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Phenylboronic acid derivatives: advancing glucose-responsive insulin delivery and multifunctional biomedical applications

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Phenylboronic acid (PBA) and its derivatives have emerged as versatile materials with significant implications in biomedical and industrial applications, particularly for glucose-responsive systems. Their unique saccharide-binding properties, dictated by their tunable pK_a, enable advanced functionalities in drug delivery and biosensing. In diabetes management, PBA-based systems ranging from bulk hydrogels to micro/nanogels and self-assembled micelles offer precise insulin delivery mechanisms that respond dynamically to glucose levels. These materials are further enhanced by their adaptability to diverse routes of administration, including subcutaneous, transdermal, and oral delivery systems. Beyond insulin delivery, multifunctional PBA derivatives combined with glucose oxidase or polymers have been utilized in diabetic wound healing, biosensing, and environment-sensitive therapeutic applications like siRNA and cancer immunotherapy. The integration of PBA into hybrid and dual-responsive platforms continues to expand its utility, paving the way for innovative solutions in personalized medicine and diagnostics. This review explores the chemistry, applications, and future prospects of PBA derivatives, emphasizing their transformative potential in creating responsive, biocompatible, and multifunctional systems for biomedical use.

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1. Introduction

PBA derivatives have gained significant attention for their unique chemical properties, enabling diverse applications across scientific and industrial fields.[1–3] The pK_a of PBA plays

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a critical role in its functionality, particularly enabling selective interactions with saccharides such as glucose.[4–8] This interaction is central to the ability of PBA to form reversible covalent bonds with diols, making it especially valuable in biomedical applications like glucose sensing and insulin delivery systems. The development of advanced PBA derivatives has further expanded their utility by tailoring specific properties such as enhanced glucose responsiveness or biocompatibility.

In the context of insulin delivery, PBA-functionalized platforms such as bulk hydrogels,[9–14] micro/nanogels,[15–19] and self-assembled micelles[20–25] have demonstrated remarkable potential. These systems utilize the glucose-binding ability of PBA to enable on-demand insulin release, providing a more physiologically responsive approach for blood glucose regulation for patients with type 1 diabetes (T1D). Beyond insulin delivery, PBA derivatives have demonstrated benefits in diabetic wound healing, where they help modulate the wound microenvironment and support tissue regeneration.[26,27] Their utility also extends to biosensing and diagnostic technologies, where PBA-based platforms enable real-time monitoring of glucose and other biological markers.[28,29]

Emerging applications have pushed the boundaries of PBA use even further. For instance, in cancer immunotherapy and siRNA delivery, PBA-containing platforms are being explored for their ability to respond to environmental cues such as pH changes or oxidative stress.[30–37] By incorporating PBA into hybrid systems, researchers have created smart carriers capable of releasing therapeutics in a more targeted and efficient manner, reducing off-target effects and improving treatment.[38] These systems contribute to reducing systemic toxicity while enhancing therapeutic efficacy.

Despite this progress, much of the existing literature tends to focus on individual applications of PBA in isolation, be it insulin delivery, wound healing, biosensing, or cancer therapy. What's often missing is a broader, integrative analysis that connects the design principles behind PBA-based materials across these different domains. Overlapping mechanisms such as glucose sensitivity, reactive oxygen species (ROS)-responsiveness, and structural tunability are rarely discussed collectively, even though they offer clear opportunities for cross-application innovation.

This review aims to bridge that gap. Rather than viewing PBA solely as a chemical functional group, we present it as a modular design strategy for creating responsive, multifunctional biomaterials. We explore how the same core chemical interactions, particularly PBA's dynamic bonding with diols, can be adapted for diverse biomedical uses, from glucose-triggered insulin release to ROS-scavenging wound dressings and tumor-targeted drug carriers. By drawing these connections, we aim to provide a more unified framework for future research and design in the field.

The novelty of this work lies in its cross-disciplinary perspective. By examining shared challenges and synergistic design opportunities, we propose a more holistic approach for the development of PBA-based platforms, one that can better support the translation of these materials into clinically relevant technologies.

2. Chemistry of phenylboronic acid

PBA and its derivatives are versatile chemical entities with wide-ranging applications in fields such as drug delivery,

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sugar sensing, diagnostics, and materials science. The significance of boron-containing compounds was notably recognized in 2010 when the Nobel Prize in Chemistry was awarded for the development of the Suzuki–Miyaura reaction, highlighting the foundational role of organoboron chemistry in modern synthesis.[39] Central to the utility of PBAs is their ability to reversibly bind *cis*-diols *via* boronate ester formation, a process governed by their Lewis acidity and pK_a. The pK_a value is a particularly critical parameter, as it dictates the acid–base equilibrium between the neutral trigonal planar (sp^2-hybridized) boronic acid and the anionic tetrahedral (sp^3-hybridized) boronate form. Diol binding predominantly occurs *via* the latter, making the pK_a a determining factor in the efficiency of saccharide recognition under physiological conditions.[40]

Most unmodified PBA derivatives exhibit pK_a values greater than 8.5, limiting their reactivity at physiological pH (~7.4). Thus, optimization strategies often focus on lowering the pK_a to enhance reactivity at near-neutral pH. This is achieved through strategic substitution on the phenyl ring, where electron-withdrawing groups (EWGs) such as $-NO_2$, $-CF_3$, or –CHO stabilize the boronate anion *via* inductive and resonance effects, thereby reducing the pK_a and enhancing Lewis acidity. In contrast, electron-donating groups like $-NH_2$ or $-OCH_3$ destabilize the anionic form and increase the pK_a, reducing diol-binding affinity.[41,42] This substituent effect can be quantitatively analyzed using Hammett constants (σ), enabling predictive tuning of boronic acid reactivity.

Furthermore, the position of substituents on the phenyl ring, whether *ortho*, *meta*, or *para*, can drastically alter pK_a values and binding properties.[43,44] *ortho*-Substituted groups, particularly those capable of intramolecular interactions such as >C═O (in 2-formylphenylboronic acid, 2-FPBA), introduce internal hydrogen bonding or tautomerization that stabilizes the tetrahedral boronate form and lowers the effective pK_a. This stabilization not only improves diol affinity but also enhances the hydrolytic stability of the boronate ester. Another *ortho*-substituted derivative, 2-((dimethylamino)methyl)phenylboronic acid, exhibits a markedly low pK_a value (~5.3), enabling strong diol binding even under mildly acidic conditions.[45,46]

A range of PBA derivatives, such as 4-formylphenylboronic acid (4-FPBA), 4-(methylcarbamoyl)phenylboronic acid, and benzoxaborole, have been studied for their binding to biologically active diols like glucose and fructose.[45] These derivatives demonstrate pK_a values ranging from 5.3 to 8.5, influenced by their substituents. Lower pK_a values, as seen in EWGs like 4-FPBA, enhance binding affinity, while higher pK_a values, observed in derivatives such as 3-acetamidophenylboronic acid, indicate weaker acidity. Benzoxaborole's cyclic structure offers additional stabilization by relieving ring strain upon ester formation, further reducing the effective pK_a.[47]

Fluoro-substituted PBA molecules, particularly fluoro-2-FPBA analogs, combine strong EWGs at the *ortho*/*meta*/*para* positions with carbonyl functionalities, resulting in dual electronic modulation that dramatically lowers the pK_a and enhances diol-binding kinetics. These compounds are especially valuable for protein–sugar interaction studies, where fluorine atoms not only influence acidity but also offer synthetic handles for selective conjugation.[48,49] Moreover, the strategic spatial arrangement of substituents next to the boronic acid moiety, especially at positions that allow resonance or steric interplay, can fine-tune both binding strength and selectivity.

Beyond simple arylboronic acids, heterocyclic PBA derivatives such as pyridylboronic acids are emerging as next-generation saccharide binders. The incorporation of nitrogen-containing heterocycles (*e.g.*, pyridine and pyrimidine) introduces additional electronic effects and hydrogen-bonding capabilities that lower pK_a and improve water solubility. For example, 3-pyridylboronic acid exhibits strong affinity toward sialic acid and pyrophosphate at near-neutral or mildly acidic pH, owing to the resonance stabilization of its boronate form and its capacity for bidentate interactions.[50] Other heterocycles, such as boronopicolinic acid and 5-pyrimidineboronic acid, also exhibit high specificity for nucleoside derivatives and phosphorylated metabolites, showing promise in targeted drug delivery and biosensing.

PBA derivatives play a critical role in stabilizing diols, a property leveraged in prebiotic RNA stabilization and drug delivery. Clinically, boronic acid derivatives like bortezomib serve as proteasome inhibitors for cancer treatment.[51] The binding of PBA to polyols, which includes diols in *threo* and *erythro* configurations, demonstrates its specificity. *threo*-1,2-Diols, for instance, provide stable binding due to reduced steric interactions, while *erythro*-1,2-diols are less stable due to steric hindrance.[52] This selectivity underscores the potential of boronic acids in designing biomaterials for targeted applications.

In conclusion, PBA and its derivatives represent a cornerstone of chemical innovation, with their properties dictated by structural modifications and pK_a values. Their ability to bind saccharides and interact with diols under specific conditions positions them as indispensable tools in sugar sensing, drug delivery, and beyond. Continued exploration of PBA derivatives holds great promise for advancing both biomedical and industrial applications.

3. PBA-based insulin delivery systems

3.1. Bulk hydrogels

A hydrogel, which is a three-dimensional network retaining substantial volume of water, is stabilized by a chemically or physically crosslinked polymeric framework.[9] By incorporating PBA into the polymer network, the hydrogel can exhibit glucose-responsive behavior under specific conditions. When glucose is introduced, it shifts the equilibrium toward boronate ester formation, which alters the interactions within the polymer network or between the polymer and surrounding water molecules.[10] This results in increased hydrophilicity, causing the polymer chains to move apart due to steric hindrance, leading to the controlled release of the encapsulated drug.

In 2017, a new device was developed by combining a hydrogel formulation with a catheter.[53] The catheter had pores aligned perpendicular to its long axis, which acted as channels for the bidirectional flow of insulin and glucose between the internal solution and the surrounding interstitial fluid. The hydrogel coating these openings functioned as a glucose-responsive barrier, controlling the rate of insulin diffusion. When implanted subcutaneously in type 1 diabetic mice, the device lowered their blood glucose levels from around 500 mg dL^{-1} to 300 mg dL^{-1} while they maintained a normal diet. A glucose tolerance test conducted on overnight-fasted diabetic mice revealed a surge in serum insulin that coincided with the blood glucose peak, indicating *in vivo* insulin release triggered by blood glucose levels. However, in spite of the promising performance, the device's clinical translation is limited by its relatively large and invasive design, the need for surgical implantation, and concerns about potential for infection at the implantation site. Additionally, the precision and responsiveness of insulin release under physiological glucose fluctuations remain suboptimal for tight glycemic control.

3.2. Micro/nanogels

Microgels used in glucose-responsive systems are typically synthesized *via* precipitation or emulsion polymerization techniques. Alternatively, self-assembly of chains can occur, driven by intra- or intermolecular PBA–diol complexation or hydrophobic interactions. Similar to bulk hydrogels, when free glucose binds to PBA, it weakens these forces, leading to the swelling or breakdown of the microgel or nanogel and initiating insulin release.

For instance, Zhou and colleagues developed glucose-responsive poly(*N*-isopropylacrylamide-*co*-phenylboronic acid) microgels using a post-modification method.[5] In this study, 3-aminophenylboronic acid (APBA) was attached onto the poly (*N*-isopropylacrylamide-*co*-acrylic acid) backbone of a cross-linked microgel made through precipitation polymerization. Upon glucose exposure (10 mM), the size of the microgel containing 10% APBA increased two-fold at room temperature under basic conditions. Likewise, an alternative team employed a direct polymerization technique to formulate PBA-containing microgels with significant expansion observed at pH 8.5 and 9.5.[17] Despite their potential, microgel systems encounter notable challenges. The glucose-responsive swelling often requires alkaline or non-physiological pH conditions (*e.g.*, pH 8.5–9.5), which limits their effectiveness under normal physiological pH (~7.4). Additionally, post-modification methods can result in uneven or incomplete functionalization of PBA groups, affecting reproducibility and consistency.

3.3. Self-assembled micelles

Introducing PBA into the hydrophobic segment has been utilized to create amphiphilic copolymers exhibiting glucose-responsive properties. For instance, a micelle system made from poly(ethylene glycol)-*block*-poly(acrylic acid-*co*-acrylamidophenylboronic acid) demonstrated glucose-triggered insulin release within the physiological glucose range. A follow-up study indicated that the coordination between the carboxylate group and PBA lowered the pK_a of PBA, which enhanced its glucose sensitivity at lower pH levels.[54] Alternatively, researchers have developed a glucose-sensitive platform by integrating a phenyl borate monomer into the amphiphilic polymer framework.[23,55] This copolymer self-assembled into core–shell micelles at pH 7.4. Upon exposure to high glucose concentrations, glucose competed with diols for binding to PBA, resulting in a transition of the polymer from amphiphilic to hydrophilic. In a glucose-rich solution (400 mg dL^{-1}), a significant increase in the release rate of insulin was observed.[22] Further investigations have explored the factors affecting glucose-responsiveness and insulin encapsulation efficiency, like the molecular size and the method of drug loading.[23] Nevertheless, lengthy and complex copolymerization processes may lead to batch-to-batch variability, hindering reproducibility and posing challenges for large-scale manufacturing.

4. Routes of administration

4.1. Subcutaneous injection-based glucose-responsive insulin delivery systems

Subcutaneous injection remains a cornerstone of insulin delivery due to its reliability and ability to provide consistent therapeutic effects. Advances in glucose-responsive insulin delivery systems aim to integrate physiological feedback mechanisms to mimic the function of the pancreas, ensuring optimal glucose regulation. Recent innovations leverage the unique properties of PBA derivatives and their interactions with glucose to develop adaptive delivery platforms. These systems demonstrate significant potential in managing diabetes through enhanced responsiveness, reduced side effects, and prolonged glycemic control.

Zhang and colleagues developed a polymeric delivery system that uses a glucose-triggered charge-reversal mechanism to release insulin (Fig. 1a).[56] This system is based on a cationic FPBA polymer, which is synthesized by modifying poly(L-lysine) with FPBA. In its unaltered form, the polymer carries a positive charge, which facilitates the efficient loading of gluconic acid-modified insulin, a negatively charged molecule. Under normal blood glucose levels, the polymer maintains its positive charge, resulting in a gradual, sustained release of insulin. However, when blood glucose levels rise during hyperglycemia, the polymer undergoes charge reversal, becoming negatively charged and leading to a rapid release of insulin. *In vitro* experiments confirmed that the polymer binds glucose and triggers insulin release, while *in vivo* studies in diabetic mice and minipigs showed that the system was able to regulate blood glucose and maintain normoglycemia for up to a week, demonstrating its potential for long-term diabetes management. Notwithstanding these advantages, limitations remain. The requirement to modify insulin with gluconic acid may complicate large-scale production and regulatory approval.

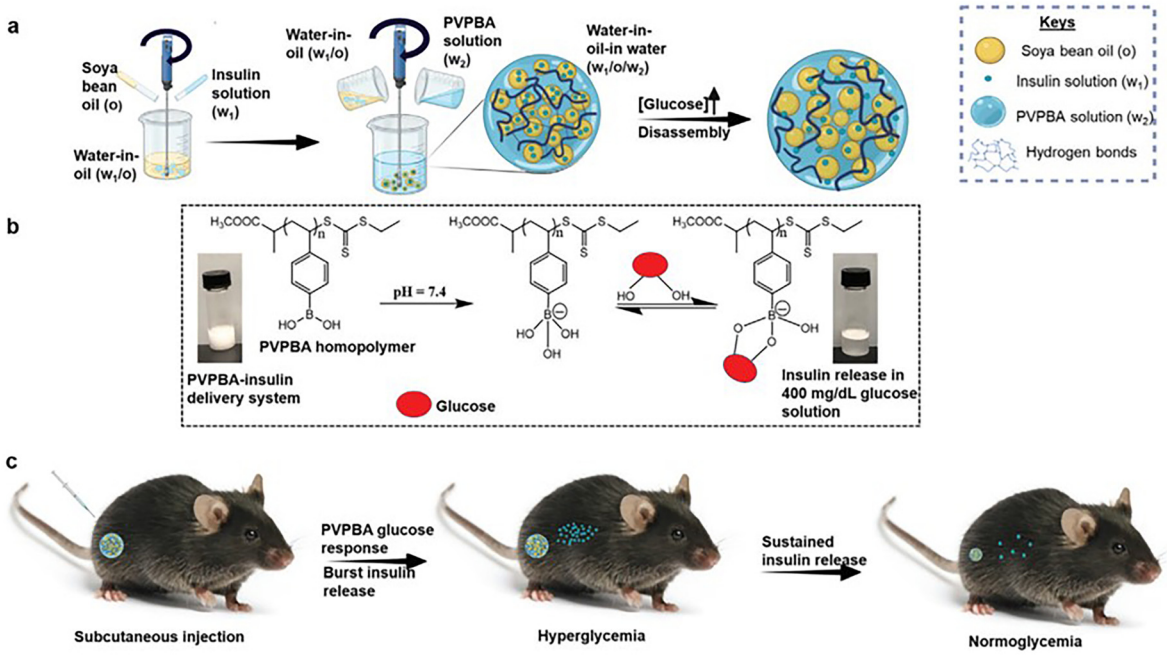

Fig. 1 A diagram illustrating the formation of a glucose-responsive gelled emulsion and its application in T1D therapy. (a) Preparation of a gelled multiple emulsion and the release of insulin *via* a glucose-responsive mechanism. (b) Insulin release from the gelled emulsion upon exposure to a hyperglycemic state. The stability of the emulsion is due to the hydrogen bonds between PBA molecules. In a hyperglycemic environment, these hydrogen bonds are broken down, leading to the destabilization of the emulsion and accelerating insulin release. (c) Treatment regimen of T1D in a streptozotocin-induced diabetes mouse model using the gelled emulsion-based insulin delivery platform. Reproduced with permission from ref. 57. Copyright 2024 Wiley-VCH Verlag GmbH.

Boakye-Yiadom *et al.* employed RAFT polymerization to synthesize a poly(4-vinylphenylboronic acid) homopolymer with exceptional emulsification and gelling properties (Fig. 1).[57] This polymer facilitated the creation of a glucose-responsive gelled water-in-oil-in-water (W/O/W) multiple emulsion for insulin delivery. The system exhibited several advantageous features, including its injectable gel-like scaffold, high glucose responsiveness, and stability under low-glucose conditions. In hyperglycemic environments, the system demonstrated self-accelerating demulsification, enabling rapid insulin release. Furthermore, this platform offers the benefit of simple preparation without requiring chemical modification of insulin, presenting a scalable and adaptive approach for diabetes management. The multistep emulsion fabrication process, while simpler than covalent modification approaches, may still face challenges in achieving batch-to-batch consistency and long-term storage stability. The system's performance *in vivo* has so far been limited to animal models, and its translational feasibility in humans remains untested, particularly regarding potential immunogenicity, biodegradability, and metabolic clearance of the polymer.

The formation of a boronate ester between PBA and glucose enhances its water solubility and has been investigated as a mechanism for triggering insulin-PBA release from delivery systems. Scientists have investigated the interaction between aliphatic PBA and blood plasma albumin as a potential glucose-responsive approach for insulin delivery.[58] This strategy involved modifying insulin with various aliphatic PBA derivatives exhibiting distinct pK_a values. In a glucose-rich medium (400 mg dL^{-1}), glucose molecules bound to the PBA moiety, converting it into a boronate ester and reducing the interactions between PBA and albumin, which in turn triggered insulin release. This engineered insulin demonstrated prolonged efficacy similar to insulin detemir and exhibited the ability to dynamically adjust its function in response to changes in blood glucose concentrations. Nonetheless, the covalent modification of insulin raises concerns regarding structural integrity, potential immunogenicity, and altered pharmacokinetics. The variability in binding affinity among different PBA derivatives and their sensitivity to pH fluctuations may also compromise the precision of glucose responsiveness, limiting their immediate clinical translatability.

These subcutaneous injection-based systems represent a leap forward in developing glucose-responsive technologies, offering a promising path toward achieving tighter glycemic control and enhancing the well-being of patients with diabetes.

4.2. Transdermal-based glucose-responsive insulin delivery systems

Transdermal glucose-responsive insulin delivery systems represent an innovative approach for diabetes management, leveraging the competitive dissociation of reversible boronate ester bonds between phenylboronic acid derivatives and diol groups

on carrier materials. This mechanism is triggered by elevated glucose levels, leading to crosslinking dissociation and enabling glucose-mediated insulin release.[59]

The pioneering work in this area was conducted by Chen *et al.*, who developed microneedle (MN) patches using hydrogels formed by poly(vinyl alcohol) (PVA) and sodium hyaluronate grafted with 4-((2-aminoethyl)carbamoyl)-3-fluorophenylboronic acid[60] or PVA combined with polyallylamine grafted with 3-carboxy-4-fluorophenylboronic acid.[61] These hydrogels were crosslinked through boronate ester bonds. In hyperglycemic conditions, glucose was expected to reduce crosslinking density, thereby facilitating a glucose-dependent insulin release. However, *in vivo* studies in type 1 diabetic rats primarily demonstrated prolonged insulin release without evidencing differential glucose responsiveness due to the absence of a non-responsive insulin-loaded MN group. While glucose-dependent release has been demonstrated *in vitro*, these MN patch systems show limited *in vivo* evidence of true glucose responsiveness due to the lack of appropriate non-responsive control groups.

Alternatively, Fu *et al.* developed a dissolving MN patch incorporating insulin-loaded mesoporous silica nanoparticles capped with zinc oxide nanoparticles (Fig. 2).[62] Dynamic boronic ester bonds between gluconamide diols and phenylboronic acid derivatives regulated insulin release through an on/off gating mechanism. Under hyperglycemic conditions, glucose cleaved the bonds, uncapping the mesopores and releasing insulin. In diabetic mice, these patches maintained normoglycemia for approximately three hours longer than subcutaneous insulin. Additionally, glucose tolerance tests and hypoglycemia assessments confirmed their glucose sensitivity, outperforming subcutaneous insulin in both efficacy and safety. Although the system shows improved glucose sensitivity and extended glycemic control in diabetic mice, challenges remain regarding the complexity of nanoparticle fabrication and the stability of dynamic boronic ester bonds under physiological conditions. The on/off gating mechanism may face variability in response times and insulin release rates *in vivo* due to fluctuating glucose levels and potential interference from other biomolecules.

Subsequent efforts focused on developing synthetic polymer hydrogels modified with pyridiniumboronic acid motifs, aiming for reversible glucose-triggered insulin release.[63] While these designs showed promise, many studies failed to demonstrate a clear glucose-specific response, primarily due to the absence of a proper non-responsive control group. However, recent advancements have addressed this gap, enhancing the reliability of these glucose-responsive systems. Chen *et al.* developed a core–shell MN patch where the shell comprised PVA and ε-polylysine modified with 4-carboxy-3-fluorophenylboronic acid, crosslinked through boronate ester bonds.[64] Under hyperglycemic conditions, glucose competitively dissociated the bonds, reducing shell density and allowing insulin to diffuse from the core. This system demonstrated glucose-dependent release *in vitro* and effectively managed daily glucose fluctuations in diabetic rats, with a reduced risk of hypoglycemia under normoglycemic conditions. However, the absence of comprehensive *in vivo* validation limits the understanding of its therapeutic efficacy and safety under physiologically dynamic conditions. Mechanical robustness and consistent skin penetration across varying skin types remain critical concerns, particularly for the dual-layer architecture. Moreover, the long-term biocompatibility and metabolic clearance of fluorophenylboronic acid-modified ε-polylysine require thorough toxicological assessment.

Together, these advancements highlight how transdermal glucose-responsive systems could pave the way for safer and more effective insulin delivery in diabetes care. That said, incorporating non-responsive controls in future studies will be essential to confidently confirm that the observed effects are truly driven by glucose responsiveness.

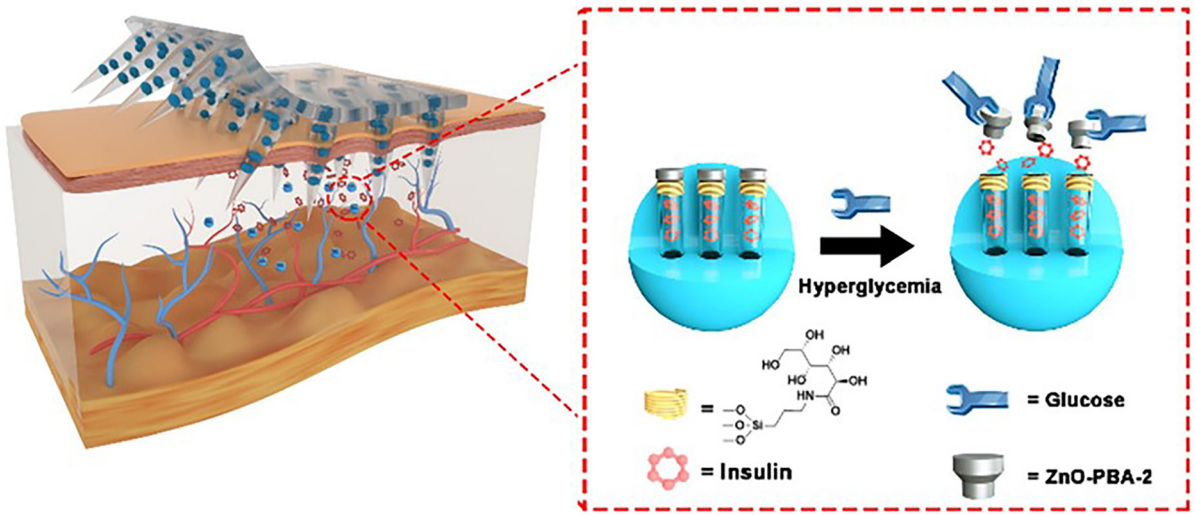

Fig. 2 Schematic illustration of a dissolving microneedle patch (SGRM patch) containing mesoporous silica nanoparticles (G-MSN@Insulin@ZnO-PBA-2) for transdermal delivery of insulin. Reproduced with permission from ref. 62. Copyright 2022 Elsevier.

4.3. Oral-based glucose-responsive insulin delivery systems

Since the discovery of insulin, oral administration has been a long-standing goal.[65] Nevertheless, insulin is rapidly broken down by enzymes in the stomach and intestinal tract, and its transport across the intestinal epithelium remains problematic.[66] Recently, Gu and colleagues designed an oral insulin delivery system aimed at regulating blood glucose levels after meals. This system involved encapsulating insulin within liposomes designed to target the neonatal Fc receptor (FcRn), which were subsequently coated with a glucose-responsive hyaluronic acid-phenylboronic acid (HA-PBA) shell.[67] Upon oral administration, the HA shell disassociated from the liposomes due to elevated blood glucose concentration in the intestine following meal ingestion. This allowed the exposed Fc portion on the surface of the liposome to bind with FcRn receptors on the small intestine, promoting the absorption of insulin across the epithelium. *In vitro* tests established that glucose-triggered exposure contributed to an increase in zeta potential, and *in vivo* studies demonstrated effective blood glucose regulation following oral insulin administration. Despite these promising results, several limitations exist. The complex structure and multi-component nature of the system raise concerns about reproducibility and scalability for large-scale manufacturing. Additionally, the efficiency of FcRn-mediated transcytosis in humans remains to be fully validated, and the stability of the HA-PBA coating in the harsh gastrointestinal environment poses a risk to the consistency of glucose-triggered release. Furthermore, variability in intestinal glucose levels among patients could affect the responsiveness and reliability of the system in clinical use.

5. Multifunctional PBA derivatives

5.1. Hybrid materials: combining PBA with polymers for dual or enhanced functionalities

Hybrid materials that integrate PBA with polymers have emerged as a promising avenue in biomedical engineering, offering dual or enhanced functionalities for various applications.[68,69] These materials utilize the unique properties of PBA, particularly its dynamic boronate ester bonding with diols, and combine them with the structural and functional versatility of polymers. Two key innovations in this field focus on developing pH-sensitive systems and biodegradable systems, each designed to address specific challenges in drug delivery and therapeutic interventions.

One significant advancement lies in the development of pH-sensitive systems that simultaneously respond to glucose and pH variations. These systems leverage the pH-dependent binding affinity of PBA to glucose, enabling precise control over drug or insulin release under specific environmental conditions. For example, in acidic microenvironments, such as inflamed tissues or tumors, the altered pH modulates the PBA–glucose interaction, triggering the release of encapsulated therapeutic agents.[70,71] This dual responsiveness enhances the efficiency and specificity of drug delivery, making these systems particularly valuable in managing conditions like diabetes and cancer. In the case of glucose-responsive insulin delivery, such materials can ensure insulin release under specific pH conditions characteristic of the target environment in response to elevated glucose levels, thereby improving glycemic control and reducing side effects.[72,73] In parallel, biodegradable systems incorporating PBA with polymers have demonstrated immense potential for improving biocompatibility. By conjugating PBA to biodegradable polymers such as poly(L-lysine),[56,72] polycaprolactone,[71,74] or natural polymers like chitosan,[75,76] researchers have created environmentally responsive materials that safely degrade within the body after delivering their therapeutic payload. This degradability not only minimizes long-term toxicity but also aligns with clinical and regulatory standards, making these systems ideal for sustained drug delivery and temporary scaffolding in regenerative medicine. For instance, glucose-responsive hydrogels formulated with biodegradable polymers provide a platform for prolonged insulin delivery, degrading gradually after the drug is released. Similarly, PBA-functionalized biodegradable nanoparticles have been developed for cancer immunotherapy, targeting tumor cells while decomposing into nontoxic byproducts post-treatment.

In summary, hybrid materials combining PBA with polymers offer a unique blend of functionality and safety, addressing critical needs in targeted and controlled drug delivery. The integration of pH-sensitive and biodegradable properties enables these materials to adapt to complex physiological environments, ensuring precision, efficacy, and reduced side effects. As research continues, these innovations are poised to transform the landscape of therapeutic interventions, fostering the development for more effective and user-friendly solutions.

5.2 Combining GOx and PBA responsive systems

Tong *et al.* designed a dual-responsive transdermal insulin delivery system integrating glucose oxidase and phenylboronic acid functionalities (Fig. 3).[77] This system used dissolvable MN patches made from polyvinylpyrrolidone and PVA, which encapsulated polymersomes loaded with insulin and glucose oxidase. The polymersomes were synthesized from an amphiphilic triblock copolymer consisting of polyethylene glycol (PEG), poly(phenylboronic acid pinacol ester), and poly(3-acrylamidophenylboronic acid), enabling two distinct glucose-responsive mechanisms.

First, the phenylboronic acid pinacol ester groups hydrolyze in the presence of hydrogen peroxide, produced during glucose oxidase-catalyzed glucose oxidation. This reaction makes the copolymer water-soluble, triggering polymersome disassembly and insulin release. Second, the 3-acrylamidophenylboronic acid groups gain a negative charge upon glucose binding under hyperglycemic conditions, causing polymer swelling. This swelling reduces the interaction between the polymer and insulin, enhancing insulin release.

The performance of the system was evaluated in diabetic rats divided into four groups: a control group using MN patches with empty polymersomes, a group receiving sub-

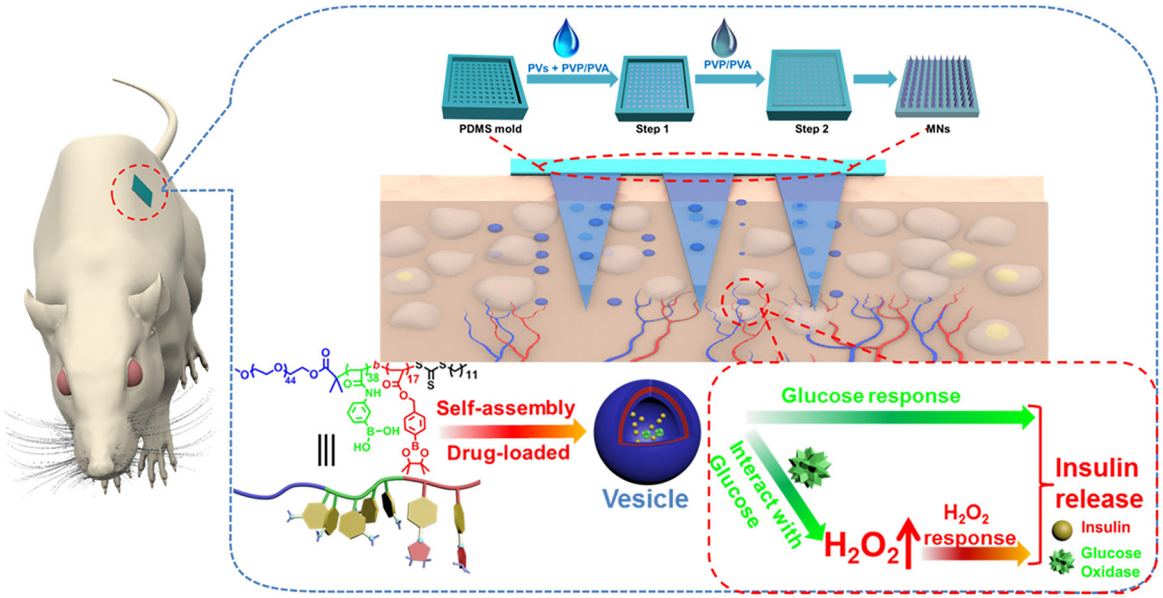

Fig. 3 Diagram illustration of fabricated MN patches and transdermal drug delivery in diabetic rats. Reproduced with permission from ref. 77. Copyright 2018 American Chemical Society.

cutaneous insulin injections (20 IU kg^{-1}), a group with glucose-responsive polymersomes containing insulin only (40 IU kg^{-1}), and a group with dual-responsive polymersomes containing both insulin (40 IU kg^{-1}) and glucose oxidase.

Results showed that the dual-responsive MN patches sustained blood glucose levels below 200 mg dL^{-1} for up to four hours, compared to only two hours for MN patches without glucose oxidase. Subcutaneous insulin injections caused a rapid drop in glucose to 80 mg dL^{-1} but failed to maintain control beyond an hour.

This study demonstrates that incorporating glucose oxidase enhances glucose-triggered insulin release, achieving more prolonged and effective glycemic control compared to single-mechanism systems. However, limitations remain, including the short duration of glycemic control (only four hours), the relatively high insulin dose required (40 IU kg^{-1}), and concerns about long-term stability and activity of glucose oxidase within the microneedles. Moreover, repeated use of GOx may induce oxidative stress or immune responses, and large-scale manufacturing of such complex triblock copolymers with consistent quality could present translational challenges.

6. Applications beyond insulin delivery

6.1 Diabetic wound healing

Diabetic wounds present significant challenges in clinical practice, primarily due to prolonged inflammation, excessive oxidative stress, impaired tissue regeneration, and susceptibility to infections. These chronic wounds, especially in individuals with uncontrolled diabetes, often fail to progress through the normal stages of wound healing, leading to complications such as ulcers, infections, and in severe cases, amputations. Therefore, addressing the unique needs of diabetic wounds requires innovative therapeutic strategies. One of the promising approaches gaining attention involves the use of PBA-based polymers in hydrogel formulations. PBA polymers, known for their ability to form dynamic boronate ester bonds, have been widely explored for glucose-responsive insulin delivery, but their potential extends far beyond this application, offering new possibilities in diabetic wound healing.

PBA-based hydrogels offer an advanced platform for localized drug delivery in response to specific microenvironmental stimuli, which is essential for managing the complex dynamics of diabetic wound healing. In particular, their ability to respond to both glucose and ROS provides a unique advantage. The diabetic wound environment is characterized by elevated glucose levels and increased oxidative stress, which not only impedes healing but also exacerbates inflammation. By utilizing the dual-responsive nature of PBA, these hydrogels can adapt to the fluctuating levels of glucose and ROS, releasing therapeutic agents precisely when and where they are needed.

6.1.1 Antibacterial properties of PBA-functionalized hydrogels. In diabetic wounds, bacterial infections are a common and serious complication. PBA-functionalized hydrogels not only support tissue repair but also possess inherent antibacterial properties, making them an ideal choice for treating infected diabetic wounds. For example, PBA-modified gelatin and oxidized hyaluronic acid can be crosslinked to form a self-healing hydrogel that actively enriches and releases curcumin in response to pH and glucose changes.[78] Curcumin, known for its antioxidant and anti-inflammatory properties, has been

shown to reverse the inflammatory microenvironment in diabetic wounds, thereby promoting wound healing. Furthermore, this hydrogel system demonstrates effective antibacterial activity, inhibiting bacterial growth and infection. The synergy between PBA-mediated drug release and the inherent bioactivity of curcumin represents a promising strategy for tackling both infection and chronic inflammation in diabetic wounds.

Additionally, a hydrogel system incorporating polyboronic acid-modified carboxymethyl chitosan and rosmarinic acid (RA) has been developed, demonstrating not only antioxidant and antibacterial properties but also the ability to promote the migration of key wound-healing cells.[79] The RAgel system, as it is called, enhances macrophage polarization to the M2 phenotype, which is crucial for resolving inflammation and promoting tissue repair. In a diabetic wound model, this hydrogel facilitated improved tissue regeneration by promoting collagen deposition and accelerating wound closure (Fig. 4a).

6.1.2 PBA polymers in antioxidant and anti-inflammatory strategies. In addition to modulating glucose and ROS levels, PBA-based hydrogels are also being developed to control inflammation, one of the most detrimental factors in diabetic wound healing. For example, a study reported the use of a hydrogel composed of hydroxybutyl chitosan and 4-carboxyphenylboronic acid that exhibits both pH and glucose-responsive drug release.[81] This self-healing hydrogel, which undergoes irreversible gelation due to the dual crosslinking network of hydrogen bonds and boronate ester interactions, promotes wound healing by enhancing cell migration, inhibiting bacterial infection, and reducing inflammation. Notably, this hydrogel system demonstrates remarkable stability even under dynamic wound conditions, such as fluctuating pH and glucose levels, making it a strong candidate for diabetic wound treatment.

Moreover, the ability of PBA-based hydrogels to scavenge ROS plays a crucial role in preventing the oxidative stress that

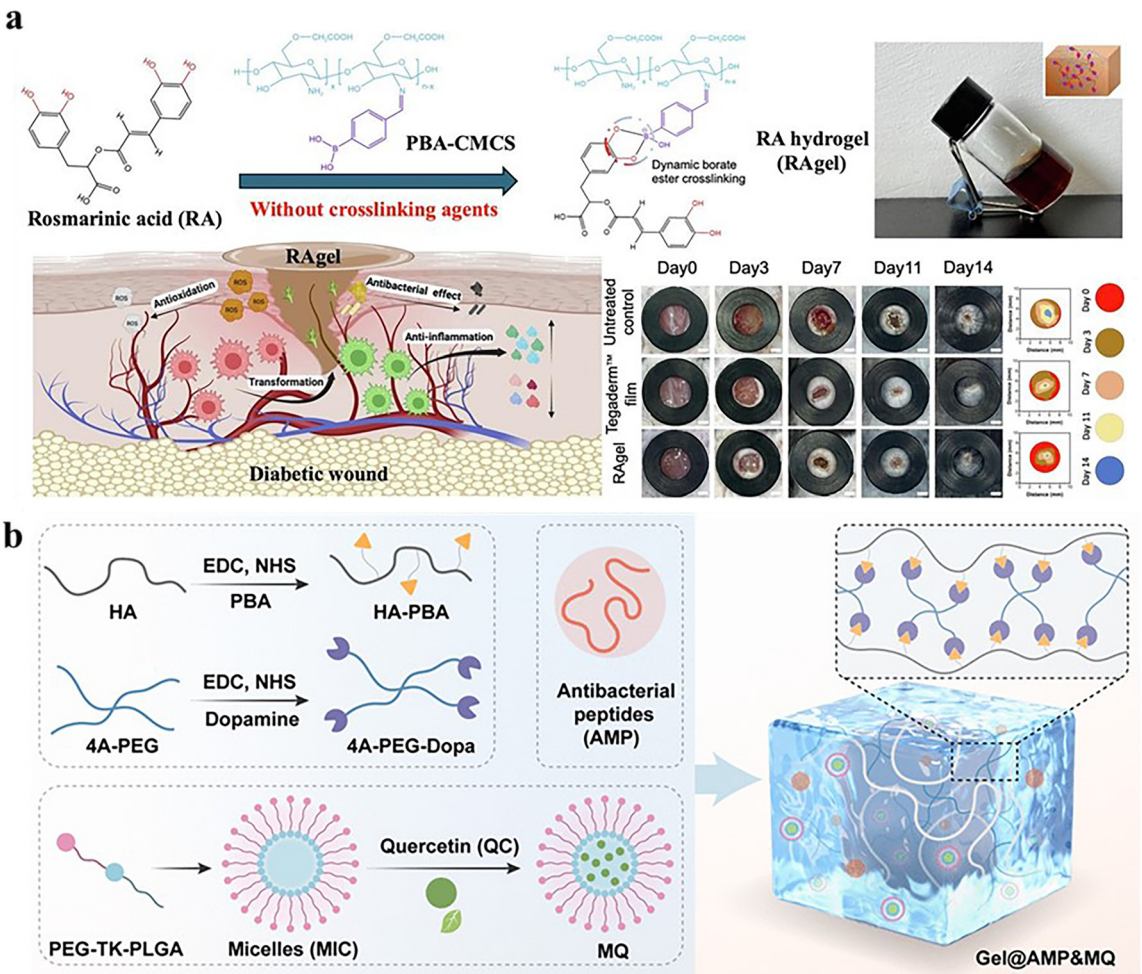

Fig. 4 (a) Schematic representation of RAgel, a polyboronic acid-modified carboxymethyl chitosan hydrogel loaded with rosmarinic acid, demonstrating its antioxidant, antibacterial, and wound healing properties in diabetic wound management. Reproduced with permission from ref. 79. Copyright 2024 Elsevier. (b) Schematic of a pH/ROS-responsive hydrogel dressing composed of HA-PBA and 4A-PEG-Dopa, loaded with antimicrobial peptides and quercetin-loaded micelles, designed for sequential antibacterial, antioxidant, and anti-inflammatory release in diabetic wound healing. Reproduced with permission from ref. 80. Copyright 2024 American Chemical Society.

impedes wound healing in diabetic patients. A noteworthy innovation in this regard is the development of a hydrogel system that integrates polyphenolic compounds like epigallocatechin gallate (EGCG) with PBA-modified gelatin. This hydrogel demonstrates glucose-responsive ROS-scavenging activity, effectively reducing oxidative stress in the wound environment and promoting tissue regeneration. Through the dissociation of boronate ester bonds, more EGCG is released as glucose levels rise, ensuring that the healing process is supported when it is most needed.

6.1.3 Multifunctional hydrogels with PBA for chronic wound management. Recent studies have demonstrated that PBA-based hydrogels can be engineered with multiple functionalities, including antioxidant, antibacterial, and anti-inflammatory properties, to address the key challenges in diabetic wound healing. For instance, the development of a hydrogel dressing composed of HA-PBA and 4-arm-PEG-dopamine (4A-PEG-Dopa) has shown promise in treating chronic diabetic wounds (Fig. 4b).[80] This hydrogel utilizes dynamic borate ester bonds to provide a scaffold that responds to the acidic and ROS-rich environment typical of diabetic wounds. Upon exposure to the acidic conditions, the hydrogel dissociates to release encapsulated antimicrobial peptides and ROS-sensitive micelles loaded with quercetin. Quercetin, an antioxidant, helps mitigate oxidative stress and promotes the M2 polarization of macrophages through the Akt/STAT6 signaling pathway. This process not only reduces inflammation but also accelerates the repair of damaged tissue, suggesting that HA-PBA-based hydrogels could serve as effective tools for improving chronic wound healing.

Similarly, hydrogels designed with HA-PBA and fulvic acid (FA) have been proposed for diabetic wound healing.[82] This system is glucose-responsive, enabling the localized and controlled release of EN106, a compound that targets the FEM1b-FNIP1 axis. EN106 plays a role in regulating inflammation and promoting tissue repair by modulating macrophage behavior. The combination of FA as a crosslinker and an anti-inflammatory agent, alongside the role of EN106 in targeting specific molecular pathways, underscores the versatility of PBA-based hydrogels in addressing both the biochemical and physiological barriers to wound healing.

In conclusion, PBA-based polymers offer a versatile and innovative solution for advancing diabetic wound healing beyond insulin delivery. Unlike conventional wound dressings and hydrogel systems, PBA-functionalized materials provide a unique combination of glucose/ROS responsiveness, dynamic drug release, and the ability to modulate inflammation and oxidative stress in real time. By capitalizing on the distinctive properties of PBA, researchers are paving the way for smart, self-regulating wound care systems that can precisely address the underlying causes of impaired healing in diabetic patients. With continued innovation and comparative performance validation against existing biomaterials, these hydrogels hold the potential to revolutionize the treatment of diabetic wounds, providing targeted, effective, and patient-centric therapies for one of the most challenging aspects of diabetes management (Table 1).

6.2 Biosensing and diagnostics

The use of PBA-modified sensors in glucose detection has revolutionized biosensing technology by exploiting the revers-

Table 1 Comparative evaluation of PBA-based systems and conventional approaches across biomedical applications

Application	System type	PBA-based systems	Conventional systems	Current limitations & future considerations
Diabetic wound healing	Drug-responsive hydrogel	Glucose-/ROS-responsive hydrogels enable on-demand release, modulate oxidative stress and inflammation	Passive or standard hydrogels lack stimuli-responsiveness and precise drug release control	- Comprehensive long-term biocompatibility studies - Tailoring responsiveness to chronic wound physiology - Scalable manufacturing for clinical translation
Glucose monitoring	Biosensor technology	Non-enzymatic PBA-modified sensors offer reversible glucose recognition, enhanced stability, and reuse	Enzyme-based sensors (*e.g.*, glucose oxidase) suffer from instability, narrow pH tolerance, and degradation	- Enhancing glucose specificity in complex biofluids - Integration into miniaturized or wearable devices - Validation under real-world physiological conditions
Cancer immunotherapy applications	Targeted delivery systems	PBA-enabled nanocarriers allow glycan-selective targeting, microenvironment-responsive release, and increased antibody stability	Traditional or immunotherapies face nonspecific distribution, systemic toxicity, and low tumor accumulation	- Optimizing tumor-selective ligand design - Evaluating immunogenicity and metabolic fate of PBA-based materials - Bridging preclinical efficacy with regulatory readiness

ible interaction of PBA with diols, such as glucose and glycoproteins. These sensors have become indispensable tools for biomedical diagnostics, offering significant advancements in sensitivity, selectivity, and functional adaptability. Unlike traditional enzymatic glucose sensors that depend on glucose oxidase, which are often limited by enzyme instability, narrow pH operating ranges, and reduced activity over time, PBA-based sensors provide enhanced chemical stability, reusability, and tunable glucose affinity under physiological conditions. Their non-enzymatic nature eliminates the need for cofactors and reduces susceptibility to biological degradation (Table 1). Beyond voltammetric platforms, the development of potentiometric sensors and fluoride-functionalized systems demonstrates the growing versatility and robustness of this approach. As such, PBA-modified sensors not only expand the landscape of glucose biosensing but are also superior to conventional systems in terms of stability, responsiveness, and long-term applicability.

6.2.1 Voltammetric sensors. PBA-modified voltammetric sensors remain a fundamental tool for glucose detection. For example, glassy carbon (GC) electrodes modified with a composite of 4-APBA and graphene oxide (GO) exhibit enhanced glucose sensitivity.[28] The high conductivity and surface area of GO improve electron transfer, while the formation of PBA–glucose complexes results in electrostatic repulsion that decreases the differential pulse voltammetry current. This strategy has enabled detection limits far superior to traditional electrodes.[83]

Similarly, bis-PBA derivatives immobilized on gold (Au) electrodes and polymer-coated electrodes using 3-hydroxyphenylboronic acid have provided selective glucose detection.[84] In these systems, sensitivity and selectivity are finely tuned through the combination of PBA specificity and the conductive properties of the electrode material. These designs enable glucose monitoring across physiologically relevant ranges, a critical requirement for clinical applications.

6.2.2 Potentiometric sensors. PBA-based glucose sensors employ potentiometric detection to measure glucose concentrations by tracking changes in electrode potential due to PBA–diol interactions. Early designs used poly(aniline boronic acid)-coated electrodes, evolving to copolymers like anilineboronic acid and alkylated thiophene for better sensitivity and lower detection limits.[85] Innovations such as nanotube structures increased surface area, while PBA-substituted poly(pyrrole) films showed potential despite requiring basic pH for operation.[86] 4-Mercaptophenylboronic acid-modified gold nanoparticles integrated into conductive polymers further improved performance, enabling broader glucose response ranges and functionality in weakly acidic environments.[87]

Ion-sensitive field-effect transistors (FETs) modified with PBA[88,89] or fluorinated PBA[90] demonstrated precise glucose detection under physiological conditions. Polymeric liquid membranes with quaternary ammonium salts exhibited glucose-selective responses, particularly with bis-PBA. Advanced materials like ferrocene boronic acid derivatives[91–96] and tetrathiafulvalene-bridged bis-PBA[97] highlighted the versatility of PBA-based sensors for sugar detection, including applications in enzymatic glucose isomerization monitoring and electrochemical sugar detection.

6.2.3 Glycoprotein sensors. PBA-modified electrodes have gained attention for the rapid and facile determination of glycoproteins due to their ability to bind specific carbohydrate residues *via* boronate ester bonds. For example, PBA-modified electrodes have been used to construct voltammetric sensors for glycated hemoglobin (HbA1c), which reflects long-term glucose levels.[98] These sensors often rely on catalytic or redox-active species like glucose oxidase or Fc-labeled antibodies to produce electrical signals, even though HbA1c itself lacks a redox-active moiety.[99] Pyrroloquinoline quinone/reduced GO composites and poly(anilineboronic acid) nanoparticles further enhance HbA1c detection with low detection limits.[100]

Additionally, PBA-based sensors have been employed for detecting various glycoproteins, including bovine serum albumin and avidin.[101] For BSA, MIP-based sensors on Au nanoparticles displayed voltammetric responses in the range of 1×10^{-11} to 1.0×10^{-5} g mL^{-1}, while avidin detection using 4MPBA-modified Au nanoparticles relied on binding affinity through boronate ester bonds. Displacement sensors utilizing glycan-coated electrodes and redox markers like FcBA showed reduced signals upon binding to Con A or *E. coli*, indicating their utility in biosensing applications.[102]

6.2.4 Miscellaneous sensors and applications. PBA derivatives have demonstrated the ability to selectively bind various compounds, including sialic acid (SA), catechol compounds, hydroxy acids like lactic acid and salicylic acid, dopamine, and inosine.[103] For SA, PBA-modified FET sensors show high selectivity due to the strong affinity of PBA to SA, useful for detecting SA in biological samples, which is a biomarker for cancers and other diseases.[104] Molecularly imprinted polymers (MIPs) constructed using PBA derivatives have been employed for dopamine[105] and inosine detection,[106] showing excellent sensitivity and wide concentration ranges.

Additionally, PBA-based sensors have been developed for bleomycin detection using oligonucleotide-modified electrodes. The sensors exhibited impedimetric and voltammetric responses due to the cleavage of oligonucleotide chains by bleomycin.[107] PBA-modified Au nanoparticles and graphene-based electrodes demonstrated redox responses, with detection limits as low as 0.2×10^{-6} M.[108]

Furthermore, PBA-modified electrodes have been used for acetyl cholinesterase-based sensors, detecting organophosphorus and carbamate insecticides at low ppb levels through enzymatic oxidation of thiocholine. Studies on FcBA derivatives have shown their potential in constructing reagentless sensors for compounds like salicylic acid,[109] fructosyl valine,[110] catechin,[111] and hypochlorite ions[112] based on changes in electrochemical properties.

In conclusion, the integration of PBA-modified sensors across voltammetric, potentiometric, glycoprotein, and miscellaneous platforms underscore their versatility and potential in biosensing. These systems leverage the reversible and specific binding of PBA to diols and saccharides, enabling real-time

detection of biomolecules with high sensitivity and selectivity. As a result, they play a key role in advancing biomedical diagnostics and real-time health monitoring.

6.3 Drug delivery for comorbid conditions

6.3.1 PBA-inspired biomaterials for cancer immunotherapy applications. Cancer immunotherapy (CI) has emerged as a transformative strategy for combating cancer by leveraging components of the immune system.[29] Over the years, various therapeutic strategies have been developed under the framework of CI, including the use of immune agents targeting molecules overexpressed by cancer cells. These approaches often involve T cells, natural killer (NK) cells, and their modified versions, such as genetically engineered chimeric antigen receptor (CAR) T or NK cells.[113] For a robust anti-tumor immune response, a cascade of events must take place: initial recognition and communication between immune cells, the activation of immune cells through cytokine release, and the infiltration and targeting of tumor cells.[114,115] These steps culminate in a robust antitumor response, marking CI as a promising field of cancer treatment.

Recent advancements in CI include cytokine therapy, immune checkpoint blockade (ICB), and dendritic cell therapy. ICB, particularly, has revolutionized cancer treatment by targeting co-inhibitory agents such as programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) and CTLA-4.[116] This strategy has demonstrated remarkable success against cancers like melanoma, breast cancer, lung cancer, and bladder cancer.[117] Another significant approach is adoptive cell transfer, which utilizes receptor-modified T cells and CAR-T or CAR-NK cells for targeted and efficient elimination of cancer cells.[118–120] Despite the promising benefits of CI, challenges like immune evasion, antigenic variation, and reduced cell persistence persist, limiting its efficacy in clinical trials.

To address these challenges, researchers have integrated advanced materials like nanoparticles and biomaterials with immune cells. Among these, PBA-mediated materials have gained significant attention. The reversible boronate ester bonds of PBA allow for controlled binding and release of cells, enhancing the targeting precision in cancer immunotherapy. However, the oxidative instability of PBA under physiological conditions poses challenges. To mitigate this, derivatives such as oxaborolones and PBA complexes with citrate, cysteine, and PEG have been developed, offering improved oxidative stability while retaining their ability for dynamic covalent bonding with glycans and amino acid residues.[121] These innovations make PBA-based materials valuable for applications in drug delivery, cancer immunotherapy, and cell spheroid formation.

PBA-mediated polymers and nanoparticles have emerged as effective drug carriers due to their stability, biocompatibility, and long circulation times.[122,123] These materials enhance immune responses while reducing systemic adverse effects.[124] For instance, in pancreatic cancer, where myeloid-derived suppressor cells (MDSCs) significantly contribute to tumor immunosuppression, PBA-functionalized polymeric nanoparticles formulated with chemotherapy drugs have been engineered.[125] These nanoparticles inhibit the recruitment of MDSCs by targeting the P-selectin/PSGL-1 pathway, effectively reducing tumor progression. Biocompatibility studies in healthy mice further confirmed the safety of these nanoparticles, highlighting their potential in CI.

One of the most significant breakthroughs in CI involves targeting immune checkpoints like programmed death-1 and programmed death-ligand 1 (PD-L1). PD-L1, a critical player in cancer immune evasion, has become a key therapeutic target in solid cancers.[126,127] While antibodies targeting PD-L1 have shown success, their limitations include poor intra-tumoral accumulation and rapid clearance.[128] To address these challenges, PBA-based nanocomplexes have been developed to enhance antibody stability and delivery. These complexes protect antibodies from degradation, prolong their circulation time, and facilitate tumor-specific accumulation. *In vivo* studies demonstrated that PBA–antibody nanocomplexes significantly increased T cell infiltration into tumors, enhancing antitumor immune responses.[129]

PBA-based materials have also been employed in gene-editing approaches for cancer therapy. For example, PBA-functionalized tecto dendrimers combined with gold nanoparticles were used for CRISPR/Cas9-mediated PD-L1 blockade.[130] This approach demonstrated superior tumor suppression compared to commercial anti-PD-L1 therapies and activated robust T-cell-mediated immune responses. Moreover, PBA-based micelle-like nanoparticles loaded with chemotherapeutic agents like doxorubicin have shown promise in remodeling the tumor immune microenvironment, further enhancing chemoimmunotherapy outcomes.[70]

In conclusion, cancer immunotherapy continues to advance steadily, opening new avenues for effective and personalized cancer treatment. Among emerging technologies, PBA-mediated materials stand out due to their unique chemical reactivity, reversible diol binding, and structural tunability. These properties confer distinct advantages over traditional immunotherapeutic platforms, such as enhanced antibody stability, improved delivery precision, and responsive modulation of the tumor microenvironment. Unlike conventional methods that often face limitations in targeting efficiency and systemic toxicity, PBA-based systems offer superior control, selectivity, and adaptability under physiological conditions (Table 1). As a result, they present a transformative approach for overcoming major obstacles in current immunotherapy. Continued research and development in this area are essential for harnessing the full clinical potential of PBA-mediated strategies, ultimately leading to more effective and durable outcomes for cancer patients worldwide.

6.3.2 Environment-sensitive siRNA delivery. The delivery of small interfering RNA (siRNA) has become a focus of interest due to its ability to silence genes with remarkable sequence specificity.[131,132] One of the most promising strategies for siRNA delivery involves the formation of polyion complex (PIC) micelles, created through electrostatic interactions between the negatively charged siRNA and cationic polymers in aqueous environments.[133] A critical challenge, however, lies in

stabilizing these micelles in the bloodstream to protect siRNA from enzymatic degradation while enabling their destabilization for siRNA release upon reaching intracellular targets.

Traditional approaches for addressing this challenge include covalent conjugation of siRNA to homing polymers,[134–138] the incorporation of hydrophobic moieties to reinforce core aggregation,[139,140] and disulfide cross-linking of the micelle core.[141,142] Although these methods are effective, they often lead to highly complex structures and preparation processes, which can limit their practicality and scalability.

An innovative solution has emerged using PBA functionalities, which provide a sophisticated yet simplified method for stabilizing PIC micelles.[143] This approach exploits the unique characteristics of PBA, which enables chemical conjugation with the ribose at the 3′-ends of siRNA strands. This interaction not only stabilizes the micelle but also facilitates intermolecular cross-linking through the bis-bidentate ribose arrangement, enhancing the structural integrity of the complex. Moreover, PBA exhibits reversible changes in hydrophobicity depending on the degree of acid dissociation[144] and ribose concentration, allowing the micelle stability to be finely tuned for extracellular and intracellular conditions.

To demonstrate this approach, researchers developed poly (ethylene glycol)-*block*-poly(L-lysine) (PEG-*b*-PLys) polymers, which were modified with 3-fluoro-4-carboxyphenylboronic acid (FPBA) to varying extents. The PEG segment had a weight-average molecular weight of 12 000, while the poly(L-lysine) block had a mean degree of polymerization of 42 (Fig. 5). Systematic optimization of the degree of PBA modification and the polymer-to-siRNA mixing ratio resulted in PIC micelles that were stable under extracellular conditions but disrupted in response to intracellular adenosine triphosphate concentrations, facilitating siRNA release.

Preliminary experiments revealed that these PBA-functionalized micelles could effectively silence the proto-oncogene polo-like kinase 1 in human renal carcinoma cells. The micelles exhibited a dose-dependent silencing effect with minimal cytotoxicity, demonstrating their potential for selective siRNA delivery. By integrating stabilization and controlled release mechanisms into a single, straightforward system, this PBA-based approach holds significant promise for advancing siRNA therapeutics.

6.4 Stability considerations across PBA-based applications

The stability of PBA-based platforms is a critical factor influencing their performance in a range of biomedical applications, including glucose-responsive insulin delivery, diabetic wound healing, and cancer drug delivery. In glucose-responsive insulin delivery systems, it is essential to maintain the structural integrity and appropriate mechanical properties of hydrogels[145] or nanoparticles[146] to ensure controlled insulin release and prevent premature leakage. Rheological studies offer valuable insights into the viscoelastic behavior and mechanical robustness of these hydrogels under physiological conditions, guiding formulation optimization. Similarly, the surface charge and colloidal stability of PBA-functionalized nanoparticles, commonly assessed through zeta potential analysis, are pivotal in determining their dispersion stability, cellular interactions, and circulation time *in vivo*. Furthermore, cell viability assays such as MTT or XTT are widely employed to evaluate the cytocompatibility of PBA-based hydrogels and nanoparticles, ensuring their safety for biomedical use.[147] Notably, these materials often exhibit a storage modulus (G') greater than the loss modulus (G''), indicating a predominantly elastic and stable gel network.[148] They also typically exhibit zeta potential values exceeding ±30 mV, indicating strong electrostatic repulsion and stable colloidal behavior, as well as excellent cytocompatibility.[149,150] These characteristics collectively support their suitability for *in vivo* applications.

However, the dynamic nature of boronate ester bonds, which respond to glucose and pH fluctuations, can lead to undesired dissociation and degradation of the materials under physiological conditions.[151] To address this, researchers have developed multi-crosslinking strategies that combine reversible boronate ester linkages with more stable covalent or hydrogen bonds.[152–155] The incorporation of robust polymeric backbones, such as PEG[156] or HA derivatives,[157] further enhances mechanical strength and enzymatic resistance,

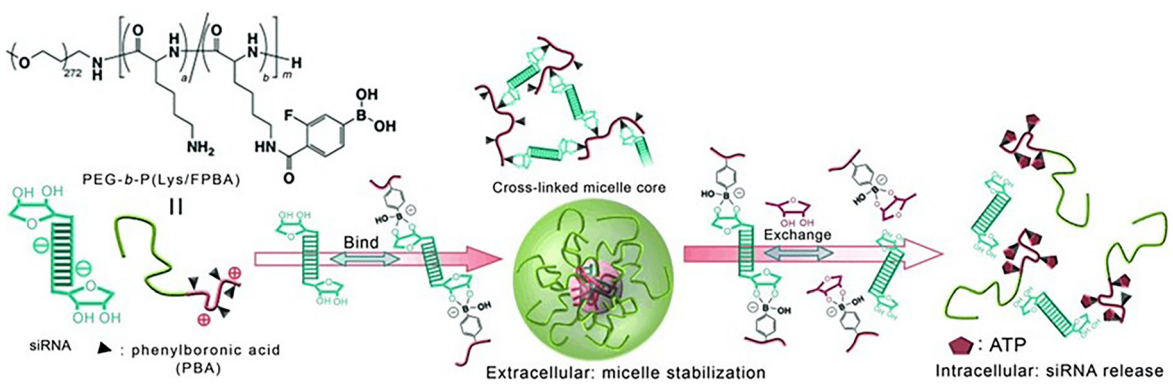

Fig. 5 Schematic illustration of the phenylboronic acid modified block copolymer assemblies for ATP-responsive siRNA delivery. Reproduced with permission from ref. 143. Copyright 2012 Wiley-VCH Verlag GmbH.

thereby extending the functional lifespan of these delivery systems.

In diabetic wound healing, PBA-based hydrogels must function effectively in a challenging microenvironment characterized by fluctuating pH, elevated glucose levels, ROS, and heightened enzymatic activity.[158–160] To maintain both responsiveness and structural integrity under these conditions, multi-stimuli-responsive designs are often employed, integrating ROS-sensitive components coupled with boronate ester moieties.[161,162] Hybrid crosslinking networks that combine dynamic and covalent bonds further enhance mechanical stability, enabling prolonged drug release and sustained wound coverage.[162] Rheological characterization in this context is particularly important to ensure the hydrogel retains sufficient mechanical strength and injectability throughout the treatment duration.

For cancer drug delivery, materials must remain stable in systemic circulation while enabling selective drug release within the acidic and enzyme-rich tumor microenvironment. PBA-based micelles and nanoparticles typically utilize hydrophobic cores to shield boronate ester bonds and encapsulated drugs from premature degradation.[163,164] Their surfaces are often modified with hydrophilic polymers such as PEG to enhance colloidal stability and extend circulation time.[50,165] Zeta potential analysis plays a critical role here as well, confirming favorable surface charge profiles that minimize aggregation and improve biocompatibility. Multi-responsive systems capable of responding to pH, ROS, and glucose stimuli enable precise, site-specific drug release while preserving carrier integrity.

Overall, achieving a balance between responsiveness and structural stability is essential for optimizing PBA-based platforms. Advanced material designs that integrate dual or multiple crosslinking mechanisms, employ robust polymer backbones, and incorporate multi-stimuli sensitivity represent promising strategies to address stability challenges and improve the clinical translation of PBA-based biomedical applications.

7. Conclusion and future perspectives

In conclusion, PBA derivatives have demonstrated remarkable potential across a broad spectrum of scientific and biomedical applications. Their ability to selectively bind with saccharides, particularly glucose, has positioned PBA as a key player in the development of glucose-responsive insulin delivery systems, contributing significantly to diabetes management. From bulk hydrogels to micro/nanogels and self-assembled micelles, PBA-based materials have shown promising results in achieving controlled and efficient insulin release, enhancing glycemic regulation, and offering a potential solution for long-term diabetes care.

Looking ahead, the future of PBA-based systems holds immense promise for further innovation and broader applications. The continued exploration of PBA derivatives in drug delivery, particularly for comorbid conditions like cancer immunotherapy, suggests new avenues for targeted therapies with reduced side effects. Additionally, the integration of PBA with polymers in biosensing and diagnostic platforms may lead to the development of more sensitive, accurate, and real-time monitoring systems for various health conditions. The potential for environment-sensitive siRNA delivery based on PBA highlights its application in personalized medicine, offering precise therapeutic interventions tailored to specific biological environments.

Moreover, future research should focus on refining PBA-based platforms to improve biocompatibility, minimize toxicity, and enhance responsiveness under diverse physiological conditions. In parallel, immunological implications warrant careful attention, especially for applications involving chronic or repeated use. While many studies demonstrate short-term safety, the potential for long-term immune activation, foreign body responses, or adaptive immunogenicity remains insufficiently explored. Thus, future studies should prioritize comprehensive immunotoxicity assessments and long-term *in vivo* evaluations to ensure the sustained safety of PBA-based systems. Integrating PBA with other responsive agents, such as glucose oxidase or smart polymers, offers new avenues for developing multifunctional, adaptable platforms. As PBA technologies continue to mature, their reach will likely expand well beyond insulin delivery into wound healing, biosensing, and complex drug delivery applications, paving the way for more effective, personalized, and responsive therapies.

Ultimately, PBA derivatives hold transformative potential, advancing biomedical research and offering innovative solutions to complex clinical challenges. Continued interdisciplinary research and development will ensure that PBA-based systems lead the way in biomedical development, fostering more effective, personalized, and responsive therapeutic strategies.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

Data will be available upon request from the corresponding author.

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