) Enhancing immunogenicity of antigens through sustained intradermal delivery using chitosan microneedles with a patch-dissolvable design. Acta Biomater 65:66-75. https://doi.org/https://doi.org/10.1016/j.actbio.2017.11.004

[71] Chu LY, Prausnitz MR (2011) Separable arrowhead microneedles. J Control Release 149(3):242-249. https://doi.org/10.1016/j.jconrel.2010.10.033

[72] Song HB, Lee KJ, Seo IH et al (2015) Impact insertion of transfer-molded microneedle for localized and minimally invasive ocular drug delivery. J Control Release 209:272-279. https://doi.org/10.1016/j.jconrel.2015.04.041

[73] Lee K, Song HB, Cho W et al (2018) Intracorneal injection of a detachable hybrid microneedle for sustained drug delivery. Acta Biomater 80:48-57. https://doi.org/10.1016/j.actbio.2018.09.039

[74] Lee J, Jang EH, Kim JH et al (2021) Highly flexible and porous silk fibroin microneedle wraps for perivascular drug delivery. J Control Release 340:125-135.

https://doi.org/10.1016/j.jconrel.2021.10.024

[75] Lee J, Kim DH, Lee KJ et al (2017) Transfer-molded wrappable microneedle meshes for perivascular drug delivery. J Control Release 268:237-246. https://doi.org/10.1016/j.jconrel.2017.10.007

[76] Song HB, Lee KJ, Seo IH et al (2015) Impact insertion of transfer-molded microneedle for localized and minimally invasive ocular drug delivery. J Control Release 209:272-279. https://doi.org/10.1016/j.jconrel.2015.04.041

[77] Oleksy M, Dynarowicz K, Aebisher D (2023) Advances in Biodegradable Polymers and Biomaterials for Medical Applications-A Review. Molecules 28(17). https://doi.org/10.3390/molecules28176213

[78] Mbituyimana B, Ma G, Shi Z et al (2022) Polymer-based microneedle composites for enhanced non-transdermal drug delivery. Applied Materials Today 29:101659. https://doi.org/https://doi.org/10.1016/j.apmt.2022.101659

[79] Yang F, Wang J, Li X et al (2022) Electrospinning of a sandwich-structured membrane with sustained release capability and long-term anti-inflammatory effects for dental pulp regeneration. Bio-Design and Manufacturing 5(2):305-317. https://doi.org/10.1007/s42242-021-00152-5

[80] Ma G, Wu C (2017) Microneedle, bio-microneedle and bio-inspired microneedle: A review. J Control Release 251:11-23. https://doi.org/10.1016/j.jconrel.2017.02.011

[81] Zhang X, Wang F, Yu Y et al (2019) Bio-inspired clamping microneedle arrays from flexible ferrofluid-configured moldings. Sci Bull (Beijing) 64(15):1110-1117. https://doi.org/10.1016/j.scib.2019.06.016

[82] Zhang X, Chen G, Sun L et al (2021) Claw-inspired microneedle patches with liquid metal encapsulation for accelerating incisional wound healing. Chem Eng J 406:126741. https://doi.org/10.1016/j.cej.2020.126741

[83] Lu Y, Ren T, Zhang H et al (2022) A honeybee stinger-inspired self-interlocking microneedle patch and its application in myocardial infarction treatment. Acta Biomater 153:386-398. https://doi.org/10.1016/j.actbio.2022.09.015

[84] Liu T, Sun Y, Jiang G et al (2023) Porcupine-inspired microneedles coupled with an adhesive back patching as dressing for accelerating diabetic wound healing. Acta Biomater 160:32-44. https://doi.org/10.1016/j.actbio.2023.01.059

[85] Yang SY, O'Cearbhaill ED, Sisk GC et al (2013) A bio-inspired swellable microneedle adhesive for mechanical interlocking with tissue. Nat Commun 4:1702. https://doi.org/10.1038/ncomms2715

[86] Seong KY, Seo MS, Hwang DY et al (2017) A self-adherent, bullet-shaped microneedle patch for controlled transdermal delivery of insulin. J Control Release 265:48-56. https://doi.org/https://doi.org/10.1016/j.jconrel.2017.03.041

[87] Jeon EY, Lee J, Kim BJ et al (2019) Bio-inspired swellable hydrogel-forming double-layered adhesive microneedle protein patch for regenerative internal/external surgical closure. Biomaterials 222:119439. https://doi.org/10.1016/j.biomaterials.2019.119439

[88] Uppu DSSM, Turvey ME, Sharif ARM et al (2020) Temporal release of a three-component protein subunit vaccine from polymer multilayers. J Control Release 317:130-141. https://doi.org/https://doi.org/10.1016/j.jconrel.2019.11.022

[89] Jung CR, Lahiji SF, Kim Y et al (2020) Rapidly Separable Micropillar Integrated Dissolving Microneedles. Pharmaceutics 12(6). https://doi.org/10.3390/pharmaceutics12060581

[90] Li W, Terry RN, Tang J et al (2019) Rapidly separable microneedle patch for the sustained release of a contraceptive. Nat Biomed Eng 3(3):220-229. https://doi.org/10.1038/s41551-018-0337-4

[91] Lee Y, Li W, Tang J et al (2021) Immediate detachment of microneedles by interfacial fracture for sustained delivery of a contraceptive hormone in the skin. J Control Release 337:676-685. https://doi.org/https://doi.org/10.1016/j.jconrel.2021.08.012

[92] Ning T, Yang F, Chen D et al (2022) Synergistically Detachable Microneedle Dressing for Programmed Treatment of Chronic Wounds. Adv Healthc Mater 11(11):2102180. https://doi.org/https://doi.org/10.1002/adhm.202102180

[93] Yang F, Niu X, Gu X et al (2019) Biodegradable Magnesium-Incorporated Poly(l-lactic acid) Microspheres for Manipulation of Drug Release and Alleviation of Inflammatory Response. Acs Appl Mater Inter 11(26):23546-23557. https://doi.org/10.1021/acsami.9b03766

[94] Ke CJ, Lin YJ, Hu YC et al (2012) Multidrug release based on microneedle arrays filled with pH-responsive PLGA hollow microspheres. Biomaterials 33(20):5156-5165. https://doi.org/10.1016/j.biomaterials.2012.03.056

[95] Vora LK, Donnelly RF, Larraneta E et al (2017) Novel bilayer dissolving microneedle arrays with concentrated PLGA nano-microparticles for targeted intradermal delivery: Proof of concept.

J Control Release 265:93-101. https://doi.org/10.1016/j.jconrel.2017.10.005

[96] Yang F, Xu C, Zhang W et al (2023) Biodegradable magnesium incorporated microspheres enable immunomodulation and spatiotemporal drug release for the treatment of osteonecrosis of the femoral head. Compos Part B-Eng 250:110430. https://doi.org/https://doi.org/10.1016/j.compositesb.2022.110430

[97] Mazzara JM, Ochyl LJ, Hong JKY et al (2019) Self-healing encapsulation and controlled release of vaccine antigens from PLGA microparticles delivered by microneedle patches. Bioeng Transl Med 4(1):116-128. https://doi.org/10.1002/btm2.10103

[98] Tran KTM, Gavitt TD, Farrell NJ et al (2021) Transdermal microneedles for the programmable burst release of multiple vaccine payloads. Nat Biomed Eng 5(9):998-1007. https://doi.org/10.1038/s41551-020-00650-4

[99] Li W, Chen JY, Terry RN et al (2022) Core-shell microneedle patch for six-month controlled-release contraceptive delivery. J Control Release 347:489-499. https://doi.org/https://doi.org/10.1016/j.jconrel.2022.04.051

[100] Makvandi P, Jamaledin R, Chen G et al (2021) Stimuli-responsive transdermal microneedle patches. Mater Today 47:206-222. https://doi.org/10.1016/j.mattod.2021.03.012

[101] Ding H, Tan P, Fu S et al (2022) Preparation and application of pH-responsive drug delivery systems. J Control Release 348:206-238. https://doi.org/10.1016/j.jconrel.2022.05.056

[102] Percival SL, McCarty S, Hunt JA et al (2014) The effects of pH on wound healing, biofilms, and antimicrobial efficacy. Wound Repair Regen 22(2):174-186. https://doi.org/10.1111/wrr.12125

[103] Mo R, Zhang H, Xu Y et al (2023) Transdermal drug delivery via microneedles to mediate wound microenvironment. Adv Drug Deliv Rev 195:114753. https://doi.org/10.1016/j.addr.2023.114753

[104] Lei X, Cheng K, Li Y et al (2023) The eradication of biofilm for therapy of bacterial infected chronic wound based on pH-responsive micelle of antimicrobial peptide derived biodegradable microneedle patch. Chem Eng J 462:142222. https://doi.org/10.1016/j.cej.2023.142222

[105] Yan G, Wang J, Hu L et al (2017) Stepwise targeted drug delivery to liver cancer cells for enhanced therapeutic efficacy by galactose-grafted, ultra-pH-sensitive micelles. Acta Biomater 51:363-373. https://doi.org/10.1016/j.actbio.2017.01.031

[106] Duong HTT, Yin Y, Thambi T et al (2018) Smart vaccine delivery based on microneedle arrays

decorated with ultra-pH-responsive copolymers for cancer immunotherapy. Biomaterials 185:13-24. https://doi.org/10.1016/j.biomaterials.2018.09.008

[107] Podual K, Doyle FJ, Peppas NA (2000) Glucose-sensitivity of glucose oxidase-containing cationic copolymer hydrogels having poly(ethylene glycol) grafts. J Control Release 67(1):9-17. https://doi.org/https://doi.org/10.1016/S0168-3659(00)00195-4

[108] Chen W, Tian R, Xu C et al (2017) Microneedle-array patches loaded with dual mineralized protein/peptide particles for type 2 diabetes therapy. Nat Commun 8(1):1777. https://doi.org/10.1038/s41467-017-01764-1

[109] Yu J, Zhang Y, Ye Y et al (2015) Microneedle-array patches loaded with hypoxia-sensitive vesicles provide fast glucose-responsive insulin delivery. Proc Natl Acad Sci U S A 112(27):8260-8265. https://doi.org/10.1073/pnas.1505405112

[110] Hu X, Yu J, Qian C et al (2017) H_2O_2-Responsive Vesicles Integrated with Transcutaneous Patches for Glucose-Mediated Insulin Delivery. Acs Nano 11(1):613-620. https://doi.org/10.1021/acsnano.6b06892

[111] Yu J, Wang J, Zhang Y et al (2020) Glucose-responsive insulin patch for the regulation of blood glucose in mice and minipigs. Nat Biomed Eng 4(5):499-506. https://doi.org/10.1038/s41551-019-0508-y

[112] Castellano JM, Narula J, Castillo J et al (2014) Promoting Cardiovascular Health Worldwide: Strategies, Challenges, and Opportunities. Rev Esp Cardiol 67(9):724-730. https://doi.org/10.1016/j.rec.2014.01.023

[113] Li L, Wang L, Liu SS et al (2019) Association between Coronary Atherosclerotic Plaque Composition and Cardiovascular Disease Risk. Biomed Environ Sci 32(2):75-86. https://doi.org/10.3967/bes2019.012

[114] Raval AJ, Parikh JK, Desai MA (2023) Perivascular patch using biodegradable polymers: Investigation of mechanical and drug elution characteristics. J Mech Behav Biomed Mater 142:105853. https://doi.org/10.1016/j.jmbbm.2023.105853

[115] Kim JH, Jang EH, Ryu JY et al (2023) Sirolimus-Embedded Silk Microneedle Wrap to Prevent Neointimal Hyperplasia in Vein Graft Model. Int J Mol Sci 24(4). https://doi.org/10.3390/ijms24043306

[116] Filova E, Parizek M, Olsovska J et al (2011) Perivascular sirolimus-delivery system. Int J Pharm

404(1-2):94-101. https://doi.org/10.1016/j.ijpharm.2010.11.005

[117] Mylonaki I, Allemann E, Saucy F et al (2017) Perivascular medical devices and drug delivery systems: Making the right choices. Biomaterials 128:56-68. https://doi.org/10.1016/j.biomaterials.2017.02.028

[118] Choi CK, Kim JB, Jang EH et al (2012) Curved biodegradable microneedles for vascular drug delivery. Small 8(16):2483-2488. https://doi.org/10.1002/smll.201200441

[119] Lee KJ, Park SH, Lee JY et al (2014) Perivascular biodegradable microneedle cuff for reduction of neointima formation after vascular injury. J Control Release 192:174-181. https://doi.org/10.1016/j.jconrel.2014.07.007

[120] Kim DH, Jang EH, Lee KJ et al (2017) A Biodegradable Microneedle Cuff for Comparison of Drug Effects through Perivascular Delivery to Balloon-Injured Arteries. Polymers-Basel 9(2). https://doi.org/10.3390/polym9020056

[121] Tzafriri AR, Edelman ER (2016) Endovascular Drug Delivery and Drug Elution Systems: First Principles. Interv Cardiol Clin 5(3):307-320. https://doi.org/10.1016/j.iccl.2016.02.007

[122] Lee K, Lee SG, Jang I et al (2018) Linear Micro-patterned Drug Eluting Balloon (LMDEB) for Enhanced Endovascular Drug Delivery. Sci Rep 8(1):3666. https://doi.org/10.1038/s41598-018-21649-7

[123] Owens CD, Gasper WJ, Walker JP et al (2014) Safety and feasibility of adjunctive dexamethasone infusion into the adventitia of the femoropopliteal artery following endovascular revascularization. J Vasc Surg 59(4):1016-1024. https://doi.org/10.1016/j.jvs.2013.10.051

[124] Lee K, Lee J, Lee SG et al (2020) Microneedle drug eluting balloon for enhanced drug delivery to vascular tissue. J Control Release 321:174-183. https://doi.org/10.1016/j.jconrel.2020.02.012

[125] Zhang X, Cheng Y, Liu R et al (2022) Globefish-Inspired Balloon Catheter with Intelligent Microneedle Coating for Endovascular Drug Delivery. Adv Sci 9(34):e2204497. https://doi.org/10.1002/advs.202204497

[126] Cheng W, Law PK (2017) Conceptual Design and Procedure for an Autonomous Intramyocardial Injection Catheter. Cell Transplant 26(5):735-751. https://doi.org/10.3727/096368916X694256

[127] Tang J, Wang J, Huang K et al (2018) Cardiac cell-integrated microneedle patch for treating myocardial infarction. Sci Adv 4(11):eaat9365. https://doi.org/10.1126/sciadv.aat9365

[128] Hu S, Zhu D, Li Z et al (2022) Detachable Microneedle Patches Deliver Mesenchymal Stromal

Cell Factor-Loaded Nanoparticles for Cardiac Repair. Acs Nano 16(10):15935-15945. https://doi.org/10.1021/acsnano.2c03060

[129] Shi H, Xue T, Yang Y et al (2020) Microneedle-mediated gene delivery for the treatment of ischemic myocardial disease. Sci Adv 6(25):eaaz3621. https://doi.org/10.1126/sciadv.aaz3621

[130] Lim S, Park TY, Jeon EY et al (2021) Double-layered adhesive microneedle bandage based on biofunctionalized mussel protein for cardiac tissue regeneration. Biomaterials 278:121171. https://doi.org/10.1016/j.biomaterials.2021.121171

[131] Yuan J, Yang H, Liu C et al (2023) Microneedle Patch Loaded with Exosomes Containing MicroRNA-29b Prevents Cardiac Fibrosis after Myocardial Infarction. Adv Healthc Mater 12(13):e2202959. https://doi.org/10.1002/adhm.202202959

[132] Bachu RD, Chowdhury P, Al-Saedi ZHF et al (2018) Ocular Drug Delivery Barriers-Role of Nanocarriers in the Treatment of Anterior Segment Ocular Diseases. Pharmaceutics 10(1). https://doi.org/10.3390/pharmaceutics10010028

[133] Falavarjani KG, Nguyen QD (2013) Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. Eye (Lond) 27(7):787-794. https://doi.org/10.1038/eye.2013.107

[134] Huang D, Chen YS, Rupenthal ID (2018) Overcoming ocular drug delivery barriers through the use of physical forces. Adv Drug Deliv Rev 126:96-112. https://doi.org/10.1016/j.addr.2017.09.008

[135] Long L, Ji D, Hu C et al (2023) Microneedles for in situ tissue regeneration. Mater Today Bio 19:100579. https://doi.org/10.1016/j.mtbio.2023.100579

[136] Datta D, Roy G, Garg P et al (2022) Ocular delivery of cyclosporine A using dissolvable microneedle contact lens. J Drug Deliv Sci Tec 70:103211. https://doi.org/https://doi.org/10.1016/j.jddst.2022.103211

[137] Roy G, Garg P, Venuganti VVK (2022) Microneedle scleral patch for minimally invasive delivery of triamcinolone to the posterior segment of eye. Int J Pharm 612:121305. https://doi.org/10.1016/j.ijpharm.2021.121305

[138] Than A, Liu C, Chang H et al (2018) Self-implantable double-layered micro-drug-reservoirs for efficient and controlled ocular drug delivery. Nat Commun 9(1):4433. https://doi.org/10.1038/s41467-018-06981-w

[139] Wu Y, Vora LK, Wang Y et al (2021) Long-acting nanoparticle-loaded bilayer microneedles for protein delivery to the posterior segment of the eye. Eur J Pharm Biopharm 165:306-318. https://doi.org/10.1016/j.ejpb.2021.05.022

[140] Wu Y, Vora LK, Mishra D et al (2022) Nanosuspension-loaded dissolving bilayer microneedles for hydrophobic drug delivery to the posterior segment of the eye. Biomater Adv 137:212767. https://doi.org/10.1016/j.bioadv.2022.212767

[141] Park SH, Jo DH, Cho CS et al (2018) Depthwise-controlled scleral insertion of microneedles for drug delivery to the back of the eye. Eur J Pharm Biopharm 133:31-41. https://doi.org/10.1016/j.ejpb.2018.09.021

[142] Lee Y, Park S, Kim SI et al (2020) Rapidly Detachable Microneedles Using Porous Water-Soluble Layer for Ocular Drug Delivery. Adv Mater Technol-Us 5(5). https://doi.org/10.1002/admt.201901145

[143] Lee K, Park S, Jo DH et al (2022) Self-Plugging Microneedle (SPM) for Intravitreal Drug Delivery. Adv Healthc Mater 11(12):e2102599. https://doi.org/10.1002/adhm.202102599

[144] Patel SR, Lin AS, Edelhauser HF et al (2011) Suprachoroidal drug delivery to the back of the eye using hollow microneedles. Pharm Res 28(1):166-176. https://doi.org/10.1007/s11095-010-0271-y

[145] Kim YC, Edelhauser HF, Prausnitz MR (2014) Targeted delivery of antiglaucoma drugs to the supraciliary space using microneedles. Invest Ophthalmol Vis Sci 55(11):7387-7397. https://doi.org/10.1167/iovs.14-14651

[146] Jung JH, Chiang B, Grossniklaus HE et al (2018) Ocular drug delivery targeted by iontophoresis in the suprachoroidal space using a microneedle. J Control Release 277:14-22. https://doi.org/10.1016/j.jconrel.2018.03.001

[147] Smart AL, Gaisford S Fau - Basit AW, Basit AW (2014) Oral peptide and protein delivery: intestinal obstacles and commercial prospects. Expert Opin Drug Del 11(8):1323-1335.

[148] Liu C, Kou Y, Zhang X et al (2018) Strategies and industrial perspectives to improve oral absorption of biological macromolecules. Expert Opin Drug Deliv 15(3):223-233. https://doi.org/10.1080/17425247.2017.1395853

[149] Liu F, Moreno P, Basit AW (2010) A novel double-coating approach for improved pH-triggered delivery to the ileo-colonic region of the gastrointestinal tract. Eur J Pharm Biopharm 74(2):311-

315. https://doi.org/10.1016/j.ejpb.2009.11.008

[150] Nelson BJ, Kaliakatsos IK, Abbott JJ (2010) Microrobots for minimally invasive medicine. Annu Rev Biomed Eng 12:55-85. https://doi.org/10.1146/annurev-bioeng-010510-103409

[151] Li J, Thamphiwatana S, Liu W et al (2016) Enteric Micromotor Can Selectively Position and Spontaneously Propel in the Gastrointestinal Tract. Acs Nano 10(10):9536-9542. https://doi.org/10.1021/acsnano.6b04795

[152] Mapara SS, Patravale VB (2017) Medical capsule robots: A renaissance for diagnostics, drug delivery and surgical treatment. J Control Release 261:337-351. https://doi.org/10.1016/j.jconrel.2017.07.005

[153] Munoz F, Alici G, Li W (2014) A review of drug delivery systems for capsule endoscopy. Adv Drug Deliv Rev 71:77-85. https://doi.org/10.1016/j.addr.2013.12.007

[154] Traverso G, Schoellhammer CM, Schroeder A et al (2015) Microneedles for drug delivery via the gastrointestinal tract. J Pharm Sci 104(2):362-367. https://doi.org/10.1002/jps.24182

[155] Chen W, Wainer J, Ryoo SW et al (2022) Dynamic omnidirectional adhesive microneedle system for oral macromolecular drug delivery. Sci Adv 8(1):eabk1792. https://doi.org/10.1126/sciadv.abk1792

[156] Abramson A, Caffarel-Salvador E, Soares V et al (2019) A luminal unfolding microneedle injector for oral delivery of macromolecules. Nat Med 25(10):1512-1518. https://doi.org/10.1038/s41591-019-0598-9

[157] Abramson A, Caffarel-Salvador E, Khang M et al (2019) An ingestible self-orienting system for oral delivery of macromolecules. Science 363(6427):611-615. https://doi.org/10.1126/science.aau2277

[158] Lee J, Lee H, Kwon SH et al (2020) Active delivery of multi-layer drug-loaded microneedle patches using magnetically driven capsule. Med Eng Phys 85:87-96. https://doi.org/10.1016/j.medengphy.2020.09.012

[159] Creighton RL, Woodrow KA (2019) Microneedle-Mediated Vaccine Delivery to the Oral Mucosa. Adv Healthc Mater 8(4):e1801180. https://doi.org/10.1002/adhm.201801180

[160] Wang Y, Sheng Aa, Jiang X et al (2023) Multidrug dissolvable microneedle patch for the treatment of recurrent oral ulcer. Bio-Design and Manufacturing 6(3):255-267. https://doi.org/10.1007/s42242-022-00221-3

[161] Ma Y, Tao W, Krebs SJ et al (2014) Vaccine delivery to the oral cavity using coated microneedles induces systemic and mucosal immunity. Pharm Res 31(9):2393-2403. https://doi.org/10.1007/s11095-014-1335-1

[162] An H, Gu Z, Zhou L et al (2022) Janus mucosal dressing with a tough and adhesive hydrogel based on synergistic effects of gelatin, polydopamine, and nano-clay. Acta Biomater 149:126-138. https://doi.org/https://doi.org/10.1016/j.actbio.2022.07.016

[163] Serpe L, Jain A, de Macedo CG et al (2016) Influence of salivary washout on drug delivery to the oral cavity using coated microneedles: An in vitro evaluation. Eur J Pharm Sci 93:215-223. https://doi.org/10.1016/j.ejps.2016.08.023

[164] Zhang X, Hasani-Sadrabadi MM, Zarubova J et al (2022) Immunomodulatory Microneedle Patch for Periodontal Tissue Regeneration. Matter-Us 5(2):666-682. https://doi.org/10.1016/j.matt.2021.11.017

[165] Caffarel-Salvador E, Kim S, Soares V et al (2021) A microneedle platform for buccal macromolecule delivery. Sci Adv 7(4). https://doi.org/10.1126/sciadv.abe2620

[166] Li XJ, Li Y, Meng Y et al (2022) Composite dissolvable microneedle patch for therapy of oral mucosal diseases. Biomater Adv 139:213001. https://doi.org/10.1016/j.bioadv.2022.213001

[167] Cheng X, Yang Y, Liao Z et al (2023) Drug-loaded mucoadhesive microneedle patch for the treatment of oral submucous fibrosis. Front Bioeng Biotechnol 11:1251583. https://doi.org/10.3389/fbioe.2023.1251583

[168] Chung MK, Wang S, On SL et al (2021) Acute and Chronic Pain from Facial Skin and Oral Mucosa: Unique Neurobiology and Challenging Treatment. Int J Mol Sci 22(11). https://doi.org/10.3390/ijms22115810

[169] Han M, Yang H, Lu X et al (2022) Three-Dimensional-Cultured MSC-Derived Exosome-Hydrogel Hybrid Microneedle Array Patch for Spinal Cord Repair. Nano Lett 22(15):6391-6401. https://doi.org/10.1021/acs.nanolett.2c02259

[170] Sasaki K, Fukakusa S, Torikai Y et al (2023) Effective nose-to-brain drug delivery using a combination system targeting the olfactory region in monkeys. J Control Release 359:384-399. https://doi.org/10.1016/j.jconrel.2023.06.005

[171] Wang Z, Yang Z, Jiang J et al (2022) Silk Microneedle Patch Capable of On-Demand Multidrug Delivery to the Brain for Glioblastoma Treatment. Adv Mater 34(1):e2106606.

https://doi.org/10.1002/adma.202106606

[172] Liu Y, Long L, Zhang F et al (2021) Microneedle-mediated vascular endothelial growth factor delivery promotes angiogenesis and functional recovery after stroke. J Control Release 338:610-622. https://doi.org/10.1016/j.jconrel.2021.08.057

[173] Li S, Li Y, Yu F et al (2022) Human Endometrium-Derived Adventitial Cell Spheroid-Loaded Antimicrobial Microneedles for Uterine Regeneration. Small 18(31):e2201225. https://doi.org/10.1002/smll.202201225

[174] Zhang X, Chen G, Wang Y et al (2022) Arrowhead Composite Microneedle Patches with Anisotropic Surface Adhesion for Preventing Intrauterine Adhesions. Adv Sci 9(12):e2104883. https://doi.org/10.1002/advs.202104883

[175] Wang N, Zhen Y, Jin Y et al (2017) Combining different types of multifunctional liposomes loaded with ammonium bicarbonate to fabricate microneedle arrays as a vaginal mucosal vaccine adjuvant-dual delivery system (VADDS). J Control Release 246:12-29. https://doi.org/10.1016/j.jconrel.2016.12.009

[176] Ma S, Li J, Pei L et al (2023) Microneedle-based interstitial fluid extraction for drug analysis: Advances, challenges, and prospects. J Pharm Anal 13(2):111-126. https://doi.org/https://doi.org/10.1016/j.jpha.2022.12.004

[177] Huang X, Liang B, Zheng S et al (2023) Microarrow sensor array with enhanced skin adhesion for transdermal continuous monitoring of glucose and reactive oxygen species. Bio-Design and Manufacturing. https://doi.org/10.1007/s42242-023-00246-2.

[178] Wang Y, Xu H, Dong Z et al (2022) Micro/nano biomedical devices for point-of-care diagnosis of infectious respiratory diseases. Medicine in Novel Technology and Devices 14:100116. https://doi.org/https://doi.org/10.1016/j.medntd.2022.100116

[179] Liu S, Jia Z, Yang F et al (2023) Flexible Transient Bioelectronic System Enables Multifunctional Active-Controlled Drug Delivery. Advanced Functional Materials 33(13):2215034. https://doi.org/https://doi.org/10.1002/adfm.202215034

[180] Bhatnagar S, Dave K, Venuganti VVK (2017) Microneedles in the clinic. J Control Release 260:164-182. https://doi.org/https://doi.org/10.1016/j.jconrel.2017.05.029

[181] Lee KJ, Jeong SS, Roh DH et al (2020) A practical guide to the development of microneedle systems—In clinical trials or on the market. Int J Pharmaceut 573:118778.

https://doi.org/https://doi.org/10.1016/j.ijpharm.2019.118778