Current Advances in Sustained Release Microneedles

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Abstract

Microneedles have been extensively investigated for intradermal delivery of drugs and vaccines due to advantages including high skin delivery efficiency, improved patient compliance, and potential for self-administration. However, traditional microneedles cannot regulate the release kinetics of payloads, limiting therapeutic utility of the biotherapeutics. Recently, several types of microneedles with sustained release properties, including slow-dissolving microneedles made of hydrophilic polymers, degradable microneedles made of hydrophobic polymers, and bioresponsive microneedles made of bioresponsive polymers, have been developed and investigated for intradermal delivery of the biotherapeutics, aiming for improving their therapeutic potency, reducing side effects and administration frequency, and further improving patient compliance. In this review, we introduced different types of microneedles that have been designed for sustained release of the payloads, summarized various applications of these microneedles, and discussed the future prospects of this technology.

Keywords
► sustained release
► polymeric microneedles
► drug delivery
► vaccines

Introduction

Microneedles are microscale structures that are designed to overcome the skin barrier for successful intradermal delivery of drugs and vaccines. They generally have a length ranging from 200 μm to 1 mm and therefore can avoid stimulating nerve endings when applied into the skin.[1–4] Compared with traditional injections with hypodermic needles, microneedle-mediated intradermal delivery of biotherapeutics have several advantages, including improved patient compliance, potential for self-administration, avoidance of needle stick injury, and infection risk due to reuse of needles.[5] Microneedles can also improve the stability of loaded biotherapeutics and potentially decrease side effects associated to systemic administration.[6–11]

Microneedles have been classified into coated, hollow, and polymer-based dissolving microneedles. The fabrication methods, various features, and applications of these microneedles have been extensively summarized and discussed in several good review articles.[1,2,12–14] Among the different types of the microneedles, dissolving microneedles which are made of fast water-soluble polymers have received particular attention as they do not result in any hazardous sharp waste after application.[15–19] They can normally dissolve within minutes and release the loaded biotherapeutics as the matrix dissolves.[18,20–22] In the past two decades, dissolving microneedles have been fabricated by using various types of biocompatible and water-soluble matrix, including hyaluronic acid (HA),[23,24] polyvinylpyrrolidone (PVP),[25,26] sucrose,[27,28] gelatin,[29] etc. Microneedles made of these polymers have shown strong mechanical strength for skin piercing and excellent biocompatibility and safety for delivery of substances from small-molecule chemical drugs to biomacromolecule protein therapeutics.[30–34] However,

most of the investigated microneedles cannot regulate the release kinetics of the encapsulated cargos due to the instant dissolution properties of the matrix. As a result, the microneedle-delivered drugs may have a short half-life and unordered distribution, which may limit their potency and cause unwanted side effects.[35]

To exploit the potential of polymeric microneedles for modulation of release properties and further improve therapeutic potency of the payloads, researchers started to design and investigate microneedles with sustained release properties.[36] Instead of rapidly dissolving and releasing the drugs after insertion, sustained release microneedles can keep the drug inside the matrix and release the payloads in a certain manner based on the dissolution or degradation properties of the polymer matrix.[36,37] The hypothesis is that the sustained release of drugs and vaccines from the microneedles could help to improve therapeutic efficacy, decrease side effects, and reduce administration frequency. To this end, several types of microneedles have been developed, including slow-dissolving microneedles made of hydrophilic polymers, degradable microneedles made of hydrophobic polymers, and bioresponsive microneedles made of bioresponsive polymers.[37] In the case of slow-dissolving microneedles, the release rate of the payloads is determined by the dissolution of the polymer after the insertion into skin. In degradable microneedles, the drug is delivered through passive diffusion or degradation of the matrix. In bioresponsive microneedles, bioresponsive polymers and micro- or nanoparticles which are sensitive to physiological signal are utilized for drug delivery in a bioresponsive manner[37] (►Table 1).

Although the research of these sustained release microneedles is in a relatively early stage, they have been used for delivery of various types of drugs and vaccines, including small-molecule chemical drugs, antibodies, protein therapeutics, and vaccines. These microneedles have been investigated for immune modulation, cancer therapy, diabetes treatment, etc. The results have shown that the sustained release of drug from the microneedles can improve therapeutic potency of the cargos and sustained release microneedles have potential to be used as a patient-friendly substitute for conventional sustained release methods. In this review, we introduced the representative types of the microneedles that have been designed for sustained release of drugs and vaccines, summarized different applications of these microneedles, and discussed the future perspective of this technology.

Representative Microneedle Types with Sustained Release Properties

Slow-Dissolving Microneedles Made of Hydrophilic Polymers

To extend the release period of drugs of dissolving microneedles, hydrophilic polymers with a slow dissolution rate in aqueous media were used. The polymers that have been studied for this type of microneedles are chitosan and polyvinyl alcohol (PVA; ►Table 2).[38–40] When selecting these polymers, the parameters that need to be carefully considered are water solubility, mechanical strength, and compatibility to drugs and vaccines. Although several new methods, including drawing lithography,[41] soft lithography,[42] and droplet-born air blowing,[43] have been developed for fabrication of polymeric microneedles, the mostly used method for preparing sustained release microneedles is the aqueous-based micromolding method.[2,12,32]

To fabricate slow-dissolving microneedles, one challenge is to dissolve the polymer in aqueous solution and obtain a relatively high concentration, which is needed for micromolding. Researchers have utilized high temperature and acidic pH for helping in dissolving the polymers with a high concentration. For example, to prepare a matrix formulation of PVA/PVP-based microneedles, Leonard et al first dissolved PVA in water to obtain a concentration of 0.67 g/mL by heating at 90°C.[40] After adding PVP, the polymer mixtures were further incubated at 60°C for 5 to 6 hours before use. In another study, chitosan was used to prepare a microneedle patch for sustained delivery of a model antigen ovalbumin (OVA). A 2% chitosan solution was first prepared by adding 2% (w/v) acetic acid. Next, excess acetic acid was removed by dialysis and excess water was removed by evaporation to obtain a 10% chitosan gel. The prepared chitosan microneedles successfully penetrated the skin, leaving the chitosan tip embedded for sustained release of OVA for over 14 days (►Fig. 1).[38] These high temperature and acidic conditions, however, may impact the structure and functionality of the loaded biotherapeutics, especially for protein and gene drugs which are sensitive to environmental conditions.[44–47]

Another strategy that can enable dissolving microneedles to release the payloads in a controlled manner is to combine nano- and microparticle technologies.[48,49] Vora et al fabricated PVP-based microneedles loaded with a mixture of poly (lactic-co-glycolic acid) (PLGA) nanoparticles and microparticles.[48] The developed system showed good mechanical and

Table 1 Different types of sustained release microneedles and their drug release mechanism

Microneedle type	Polymer matrix	Drug release mechanism
Slow-dissolving microneedles made of hydrophilic polymers	Slowly water-dissolving polymers	Released together with the dissolution of matrix
Degradable microneedles made of hydrophobic polymers	Non-water soluble and degradable polymers	Released through passive diffusion or degradation of polymer
Bioresponsive microneedles made of bioresponsive polymers	Biodegradable and bioresponsive polymers	Released in responding to physiological signals

Table 2 Representative microneedle types for sustained delivery of biotherapeutics

Microneedle type	Polymer matrix	Delivered biotherapeutics	Ref.
Slow-dissolving microneedles made of hydrophilic polymers	Chitosan	OVA	38
	Chitosan	Calcein, BSA	39
	PVA	Sulforhodamine B, inactivated influenza virus	40
	PVP, PLGA	Vitamin D3	48
	PVA, PLGA	Alexa 488, Cy5	49
Degradable microneedles made of hydrophobic polymers	PLGA	Calcein, BSA	50
	PLGA	Sulforhodamine B, inactivated influenza virus	40
	PLA	Methotrexate	51
	PLGA	Rhodamine	52
	PLGA	OVA	53
	PLGA, PLA	Levonorgestrel	54
	PLGA	OVA	62
	Crystallized silk fibroin	OVA	56
	Crosslinked MeHA	Anti-PD-1	57
	Genipin-crosslinked gelatin	Insulin	58
	Crystallized silk fibroin	Antibiotic	60
	PS-PAA	Insulin	113
	Crosslinked MeHA	Tumor lysate	61
	Crosslinked MeHA	Insulin	63
	Crosslinked MeHA	Insulin	64
	Crosslinked MeHA	Checkpoint inhibitors	65
Bioresponsive microneedles made of bioresponsive polymers	Crosslinked MeHA	Insulin	79
	Crosslinked PVA	Insulin	66
	Crosslinked MeHA	Insulin	80
	Crosslinked alginate	Exendin-4	67

Abbreviations: BSA, bovine serum albumin; OVA, ovalbumin; PLA, polylactic acid; PLGA, poly(lactic-co-glycolic) acid; PVA, polyvinyl alcohol; PVP, polyvinylpyrrolidone.

insertion profiles, and can continuously release a model drug for over 5 days. In another study, Ke et al developed PVP based dissolving microneedles loaded with pH-sensitive PLGA microparticles for multidrug release in sequence. In the first step, the microneedles quickly dissolved and released the free drug as well as another drug encapsulated in PLGA microparticles. In the subsequent step, the delivered microparticles disassembled due to the acidic pH of the skin and released the second drug. This system has potential for use of some clinical applications in which drugs need to be administered in sequence.[49] However, in the studies mentioned above, the authors did not investigate the application of the developed microneedles in real disease models. Additionally, the relatively low loading capacity of the polymeric nanoparticles may limit the overall drug loading capacity of the microneedles.

Degradable Microneedles Made of Hydrophobic Polymers

Except utilizing dissolving microneedles for sustained drug release, researchers also designed degradable microneedles by using nonsoluble and hydrophobic polymers for sustained release of drugs. The polymers that have been used are polylactic acid and PLGA, which have good biocompatibility and biodegradability (►**Table 2**).[40,50–54] Degradable microneedles made of these polymers have shown sufficient mechanical strength for skin insertion and a slow degradation rate for sustained release of the payloads. Hydrophobic drugs can be directly dissolved and mixed with the polymer in organic solution for drug loading during the micromolding process.[51] In most of the cases, the polymers need to be melted at a high temperature above 135 °C in order to fill the microcavities of the molds.[50,53] The high temperature and
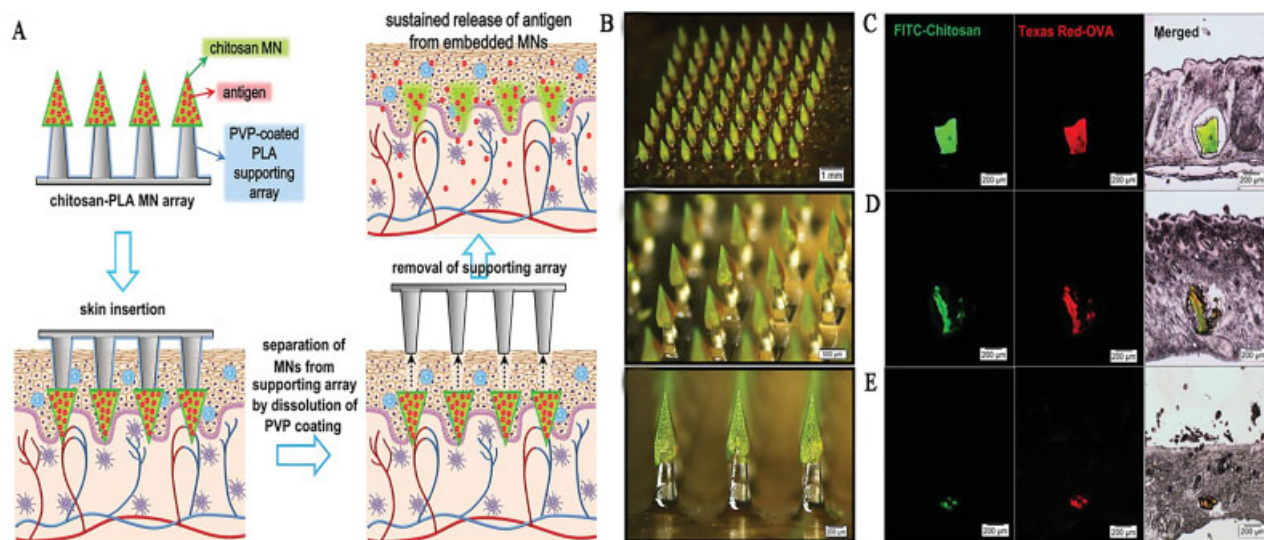
Fig. 1 Chitosan-based microneedles for sustained release of OVA. (**A**) Schematic illustration of the fabrication process. (**B**) Bright-field images of the microneedles. (**C–E**) Confocal images of the insertion sites after 1 day (**C**), 1 week (**D**), and 2 weeks (**E**). OVA, ovalbumin. (Adapted with permission from Chen et al 2013[38].)

organic solvent used in this method could cause the loss of drug efficacy.[55] The loading of hydrophilic drugs can be a challenge due to the immiscible nature of the drug and microneedle matrix. In some studies, hydrophilic drugs were first encapsulated into nano- or microparticles, and the particles were incorporated into the microneedles in the next step.[50,52]

Preparing degradable microneedles by postprocessing is an interesting alternative method that has been developed recently for overcoming the drawbacks mentioned above.[56–65] This approach combines the advantages of easiness for drug loading of dissolving microneedles during the preparation process and sustained release properties of biodegradable polymers. To prepare the microneedles, chemically modified water-soluble polymers were first used for the loading of drugs and vaccines. After molding, the fabricated microneedles were crosslinked or crystallized by chemical or physical treatments including UV exposure, organic solvent treatment, etc. After the postprocessing, the polymers became non-water soluble and thereby could slowly release the drug during degradation. Studies have shown that the crosslinked or crystallized microneedles can significantly improve the stiffness of microneedles and extend the release time of the payloads. The matrices used for this type of microneedles include crosslinked methacrylated hyaluronic acid (MeHA),[57,61,63–65] crosslinked PVA,[66] genipin-crosslinked gelatin,[58] crystallized silk fibroin,[59,60] and crosslinked alginate.[67]

Researchers from Gu et al's group fabricated crosslinked MeHA microneedles and applied them for the delivery of checkpoint inhibitors, tumor lysates, and insulin (►**Fig. 2**).[57,61,63–65] HA was first modified with a methyacrylamide group and filled into micromolds together with methylenebisacrylamide and a photoinitiator for microneedle fabrication. After UV exposure, the polymers form a water-insoluble network entrapping the drug, allowing for sustained release of drug for over several days.[57,61,65] The

methyacrylation rate of HA and the exposure time to UV light have been shown to influence the mechanical strength of microneedles and release properties of the payloads. Similarly, they modified PVA with the methyacrylamide group and fabricated crosslinked PVA microneedles for sustained release of payloads.[66]

Silk fibroin can be used for microneedle preparation due to their excellent mechanical properties, biocompatibility, and biodegradability.[68,69] However, microneedles made of silk fibroin without any processing cannot control the release rate of the payloads.[70] Recent studies showed that the degradation rate of silk fibroin and the diffusion rate of the payloads can be controlled by postprocessing the microneedles with methanol or high humidity exposure, by changing the secondary structure of the silk fibroin.[71–73] Tsioris et al modified silk fibroin with water vapor annealing for modulation of the degradation properties of silk fibroin. They showed that the processed silk fibroin had higher content of β sheet secondary structure, and the drug release rate was decreased by 5.6-fold compared with nonmodified microneedles.[60] Jiyong et al. treated silk-fibroin-based microneedles with methanol, and found that the exposure time to methanol can be used to control the drug release rate.[59]

Bioresponsive Microneedles Made of Bioresponsive Polymers

The slow-dissolving microneedles and degradable microneedles can deliver the loaded drugs and vaccines in a sustained manner, which is predetermined by the dissolution and biodegradation rate of the polymers. Bioresponsive microneedles, in contrast, can respond to the physiological signal and release the payloads smartly according to the change of the physiological signals.[74,75] This character of the microneedles can be achieved via the loading of drugs in bioresponsive polymers or secondary encapsulation of drugs in physiological signal-sensitive micro- or nanoparticles.[76–78] The microneedles keep

Fig. 2 Crosslinked MeHA microneedles used for delivery of checkpoint inhibitors and tumor lysates. (**A**) Schematic of anti-PD-1 delivery by crosslinked MeHA microneedles. (**B**) Scanning electron microscopy (SEM) image of anti-PD-1-loaded microneedles. (**C**) In vitro release of anti-PD-1 from crosslinked MeHA microneedles. (**D**) Schematic of sustained delivery of tumor lysates by crosslinked MeHA microneedles. (**E**) SEM image of tumor-lysate-loaded microneedles. (**F**) In vitro release of tumor lysates from the microneedles. MeHA, methacrylated hyaluronic acid. (Adapted with permission from Wang et al 2016[57] and Ye et al 2017[61].)

the drug in the matrix, while the particles can respond to the physiological signals and release the drug in a sustained manner.

The bioresponsive microneedles that have been reported in the literature are mainly glucose-responsive ones (►**Table 2**).[66,79,80] In this system, the glucose oxidase is an essential component which is normally encapsulated inside of nanoparticles embedded in the microneedle matrix. The glucose oxidase can catalyze the oxidation of high concentration of blood glucose and produce H_2O_2, which in turn stimulates the release of insulin from H^+- or hypoxia-sensitive nanoparticles. This process finally can lead to a closed loop and regulate the insulin delivery in a bioresponsive manner. For example, researchers fabricated bioresponsive microneedles loaded with pH-sensitive and insulin-loaded nanoparticles. The H_2O_2 produced from the oxidation of glucose by glucose

oxidase successfully triggered the release of insulin from the nanoparticles.[66,80] In these two studies, the outer layer of microneedles was loaded with a catalyzing enzyme for scavenging excess H_2O_2 to protect normal tissues from injury caused by oxidative stress.[66] Similarly, Chen et al fabricated crosslinked alginate microneedles loaded with dual-mineralized nanoparticles for encapsulation of exendin-4 and glucose oxidase separately. The H^+ produced by enzyme oxidation of blood glucose stimulated the disassembling of mineralized nanoparticles, leading to bioresponsive release of insulin.[79]

Application of Microneedles with Sustained Delivery Properties

Fast dissolving microneedles have the limitation that the drug release patterns cannot be precisely controlled. Sustained

release microneedles open up new therapeutic utility for applications which require constant delivery of the drugs. The microneedles with sustained delivery properties can potentially be used to improve therapeutic potency, decrease administration frequency, and reduce side effects. The applications that have been investigated so far are immune modulation, cancer therapy, and diabetes treatment.

Immune Modulation

The skin harbors abundance of antigen-presenting cells, including Langerhans cells in the epidermis and dendritic cells in the dermis, making the skin an important site for vaccination.[81–85] It has been shown that intradermal vaccination can result in stronger immune responses as compared with subcutaneous and intramuscular vaccinations.[86–89] Furthermore, the vaccination using microneedles can avoid pain sensation and significantly reduce the stress of recipients as compared with injection by traditional hypodermic needles, which is especially important for vaccination of young children.[90,91]

Sustained release microneedles can be used to further improve the immunogenicity of the loaded antigen. During natural infection with microorganism, the pathogens replicate typically over several weeks and therefore continuously expose the antigen to the immune system. As a result, the induced immune response is normally strong.[92,93] Previous studies have also shown that the sustained delivery of antigens and adjuvants from nanoparticles can potentially increase the immune responses.[94–97] Microneedles with a sustained release behavior can be used as a painless and patient-friendly alternative mimicking this natural infection for improving the immunogenicity of antigens.[53,56] One study showed that by using silk-fibroin-fabricated microneedles for sustained delivery of loaded OVA, the elicited antibody titers was 10-fold higher than that elicited by traditional hypodermic-needle-injected antigens (►**Fig. 3**).[56] The same group also investigated PLGA-based microneedles for intradermal delivery of OVA and found that the sustained delivery of OVA significantly increased T-cell responses although did not improve antibody titers.[53]

Another disadvantage of traditional hypodermic-needle-mediated immunization is that normally multiple injections are needed to stimulate robust immune responses.[98] As a result, the recipients may fail to follow the entire program for successful immunization. On the other hand, these disadvantages bring several burdens for caregivers, especially during large vaccination campaigns. The use of sustained release microneedles for vaccination thereby has potential to significantly improve the vaccine coverage and reduce the work of caregivers.[99] To the best of the authors' knowledge, however, there are no studies reported to date investigating the potential of sustained release microneedles for reducing immunization frequency.

Cancer

Recently, cancer treatment with immune therapy by harnessing the immune system has achieved great progress, including immunotherapy by using checkpoint inhibitors and cancer vaccines. These strategies aim at stimulating the immune system or remodeling the tumor microenviron-

ment, and finally eliciting potent CD8$^+$ T-cell responses for clearance of cancerous cells.[100–102] Immunotherapy strategies by using anti-PD-1 and anti-CTLA-4 have achieved encouraging results in clinical trials and are now revolutionizing cancer treatments.[103] However, the response rate is relatively low and cancer-type-dependent.[104,105] Researchers have tried to combine different immune reagents and treatment strategies to achieve synergetic antitumor efficacy. Microneedles with sustained release properties provide a good platform for this purpose for remodeling immune microenvironments and stimulating the immune system.

Wang et al developed a self-degradable microneedle patch composed of anti-PD-1 and glucose oxidase that are loaded in pH-sensitive dextran nanoparticles. After insertion into the skin, the pH was decreased due to the oxidation of glucose and production of H$^+$, which triggered the degradation of the nanoparticles for sustained release of anti-PD-1. This self-degradable microneedles induced stronger immune responses and antitumor potency compared with microneedles without self-degradation property.[57] Ye et al loaded B16F10 tumor lysates and photothermal reagents in crosslinked MeHA microneedles. The results showed that the developed microneedles could continuously release loaded tumor lysates under exposure to laser light. This combined strategy elicited potent antitumor effects and significantly increased the survival rate of tumor-bearing mice.[61] They also developed crosslinked MeHA microneedles for co-loading of anti-PD-1 and IDO (indoleamine 2,3-dioxygenase) inhibitor 1-MT. The sustained release of these two inhibitors successfully enhanced the retention of the checkpoint inhibitors in the tumor microenvironment. This system finally demonstrated a synergistic treatment effect against B16F10 mouse melanoma.[65]

Diabetes

For diabetes, subcutaneous injection and pump-mediated infusion of insulin are the main treatment strategies.[106] These delivery strategies, however, could cause complications including acute pain and inflammation due to frequent administrations for maintaining an appropriate blood concentration of insulin. Under this context, researchers have investigated the microneedle system for noninvasive and convenient intradermal delivery of insulin.[38,107–109] However, there are two limitations of these microneedle systems. First, the investigated microneedle systems cannot control the delivery kinetics of insulin and therefore have a short lasting time for glucose control. Second, the delivered dose of insulin is predetermined and there is a risk that the administrated insulin may exceed the amount that is needed, causing hypoglycemia which can be severe and lethal.[110–112] To extend the release time of insulin from the microneedle system, researchers utilized biodegradable microneedles for sustained release of insulin.[58,113] These systems have shown to be able to extend the release of insulin and maintain the glucose level in a stable range within 10 to 12 hours. For instance, Chen et al fabricated genipin-crosslinked gelatin microneedles for sustained delivery of insulin. They observed that the crosslinking degree of gelatin could affect the mechanical strength and release profile of the microneedles. The microneedles with a higher crosslinking degree
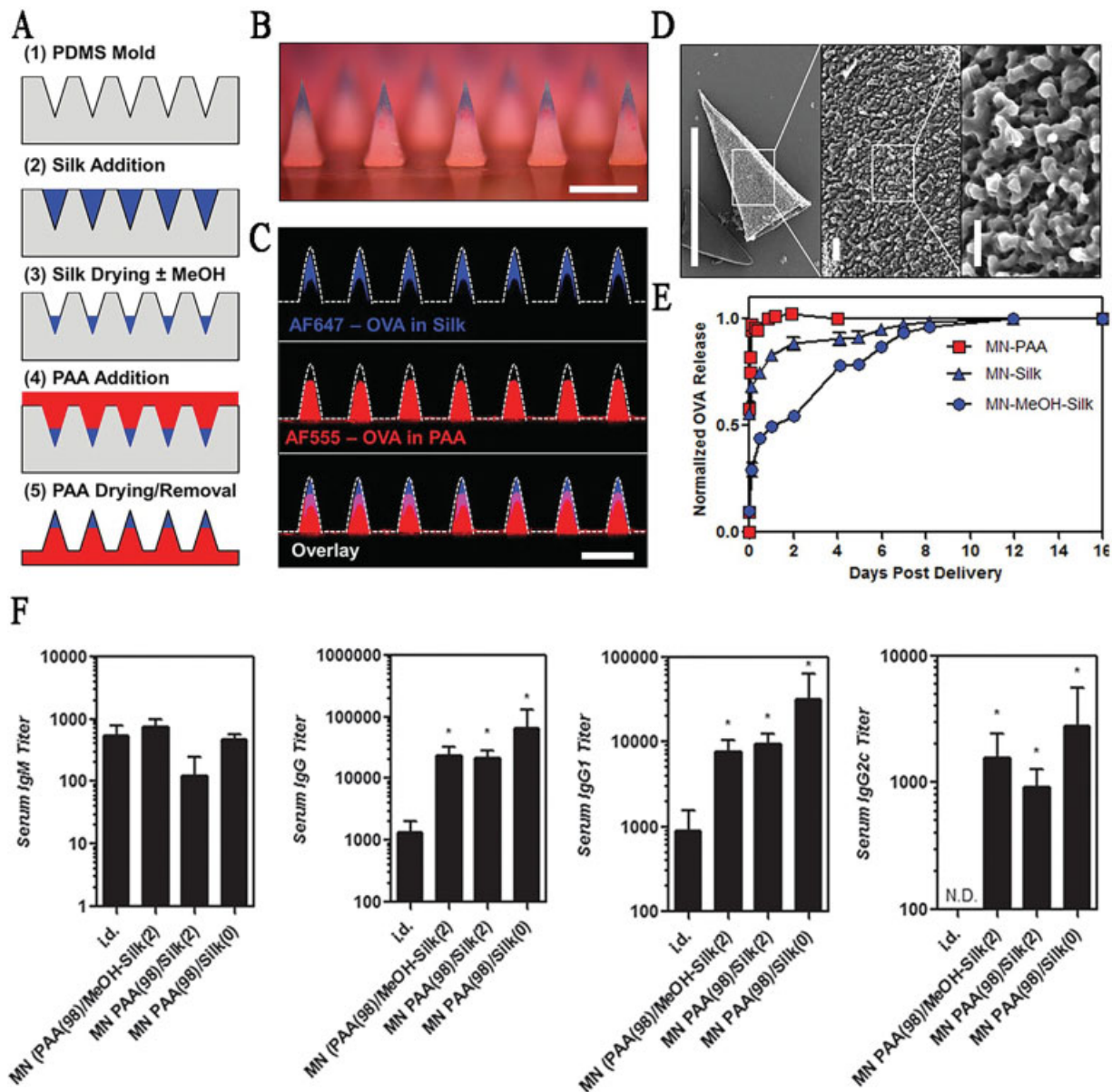
Fig. 3 Crystallized silk fibroin microneedles used for modulation of immune response. (**A**) Schematic of fabrication of microneedles. (**B**) Optical images of OVA-loaded microneedles. (**C**) Confocal images of OVA-loaded microneedles. (**D**) SEM image of a single microneedle. (**E**) In vitro release of OVA from the microneedles. (**F**) Antibody immune responses after immunization with the sustained release microneedles in mice. OVA, ovalbumin; SEM, scanning electron microscopy. (Adapted with permission from DeMuth et al 2014[56].)

could more prolong the release of insulin and improve the therapeutic effectiveness of insulin as compared with traditional subcutaneous injection.[58] Seong et al fabricated microneedles with a bullet shape made of swellable polystyrene-block-poly(acrylic acid) (PS-PAA) for intradermal delivery of insulin. They showed that after inserting microneedles into the skin, the loaded insulin could be delivered through passive diffusion due to the swelling of the tip matrix. The in vitro release study showed that the microneedles had released around 60% of the payloads for over 12 hours. In a rat diabetes animal model, the microneedle administration had led to a gradual decrease of blood glucose levels for over 8 hours.[113]

One risk of traditional insulin injection is that excess insulin may cause hypoglycemia. Therefore, a new "smart" system for insulin delivery is urgently needed that can deliver desirable

amounts of insulin when the blood glucose level is high while maintaining the basal release rate of insulin when the blood glucose level is normal. To this end, researchers developed bioresponsive microneedles that can precisely release the loaded insulin in response to the blood glucose level, as discussed in the section of "bioresponsive microneedles." This system could help create a closed loop for insulin delivery, avoiding the risk of excessive delivery of the drug. Zhang et al developed crosslinked MeHA bioresponsive microneedles for entrapment of insulin and glucose oxidase. The results showed that the developed system can effectively regulate the blood glucose level within a normal range for around 12 hours after administration of one microneedle patch on a diabetic mice model (►**Fig. 4**).[66,80] Wang et al also investigated the multiple microneedle administration and monitored the blood glucose

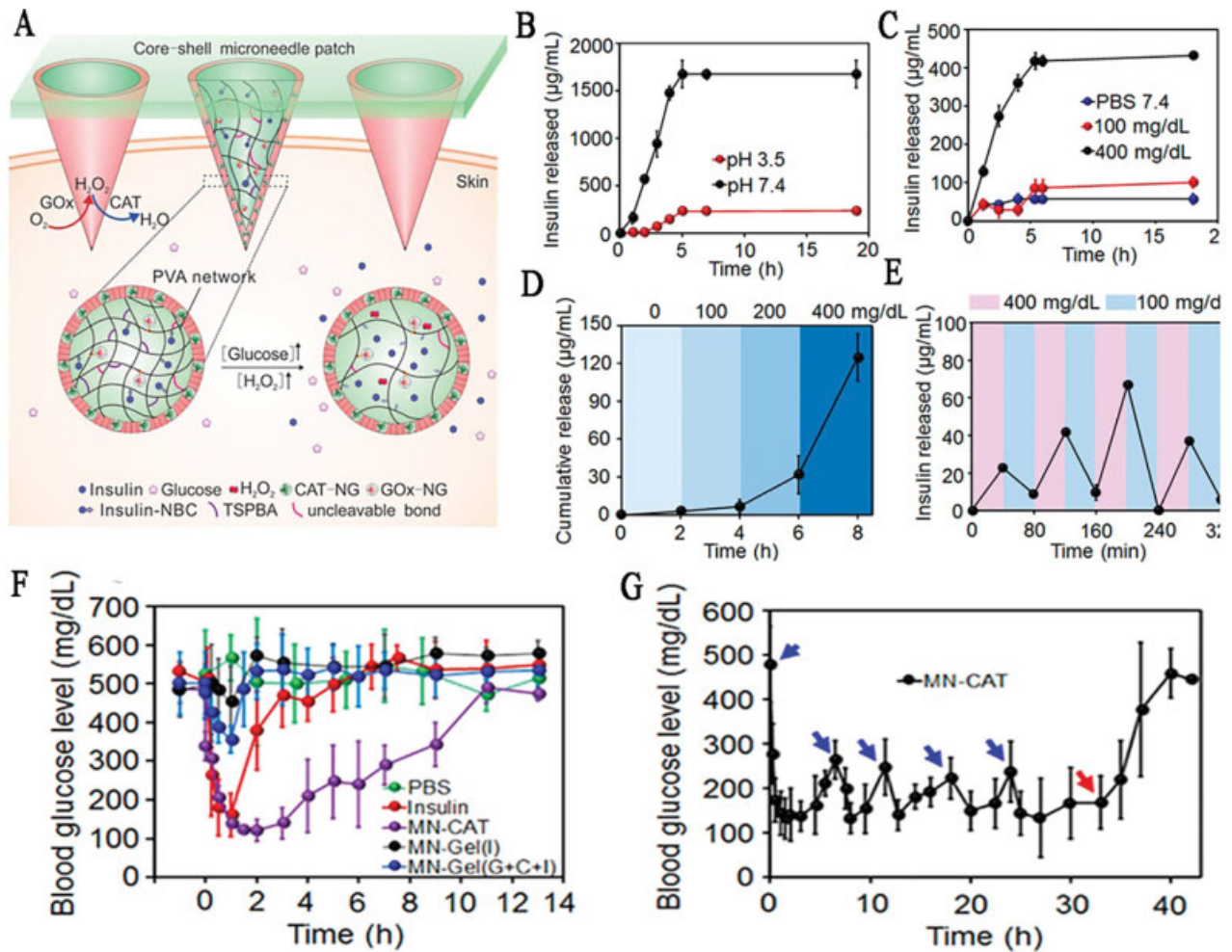**Fig. 4** Crosslinked PVA-based bioresponsive microneedles for regulation of blood glucose level. (**A**) Schematic of fabrication of microneedles. (**B**) The release of insulin from crosslinked PVA gel at different pH values. (**C**) The release of insulin from crosslinked PVA gel at different glucose concentrations. (**D**) The release of insulin with different concentrations of glucose. (**E**) Self-regulated release of insulin in response to glucose level. (**F**) The blood glucose level for over 14 hours after application of one microneedle patch on diabetes mice model. (**G**) The blood glucose level for over 40 hours after application of multiple microneedle patches on diabetes mice model. PVA, polyvinyl alcohol. (Adapted with permission from Ye et al 2016[66].)

level for 40 hours. They found that within this time period, the blood glucose level was regulated to a narrow range between 100 and 250 mg/dL without any hypoglycemia observed.[66]

Other Applications

The sustained release microneedles were also investigated for other applications, including ocular disease,[51] contraception,[54] and antibacterial.[60] In these studies, the microneedles were used to maintain and achieve sufficient therapeutical levels of the payloads with less administration frequency, aiming for better patient acceptance, improved safety, and stronger therapeutic efficacy.

Conclusion and Perspectives

Sustained release microneedles have shown superior delivery efficacy as compared with fast-dissolving microneedles. However, there are still several aspects that need to be further investigated or optimized. First, the small drug loading capacity of the microneedles due to their small size and volume is a limiting factor for their clinical translation. Researchers have utilized centrifugation, repeated filling, and evaporation for enrichment of drug solution or drug-loaded nanoparticles in microcavities.[66,67] Other ways for increasing the drug-loading capacity could be enlarging the size of the microneedle patch or developing new polymers with higher solubility or packing capacity of drug molecules. Second, the strategies which have been used for preparing sustained release microneedles often include intense physical/chemical procedures that may impact the structure or functionality of biotherapeutics, such as high temperature, use of organic solvent or UV light. New methods for minimizing the use of these intense conditions are still needed. Lastly, the effect of different release kinetics of the payloads from microneedle matrix on drug potency has not been systemically studied. Several studies have shown that by simply adjusting the components of the microneedle matrix or adjusting chemical modification level of the polymers, the release kinetics can be regulated and optimized. More in-detailed mechanism and comparison studies are needed.

Currently, there are dozens of clinical trial reports on investigating microneedle systems for treating diabetes, psoriatic plaques, topical anesthesia, and influenza vaccination.[37,114,115] In most of these studies, commercially available hollow-microneedle systems were used while the clinical studies of polymeric microneedles are limited.[116–120] Two phase I studies have investigated the piercing ability and safety of HA-based dissolving microneedles. The results showed that with the assistance of an applicator, the microneedles can be reproducibly penetrated into the skin with no obvious side effect.[121,122] In another phase I clinical study, the safety and immunogenicity of HA-based dissolvable microneedles for delivery of H1N1, H3N2, and B seasonal influenza virus vaccine strains have been studied. The results showed that the designed microneedle patch is tolerable and can induce robust immune response.[5] These studies revealed the potential for clinical translation of polymer microneedles. However, as far as we know, there are no clinical studies reported to date on the sustained release microneedles.

In conclusion, the microneedles with sustained release properties of drugs or vaccines have been successfully developed and applied for immune modulation and disease treatment in mice models. Many of them have shown superior potency than traditional fast-dissolving microneedles or free drug/vaccine formulations, revealing the potential of this strategy to be used as a patient-friendly replacement for conventional sustained release methods. Future success of this technology and clinical translation will rely on the combined efforts from researchers of engineering, pharmaceuticals, and immunology.

Conflict of Interest
None declared.

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