



A boronate gel-based synthetic platform for closed-loop insulin delivery systems

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Abstract

Diabetes is one of the most devastating global diseases with an ever-increasing number of patients. Achieving persistent glycemic control in a painless and convenient way is an unmet goal for diabetes management. Insulin therapy is commonly utilized for diabetes treatment and usually relies on patient self-injection. This not only impairs a patient's quality of life and fails to precisely control the blood glucose level but also brings the risk of life-threatening hypoglycemia. "closed-loop" insulin delivery systems could avoid these issues by providing on-demand insulin delivery. However, safety concerns limit the application of currently developed electronics-derived or enzyme-based systems. Phenylboronic acid (PBA), with the ability to reversibly bind glucose and a chemically tailored binding specificity, has attracted substantial attention in recent years. This focus review provides an overview of PBA-based versatile insulin delivery platforms developed in our group, including new PBA derivatives, glucose-responsive gels, and gel-combined medical devices, with a unique "skin layer" controlled diffusion feature.

Introduction

As the seventh leading cause of death, diabetes mellitus is one of the most challenging global issues [1, 2]. More than 463 million people were living with diabetes in 2019, and the number is expected to increase dramatically to 700 million in 2045 [3]. Insulin is commonly used for the treatment of patients with type I and advanced type II diabetes and is usually self-administered by subcutaneous injection multiple times per day [4–6]. It is difficult to maintain persistent glycemic control, and more importantly,

hypoglycemia caused by overdose may lead to behavioral and cognitive disturbance, brain damage, or even death [7, 8]. Therefore, "closed-loop" insulin delivery systems mimicking the pancreas to secrete insulin in response to hyperglycemia are highly desirable [9–11]. Electronics-based artificial pancreas can efficiently control blood glucose levels and reduce the risk of hypoglycemia [9, 12, 13]. However, its high cost, risk of electronic failures, discomfort associated with needle-tipped catheter insertion under the skin, a long time to establish a learning curve, and frequent calibration limit its wide application [14, 15].

Consequently, electronics-free, chemically controlled glucose-responsive systems have attracted constant research interest [16–18]. Compared to the widely exploited glucose-sensitive enzymes such as glucose oxidase (GO_x) and glucose-binding proteins such as concanavalin A (Con A), synthetic phenylboronic acid (PBA) has advantages due to its high stability, durable glucose sensitivity, suitability for large-scale production, and lack of denaturation and immunotoxicity concerns [19–22]. It can reversibly bind with 1,2- or 1,3-cis-diols, including glucose, through boronate ester formation in an aqueous solution [23, 24]. By fine-tuning the stereochemistry and electronic affinity, the binding strength and specificity of PBA with glucose can be well controlled [25–27]. All these characteristics make PBA an attractive candidate for glucose sensing and self-regulated insulin delivery.

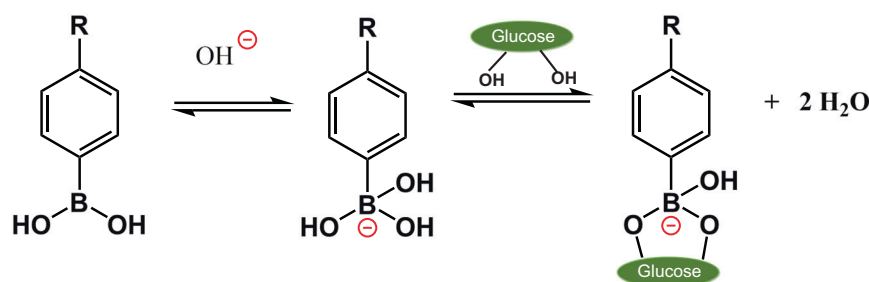
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Scheme 1 Glucose-dependent equilibria of PBA derivatives

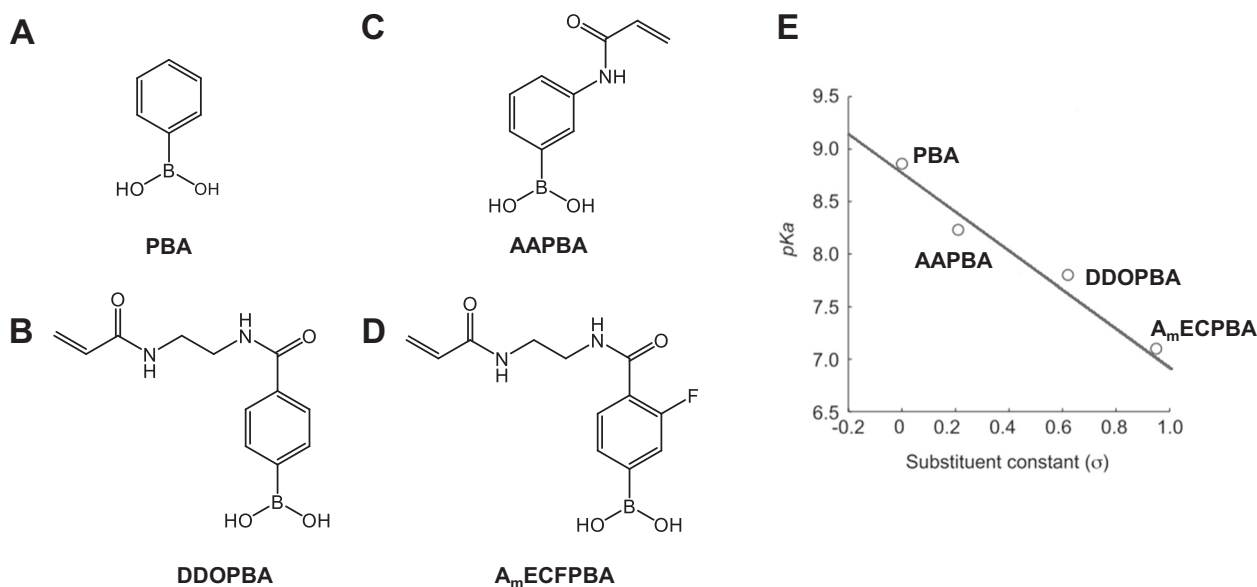


Fig. 1 Chemical structure of **A** PBA and **B–D** its derivatives. **E** The linear relationship between pK_a values and substituent constants of various PBAs

In this focus review, we summarized the recent progress our group achieved in the area of PBA-based glucose-responsive systems for self-regulated insulin delivery, including PBA monomers with decreased pK_a values, PBA-based glucose-responsive gels, and PBA gel-combined catheter and hollow fiber medical devices. Their therapeutic effectiveness was validated in vivo. In addition, PBA hydrogels containing microneedles (MNs) for noninvasive transdermal application will be described.

PBA monomers with decreased pK_a values

As a Lewis acid, PBA in aqueous solution exists in equilibrium between a neutrally charged trigonal planar state and an anionic tetrahedral form in dynamic balance [28, 29]. When the pH of the solution is below the pK_a of PBA, most of the moieties are in neutral form and relatively hydrophobic. When the pH value is above the pK_a of PBA, the majority of the moieties are negatively charged. Upon the addition of glucose, the anionic

tetrahedral form can covalently bind with glucose in a reversible way, shifting the equilibrium toward the anionic form of PBA (Scheme 1) [30–32]. As a result, it is commonly observed that the apparent pK_a of PBA decreases with the addition of glucose [33]. Such a glucose-dependent change in the PBA equilibria, when taking place in a gel network, translates into a change in the counterions' osmotic pressure, which dramatically affects the state of hydration of the gel. This dynamic PBA–glucose interaction gives PBA-functionalized materials great potential in glucose-responsive drug delivery [23, 34]. However, at physiological pH, charged phenylboronate, which is responsible for the complex with glucose, is formed in a limited fraction due to the relatively high pK_a of PBA (typically around 9, Fig. 1A) [35]. Thus, the pK_a of PBA needs to be decreased to achieve adequate function under physiological pH [36, 37].

In our group, a variety of PBA derivatives containing electron-withdrawing substituents on the phenyl ring were reported. By the introduction of a para-positioned carbonyl group into the phenyl ring, 4-(1,6-dioxo-2,5-diaza-7-oxamyl) phenylboronic acid (DDOPBA, Fig. 1B) was

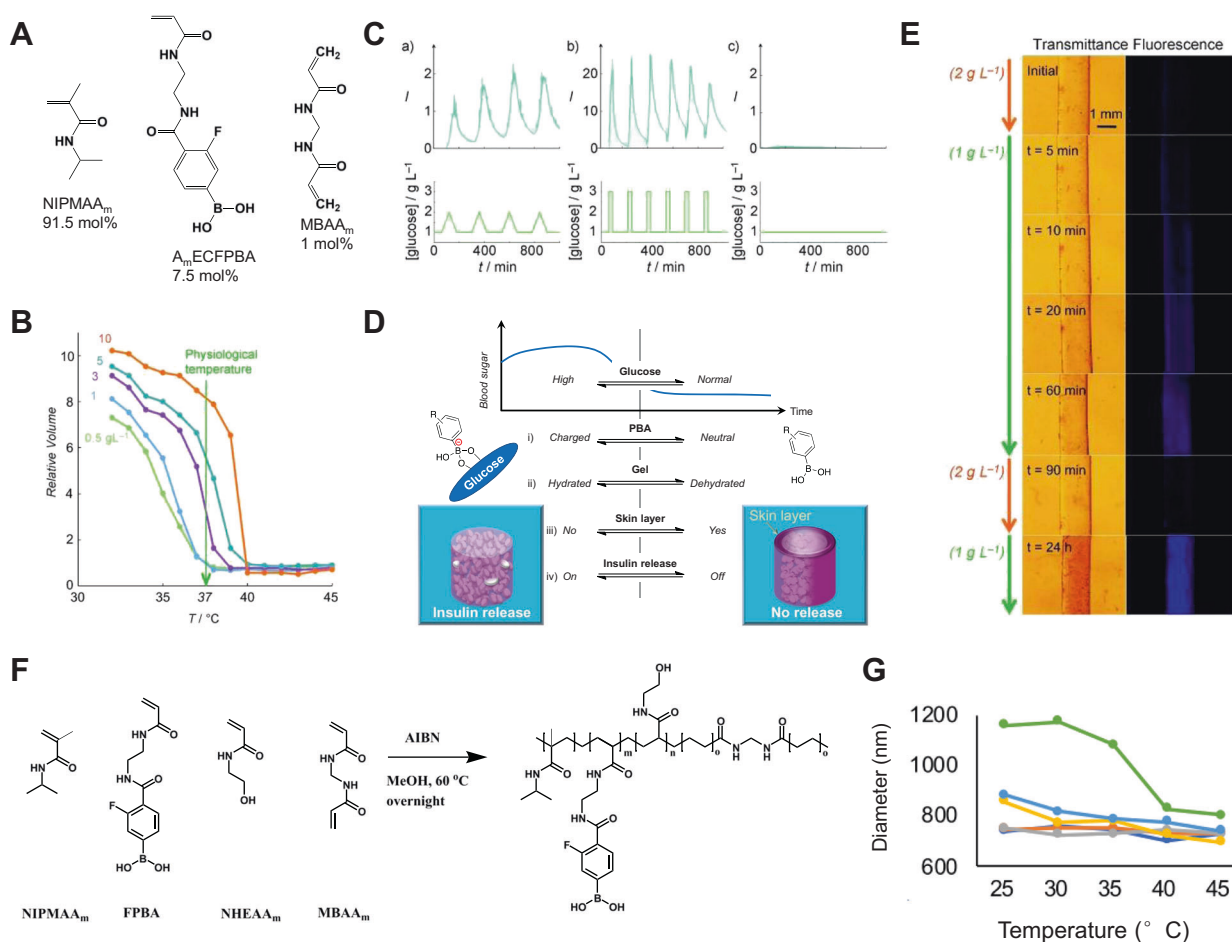


Fig. 2 **A** Optimized monomers and their molar amounts in the gel solution to achieve glucose responsiveness under physiological conditions. **B** Phase diagram of the gel showing the equilibrium volume changes under various temperatures and glucose concentrations at pH 7.4. **C** Time-course changes in the fluorescence intensity of FITC-insulin released from the gel under physiological conditions and the temporal patterns of the fluctuation in glucose concentration.

D Schematic of “skin layer” controlled self-regulated insulin release.

E Time-course transmittance and fluorescence images of a cylinder-shaped gel under different glucose concentrations. **F** Chemical structure of the gel with a temperature-independent function. **G** Phase diagrams showing the diameter change of the gel with optimized formulation at various glucose concentrations. Reproduced with permission from refs. [40, 45, 46]

synthesized [33, 38, 39]. Compared to its counterpart 3-acrylamidophenylboronic acid (AAPBA, $pK_a = 8.2$, Fig. 1C) with a meta-positioned amide group [23], DDOPBA shows a reduced pK_a value of 7.8 due to the relatively larger substituent constant ($\sigma = 0.62$) of the para-positioned carbonyl group and its strong electron-withdrawing effect. To further decrease the pK_a , a meta-fluoro group with a strong electron affinity to the phenyl ring was introduced to DDOPBA [40]. Usually, a fluorocarbon group is very hydrophobic, which may reduce the phase transition temperature of the PBA-bearing gel and limit its application [41]. However, the new derivative 4-(2-acrylamidoethylcarbamoyl)-3-fluorophenylboronic acid (A_m ECFPBA, Fig. 1D) containing para-carbamoyl and meta-fluoro substituents is capable of decreasing this side effect. The pK_a value is decreased to 7.2, which is ideally lower than the physiological pH.

PBA-based glucose-responsive gels

To take one step further, A_m ECFPBA was combined with acrylamide and methacrylamide to create copolymer gels for on-demand insulin delivery [40, 42]. By fine-tuning the hydrophobic/hydrophilic balance, the synthesized gel with an optimized formulation (NIPMAAm: A_m ECFPBA:MBAAm = 91.5:7.5:1, Fig. 2A) displayed a volume phase transition corresponding to the glucose concentration, with a threshold value of normal glucose level (100 mg/dL) at physiological conditions (pH 7.4, temperature 37 °C, Fig. 2B). Figure 2C shows the time-course insulin release profile from the gel under different glucose treatment patterns under physiological conditions. The release of insulin from the PBA gel was well correlated with the glucose pattern change. Furthermore, when increasing the glucose concentration from 1–2 to 3 g/L, a tenfold increase in the insulin release rate was observed.

Under normoglycemia conditions for at least 16 h, no insulin release was detected. These results demonstrate that this protein-free, totally synthetic PBA gel can function as a self-regulated insulin delivery system that is capable of tightly regulating the released insulin dosage without the risk of causing hypoglycemia.

The mechanism of self-regulated insulin release was further explored. As explained in Fig. 2D, due to the glucose-dependent shift in the equilibria of PBA, upon an abrupt decrease in glucose concentration, the surface of a PBA-containing gel changes rapidly from a swollen hydrophilic state into a shrunken hydrophobic state. The thus-formed “skin layer,” which is a microscopically thin, dehydrated layer [43], was able to control the diffusion of the loaded insulin molecules. Since the binding of PBA with glucose is reversible, if the glucose concentration rises again, the skin layer disappears with gel hydration, and the amount of insulin released is restored. Hence, by optimizing the chemical structure of PBA (tuning the pK_a), the cross-linking density, and the molar ratio of various monomers, the skin layer could rapidly form at normal blood glucose levels, thus effectively switching insulin release in a “gated” manner when hitting the normoglycemia level under physiologically relevant conditions [26, 42, 44].

The formation of the expected skin layer was confirmed by confocal microscopy with 8-anilino-1-naphthalene sulfonic acid (ANS) as an environmentally responsive pigment. Since the fluorescence intensity of ANS is increased when the permittivity of its surrounding environment decreases, the formation of the skin layer, which leads to reduced water content on the gel surface, could be visualized by this method [40]. As shown in Fig. 2E, under hyperglycemic conditions (2 g/L), negligible fluorescence intensity was observed due to hydration of the gel. Instead, a dramatic increase in fluorescence intensity is observed when decreasing the glucose concentration to the normal blood sugar level (1 g/L), indicating the formation of the skin layer. When returning to the hyperglycemic state, the fluorescence suddenly disappeared, confirming the reversible formation of the skin layer. Thus, this gel system could effectively switch insulin release in a “gated” manner after reaching the normoglycemia level of glucose.

To further eliminate the safety concern that hampers the clinical application of the gel, its temperature dependency should be minimized. One straightforward approach is to decrease the thermosensitive NIPMAA_m fraction. However, this consequently increases the A_mECFPBA fraction and thus leads to excessively enhanced hydrophobicity and results in loss of function under physiological temperature [40]. To solve this dilemma, hydrophilic *N*-hydroxyethylacrylamide (NHEAA_m)-bearing hydroxyl groups were introduced in the gel network to serve as intermolecular cross-linkers via boronate ester formation with

A_mECFPBA while also increasing the hydrophilicity of the overall network (Fig. 2F). By fine-tuning the hydrophobic/hydrophilic balance, the optimum formulation (NIPMAA_m:FPBA:NHEAA_m:MBAA_m = 39.56:16.95:38.48:5.00) achieved a temperature-independent closed-loop function in the temperature range of 25–45 °C (Fig. 2G), which is critical for in vivo application to avoid unwanted burst insulin release immediately after implantation.

PBA gel-combined devices

Our totally synthetic gel-based technology, taking advantage of the skin-layer mechanism, should offer crucial advantages over those involving proteins or nanoparticle formulations in terms of establishing both acute- and long-term release controls. In addition, the readiness of the preparation enables a combination with existing medical devices. Based on this idea, we developed a catheter-combined device [45]. Figure 3A shows the morphology and preparation method of this catheter-combined device. The pregel solution was loaded into a 4-French silicone catheter bearing penetrating openings to fill the whole inner wall and the openings, followed by gelation upon heating. Glucose-dependent insulin release could be well controlled by the skin layer formed in the openings (Fig. 3B). To increase the biocompatibility and reinforce the mechanical integrity, the surface of the device was coated with poly(ethylene glycol). The gel-modified catheter was then cut into 15-mm long pieces and connected with another non-treated long catheter (11 cm) serving as an insulin reservoir. This catheter device meets the clinical biosafety requirements according to in vitro cytotoxicity and histological examinations (Fig. 3C).

The therapeutic effectiveness of the catheter device was evaluated in vivo. In the glucose tolerance test (Fig. 3D), the glucose-lowering effect was observed as soon as 15 min after glucose injection in healthy mice implanted with a gel-combined catheter. In line with this, a remarkable increase in serum insulin was detected synchronized with acute glucose injection. More advantageously, therapeutic effectiveness was well maintained even after 3 weeks of implantation. These results clearly demonstrate the durability and stability of this device. The glucose-responsive insulin release of this device was further examined in diabetic mice. A significant decrease in blood glucose concentration was noted in diet-induced type II diabetic mice treated with the recombinant human insulin-loaded catheter device (Fig. 3E). More importantly, the device treatment remarkably decreased the serum mouse C-peptide concentration (Fig. 3F), indicating that the device effectively mitigates obesity-induced hyperinsulinemia. Figure 3G shows the glucose tolerance test in STZ-induced type I diabetic mice. The catheter device effectively decreased the blood glucose

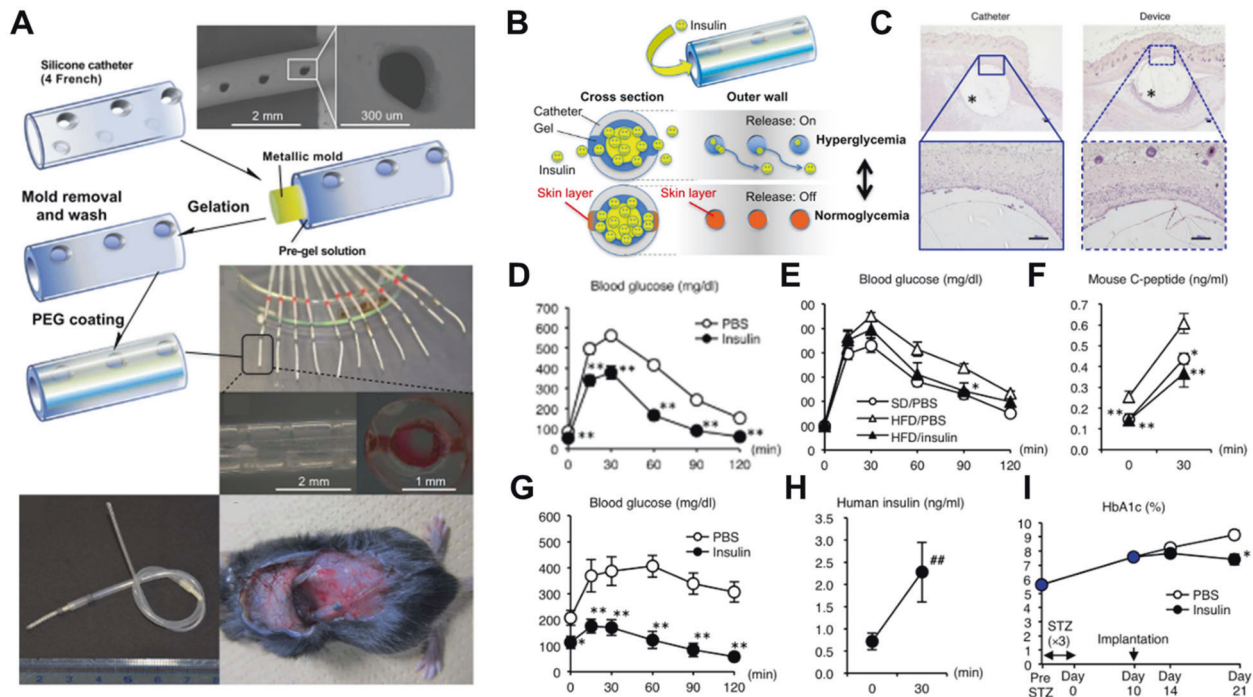


Fig. 3 **A** Morphology and fabrication method of the catheter-combined device. **B** Schematic of glucose-responsive insulin regulated by the skin layer. **C** H&E staining images showing the subcutaneous tissue surrounded by the implanted catheters. **D** Glucose tolerance test (GTT) of healthy mice implanted with catheter devices containing PBS and

human insulin. **E** Blood glucose concentration and **F** mouse C-peptide concentration of type II diabetic mice in the GTT. **G** Blood glucose concentration and **H** human serum insulin concentration of type I diabetic mice in the GTT. **I** HbA1c levels of type I diabetic mice implanted with devices. Reproduced with permission from ref. [45]

concentration to a normal level within 1 h and effectively controlled glucose fluctuation. Considerably increased human insulin was detected in the serum (Fig. 3H), and a significantly decreased hemoglobin A1c (HbA1c) level was observed in type I diabetic mice treated with the insulin-containing device after 21 days (Fig. 3I). This smart catheter-combined device could show therapeutic effectiveness under both insulin-deficient and insulin-resistant conditions, suggesting its potential for clinical application.

To further explore the scalability and efficacy for daily blood glucose fluctuations, we recently developed a hollow fiber-combined device that is scaled suitably for rats [46]. Due to the diffusion-dependent nature of the gel, the insulin release rate could be easily scaled up by increasing the surface area of the gel. Hence, we introduce a thin coating of the gel with temperature-independent behavior throughout the hemodialysis fiber to develop a hollow fiber device (Fig. 4A). Compared to the previously described catheter-combined device, this hollow fiber device consists of 25 fibers and thus dramatically increases the diffusion-active surface area. The gel-installed region was protected by a cellulose dialysis membrane to prevent fibrillation during implantation and connected with an insulin reservoir by glue (Fig. 4B). In vitro insulin release challenged by different glucose patterns was investigated and further analyzed by a mathematical model to

gain a quantitative basis for scaling. In vivo evaluation in type I diabetic rats was performed, and the weight was approximately ten times that of the mice. The in vivo results suggest that the subcutaneously implanted device responded rapidly to acute blood glucose level changes and that the blood glucose-lowering effect was sustainable for at least 7 days (Fig. 4C). Figure 4D shows remarkably decreased HbA1c levels in the diabetic rats treated with the insulin-loaded device. No significant change in the population of white blood cells was observed, suggesting its biosafety. Remarkably, this device could even show a marked benefit in coping with glucose spike-like symptoms (daily glucose fluctuations) over the timescale of a day, to our knowledge, for the first time using an electronics-free system (Fig. 4E). Recent clinical studies have revealed that not only sustained elevation of blood glucose levels but also glucose fluctuation represents key determinants for diabetic complications and mortality, thus forming the consensus that care must be taken to evaluate the daily blood glucose fluctuations as much as the commonly used fasted blood glucose levels and HbA1c to maximize the efficacy of the treatment. With inherent stability, diffusion-dependent scalability, and week-long and acute glucose responsiveness, our PBA gel technology may offer a low-cost alternative to current electronics-based approaches.

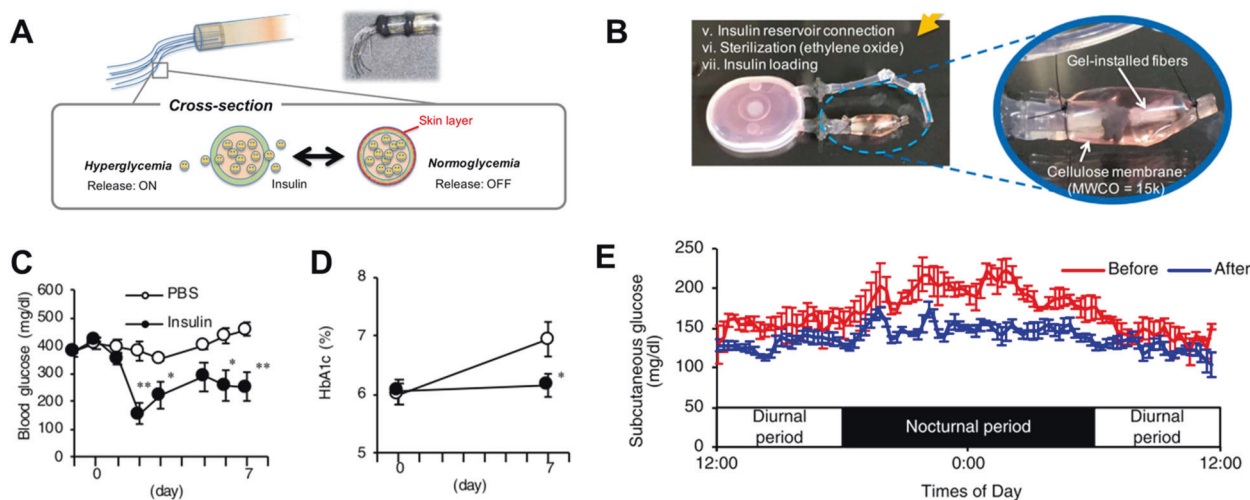


Fig. 4 **A** Schematic of the gel-combined hollow fiber with closed-loop functionality. **B** The appearance of the hollow fiber device. **C** The blood glucose concentration of type I rats implanted with hollow fiber devices containing PBS or human insulin. **D** HbA1c levels of type I

rats before and after 7 days of implantation. **E** Daily glucose fluctuations in mildly diabetic rats before and after device implantation. Reproduced with permission from ref. [46]

PBA gel containing MNs

Traditional insulin injection is painful and inconvenient and may be associated with microbial contamination and nerve damage [5, 6]. MN technology has the possibility to overcome these limitations. MNs typically contain sharper needles than hypodermic needles, with a length range of approximately several hundred micrometers [47, 48]. These characteristics enable MNs to effectively disrupt the stratum corneum, which is the main barrier that hampers the transdermal delivery of insulin [49–51]. Since MNs only form microscale channels on the skin and the needle length is not long enough to reach the nerve endings in the dermis, an MN patch is minimally invasive and could eliminate injection pain [52–54]. By incorporating glucose-sensitive elements into MNs, it is promising to achieve on-demand painless insulin delivery without human intervention [55–57].

Our recent work reported an enzyme-free MN array patch composed of a PBA-containing hydrogel that established sustained and acute glucose-responsive insulin delivery (Fig. 5A) [58]. To ensure sufficient mechanical strength for skin insertion, biocompatible and mechanically robust silk fibroin derived from the silkworm *Bombyx mori* was incorporated into the NIPAA_m/A_mECFPBA hydrogel to form a semi-interpenetrating network (Fig. 5B). As shown in Fig. 5C, an increased wall thickness was observed in the cross-sectional morphology of the silk fibroin-containing semi-interpenetrating network hydrogel. Methanol treatment to physically crosslink the silk fibroin via intermolecular β -sheet crystallization further enhanced the surface roughness, indicating improved mechanical strength. To fabricate MNs utilizing this hybrid hydrogel, six fabrication methods were investigated and compared [59]. The two-layer strategy,

which allows the needle region to be formed by the semi-interpenetrating network hydrogel and the base layer part to be fabricated by silk fibroin, was chosen for MN fabrication, as it successfully formed sharp needle tips and avoided deformation of the base layer (Fig. 5D). Figure 5E shows the uniform distribution of insulin and hydrogel throughout the needle region. Due to the incorporation of mechanically robust silk fibroin, the MN array patch displayed considerably stronger mechanical strength than the other polymeric MNs and was capable of effectively penetrating the skin to create micropores for transdermal insulin delivery (Fig. 5F). The MN array patch was highly stable in an aqueous environment, showing no deformation and negligible weight loss even after 2 months of incubation in pH 7.4 PBS at 37 °C (Fig. 5G). More advantageously, as seen in Fig. 5H, acute and long-term insulin release in a manner that is highly synchronized with the glucose pattern was observed in this MN patch. Weekly long glucose-responsive insulin release could be achieved by reloading insulin in the drug reservoir, indicating its potential to provide long-term glycemic control without human intervention.

However, safety concerns remain because gel behavior is highly dependent on temperature, and skin temperature is remarkably affected by a number of factors, such as exercise, illness, and environmental changes. To solve this problem, the abovementioned temperature-independent formulation was applied to the MN patch [60], where the content of NHEAA_m was carefully optimized (Fig. 6A). As demonstrated in the phase diagram (Fig. 6B), with the optimized hydrogel formulation, that is, 60.7-mol% NIPAA_m, 10.7-mol% A_mECFPBA, and 23.8-mol% NHEAA_m, the glucose-dependent change in hydration was established in a temperature-insensitive fashion. A porous structure was

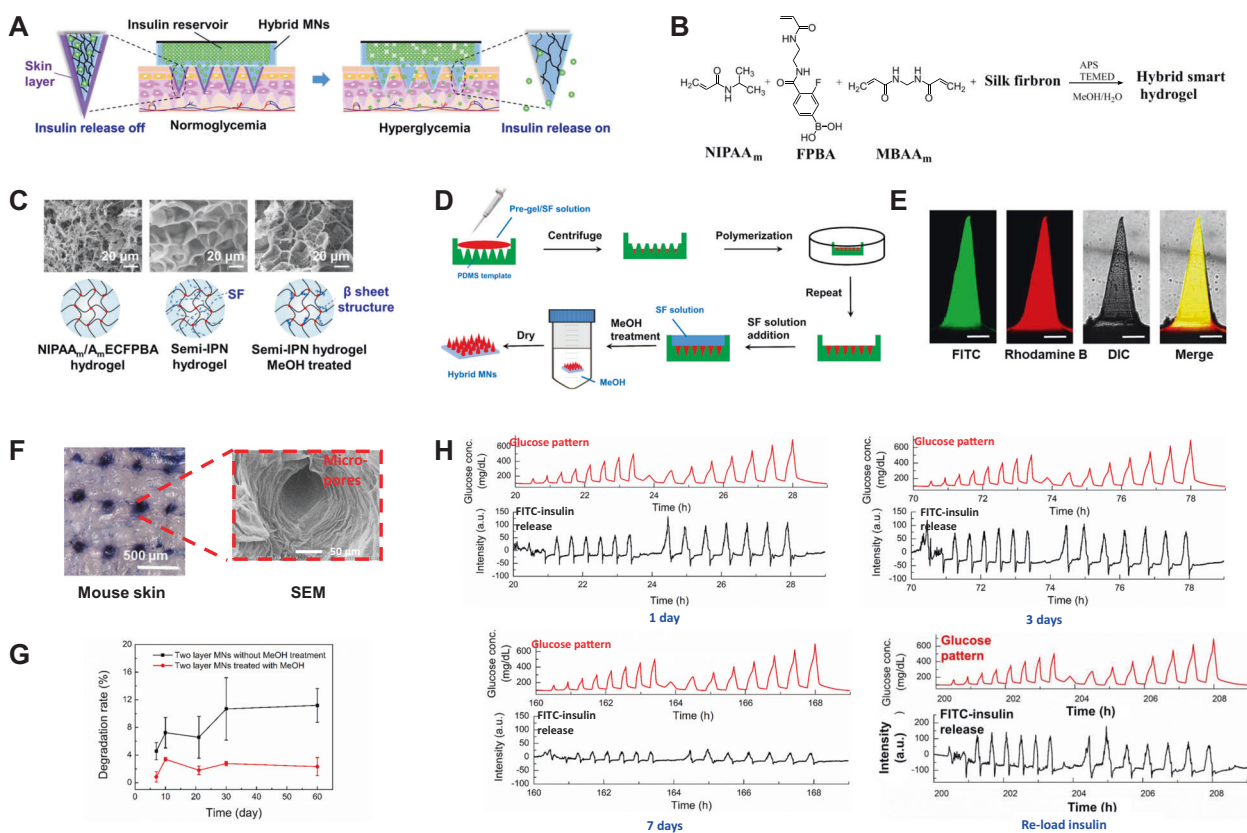


Fig. 5 **A** Schematic of a glucose-responsive gel combined with an MN array patch. **B** Synthesis of silk fibronin-composed semi-interpenetrating network hydrogel. **C** Cross-sectional SEM images of hydrogels. **D** Schematic of MN fabrication using a two-layer method. **E** Distribution of FITC-insulin and rhodamine B-traced hydrogels in the MN

array patch. **F** Micropores formed on the mouse skin after MN treatments. **G** Long-term stability assay of the MN array patch. **H** In vitro glucose-responsive insulin release from the MN array patch on days 1, 3, and 7 after insulin reloading. Reproduced with permission from ref. [58]

observed in this gel, indicating suitability for drug delivery (Fig. 6C). The gel was fabricated into a totally synthetic MN array patch using a two-layer strategy as described above, using crystallized PVA as the base layer (Fig. 6D, E). Rapid insulin release control of the two-layer MNs to the programmed glucose pattern was observed over a wide range of temperatures (28–39 °C, Fig. 6F), which could successfully eliminate the safety concerns of inadequate insulin release due to skin temperature changes. Due to the skin-layer driven diffusion mode, this temperature-insensitive MN patch could also provide glucose-responsive insulin release for several days, which shows advantages compared to the other glucose-sensitive MN patches that rely on GO_x . Insulin pharmacokinetics could be further tailored by chemical modification of the PBA and hydrogel, thus showing promise for personalized treatment.

Conclusions

This focus review describes the up-to-date progress of PBA-based versatile delivery platforms developed in our group

for on-demand insulin delivery. Due to the inherent advantages of PBA, our smart gel technology could provide diabetic patients with long-lasting, rapid on-demand insulin delivery as an alternative to traditional methods. By combining the smart gel with well-established medical devices such as catheters and MNs, convenient and effective insulin treatment could be achieved in a user-friendly, less invasive, and inexpensive way, which not only benefits patients in developing countries that have limited access to healthcare facilities but also less motivated patients such as the elderly, infants, and people who have trypanophobia.

Chemically controlled glucose-responsive insulin systems that are based on GO_x , Con A, and PBA possess great advantages compared to manual subcutaneous injection. However, to transition from research to clinical practice, several challenges need to be addressed, including the precise control of insulin release behavior, large-scale production and quality control, and their bio-safety and clinical effectiveness. Our continuous efforts will be devoted to optimizing the gel's release control ability, simplifying the fabrication methods to realize

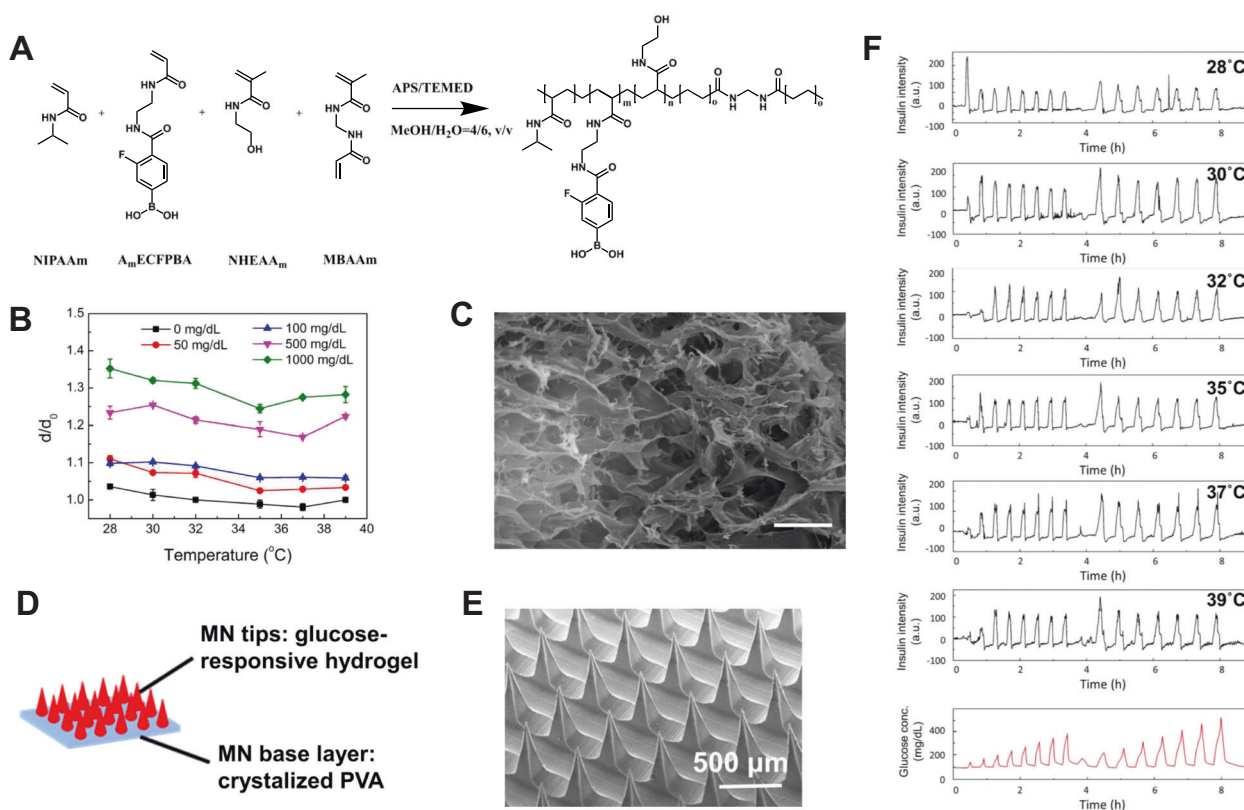


Fig. 6 **A** Chemical structure of the temperature-stable boronate gel. **B** Phase diagrams showing the gel diameter change under various glucose concentrations and temperatures. **C** Cross-sectional SEM images of the gel. **D** Schematic representation and morphology of the

totally synthetic MN array patch. **F** In vitro insulin release from the MN array patch at various temperatures and the temporal pattern of the fluctuation in glucose concentration. Reproduced with permission from ref. [60]

industrial mass production, and validating its effectiveness in clinical trials. By addressing these issues, our smart gel-based technology will have great potential to impact future diabetes treatment.

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Compliance with ethical standards

Competing interests The authors declare no competing interests.

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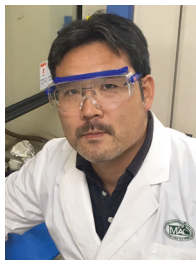
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