

Innovations and challenges in bioresponsive materials for effective drug delivery in diabetes mellitus

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ABSTRACT

Bioresponsive materials have gained prominence as innovative tools for advancing drug delivery systems, particularly in managing type 1 and type 2 diabetes mellitus. These materials respond to biological stimuli such as pH, glucose, enzymes, or temperature, thereby enabling spatiotemporally controlled drug release. This review examines recent progress in the design strategies, activation mechanisms, and therapeutic applications of these materials in diabetes care. Key focus areas include macromolecular insulin delivery systems and oral hypoglycemic agents, with emphasis on their efficacy in regulating blood glucose homeostasis. Despite their promise, challenges persist in translating these technologies to clinical practice, including scalability limitations, insufficient clinical validation, regulatory hurdles, and healthcare system compatibility. Current therapeutic shortcomings, such as frequent injections and adverse effects compromising patient adherence, are discussed. By synthesizing contemporary research developments and implementation barriers, this work provides critical insights into optimizing bioresponsive platforms for clinical translation. Our analysis underscores the need for interdisciplinary approaches to address technical and practical constraints, and ultimately engineer patient-centric, scalable solutions that enhance therapeutic outcomes and quality of life. Future directions include bridging material innovation with clinical needs to develop next-generation diabetes management systems.

Keywords: Bioresponsive, biomaterials, drug delivery, glucose, diabetes

1. INTRODUCTION

As of 2021, approximately 537 million people worldwide had diabetes, 90% of whom had type 2 diabetes mellitus (T2DM). This number is projected to reach 783 million by 2045 [1]. Numerous medications have been investigated for their efficacy in decreasing complications associated with diabetes mellitus (DM). Whereas insulin remains essential for type 1 diabetes management, T2DM treatment often combines insulin with oral antidiabetic drugs [2]. However, current delivery methods face substantial challenges. Injectable insulin causes local adverse effects (e.g., swelling or erythema), whereas oral medications may trigger gastrointestinal complications (e.g., nausea or diarrhea) [3, 4]. These challenges contribute to decreasing patient compliance, yet lifelong treatment is

required for managing DM. Using bioresponsive materials in drug delivery has emerged as a promising solution to address these limitations.

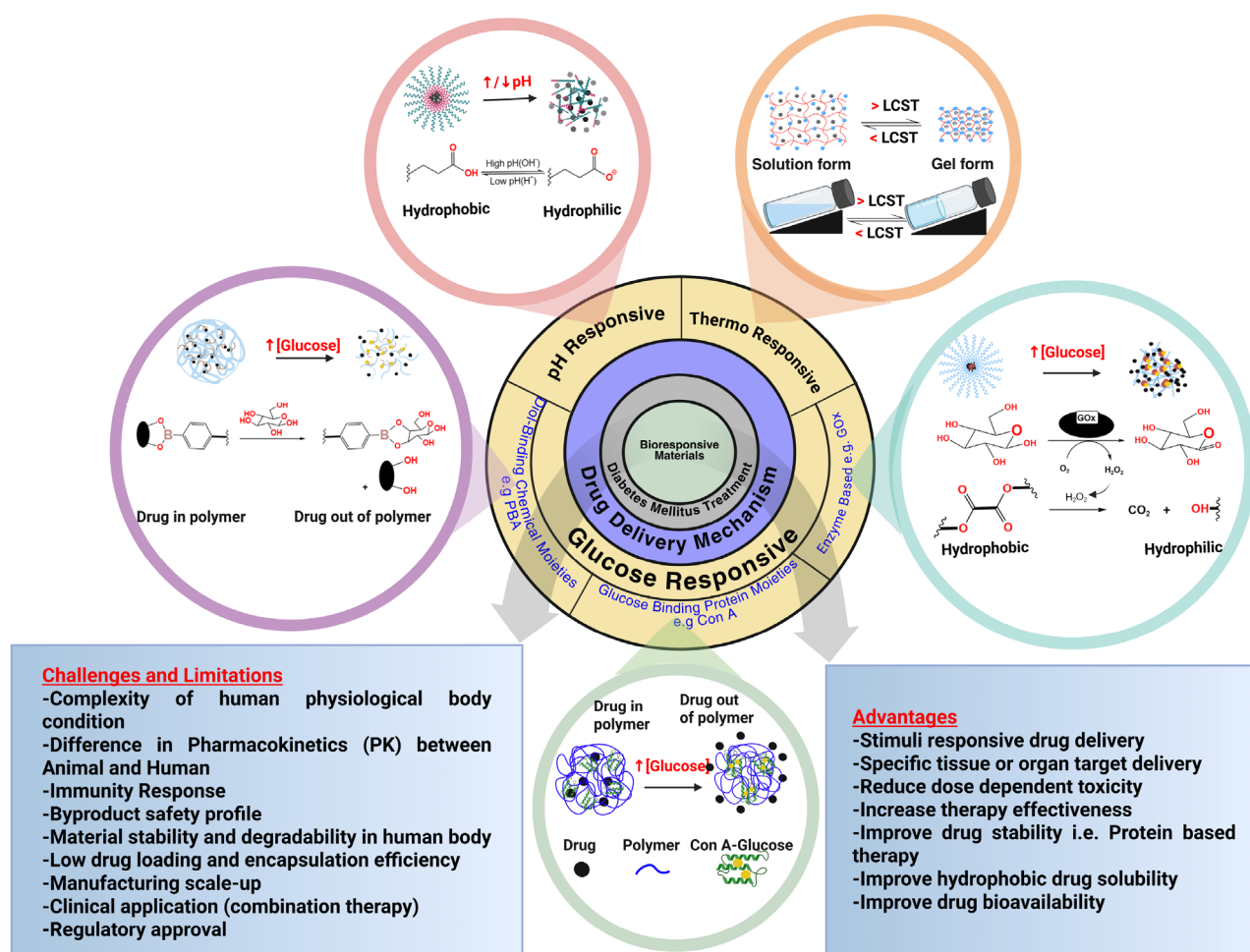
A drug delivery system (DDS) is an interface, designed as either a drug formulation or a device, that facilitates the administration of therapeutics into the body. The primary goal of DDSs is to enhance pharmacodynamic and pharmacokinetic properties, increase therapeutic efficacy, and ensure patient safety throughout treatment while minimizing undesirable effects caused by nonspecific drug distribution [5, 6]. Various DDSs have been developed, including organic nanoparticles such as dendrimers, micelles, liposomes, polymers, and ferritin; inorganic nanoparticles, such as quantum dots and gold nanoparticles; and hydrogels [7].

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In diabetes treatment, not all drug delivery routes are suitable for every medication. For example, complex and unstable drugs such as insulin cannot currently be administered orally, because they are degraded in the gastrointestinal tract. However, advancements in innovation may make oral insulin delivery feasible. Enhancing existing delivery systems or developing novel systems would provide substantial advantages in diabetes management. Bioresponsive materials are specially designed materials that undergo physical or chemical transformations in response to specific biological triggers, such as pH, glucose level, temperature, or enzymes. These transformations enable the controlled release of therapeutic agents, which can be used for treatment and diagnosis [8]. Recently, bioresponsive materials have become a critical component in DDS development. These materials offer several advantages over conventional DDSs, primarily because of their ability to respond specifically to biological triggers.

This specificity ensures targeted drug release at the disease site and consequently decreases toxicity risk. Additionally, these materials enable sustained and on-demand drug release, thus enhancing efficacy by ensuring that the drug is delivered to the proper site at the proper time. These advancements ultimately decrease the need for frequent monitoring of diabetes patients and improve treatment compliance [9, 10].

Herein, we present recent findings regarding the application of bioresponsive materials in developing advanced formulations for enhancing the delivery of antidiabetic medications (**Scheme 1**). This review provides an overview of current research progress, including a detailed examination of delivery mechanisms. Additionally, we identify the challenges associated with developing and implementing bioresponsive materials in diabetes DDSs. Finally, we explore future perspectives that offer valuable insights into potential innovations in diabetes drug delivery.



Scheme 1 | Schematic diagram illustrating bioresponsive materials for drug delivery triggered by glucose, temperature, and pH, along with their advantages and challenges in the effective treatment of diabetes mellitus.

2. BIORESPONSIVE MATERIALS, MECHANISMS, AND APPLICATIONS IN DIABETES MELLITUS TREATMENT

2.1 pH-sensitive materials

pH-sensitive biomaterials undergo structural changes (e.g., swelling/dissociation) in specific-pH environments and subsequently release therapeutic agents. Their responsiveness originates from ionizable compounds incorporated into polymers via chemical reactions or self-assembly [6, 11-15]. Examples include 1) acrylic acid, which ionizes ($-\text{COOH} \rightarrow -\text{COO}^-$) at high pH, thus increasing hydrophilicity [16]; 2) sulfonamide, which loses electrons at high pH via oxygen atoms, thus enhancing water affinity [17, 18]; and 3) sodium alginate (SA), which forms hydrogen bonds with carboxyl groups ($-\text{COOH}$) at low pH (1.2), thus decreasing electrostatic repulsion and swelling, whereas at high pH (6.8), ionized $-\text{COO}^-$ groups induce repulsion, promoting water uptake [19, 20]. Ionization increases polymer

matrix hydrophilicity through negative charge density, thereby enhancing solubility and drug release. This pH-dependent behavior makes such biomaterials ideal for oral antidiabetic drugs (e.g., insulin) that require protection against gastric acidity (Figure 1).

2.1.1 Applications of pH-sensitive materials in diabetes management. The use of ionizable acrylic acid in developing pH-sensitive materials has demonstrated effective drug release under high-pH conditions. Guo and Li have constructed an acrylic acid-functionalized chitosan system to encapsulate compound 1 (an antidiabetic agent). *In vitro* studies have revealed pH-dependent release profiles, with 32.5% release at pH 4, 56% at pH 7, and 42.1% at pH 10 [21].

Bhosale et al. have developed pH-sensitive antidiabetic pellets by using a polymethylmethacrylate-grafted gellan gum (PMMA-g-GG) framework incorporating acrylic acid functional groups. These pellets encapsulated metformin HCl. *In vitro* studies showed negligible

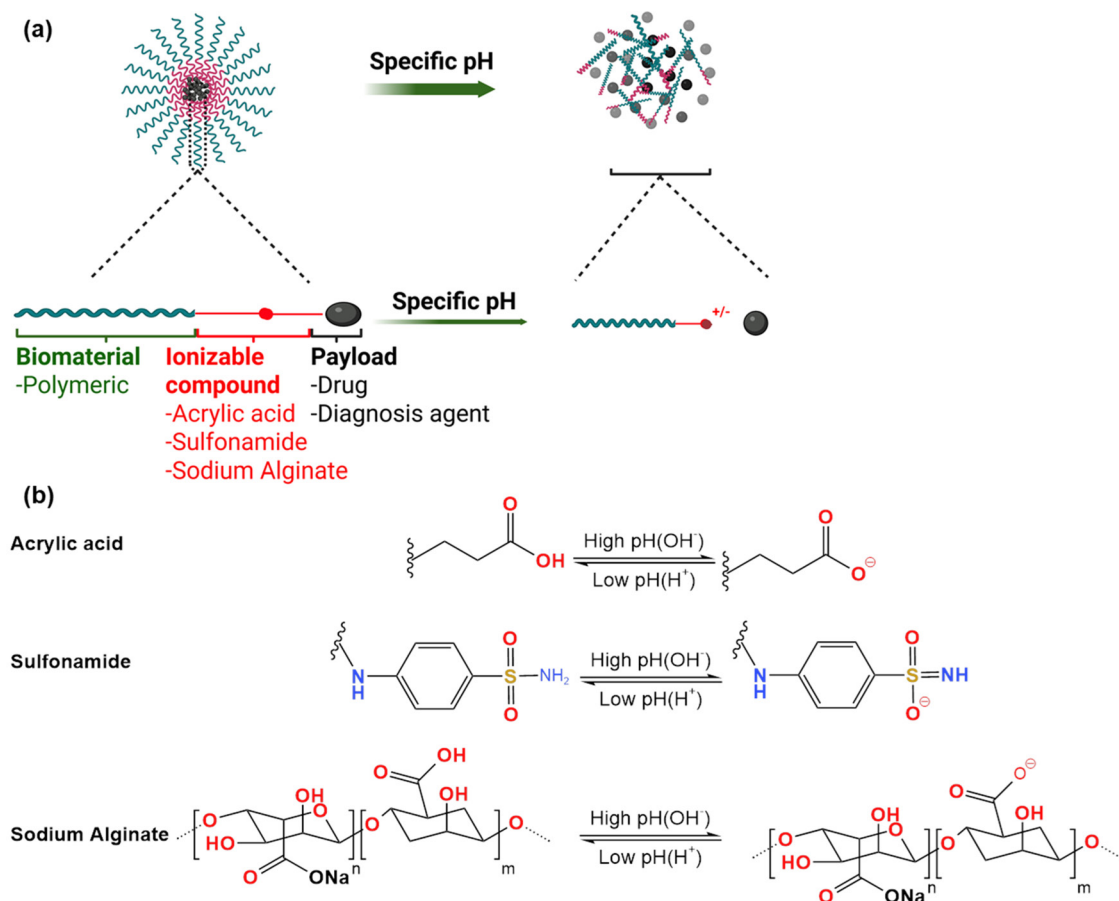


Figure 1 | Biomaterial functionalized with pH-responsive compound.

(a) Schematic representation of a polymer encapsulating a drug to form nanoparticles achieving drug release under specific pH conditions. (b) pH-sensitive compounds ionize at high pH, thus increasing polymer hydrophilicity and facilitating drug release. In contrast, at low pH, they become unionized and hydrophobic, thus hindering drug release.

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release (pH 1.2) in gastric conditions but substantial release (pH 6.8) under intestinal conditions. The proposed mechanism is that the carboxyl groups of PMMA-g-GG remain unionized at low pH, thereby forming hydrogen bonds that rigidify the polymer and inhibit swelling. At higher pH, ionization of acrylic acid carboxyl groups disrupts the hydrogen bonds, thus softening the polymer, enhancing water uptake, and ultimately promoting drug release [22].

Sulfonamide groups, another class of pH-responsive compounds, have been integrated into biomaterials to enable pH-sensitive drug release. Trinh et al. have designed a dual pH- and temperature-sensitive hydrogel by combining oligomeric serine sulfonamide (pH responsive) with poly(lactide)-*b*-poly(ethylene glycol) (thermosensitive), thereby forming a penta-block copolymer. When loaded with antidiabetic nanoparticles, the hydrogel exhibits a solution state at high pH (8.6) and room temperature. This behavior is attributable to sulfonamide ionization: at elevated pH, electron withdrawal by sulfonamide oxygen atoms and electron donation by secondary amine protons increase polymer hydrophilicity and consequently facilitate drug release. In contrast, the hydrogel maintains a gel state at physiological pH (7.4) [23].

SA, a coating material with inherent pH-responsive solubility (soluble in basic conditions and insoluble in acidic environments), has also been used. For instance, Ren et al. have developed an oral SA-coated hydrogel encapsulating insulin-loaded *Chlorella vulgaris*. Insulin release reached 22.06% at gastric pH (1.8) but surged to 96.92% at intestinal pH (7.2) [24]. Similarly, Zhang et al. have designed an oral-pH-sensitive nanohydrogel using *o*-carboxymethyl chitosan and SA, in which electrostatic interactions led to formation of insulin-loaded nanoparticles. The release profiles showed 50% release at pH 6.8 (48 hours), and 68.7% release at pH 7.4 (48 hours) [25].

Apart from incorporating pH-sensitive ionizable compounds into polymers, polymers with pH-responsive release can be achieved through careful modulation of ionic interaction and hydrogen bonding. Fetouh et al. have used chitin-grafted guar gum (chitin-g-GG) to encapsulate insulin, on the basis of bond formation through ionic interaction with the –OH group of GG and hydrogen bonding with the acetyl group of chitin. The system demonstrated pH-responsive insulin release, in which no release of insulin occurred at pH 1.2, whereas sustained release of insulin was observed at pH 7.4 [26].

2.2 Temperature-sensitive (thermosensitive) materials

Temperature-sensitive materials respond to specific temperature changes in their environment, thus exhibiting a miscibility gap at either high or low temperatures [6, 27]. These temperature-induced alterations in material properties may manifest as swelling or transitions between solution and gel states [6]. On the basis of their phase behavior, these materials are classified into

two categories: (i) lower critical solution temperature (LCST) materials, which become insoluble after heating above their LCST (Figure 2), and (ii) upper critical solution temperature materials, which become soluble after heating above their upper critical solution temperature. Analogous transitions in hydrogels are termed lower critical gelation temperature and upper critical gelation temperature [29, 30].

Common LCST-type polymers include poly(*N*-isopropylacrylamide) (PNIPAAm); poly(*N,N*-dimethylacrylamide); poly(methyl vinyl ether); poly(*N*-vinylcaprolactam); poly(ethylene oxide) (PEO); poly(ethylene oxide-co-propylene oxide) copolymers; poly(*N*-substituted acrylamides); poly(*N*-acryloyl pyrrolidine); poly(*N*-acryloyl piperidine); poly(acryloyl-L-amino acid ester); poly(ethyl oxazoline); and alcohol-based derivatives, such as hydroxypropyl acrylate, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, methylcellulose, and poly(vinyl alcohol) [6, 29, 31].

The LCST mechanism involves hydrogen bonding between polymers and water below the LCST, thereby enabling dissolution. Above the LCST, increased intra- and inter-chain hydrophobic interactions drive a coil-to-globule transition that results in polymer collapse [32, 33]. Notably, incorporating pH-sensitive monomers into thermosensitive polymers enhances pH responsiveness, because of the hydrophilic nature of ionized pH-sensitive groups. Even minimal amounts of pH-sensitive monomers can disrupt the LCST behavior of dominant monomers [27, 34].

2.2.1 Applications of temperature-sensitive materials in diabetes management. Using temperature-sensitive materials (particularly LCST systems) in diabetes treatment offers advantages such as controlled and sustained release of antidiabetic drugs. These materials undergo a solution-to-gel transition at physiological temperatures (e.g., room temperature to body temperature), thereby enabling non-invasive delivery via transdermal microneedles, oral, intravaginal, or rectal routes [35]. Yao et al. have developed a subcutaneously delivered thermosensitive biomaterial by integrating PNIPAAm and graphene oxide to mimic islet cells, which encapsulate insulin. The system maintains normal blood glucose concentrations in diabetic mice [36]. Microneedle array patches have gained prominence in diabetes research, because of their minimally invasive nature, painless self-administration, and compatibility with peptide/protein drugs such as insulin [37]. For instance, Li et al. have developed PNIPAAm-grafted gelatin microneedles for insulin delivery. *In vitro* studies showed 100% drug release at room temperature and 42% at 37°C. *In vivo* tests confirmed sustained insulin release and greater efficacy than that of non-thermosensitive systems. This behavior stems from strengthened polymer-protein interactions above the LCST (solution-to-gel transition), which restrict drug release, whereas weakened interactions below the LCST promote drug diffusion [38].

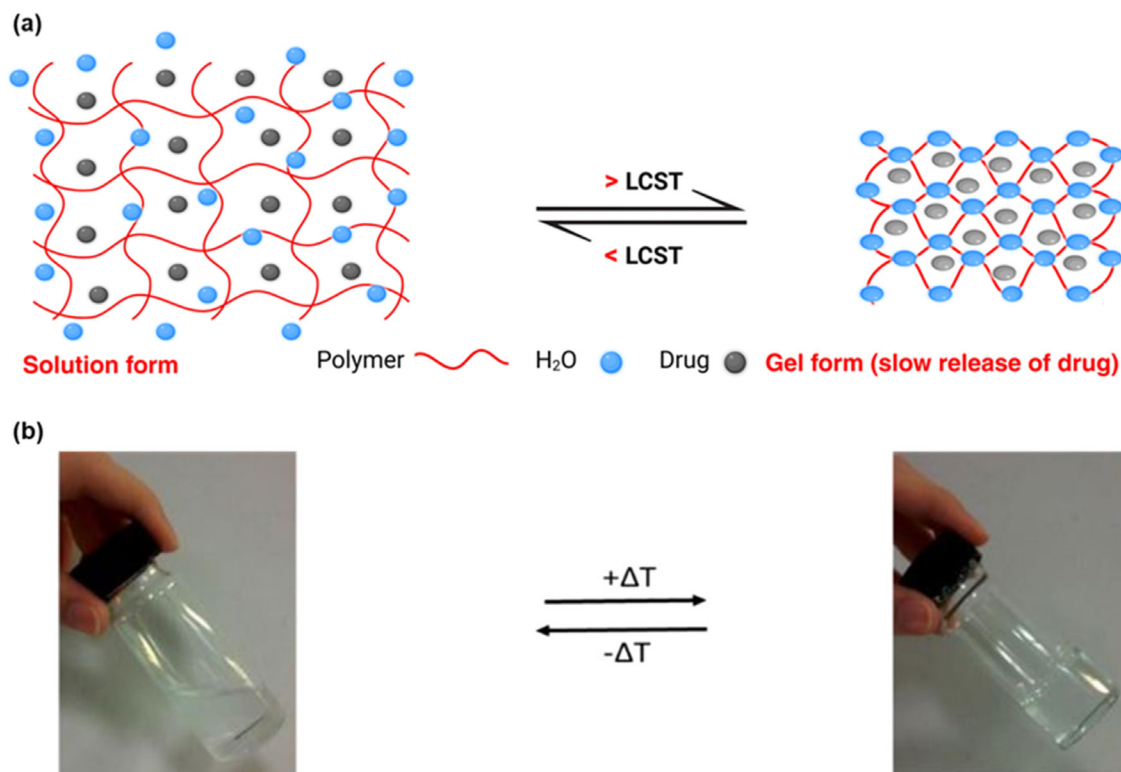


Figure 2 | Thermo-gelation mechanism of biomaterials.

(a) Schematic representation of a polymer-encapsulated drug system exhibiting LCST. Below the LCST, the material is in solution form, whereas above the LCST, it forms a gel with slow drug release. (b) Photographic image of a drug-loaded hydrogel demonstrating a reversible phase transition from solution to gel above the lower critical solution temperature (LCST), and from gel to solution below the LCST. Reproduced with permission [28]. Copyright 2019 Springer Nature.

2.2.2 Alternative thermosensitive materials. Beyond PNIPAAm, poly(lactide-co-glycolide) (PLGA) demonstrates temperature-sensitive drug release and biocompatibility, and undergoes solution-to-gel transitions near body temperature [39]. Dutta et al. have designed an injectable PLGA-PEG-PLGA triblock copolymer hydrogel (lower critical gelation temperature 34°C) encapsulating insulin and GLP-1 analogs. *In vivo*, insulin release persisted for ~100 hours, and glycemic control was maintained for 72 hours, whereas free insulin was undetectable after 24 hours [40]. Similarly, Trinh et al. have engineered a pH-thermosensitive OS-PLA-PEG-PLA-OS hydrogel incorporating chitosan-insulin nanoparticles. The system transitions from solution (15°C) to gel (37°C), thereby forming a subcutaneous depot for sustained insulin release and achieving 60-hour glycemic control in mice [41].

Other temperature-sensitive materials, such as PEO and poly(propylene oxide), are also classified as LCST polymers. These materials can be copolymerized to form a tri-block copolymer known as Pluronics, which includes two hydrophilic PEO blocks linked by a hydrophobic poly(propylene oxide) block. Pluronic F-68 and F-127 have been approved by the U.S. FDA for biomedical use

[42]. Various studies have used Pluronic F-127 in temperature-sensitive drug delivery applications [28, 43]. Mansoor et al. have designed a glucose- and temperature-sensitive hydrogel by using Pluronic F127 to link chitosan (structural stability) and concanavalin A (Con A; glucose sensing). At physiological pH (7.4) and 37°C, a solution-to-gel transition facilitated 97% insulin release over 7 days [44].

Poly(diethyleneglycol methylethermethacrylate) (PDEGMA), with tunable LCST (12–47°C via monomer ratio adjustments), has been used for glucose- and temperature-sensitive insulin delivery [45]. Wu et al. have synthesized P(AAPBA-*b*-DEGMA) nanoparticles that achieve slow insulin release at elevated temperatures *in vitro* while sustaining normoglycemia for 48 hours *in vivo* [46].

LCST materials can be tailored for specific applications by adjustment of monomer ratios or polymer molecular weights during synthesis, thus enabling precise control of drug release profiles.

2.3 Glucose-sensitive materials

Glucose-sensitive biomaterials can detect glucose levels in their surrounding environment [47]. These materials

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include hydrogels, polymer nanoparticles, liposomes, and micelles [48]. When functionalized with glucose-sensing moieties, they respond to glucose fluctuations or secondary signals associated with glucose concentration changes, such as H_2O_2 levels, pH variations, and O_2 concentrations. After encountering these stimuli, the biomaterials undergo structural alterations that modify their physicochemical properties, thereby triggering controlled drug release [49].

Three primary mechanisms enable glucose sensitivity in these systems: (i) glucose oxidase (GOx) catalyzes glucose oxidation, thus decreasing glucose concentrations while generating hydrogen peroxide (H_2O_2); (ii) glucose-binding proteins, such as Con A, selectively bind glucose through specific molecular interactions; (iii) diol-binding chemical groups, such as phenylboronic acid (PBA) and its derivatives, form reversible covalent bonds with glucose and consequently induce conformational changes in the biomaterial [47-49]. These mechanisms are critical in glucose-responsive DDSs, particularly for diabetes management, because they enable release of therapeutic agents in a glucose-dependent manner. The following sections detail their operational principles and applications in diabetes therapy.

2.3.1 Enzyme-based mechanism. GOx catalyzes the oxidation of glucose to gluconic acid and hydrogen peroxide (H_2O_2) in the presence of oxygen and subsequently

creates a hypoxic microenvironment [50, 51] (Figure 3a). These reaction products generate distinct microenvironments: an acidic microenvironment through gluconic acid production, an oxidative microenvironment through H_2O_2 generation, and a hypoxic microenvironment via oxygen consumption during glucose oxidation [52, 53]. Through the use of biomaterials sensitive to acidic, oxidative, and hypoxic microenvironments, structural modifications such as enhanced hydrophilicity can be induced to facilitate drug release. This release is achieved by incorporation of functional groups that respond to microenvironmental signals into the biomaterial. Notably, the intensity of these stimuli depends on glucose concentration, which in turn determines the degree of biomaterial structural modification. Under normal glucose concentrations, minimal or no structural modification occurs, whereas elevated glucose concentrations lead to greater modifications and enhanced drug delivery.

Examples of acid- and oxidative-sensitive functional groups in biomaterials include oxalate [54, 55]; sulfide and propylene sulfide [56, 57]; PBA and boronate ester bonds [58]; thioether-based groups such as thiomorpholine amide (TMAM), 3-methylthiopropylamide (TPAM), and 4-(methylthio)benzylamide (TPhAM) [59]; thioketals [60]; and selenium (Se) and tellurium (Te) analogs of ethers, including selenoethers, diselenides, and telluroethers [61-63] (Figure 3b).

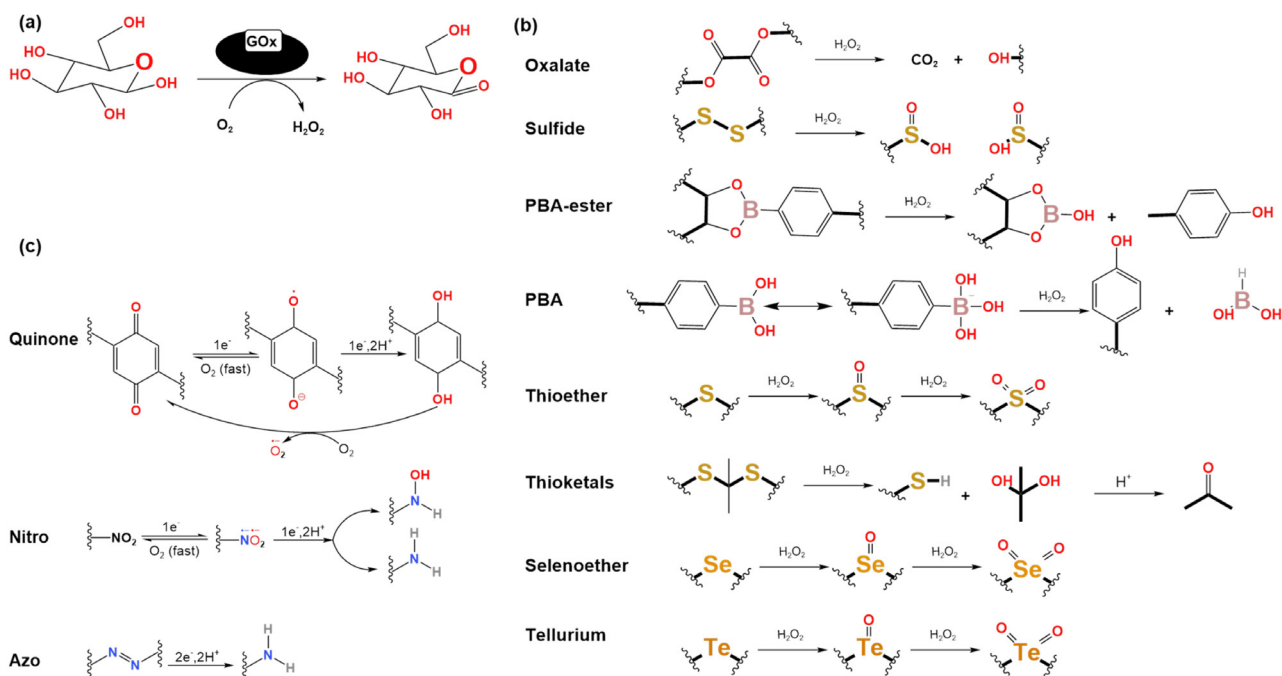


Figure 3 | GOx-mediated glucose-responsive material.

(a) Conversion of glucose to gluconic acid and H_2O_2 by GOx in the presence of oxygen. (b) Oxidation of an Oxidative-sensitive functional group in the presence of H_2O_2 , which increases system hydrophilicity and facilitates drug release. (c) Reversible reduction of a hypoxia-sensitive functional group under diminished O_2 concentrations, which enhances drug release by increasing system hydrophilicity.

Examples of hypoxia-sensitive functional groups include the following (Figure 3c):

- (i) Quinone analogs (e.g., indolequinone) that undergo one-electron reduction and form semi-quinone radical anions under hypoxia, with subsequent reduction to semiquinone radicals and hydroquinone. This reversible reaction is inhibited under normoxic conditions [64, 65].
- (ii) Nitro groups (e.g., nitroimidazole derivatives), whose R-NO₂ moiety is reduced to free radical anions under hypoxia, and is followed by further reduction to hydrophilic hydroxylamine (R-NH(OH)) or amine (R-NH₂), thereby inducing structural modifications for payload release [66-68].
- (iii) Azo groups (e.g., azobenzene) forming hypoxia-sensitive linkers (R-N=N-R) that undergo reductive cleavage of N=N bonds under hypoxia and subsequently release the payload [69-72].

GOx has been widely used in biomaterials for glucose-triggered drug delivery. Recent advances are described below.

2.3.1.1 Injectable hydrogels

Zhang et al. have developed a chitosan-based injectable hydrogel self-assembled from phenyl boronic acid-modified chitosan (CSPBA), benzaldehyde-capped polyethylene glycol (PEG) (PEGCHO), and PVA, crosslinked via (i) PBA-ester bonds (CSPBA-PVA) and (ii) amide bonds (CS-PEGCHO), to encapsulate GOx, catalase (CAT), and insulin. Under hyperglycemia, GOx-generated gluconic acid reduces amide bonds ($-N=C- \rightarrow -NH_2$), whereas H₂O₂ oxidizes PBA-ester to phenol, thereby triggering hydrogel degradation and insulin release (Figure 4a). The system has been found to maintain normoglycemia for 11 days *in vivo* [73] (Figure 4b, c).

2.3.1.2 Microneedle patches

Hypoxia/H₂O₂ dual-responsive system: Yu et al. have designed microneedles containing PEG-poly(Ser-S-NI) nanoparticles encapsulating GOx and insulin. High glucose levels induce H₂O₂-mediated thioether oxidation ($S \rightarrow$ sulfone) and hypoxia-driven nitroimidazole reduction ($NO_2 \rightarrow NH_2$), thus enhancing hydrophilicity for insulin release. This system has been found to regulate glucose in diabetic mice for 10 hours [74].

H₂O₂-responsive mesoporous silica nanoparticles: Xu et al. have engineered mesoporous silica nanoparticles modified with ICBE and α -cyclodextrin. H₂O₂ oxidizes ICBE boronate esters to phenol, thus disrupting α -CD crosslinks and releasing insulin. *In vitro* H₂O₂ exposure increased insulin release from 18.5% to 72.4%, whereas *in vivo* efficacy lasted 4.5 hours vs. 2 hours with conventional insulin [75].

MOF-based Microneedles: Yang et al. developed co-doped ZIF-8 nanoparticles (Ins/GOx@Co-ZIF-8) embedded in PVA/SiO₂-EDTA microneedles. Acidic conditions dissociate the MOF via 2-methylimidazole protonation,

thus releasing insulin. Co²⁺ mimics CAT, thus resulting in H₂O₂ degradation, whereas EDTA chelates excess Co²⁺. Although pH 5.0 triggered 80% insulin release, negligible release was observed at pH 7.4 [76].

2.3.1.3 Multi-stimulus systems

Luo et al. designed a dual-nanoparticle microneedle patch comprising (i) pH-sensitive mPEG-b-PHMEMA nanoparticles (SNP(I)) for insulin, and (ii) mPEG-b-PCHMA nanoparticles (iSNP(G+C)) loaded with GOx/CAT. Gluconic acid protonates PHMEMA amines, thus enhancing hydrophilicity for insulin release, whereas CAT scavenges H₂O₂, thereby protecting GOx. At 400 mg/dL glucose, 90% of insulin was released within 4 hours, whereas 30% was released at 100 mg/dL. Combined nanoparticles extended normoglycemia to 8 hours vs. 2 hours for SNP(I) alone [77].

2.3.1.4 Gas-driven release

Ullah et al. have created a porous polymer-coated microneedle through LBL assembly of NaHCO₃/PVA/GOx/insulin/PLGA. Gluconic acid decomposes NaHCO₃ to CO₂, thus generating pressure that ruptures the PLGA layer (Figure 5a). *In vitro* tests showed 50% insulin release in 1 hour and 100% in 6 hours at 400 mg/dL glucose (Figure 5c), whereas *in vivo* glucose control lasted 10 hours [78] (Figure 5d).

2.3.1.5 Enzyme-functionalized biomaterials for addressing diabetes complications

Beyond the well-identified complications associated with DM, such as retinopathy, neuropathy, chronic kidney disease, cardiovascular disease, and cerebrovascular disease [79], people with diabetes experience elevated susceptibility to bone fractures, delayed healing [80, 81], and chronic diabetic wounds [82]. By using enzyme-functionalized biomaterials, such as those incorporating GOx, targeted drug delivery can be achieved to address these complications effectively.

2.3.1.5.1 Bone regeneration

Gong et al. have developed an Mg²⁺/gallic acid MOF hydrogel in which GOx-generated acidity releases Mg²⁺, thereby promoting angiogenesis. Use of this hydrogel in diabetic mice has been shown to enhance bone repair [83]. In hyperglycemia, an acidic microenvironment is created because of the formation of gluconic acid from glucose oxidation with GOx, thereby facilitating reduction of the bond between Mg²⁺ and gallic acid, leading to MOF dissociation and release of Mg²⁺, and facilitating angiogenesis. The hydrogel has been demonstrated to achieve significant improvement in bone regeneration in diabetic mice.

2.3.1.5.2 Wound healing

Wu et al. have designed Fe²⁺-coordinated GOx-poly(LAAm) hydrogels with multi-enzyme activity (GOx/CAT/superoxide dismutase), thereby decreasing glucose,

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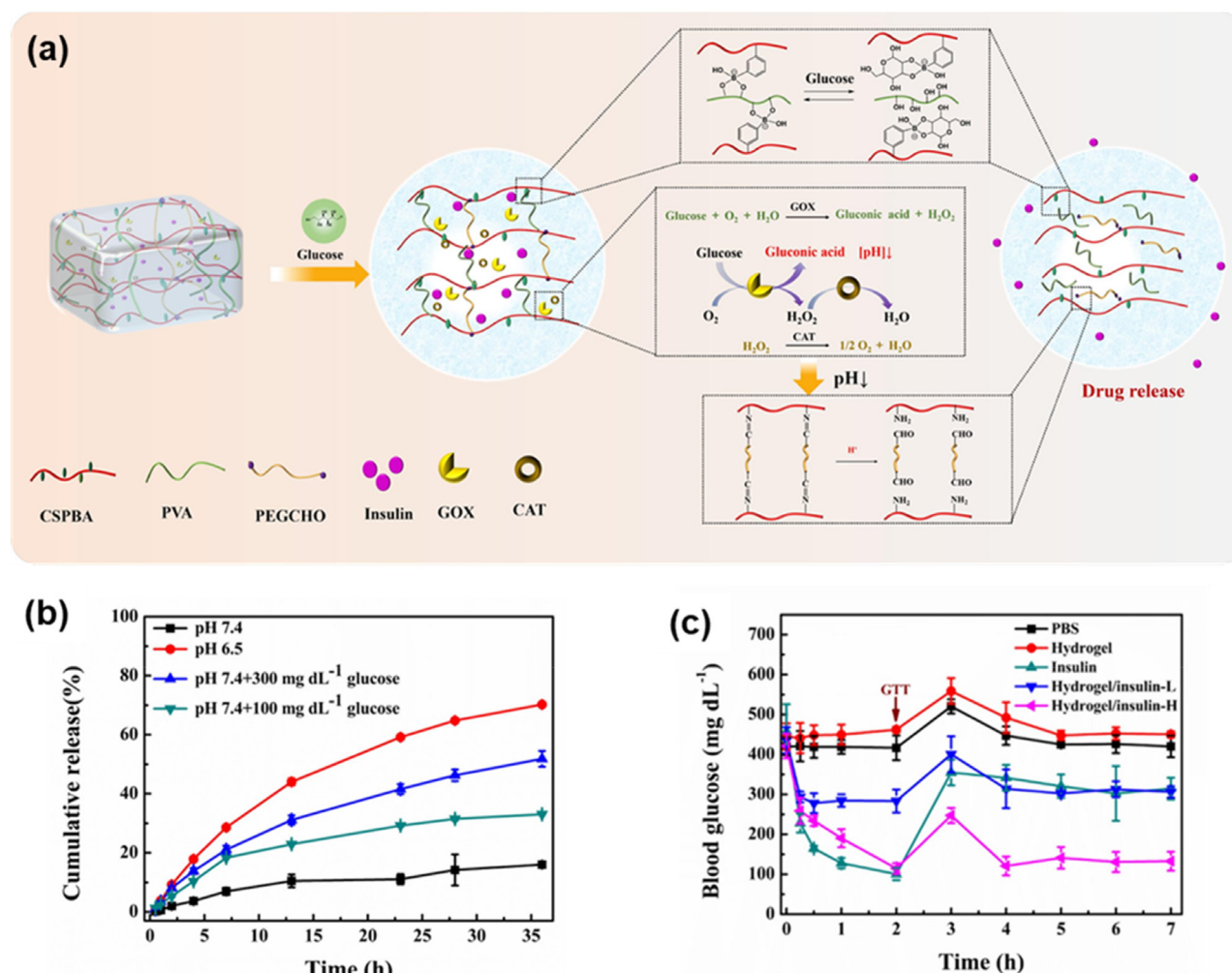


Figure 4 | Multi-stimulus-responsive system.

(a) Schematic illustrating a hydrogel system with glucose- and pH-responsive elements, depicting the mechanism of drug release triggered by glucose and pH changes. (b) *In vitro* release of insulin in a solution with different glucose concentrations and pH levels. (c) *In vivo* blood glucose monitoring, 2 hours after treatment, in rats subjected to glucose tolerance test (GTT). Reproduced with permission [73]. Copyright 2023 Elsevier B.V.

reactive oxygen species (ROS), and inflammation, while increasing wound oxygenation. With use of these hydrogels, diabetic wounds healed comparably to normal wounds within 15 days. GOx coordinates with Fe²⁺ and forms uni-molecular GOx-poly(LAAM) with multi-enzyme activity, including GOx, CAT, and superoxide dismutase activity. Consequently, glucose levels, ROS, inflammation, and infection decrease, whereas O₂ levels increase in the wound microenvironment, thus promoting healing [84].

2.3.1.5.3 Real-time monitoring

Beyond treatment of DM and its complications, effective disease monitoring is essential. Enzyme-functionalized biomaterials, such as those incorporating GOx, offer precise real-time glucose monitoring. Hsu et al. have integrated an MnO₂/GOx-TMB biosensor into methacrylated

gelatin microneedles. H₂O₂ oxidizes 3,3',5,5'-tetramethyl benzidine (TMB) (–NH₂ → =NH), thereby inducing a color shift (colorless → blue) amenable to smartphone-based glucose detection for real-time monitoring [85] (Figure 5b).

2.3.2 Mechanism based on glucose-binding-protein moieties.

Glycan-binding proteins (GBPs) recognize and bind specific glycans, and subsequently mediate cellular processes [86]. In mammals, six common carbohydrates—galactose, *N*-acetylgalactosamine, *N*-acetylglucosamine, mannose, sialic acid, and fucose—exhibit specific binding to GBPs [86]. GBPs are classified into two groups: lectins and sulfated glycosaminoglycans [87]. Lectins contain carbohydrate recognition domains and are subdivided into types C, P, I, L, and R, whereas sulfated glycosaminoglycans interact primarily with heparin, chondroitin, and

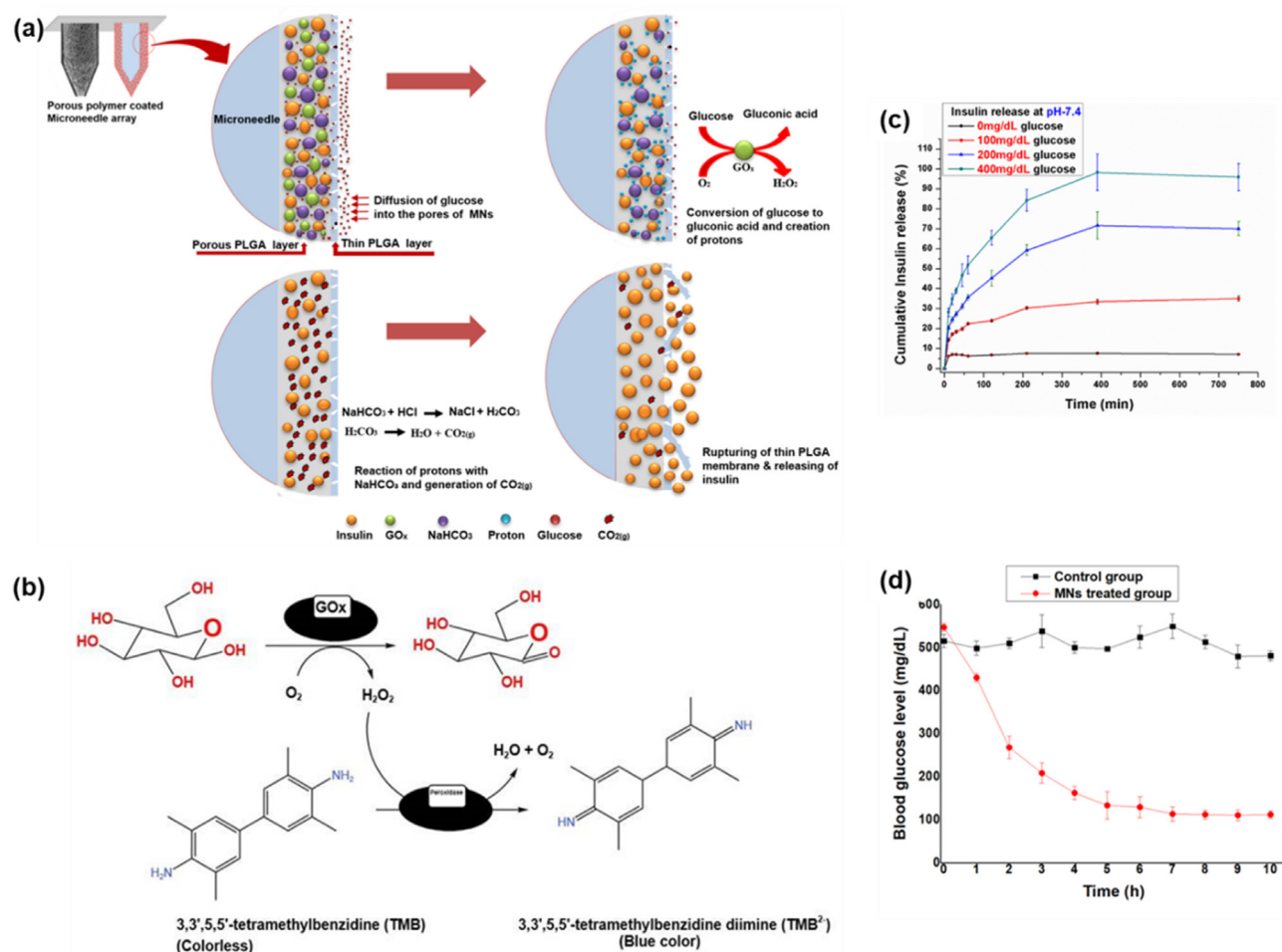


Figure 5 | GOx-mediated glucose-responsive biomaterial in glucose control and monitoring.

(a) Schematic presentation of a glucose-response microneedle patch. (b) Schematic mechanism illustrating the oxidation of TMB from colorless to blue state in the presence of high glucose concentrations, by using GOx and peroxidase reaction for blood glucose detection and monitoring. (c) *In vitro* study demonstrating the effectiveness of the microneedle array patch response under various glucose concentrations. (d) *In vivo* study demonstrating the effectiveness of microneedles in maintaining normal blood glucose levels in rats. Reproduced with permission [78]. Copyright 2020, MDPI.

dermatan [88]. Because of their carbohydrate-binding properties, lectins are widely used in glucose-responsive systems, and Con A has been extensively studied for drug delivery [89].

Con A-mediated drug delivery relies on competitive binding between glucose and polysaccharide-modified drugs/materials. Formulations often incorporate polysaccharide-conjugated drugs or polymers, thus forming drug-Con A or polymer-Con A complexes. Under hyperglycemic conditions, glucose displaces polysaccharides from Con A binding sites, thereby triggering direct drug release or polymer-degradation-mediated release [90, 91] (Figure 6a).

A critical challenge in designing Con A-based systems is balancing binding affinity. Many polysaccharides exhibit stronger Con A affinity than glucose, thus potentially impairing glucose sensitivity [93]. To

address this challenge, chemical modifications of polysaccharides (e.g., cinnamic acid-modified dextran [92], methacrylate-modified dextran [93, 94], and carboxylate-modified pullulan [95]) have been used to decrease Con A binding capacity and enhance glucose competitiveness.

2.3.2.1 Nanogels for peptide delivery

Use of Con A in delivering diabetic drugs has been successfully demonstrated. Bai et al. have developed a Con A-oxidized starch nanogel (Ngel-EX) for exenatide (EX) delivery. The nanogel was synthesized via dual crosslinking involving (i) interaction between oxidized starch (OS) glucose units and Con A binding sites, and (ii) amide bonds between OS carboxyl groups and Con A amino groups. The negatively charged nanogel encapsulated positively charged EX via electrostatic interactions.

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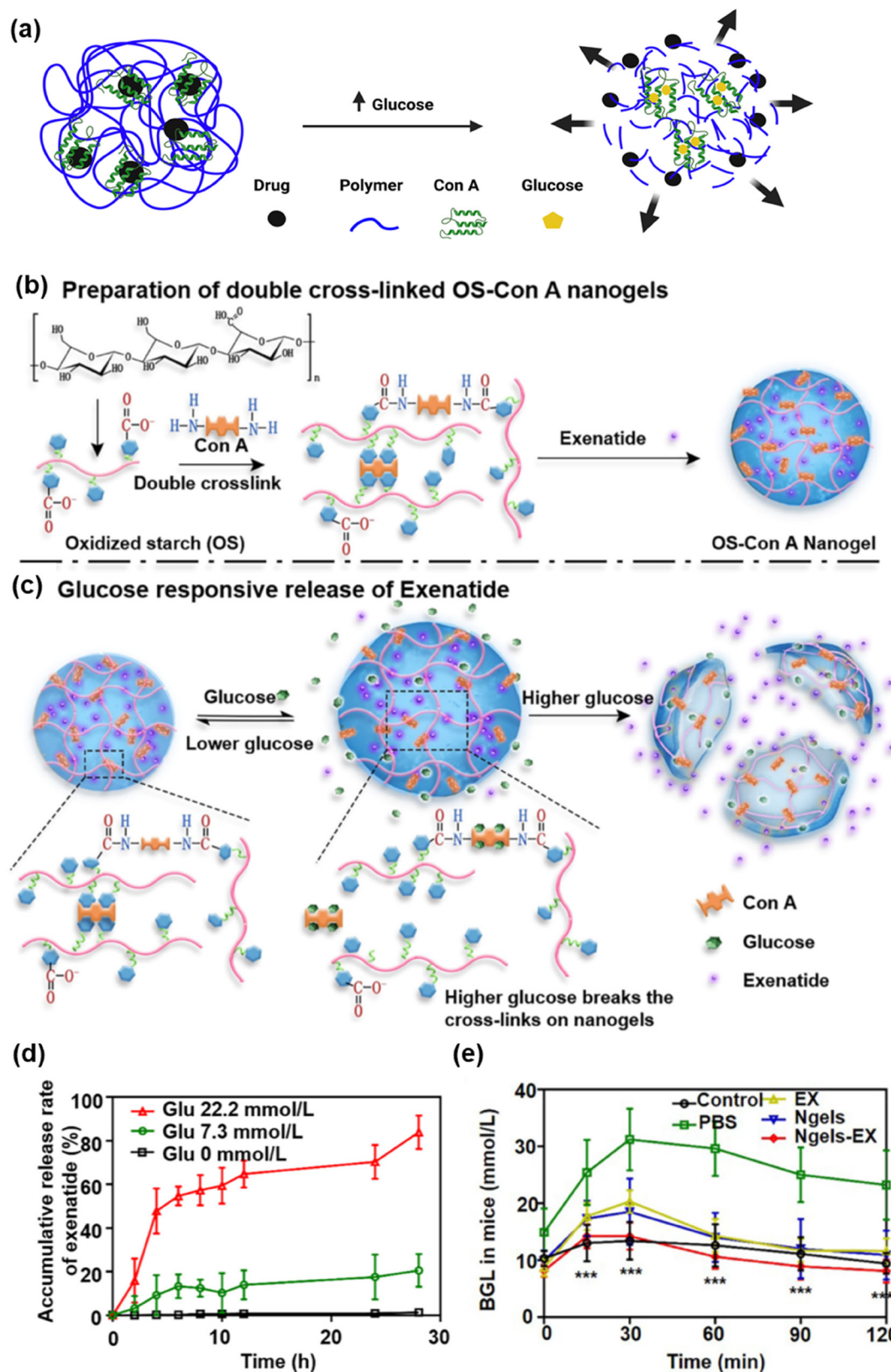


Figure 6 | Con A-mediated glucose-responsive material.

(a) Proposed synthetic route of OS-Con A nanogel. (b) Schematic representation of a polymer modified with Con A for encapsulating a drug in nanoparticles and achieving drug release under hyperglycemic conditions. (c) Schematic representation of the glucose-responsive mechanism of release of exenatide by nanogels. (d) *In vitro* exenatide release rates under various glucose concentrations, demonstrating the effective glucose-responsive drug release of the system. (e) *In vivo* blood glucose monitoring following a glucose tolerance test (GTT) 2 hours after drug administration to diabetic mice receiving various formulations or control healthy mice. Reproduced with permission [96]. Copyright 2022 Elsevier B.V.

Under hyperglycemia, glucose displaced OS from Con A, thus disrupting the nanogel structure and releasing 85% of EX within 28 hours (vs. 20% under normal glucose). In diabetic mice, Ngel-EX maintained normoglycemia for 48 hours [96] (Figure 6b–e).

2.3.2.2 Fucoidan-based oral insulin nanoparticles

Fucoidan is a polysaccharide providing many biological advantages, including anti-inflammatory and antioxidant effects, and alleviation of metabolic syndrome [97]. Zhou et al. have designed fucoidan-Con A nanoparticles for oral insulin delivery. Con A's lower affinity for fucoidan than glucose enables efficient glucose-responsive release. Nanoparticles (composed of vitamin B12, fucoidan, and Con A) released $30.7 \pm 1.3\%$ insulin within 1 hour at 400 mg/dL glucose (vs. $17.3 \pm 1.3\%$ at 100 mg/dL). In diabetic mice, the system stabilized blood glucose for 8 hours with minimal hypoglycemia [98].

2.3.2.3 Pullulan hydrogel for insulin delivery

Pullulan is another important polysaccharide whose biocompatibility and remarkable properties favor its use in the pharmaceutical industry [99]. Lin et al. have fabricated a glucose-sensitive hydrogel by using carboxylated pullulan and Con A. An amide bond forms between the carboxyl group ($-\text{COOH}$) of Pullulan and the amino group ($-\text{NH}_2$) of Con A. Glucose competitively binds Con A under hyperglycemia, thus inducing hydrogel swelling and insulin release. The system achieves concentration-dependent release, with higher glucose levels accelerating insulin discharge [95].

2.3.2.4 Thermo-responsive hydrogels

Mansoor et al. have constructed a glucose-responsive hydrogel composed of thermo-responsive carboxylated-modified Pluronic F127 (PL), chitosan, and Con A. The hydrogel was prepared through EDC/NHS coupling. An amide bond formed between the carboxyl group ($-\text{COOH}$) of PL and the amino groups ($-\text{NH}_2$) of chitosan and Con A, thereby encapsulating insulin within the structure. At 37°C (PL's lower critical solution temperature), the solution transitioned to a gel, thereby encapsulating insulin. Hyperglycemia triggered hydrogel swelling, releasing 97% insulin over 7 days [44].

2.3.2.5 Glucose-responsive liposomes

Con A has also been used in glucose-responsive liposome drug delivery. Govardhane and Shende have developed Con A-conjugated liposomes for phthalocyanine (PC)

delivery. Liposomes (composed of PC, lipids, cholesterol, and stearylamine) were prepared via thin-film hydration and functionalized with Con A by using EDC/NHS. The system demonstrated glucose-dependent PC release for diabetes management [100].

Additionally, Con A has been used in glucose monitoring through the development of glucose sensors. For example, Wei et al. have constructed a Con A hydrogel-based photonic device for glucose sensing [101], whereas Yin et al. have fabricated a Con A-hydrogel-based sensor [102]. By exploiting Con A's specificity for glucose binding, these sensors achieved high sensitivity for glucose monitoring.

Current Con A-based systems show promising glucose responsiveness and biocompatibility but require further optimization, such as (i) fine-tuning polysaccharide modifications to balance binding affinity and stability, (ii) enhancing release precision in complex physiological environments, and (iii) exploring novel polysaccharide-Con A combinations for broader applications. Advancements in material design and delivery strategies are expected to strengthen Con A-based systems as next-generation solutions for diabetes management.

2.3.3 Mechanism based on diol-binding chemical moieties. Boron-containing compounds encompass five primary categories: (i) boron-nitrogen bond molecules (e.g., diazaborinines and boron nitride), (ii) boron-based fluorophores (e.g., BODIPY), (iii) borole derivatives (e.g., benzoxaboroles), (iv) boronic acids (e.g., PBA), and (v) icosahedral boron clusters (e.g., carboranes) [103]. Among these, boron-based stimuli-responsive biomaterials have shown substantial potential in DDSs, because of their sensitivity to physiological triggers including pH, ROS, temperature fluctuations, light exposure, and saccharide concentrations (e.g., glucose) [104]. Notably, boronic acids, particularly PBA, have emerged as promising candidates for glucose-responsive diabetes therapies, owing to their structural versatility and ability to form reversible ester bonds with diol-containing compounds [104].

2.3.3.1 Mechanistic basis of PBA responsiveness

The glucose-responsive mechanism relies on PBA's ability to establish dynamic covalent bonds with 1,2- or 1,3-diol groups. Under hyperglycemic conditions, glucose competitively displaces bound diol-containing compounds through ester bond formation with PBA, thus triggering payload release [105] (Figure 7a, b). This process

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is governed by a structure-reactivity relationship that modulates binding affinities among PBA, diol-containing compounds, and glucose. Critical parameters influencing system performance include PBA's pKa, environmental pH, and molecular architecture, all of which require optimization to enhance glucose specificity and release kinetics [106, 107].

2.3.3.2 PBA-based drug delivery systems

Recent advances in PBA-engineered glucose-responsive biomaterials have highlighted their therapeutic potential.

2.3.3.2.1 Injectable polymers

Xu et al. have developed a polymeric nano-membrane made of polydopamine and glucose-sensitive 4-carboxy-3-fluorophenylboronic acid grafted poly-L-lysine (PLL-FPBA) encapsulating insulin crystals. Under hyperglycemia, glucose binding to PBA results in highly negative charge in both PLL-FPBA and polydopamine; this negative charge weakens the crosslinked structure and consequently increases insulin release. The system demonstrated effective glucose-responsive insulin release by controlling blood glucose in the normal range for more than 4 weeks in diabetic mice and more than 3 weeks in diabetic minipigs [108]. In addition, Wang et al. have

synthesized a subcutaneous injectable glucose-responsive polymer comprising poly(ethylene glycol) linked to 4-carboxy-3-fluorophenylboronic acid grafted poly-L-lysine (PEG-PLL-FPBA), encapsulating insulin. The system maintained normal blood glucose concentrations in diabetic mice for as many as 20 hours [109].

2.3.3.2.2 Oral insulin nanoparticles

Sharmah et al. have developed an oral insulin delivery system using carboxylic acid-modified PBA (PBA-COOH) and amine-functionalized cerium oxide (NC-NH₂). EDC/NHS coupling formed amide bonds between components, whereas dextran established boronate ester linkages with PBA for insulin encapsulation. Under 25 mM glucose (hyperglycemia), competitive displacement of dextran induced nanoparticle swelling and released 81.04% of insulin over 48 hours, representing a sevenfold increase over normoglycemic conditions (5 mM glucose). *In vivo* studies demonstrated 12-hour glycemic control in diabetic mice [110]. Ji et al. have prepared an oral glucose-responsive system, comprising a copolymer complex of polycarboxybetaine and FPBA-modified poly(2-aminoethyl methacrylate), to deliver insulin. The system demonstrated effective control and maintained normal blood glucose levels in a type 1 diabetes mouse model without risk of hypotension for as many as 16 hours [111].

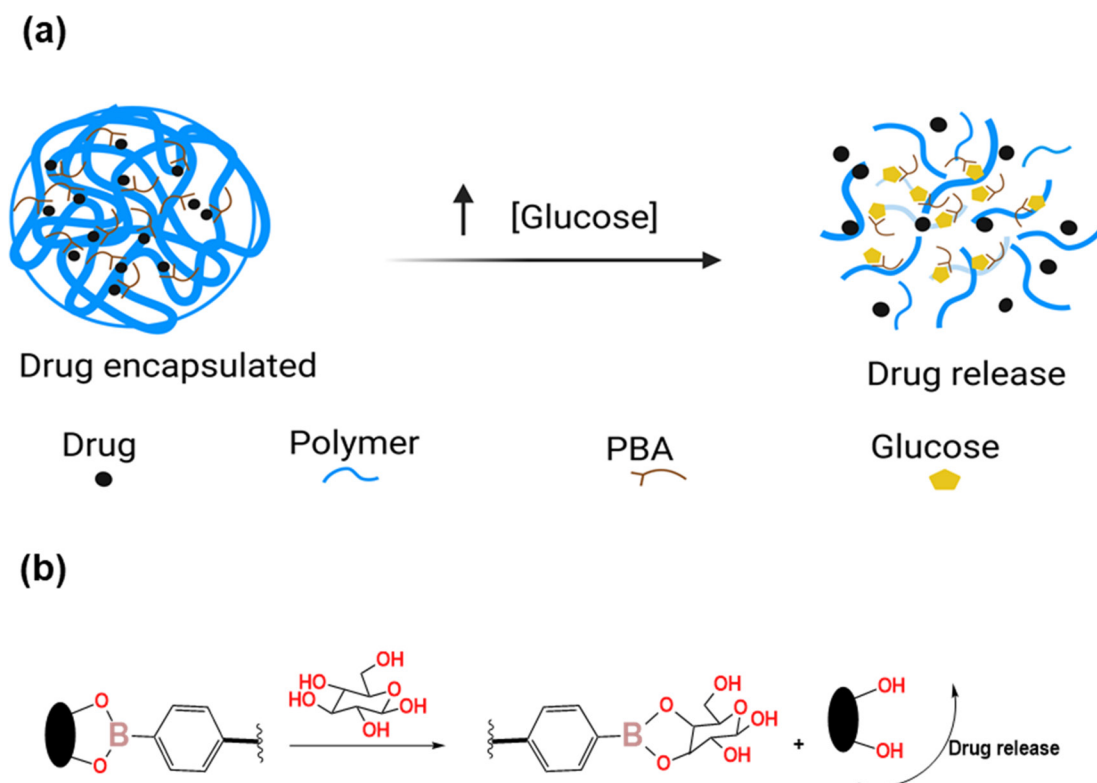


Figure 7 | PBA-integrated glucose-responsive biomaterial drug delivery.

(a) Schematic representation of a polymer encapsulating a drug to form nanoparticles that release the drug under hyperglycemic conditions. (b) Schematic representation of the drug release mechanism of biomaterials containing PBA in the presence of glucose.

2.3.3.2.3 Polymer microneedles

Wang et al. expanded the concept of polymer microneedles by using a chitosan-PBA (CS-PBA)/PVA-PVP microneedle system featuring dual responsiveness, wherein initial CS-PBA nanoparticle swelling and secondary PBA-PVA aggregation prevent uncontrolled insulin release. This design maintained normoglycemia in diabetic mice for 8 hours without posing a risk of hypoglycemia [112].

2.3.3.2.4 Enhanced-specificity hydrogels

PBA exhibits a lower binding affinity toward glucose than other polysaccharides [106]. Furthermore, PBA is prone to non-specific binding to other analytes present in the body, such as fructose and lactate [113]. To address PBA's inherent limitations—including preferential binding to fructose/lactate and suboptimal glucose affinity at physiological pH (pKa 8.2–8.6 vs. pH 7.4). Xiang et al. have designed a diboronate hydrogel using di-3-pyridylboronic acid (DiPBA) and 4-arm polyethylene glycol (4aPEG). This system achieved 70% insulin release at 22 mM glucose and 25% at 2.3 mM, and maintained specificity against competing analytes [114]. Similarly, Xian et al. have developed an injectable thermal-responsive hydrogel combining Pluronic F127 with azide-PBA, which sustained euglycemia for 8 hours after injection [115]. Xian et al. have modified insulin with a moiety with high binding affinity for glucose, DiPBA. This modified insulin was encapsulated in dendrimers and administered subcutaneously. The system demonstrated high-specificity glucose-responsive insulin release by maintaining normal glucose concentrations in a diabetic pig model for 1 week [116].

2.3.3.2.5 Dual-responsive micelles

Liu et al. have created glucose/H₂O₂ dual-responsive micelles (PEG-b-PAPBE) encapsulating GOx and insulin. Hyperglycemia activated two pathways: (i) glucose-PBA esterification and (ii) GOx-mediated gluconic acid/H₂O₂ production, H₂O₂ oxidized boronic esters. Insulin release increased from 20% (0 g/L glucose) to 77% (5 g/L), and 12-hour glycemic control was achieved *in vivo* [117].

2.3.3.3 Overcoming physiological limitations

Another issue associated with the PBA glucose response is that the pKa of PBA is usually between 8.2 and 8.6; consequently, under physiological pH (approximately 7.4), PBA shows a weak glucose response. Consequently, its applications under physiological conditions are limited, because a higher pH value is required to achieve effective glucose binding and drug release. The addition of electron-withdrawing groups on the benzene ring can improve the pKa [118]. Zhang et al. have synthesized a polysulfonamide-PBA copolymer (p(SAPBA-co-NVCL)) with optimized pKa (7.4), which achieved effective glucose responsiveness at physiological pH. The hydrogel demonstrated sustained insulin release over 12 hours in diabetic models [119].

2.3.3.4 PBA-functionalized biomaterials for addressing diabetes complications

Beyond drug delivery applications, PBA has been used in fabricating glucose-monitoring biosensors [120, 121], in the treatment of other diabetes-associated complications, such as nephropathy [122, 123], diabetic wound healing [124, 125], and bone regeneration [126, 127]. These developments underscore PBA's expanding role in creating precision therapies for diabetes and its complications. However, challenges in analyte specificity and physiological optimization warrant continued investigation.

3. ADVANTAGES OF BIORESPONSIVE DRUG DELIVERY SYSTEMS

With the development of advanced DDSs, biomaterials are increasingly used as essential tools, because of their favorable properties. Biomaterials offer numerous advantages, including the ability to deliver payloads (drugs or agents) in a sustained and controlled manner, triggered by specific stimuli such as pH, ROS, glucose, or temperature [10]. They also address challenges associated with conventional dosage forms (e.g., tablets; capsules; oral solutions, such as syrups; and injectables) [128–130] (Table 1). Additionally, biomaterials increase the stability of drugs such as proteins and peptides (e.g., insulin), which are inherently unstable and susceptible to degradation caused by enzymatic activity or pH fluctuations in the body. Encapsulating these drugs within biomaterial-based nanoshells prevents premature degradation and ensures targeted release at desired sites [130, 135]. The H₂O₂ byproduct generated by GOx-mediated biomaterials is critical for biosafety within the body at low, acceptable concentrations, given that it functions as a specific signaling molecule in cellular processes [136]. For example, it activates signaling pathways such as mitogen-activated protein kinase and phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), which play important roles in cell proliferation [137]. Nevertheless, biosafety is concentration dependent, and high H₂O₂ levels pose a risk of cellular damage [138]. Management of blood glucose in people with diabetes is associated with a risk of hypoglycemia after administration of small-molecule antidiabetic drugs, e.g., metformin HCL overdose [139], and macromolecule antidiabetic drugs, e.g., insulin overdose [140]. Biomaterials can be used to prevent hypoglycemia incidence. For example, Chen et al. synthesized a PBA-functionalized peptide amphiphile, which restores normal blood glucose levels in diabetic mice with insulin-induced hypoglycemia [141].

Biomaterials further decrease immune reactions and enhance bioavailability by prolonging drug circulation time in the bloodstream. For instance, PEG nanoparticles have been shown to extend circulation time and minimize immune recognition [142, 143]. Their design flexibility enables the delivery of both small-molecule

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Table 1 | Differences between conventional dose formulations and biomaterial-based dose formulations.

Drug delivery outcome	Conventional dose formulation (e.g., tablet, capsule, oral solution injectable)	Biomaterial-based dose formulation (e.g., polymeric nanoparticles, lipid nanoparticles, liposomes, hydrogels)	Reference
Drug release	Limited control of drug release, often resulting in burst release, elevated drug clearance, and heightened toxicity.	Controlled and sustained drug release, reducing drug clearance.	[10]
Biological drugs (e.g., insulin)	Prone to degradation and rapid clearance, thus negatively affecting drug efficiency.	Protection of biological drugs against degradation, thus increasing therapeutic half-life and efficacy.	[131, 132]
Poorly soluble drugs	Decreased bioavailability due to limited absorption in the bloodstream.	Enhanced bioavailability through improved absorption mechanisms.	[133]
Dosing frequency	Rapid degradation and clearance require frequent dosing, thereby increasing the risk of dose-associated adverse effects and toxicity and decreasing patient compliance.	Controlled and sustained release decreases dosing frequency, lowers adverse effects and toxicity, increases patient compliance, and is particularly beneficial for chronic conditions requiring lifetime medication (e.g., diabetes mellitus).	[10, 129]
Drug stability in storage and transportation (e.g., insulin)	Stability challenges due to insufficient protection make drugs vulnerable to harsh environmental conditions during storage and transportation, thus decreasing therapeutic quality.	Enhanced stability through polymer-based delivery systems, thereby ensuring drug integrity and efficacy during storage and transportation, even in challenging environments.	[129]
Multi-drug delivery	Systems are limited, thus leading to the delivery of a single drug at a time.	Can be engineered to carry multiple drugs and release them in a controllable manner.	[134]

antidiabetic drugs (e.g., metformin HCl) and macromolecules such as peptides (e.g., insulin). These formulations can be administered via multiple routes, including oral, transdermal, inhalation, intramuscular, intravenous, subcutaneous, intra-vaginal, and rectal delivery. This versatility supports personalized treatment approaches by accommodating variations in patient responses due to factors including age, disease progression, sex, genetic conditions, and ethnicity [144].

Collectively, these advantages position biomaterials as indispensable components of advanced DDSs that may markedly enhance patient safety and compliance during DM treatment.

4. CHALLENGES IN DEVELOPING BIORESPONSIVE DRUG DELIVERY SYSTEMS

The development of bioresponsive materials for DDSs, from laboratory settings to clinical trials and ultimately to market approval, faces numerous technical, scientific, and regulatory challenges. Overcoming these hurdles is critical to ensuring the delivery system's reliability, safety, and efficacy. Human physiological conditions are highly complex, and present barriers such as the mucus layer (physiological barrier), metabolizing enzymes (biochemical barrier), immune responses, and pH gradients (chemical barriers) [145]. These factors substantially influence the performance of bioresponsive materials designed to respond to specific stimuli, such as pH, glucose, enzymatic activity, or ROS. Off-target effects may arise when materials undergo undesired activation in regions mimicking target conditions, thus undermining

DDS specificity and efficacy. Such limitations underscore the gap in findings between *in vitro* studies, which often poorly predict *in vivo* outcomes, and the complexities of human physiology. Preclinical translation is further complicated by discrepancies between animal models and human immune or physiological responses [146] (Figure 8).

Biocompatibility remains a critical concern, because these materials must safely release drugs within the body over prolonged periods. Ideally, they should degrade without accumulating or producing toxic byproducts. However, even widely used biomaterials such as PEG—which was long considered the gold standard—can provoke immune reactions, thus posing safety risks and limiting clinical utility [143, 147, 148]. A key technical challenge lies in modifying materials to evade immune detection without compromising their responsiveness. Additionally, interactions between these materials and immune system components remain poorly understood [149, 150]. Balancing material stability and controlled degradability is another critical hurdle. Excessive stability risks accumulation and toxicity, whereas premature degradation leads to off-target drug release and diminished efficacy. Limited data on degradation kinetics and byproduct profiles under diverse physiological conditions further complicate safety assessments [151].

Many bioresponsive nanoscale systems also have low drug-loading capacities or encapsulation efficiencies, particularly for hydrophobic drugs and macromolecules, such as proteins and peptides (e.g., insulin), thus resulting in subtherapeutic dosing [152, 153]. Furthermore, scaling up production presents additional challenges:

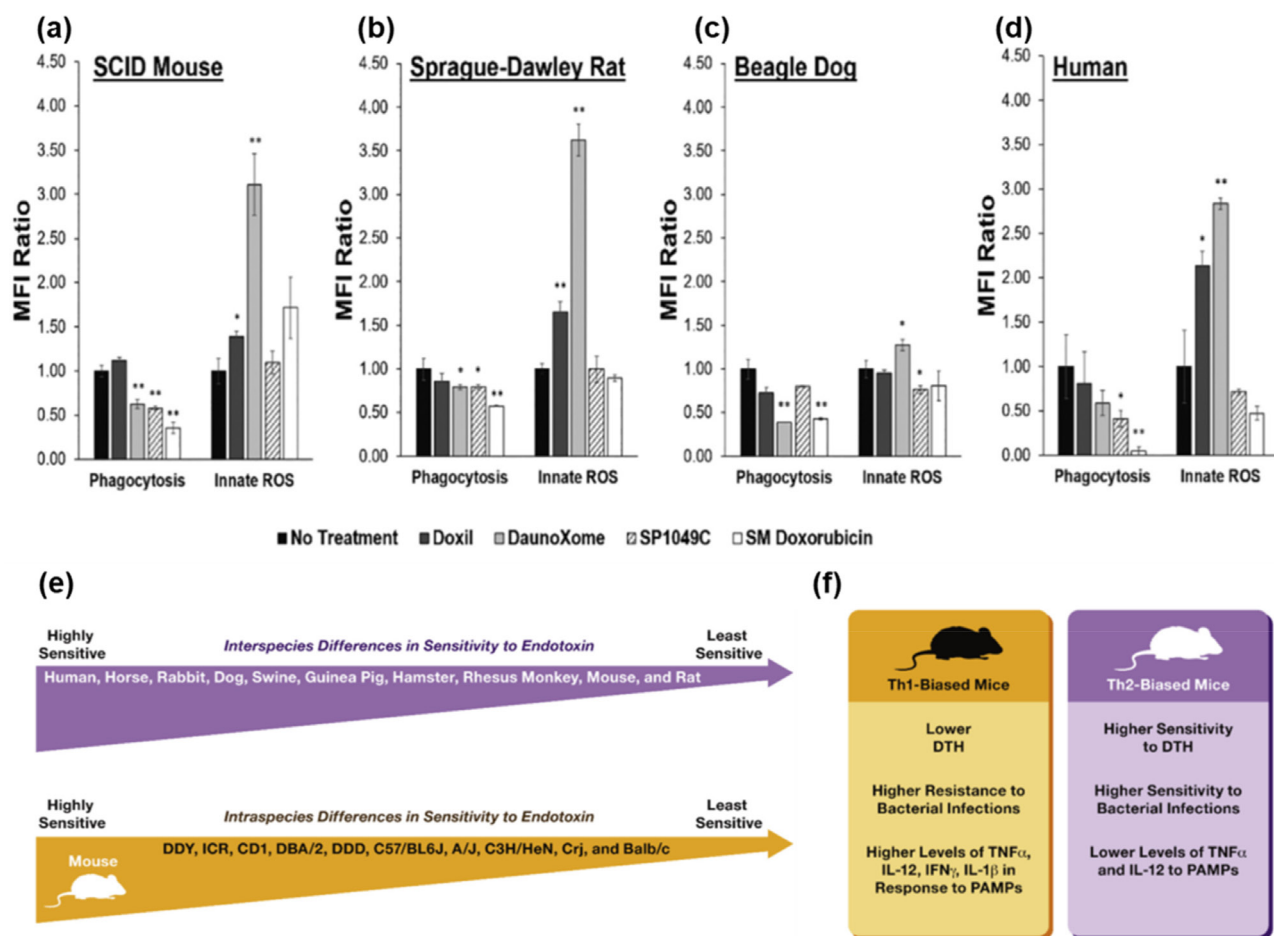


Figure 8 | Pre-clinical and Clinical challenges.

(a), (b), (c), and (d) Drug nanoparticle clearance by phagocytic cells of the mouse, rat, dog, and human mononuclear phagocytic system (MPS), respectively. (e) and (f) Inter- and intra-species differences in immune response. Reproduced with permission [146]. Copyright 2018 Elsevier B.V.

nanomaterial synthesis often relies on costly, complex processes, and minor manufacturing variations can unpredictably alter stimuli responsiveness and drug release profiles [154-156]. The lack of data on material interactions with co-administered drugs further diminishes clinical confidence and hinders integration into combination therapies. These issues collectively impede the clinical use of nanoscale bioresponsive systems.

Furthermore, even after overcoming technical barriers, securing regulatory approval remains daunting. Bioresponsive DDSs often involve novel materials and mechanisms requiring gathering of extensive clinical data on safety, biocompatibility, efficacy, and stability—a time- and resource-intensive process. The absence of standardized evaluation protocols for preclinical and clinical stages exacerbates delays. For example, whereas chitosan is classified as “Generally Recognized As Safe” (GRAS) by the USFDA for food additives, its use in biomaterial-based DDS remains limited because of regulatory ambiguities [157]. These aspects highlight the urgent

need for updated frameworks tailored to advanced bio-responsive systems.

These challenges have starkly narrowed the pipeline for bioresponsive DDS. Few systems reach clinical trials, and even fewer demonstrate satisfactory performance. According to Namoiit, only 486 clinical trials involving nanoparticles were conducted between 2002 and 2021. Most were in early phases (phase I: 37%; phase II: 45%), whereas fewer progressed to phase III (9%) or phase IV (4%) [158]. Similarly, Lele et al. have reported that only 6% of 834 biomaterial-associated clinical trials focused on nano-biomaterials for drug delivery, and phase I-IV trials accounted for 9%, 35%, 13%, and 2%, respectively [159].

5. FUTURE DIRECTIONS AND CONCLUSION

The future of biomaterials in drug delivery holds substantial promise for enhancing the effectiveness and patient-friendliness during the course of DM management. Notable advancements in biomaterials have led

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to the development of intelligent, bioresponsive DDSs that overcome the limitations of conventional (traditional) therapies.

DM is a chronic condition that requires lifelong management through precise control of blood glucose levels and frequent use of medication such as insulin. Recent innovations in biomaterials have shown promise in achieving oral insulin delivery. For example, ORMD-0801 has demonstrated favorable results and is progressing to phase III clinical trials [131]. In addition, Capsulin in phase IIb is safe and effective for patients with early-stage T2DM [160]. Smart microneedle array patches, which are painless and release insulin on demand, are being explored in several ongoing clinical trials, which have shown promising outcomes [132, 161, 162]. This delivery method would provide advantages to patients by avoiding multiple subcutaneous injections of insulin, which are associated with lipoatrophy, lipohypertrophy, and local reactions such as erythemic, pruritic, wheal, and flare reactions [163].

Considering the challenge of off-target activation in bioresponsive materials due to unintended triggering in regions mimicking target conditions, multi-stimulus-responsive biomaterials must be designed. These advanced systems can enhance specificity by responding to a combination of physiological triggers such as glucose, temperature, and pH [164], and also facilitate personalized medicine [165] by tailoring the system's response to individual patient physiology. A major hurdle in clinical translation stems from reliance on preclinical animal models to estimate human dosing, despite substantial pharmacokinetic differences among species [146] (Figure 8). These interspecies variations are likely to contribute to the high failure rate of biomaterial-based therapies in clinical trials. Success in this arena requires meticulous selection of preclinical models supported by robust scientific understanding.

Regulatory approval remains another critical challenge, particularly given the inconsistent guidance across regulatory agencies. The U.S. FDA has taken progressive steps by developing tools, methods, and nanotechnology-specific guidance documents to support industry compliance and streamline approvals [166]. However, other regulatory bodies must establish similar frameworks to harmonize standards and accelerate the approval of innovative biomaterial-based therapies.

ABBREVIATIONS

T2DM: type 2 diabetes mellitus; DM: diabetes mellitus; DDS: drug delivery system; NPs: nanoparticles; LCST: lower critical solution temperature; PBA: phenyl boronic acid; GOx: glucose oxidase; Con A: concanavalin A; GTT: glucose tolerance test; GBP: glycan binding protein.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS STATEMENT

No direct interactions with human or animal subjects were involved. Therefore, ethical approval and informed consent were not required.

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CONFLICTS OF INTEREST

All listed authors have no conflicts of interest.

CONSENT FOR PUBLICATION

Not applicable.

REFERENCES

- [1] Magliano D, Boyko EJ: *IDF Diabetes Atlas*. 10th edition. Brussels: International Diabetes Federation; 2021.
- [2] Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, KradjanWA, et al.: *Koda-Kimble and Young's Applied Therapeutics - The Clinical Use of Drugs*. 10th edition. USA: Lippincott Williams & Wilkins; 2013.
- [3] Blumer I: Severe, Delayed Insulin Detemir Injection Site Reaction. *Diabetic Medicine* 2008, 25:1008.
- [4] Neel N, Ghobara Y, Turkmani M: Liraglutide-induced Injection Site Reaction. *Journal of Dermatology and Dermatologic Surgery* 2019, 23:97–98.
- [5] Jain KK: An Overview of Drug Delivery Systems. In *Drug Delivery Systems*. Edited by Jain KK. New York, NY: Springer New York; 2008:1–54.
- [6] Devarajan PV, Jain S (Eds): *Targeted Drug Delivery: Concepts and Design*. Cham: Springer International Publishing; 2015.
- [7] Grumezescu AM: *Nanobiomaterials in Drug Delivery: Applications of Nanobiomaterials*. Kidlington, Oxford, UK: William Andrew is an imprint of Elsevier; 2016.
- [8] Ulijn RV, Bibi N, Jayawarna V, Thornton PD, Todd SJ, Mart RJ, et al.: Bioresponsive Hydrogels. *Materials Today* 2007, 10:40–48.
- [9] Singh P, Carrier A, Chen Y, Lin S, Wang J, Cui S, et al.: Polymeric Microneedles for Controlled Transdermal Drug Delivery. *Journal of Controlled Release* 2019, 315: 97–113.
- [10] Alavi SE, Alharthi S, Alavi SZ, Raza A, Shahmabadi HE: Bioresponsive Drug Delivery Systems. *Drug Discovery Today* 2024, 29:103849.
- [11] Gupta P, Vermani K, Garg S: Hydrogels: From Controlled Release to pH-responsive Drug Delivery. *Drug Discov Today* 2002, 7:569–579.
- [12] Zhang Y, Li P, Pan H, Liu L, Ji M, Sheng N, et al.: Retinal-conjugated pH-sensitive Micelles Induce Tumor Senescence for Boosting Breast Cancer Chemotherapy. *Biomaterials* 2016, 83:219–232.
- [13] Bae Y, Jang W-D, Nishiyama N, Fukushima S, Kataoka K: Multifunctional Polymeric Micelles with Folate-mediated Cancer Cell Targeting and pH-Triggered Drug Releasing

- Properties for Active Intracellular Drug Delivery. *Molecular BioSystems* 2005, 1:242–250.
- [14] Guo WX, Hu LF, Feng YH, Chen BZ, Guo XD: Advances in Self-assembling of pH-sensitive Polymers: A Mini Review on Dissipative Particle Dynamics. *Colloids and Surfaces B: Biointerfaces* 2022, 210:112202.
 - [15] Al-Shaeli M, Benkhaya S, Al-Juboori RA, Koyuncu I, Vatanpour V: pH-responsive Membranes: Mechanisms, Fabrications, and Applications. *Science of the Total Environment* 2024, 946:173865.
 - [16] Chen Y, Sun P: pH-Sensitive Polyampholyte Microgels of Poly(Acrylic Acid-co-Vinylamine) as Injectable Hydrogel for Controlled Drug Release. *Polymers* 2019, 11:285.
 - [17] Shim WS, Kim SW, Lee DS: Sulfonamide-Based pH- and Temperature-Sensitive Biodegradable Block Copolymer Hydrogels. *Biomacromolecules* 2006, 7:1935–1941.
 - [18] Bae YH, Park SY: PH-Sensitive Polymer Containing Sulfonamide and Its Synthesis Method. US6103865A; 2020 [https://patents.google.com/patent/US6103865A/en] Accessed on date 20 September 2024.
 - [19] Abka-khajouei R, Tounsi L, Shahabi N, Patel AK, Abdelkafi S, Michaud P. Structures, Properties and Applications of Alginates. *marine drugs* 2022, 20:364. https://doi.org/10.3390/md20060364.
 - [20] Wardhani DH, Aryanti N, Aziz A, Firdhaus RA, Ulya HN. Ultrasonic degradation of alginate: A matrix for iron encapsulation using gelation. *Food Bioscience* 2021, 41: 100803.
 - [21] Guo S, Li H: Chitosan-Derived Nanocarrier Polymers for Drug Delivery and pH-Controlled Release in Type 2 Diabetes Treatment. *Journal of Fluorescence* 2024. https://doi.org/10.1007/s10895-024-03810-w.
 - [22] Bhosale RR, Gangadharappa HV, Osmani RAM, Gowda DV: Design and Development of Polymethylmethacrylate-grafted Gellan Gum (PMMA-g-GG)-based pH-sensitive Novel Drug Delivery System for Antidiabetic Therapy. *Drug Delivery and Translational Research* 2020, 10:1002–1018.
 - [23] Trinh TA, Le TMD, Nguyen HT, Nguyen TL, Kim J, Huynh DP, et al.: pH-Temperature Responsive Hydrogel-Mediated Delivery of Exendin-4 Encapsulated Chitosan Nanospheres for Sustained Therapeutic Efficacy in Type 2 Diabetes Mellitus. *Macromolecular Bioscience* 2023, 23:2300221.
 - [24] Ren C, Zhong D, Qi Y, Liu C, Liu X, Chen S, et al.: Bioinspired pH-Responsive Microalgal Hydrogels for Oral Insulin Delivery with Both Hypoglycemic and Insulin Sensitizing Effects. *ACS Nano* 2023, 17:14161–14175.
 - [25] Zhang H, Gu Z, Li W, Guo L, Wang L, Guo L, et al.: pH-sensitive O-carboxymethyl Chitosan/Sodium Alginate Nanohydrogel for Enhanced Oral Delivery of Insulin. *International Journal of Biological Macromolecules* 2022, 223:433–445.
 - [26] Fetouh HA, Aleem EEA, Mohammed NH, Aldesouky JMA, Ismail AM: Formulation of New Drug Delivery Systems for Insulin from Natural Bioactive Biocompatible Polymers. *Scientific Reports* 2025, 15:3941.
 - [27] Hoffman AS: "Intelligent" Polymers in Medicine and Biotechnology. *Artificial Organs* 1995, 19:458–467.
 - [28] Chatterjee S, Hui PC, Kan CW, Wang W: Dual-responsive (pH/Temperature) Pluronic F-127 Hydrogel Drug Delivery System for Textile-based Transdermal Therapy. *Scientific Reports* 2019, 9:11658.
 - [29] Schmaljohann D: Thermo- and pH-Responsive Polymers in Drug Delivery. *Advanced Drug Delivery Reviews* 2006, 58:1655–1670.
 - [30] Gong C, Qi T, Wei X, Qu Y, Wu Q, Luo F, et al.: Thermosensitive Polymeric Hydrogels As Drug Delivery Systems. *Current Medicinal Chemistry* 2013, 20: 79–94.
 - [31] Aoki T, Kawashima M, Katono H, Kawashima M, Katono H, Sanui K, et al.: Temperature-Responsive Interpenetrating Polymer Networks Constructed with Poly(acrylic acid) and Poly(N,N-dimethylacrylamide). *Macromolecules* 1994, 27:947–952.
 - [32] Zareie HM, Volga Bulmus E, Gunning AP, Hoffman AS, Piskin E, Morris VJ: Investigation of a Stimuli-responsive Copolymer by Atomic Force Microscopy. *Polymer* 2000, 41:6723–6727.
 - [33] Zhang X-Z, Yang Y-Y, Chung T-S, Ma KX: Preparation and Characterization of Fast Response Macroporous Poly(N-isopropylacrylamide) Hydrogels. *Langmuir* 2001, 17:6094–6099.
 - [34] Dong L, Hoffman AS: A Novel Approach for Preparation of pH-sensitive Hydrogels for Enteric Drug Delivery. *Journal of Controlled Release* 1991, 15:141–152.
 - [35] Khan B, Arbab A, Khan S, Fatima H, Bibi I, Chowdhry NP, et al.: Recent Progress in Thermosensitive Hydrogels and Their Applications in Drug Delivery Area. *MedComm – Biomaterials and Applications* 2023, 2:55.
 - [36] Yao X, Gong Z, Yin W, Li H, Douroumis D, Huang L: Islet Cell Spheroids Produced by a Thermally Sensitive Scaffold: A New Diabetes Treatment. *Journal of Nanobiotechnology* 2024, 22:657.
 - [37] Peña-Juárez MC, Guadarrama-Escobar OR, Escobar-Chávez JJ: Transdermal Delivery Systems for Biomolecules. *Journal of Pharmaceutical Innovation* 2022, 17:319–332.
 - [38] Li JY, Feng YH, He YT, Hu LF, Liang L, Zhao ZQ, et al.: Thermosensitive Hydrogel Microneedles for Controlled Transdermal Drug Delivery. *Acta Biomaterialia* 2022, 153:308–319.
 - [39] Kapoor DN, Bhatia A, Kaur R, Sharma R, Kaur G, Dhawan S: PLGA: A Unique Polymer for Drug Delivery. *Therapeutic Delivery* 2015, 6:41–58.
 - [40] Dutta K, Das R, Ling J, Monibas RM, Carballo-Jane E, Kekec A, et al.: In Situ Forming Injectable Thermoresponsive Hydrogels for Controlled Delivery of Biomacromolecules. *ACS Omega* 2020, 5:17531–17542.
 - [41] Trinh TA, Duy Le TM, Ho HGV, To TCT, Nguyen VVL, Huynh DP, et al.: A Novel Injectable pH-temperature Sensitive Hydrogel Containing Chitosan–insulin Electrospayed Nanosphere Composite for an Insulin Delivery System in Type I Diabetes Treatment. *Biomaterials Science* 2020, 8:3830–3843.
 - [42] Khaliq NU, Lee J, Kim S, Sung D, Kim H: Pluronic F-68 and F-127 Based Nanomedicines for Advancing Combination Cancer Therapy. *Pharmaceutics* 2023, 15:2102.
 - [43] Chatterjee S, Hui PC, Wat E, Kan C-w, Leung P-C, Wang W: Drug Delivery System of Dual-responsive PF127 Hydrogel with Polysaccharide-based Nano-conjugate for Textile-based Transdermal Therapy. *Carbohydrate Polymers* 2020, 236:116074.
 - [44] Mansoor S, Adeyemi SA, Kondiah PPD, Choonara YE: A Closed Loop Stimuli-responsive Concanavalin A-Loaded Chitosan–Pluronic Hydrogel for Glucose-Responsive Delivery of Short-Acting Insulin Prototyped in RIN-5F Pancreatic Cells. *Biomedicines* 2023, 11:2545.
 - [45] Rangelov S, Simon P, Toncheva-Moncheva N, Dimitrov P, Gajewska B, Tsvetanov CB: Nanosized Colloidal Particles from Thermosensitive Poly(methoxydiethyleneglycol

Review Article

- methacrylate)s in Aqueous Media. *Polymer Bulletin* 2012, 68:2175–2185.
- [46] Wu JZ, Williams GR, Li HY, Wang D, Wu H, Li SD, et al.: Glucose- and Temperature-sensitive Nanoparticles for Insulin Delivery. *International Journal of Nanomedicine* 2017, 12:4037–4057.
- [47] Saeed M, Elshaer A: Glucose-sensitive Materials for Delivery of Antidiabetic Drugs. *Engineering Drug Delivery Systems* 2020, 203–228.
- [48] Yao Y, Ji K, Wang Y, Gu Z, Wang J: Materials and Carriers Development for Glucose-Responsive Insulin. *Accounts of Materials Research* 2022, 3:960–970.
- [49] Yu J, Zhang Y, Bomba H, Gu Z: Stimuli-responsive Delivery of Therapeutics for Diabetes Treatment. *Bioengineering & Translational Medicine* 2016, 1:323–337.
- [50] Santos Aguilar JGD: Applications of High-pressure Homogenization on Microbial Enzymes. *Effect of High-Pressure Technologies on Enzymes* 2023, 373–403.
- [51] Bauer JA, Zámocká M, Majtán J, Bauerová-Hlinková V: Glucose Oxidase, an Enzyme “Ferrari”: Its Structure, Function, Production and Properties in the Light of Various Industrial and Biotechnological Applications. *Biomolecules* 2022, 12:472.
- [52] Moresi M, Parente E: Fermentation (Industrial) | Production of Some Organic Acids (Citric, Gluconic, Lactic, and Propionic). In *Encyclopedia of Food Microbiology*. 2nd edition. Edited by Batt CA, Tortorello ML. Oxford: Academic Press; 2014; 804–815.
- [53] Ransy C, Vaz C, Lombès A, Bouillaud F: Use of H₂O₂ to Cause Oxidative Stress, the Catalase Issue. *International Journal of Molecular Sciences* 2020, 21:9149.
- [54] Kwon J, Kim J, Park S, Khang G, Kang PM, Lee D: Inflammation-Responsive Antioxidant Nanoparticles Based on a Polymeric Prodrug of Vanillin. *Biomacromolecules* 2013, 14:1618–1626.
- [55] Kim E-H, Chung D-Y, Park J-H, Yoo J-H: Dissolution of Oxalate Precipitate and Destruction of Oxalate Ion by Hydrogen Peroxide in Nitric Acid Solution. *Journal of Nuclear Science and Technology* 2000, 37:601–607.
- [56] Scott EA, Stano A, Gillard M, Maio-Liu AC, Swartz MA, Hubbell JA: Dendritic Cell Activation and T cell Priming with Adjuvant- and Antigen-loaded Oxidation-sensitive Polymersomes. *Biomaterials* 2012, 33:6211–6219.
- [57] Rehor A, Hubbell JA, Tirelli N: Oxidation-Sensitive Polymeric Nanoparticles. *Langmuir* 2005, 21:411–417.
- [58] Oide Y, Iwasaki M, Yoshida K, Sato K: Preparation of Multilayer Films Using the Negative Charge of Phenylboronic Acid and Its Response to pH Change, Fructose, and Hydrogen Peroxide. *Colloid and Polymer Science* 2018, 296:1573–1580.
- [59] Van Der Vlies AJ, Xu J, Ghasemi M, Bator C, Bell A, Rosoff-Verbit B, et al.: Thioether-based Polymeric Micelles with Fine-tuned Oxidation Sensitivities for Chemotherapeutic Drug Delivery. *Biomacromolecules* 2022, 23:77–88.
- [60] Pan Q, Deng X, Gao W, Chang J, Pu Y, He B: ROS Triggered Cleavage of Thioether Moiety to Dissociate Prodrug Nanoparticles for Chemotherapy. *Colloids and Surfaces B: Biointerfaces* 2020, 194:111223.
- [61] Orian L, Flohé L: Selenium-Catalyzed Reduction of Hydroperoxides in Chemistry and Biology. *Antioxidants* 2021, 10:1560.
- [62] Cao W, Gu Y, Li T, Xu H: Ultra-sensitive ROS-responsive Tellurium-containing Polymers. *Chemical Communication* 2015, 51:7069–7071.
- [63] Loub J: The Oxides and Oxyacids of Tellurium. *Collection of Czechoslovak Chemical Communications* 1993, 58:1717–1738.
- [64] Everett SA, Swann E, Naylor MA, Stratford MR, Patel KB, Tian N, Newman RG, et al.: Modifying Rates of Reductive Elimination of Leaving Groups from Indolequinone Prodrugs: A Key Factor in Controlling Hypoxia-selective Drug Release. *Biochemical Pharmacology* 2002, 63:1629–1639.
- [65] Naylor MA, Swann E, Everett SA, Jaffar Mm Nolan J, Robertson N: Indolequinone Antitumor Agents: Reductive Activation and Elimination from (5-Methoxy-1-methyl-4,7-dioxindol-3-yl)methyl Derivatives and Hypoxia-selective Cytotoxicity In Vitro. *Journal of Medicinal Chemistry* 1998, 41:2720–2731.
- [66] Xia Y, Duan S, Han C, Jing C, Xiao Z, Li C: Hypoxia-responsive Nanomaterials for Tumor Imaging and Therapy. *Frontiers in Oncology* 2022, 12:1089446.
- [67] Yu J, Zhang Y, Ye Y, DiSanto R, Sun W, Ranson D, et al.: Microneedle-array Patches Loaded with Hypoxia-sensitive Vesicles Provide Fast Glucose-responsive Insulin Delivery. *Proceedings of the National Academy of Sciences of the United States of America* 2015, 112:8260–8265.
- [68] Jeon SI, Kim HJ, Lee JH, Ahn C-H: Development of a Hypoxia-Sensitive Material Producing Fluorescence and Ultrasound Signals. *Macromolecular Research* 2022, 30:909–916.
- [69] Filipczak N, Joshi U, Attia SA, Berger Fridman I, Cohen S, Konry T, et al.: Hypoxia-sensitive Drug Delivery to Tumors. *Journal of Controlled Release* 2022, 341:431–442.
- [70] Mashreghi M, Faal Maleki M, Askarizadeh A, Farshchi H, Farhoudi L, Nasrollahzadeh MS, et al.: A Novel and Easy to Prepare Azo-based Bioreductive Linker and Its Application in Hypoxia-sensitive Cationic Liposomal Doxorubicin: Synthesis, Characterization, In vitro and In vivo Studies in Mice Bearing C26 Tumor. *Chemistry and Physics of Lipids* 2022, 247:105226.
- [71] Le T-N, Lin C-J, Shen YC, Lin KY, Lee CK, Huang CC, et al.: Hyaluronic Acid Derived Hypoxia-Sensitive Nanocarrier for Tumor Targeted Drug Delivery. *ACS Applied Bio Materials* 2021, 4:8325–8332.
- [72] Galieva F, Khalifa M, Akhmetzyanova Z, Mironova D, Burilov V, Solovieva S, et al.: New Supramolecular Hypoxia-Sensitive Complexes Based on Azo-Thiacalixarene. *Molecules* 2023, 28:466.
- [73] Zhang J, Chen F, Yu D, Liang Z, Dai F, Liang H, et al.: Chitosan-based Injectable Hydrogels with Dual Glucose Sensors for Precise Control of Insulin Release and Diabetes Mellitus Therapy. *International Journal of Pharmaceutics* 2023, 643:123246.
- [74] Yu J, Qian C, Zhang Y, Cui Z, Zhu Y, Shen Q, et al.: Hypoxia and H₂O₂ Dual-Sensitive Vesicles for Enhanced Glucose-Responsive Insulin Delivery. *Nano Letters* 2017, 17:733–739.
- [75] Xu B, Jiang G, Yu W, Liu D, Zhang Y, Zhou J, et al.: H₂O₂-Responsive Mesoporous Silica Nanoparticles Integrated with Microneedle Patches for the Glucose-monitored Transdermal Delivery of Insulin. *Journal of Materials Chemistry B* 2017, 5:8200–8208.
- [76] Yang X-X, Feng P, Cao J, Liu W, Tang Y: Composition-engineered Metal–Organic Framework-Based Microneedles for Glucose-Mediated Transdermal Insulin Delivery. *ACS Applied Materials & Interfaces* 2020, 12:13613–13621.

- [77] Luo F-Q, Chen G, Xu W, Zhou D, Li J-X, Huang Y-C, et al.: Microneedle-array Patch with pH-sensitive Formulation for Glucose-responsive Insulin Delivery. *Nano Research* 2021, 14:2689–2696.
- [78] Ullah A, Choi HJ, Jang M, An S, Kim GM: Smart Microneedles with Porous Polymer Layer for Glucose-Responsive Insulin Delivery. *Pharmaceutics* 2020, 12:606.
- [79] CDC: *National Diabetes Statistics Report 2020 Estimates of Diabetes and Its Burden in the United States*. National Statistic Report; 2020.
- [80] Napoli N, Chandran M, Pierroz DD, Abrahamsen B, Schwartz AV, Ferrari SL, On behalf of the IOF Bone and Diabetes Working Group: Mechanisms of Diabetes Mellitus-induced Bone Fragility. *Nature Reviews. Endocrinology* 2017, 13:208–219.
- [81] Hofbauer LC, Busse B, Eastell R, Ferrari S, Frost M, Müller R, et al.: Bone Fragility in Diabetes: Novel Concepts and Clinical Implications. *The Lancet Diabetes & Endocrinology* 2022, 10:207–220.
- [82] Dasari N, Jiang A, Skochdopole A, Chung J, Reece EM, Vorstenbosch J, et al.: Updates in Diabetic Wound Healing, Inflammation, and Scarring. *Seminars in Plastic Surgery* 2021, 35:153–158.
- [83] Gong Y, Gan Y, Wang P, Gong C, Han B, Li P, et al.: Injectable Foam-Like Scaffolds Release Glucose Oxidase-Integrated Metal–Organic Framework Hybrids for Diabetic Bone Defects. *Applied Materials Today* 2024, 38:102190.
- [84] Wu Y, Lyu Y, Li L, Zhou K, Cai J, Wang X, et al.: Unimolecular Cascaded Multienzyme Conjugates Modulate the Microenvironment of Diabetic Wound to Promote Healing. *Biomacromolecules* 2024, 25:43–54.
- [85] Hsu W-L, Huang C-Y, Hsu Y-P, Hwang T-L, Chang S-H, Wang H-YJ, et al.: On-skin Glucose-biosensing and On-demand Insulin-Zinc Hexamers Delivery Using Microneedles for Syringe-free Diabetes Management. *Chemical Engineering Journal* 2020, 398:125536.
- [86] Krautter F, Iqbal AJ: Glycans and Glycan-Binding Proteins as Regulators and Potential Targets in Leukocyte Recruitment. *Frontiers in Cell and Developmental Biology* 2021, 9:624082.
- [87] Taylor ME, Drickamer K, Imberty A, van Kooyk Y, Schnaar RL, Etzler ME, et al.: Discovery and Classification of Glycan-Binding Proteins. In *Essentials of Glycobiology*. 4th edition. Edited by Varki A, Cummings RD, Esko JD, Freeze HH, Stanley P, Bertozzi CR, et al. NY: Cold Spring Harbor Laboratory Press; 2022 [http://www.ncbi.nlm.nih.gov/books/NBK579947/] Accessed on date 28 September 2024.
- [88] Taylor ME, Drickamer K, Imberty A, van Kooyk Y, Schnaar RL, Etzler ME, et al.: Comparison of Two Major Classes of Glycan-Binding Proteins. In *Essentials of Glycobiology*. 4th edition. Edited by Varki A, Cummings RD, Esko JD, Freeze HH, Stanley P, Bertozzi CR, et al.: Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press; 2022. [https://www.ncbi.nlm.nih.gov/books/NBK579961/]. Accessed on date 28 September 2024.
- [89] Bercea M, Lupu A: Recent Insights into Glucose-Responsive Concanavalin A-Based Smart Hydrogels for Controlled Insulin Delivery. *Gels* 2024, 10:260.
- [90] Sato K, Imoto Y, Sugama J, Seki S, Inoue H, Odagiri T, et al.: Sugar-Induced Disintegration of Layer-by-Layer Assemblies Composed of Concanavalin A and Glycogen. *Langmuir* 2005, 21:797–799.
- [91] Yin R, Wang K, Du S, Chen L, Nie J, Zhang W: Design of Genipin-crosslinked Microgels from Concanavalin A and Glucosyloxyethyl Acrylated Chitosan for Glucose-responsive Insulin Delivery. *Carbohydrate Polymers* 2014, 103:369–376.
- [92] Yin R, Wang K, Han J, Nie J: Photo-crosslinked Glucose-sensitive Hydrogels Based on Methacrylate Modified Dextran–concanavalin A and PEG Dimethacrylate. *Carbohydrate Polymers* 2010, 412–418.
- [93] Yin R, Bai M, He J, Nie J, Zhang W: Concanavalin A-sugar Affinity Based System: Binding Interactions, Principle of Glucose-responsiveness, and Modulated Insulin Release for Diabetes Care. *International Journal of Biological Macromolecules* 2019, 124:724–732.
- [94] Bai M, He J, Kang L, Nie J, Yin R: Regulated Basal and Bolus Insulin Release from Glucose-Responsive Core-Shell Microspheres Based on Concanavalin A-Sugar Affinity. *International Journal of Biological Macromolecules* 2018, 889–899.
- [95] Lin K, Yi J, Mao X, Wu H, Zhang LM, Yang L: Glucose-sensitive Hydrogels from Covalently Modified Carboxylated Pullulan and Concanavalin A for Smart Controlled Release of Insulin. *Reactive and Functional Polymers* 2019, 139:112–119.
- [96] Bai J, Zhang H, Yang Z, Li P, Liu B, Li D, et al.: On Demand Regulation of Blood Glucose Level by Biocompatible Oxidized Starch-Con A Nanogels for Glucose-responsive Release of Exenatide. *Journal of Controlled Release* 2022, 352:673–684.
- [97] Wang Y, Xing M, Cao Q, Ji A, Liang H, Song S: Biological Activities of Fucoidan and the Factors Mediating Its Therapeutic Effects: A Review of Recent Studies. *Marine Drugs* 2019, 17:183.
- [98] Zhou J, Ma H, Guan M, Feng J, Dong X, Wei Y, et al.: Anti-inflammatory Fucoidan-ConA Oral Insulin Nanosystems for Smart Blood Glucose Regulation. *International Journal of Pharmaceutics* 2024, 659:124250.
- [99] Aquinas N, Chithra CH, Bhat MR: Progress in Bioproduction, Characterization and Applications of Pullulan: A Review. *Polymer Bulletin* 2024, 81:12347–12382.
- [100] Govardhane S, Shende P: Phthalocyanine-based Glucose-responsive Nanocochleates for Dynamic Prevention of β -cell Damage in Diabetes. *Journal of Liposome Research* 2024, 34:44–59.
- [101] Wei H, Han L, Yin R, Yang T, Liu Y, Mou C, et al.: Micro-3D Printed Concanavalin A Hydrogel Based Photonic Devices for High-sensitivity Glucose Sensing. *Sensors and Actuators B: Chemical* 2023, 386:133707.
- [102] Yin R, Xin J, Yang D, Gao Y, Zhang H, Qian Z, et al.: High-Linearity Hydrogel-Based Capacitive Sensor Based on Con A-Sugar Affinity and Low-Melting-Point Metal. *Polymers* 2022, 14:4302.
- [103] Grams RJ, Santos WL, Scorei IR, Abad-García A, Rosenblum CA, Bita A, et al.: The Rise of Boron-Containing Compounds: Advancements in Synthesis, Medicinal Chemistry, and Emerging Pharmacology. *Chemical Reviews* 2024, 124:2441–2511.
- [104] Das BC, Chokkalingam P, Masilamani P, Shukla S, Das S: Stimuli-Responsive Boron-Based Materials in Drug Delivery. *International Journal of Molecular Sciences* 2023, 24:2757.
- [105] Shiino D, Murata Y, Kataoka K, Koyama Y, Yokoyama M, Okano T: Preparation and Characterization of a Glucose-Responsive Insulin-releasing Polymer Device. *Biomaterials* 1994, 15:121–128.

Review Article

- [106] Brooks WLA, Deng CC, Sumerlin BS: Structure–Reactivity Relationships in Boronic Acid–Diol Complexation. *ACS Omega* 2018, 3:17863–17870.
- [107] Yan J, Springsteen G, Deeter S, Wang B: The Relationship Among pK_a , pH, and Binding Constants in the Interactions between Boronic Acids and Diols—It is Not as Simple as It Appears. *Tetrahedron* 2004, 60:11205–11209.
- [108] Xu J, Zhang Y, Zhao S, Zhang J, Wang Y, Liu W, et al.: A Bioinspired Polymeric Membrane-enclosed Insulin Crystal Achieves Long-term, Self-regulated Drug Release for Type 1 Diabetes Therapy. *Nature Nanotechnology* 2025, 20:697–706.
- [109] Wang Y, Chen P, Liu W, Wei X, Zhang J, Wei X, et al.: Injectable Nanosized Formulation for Glucose-responsive Insulin Delivery. *Nano Today* 2023, 51:101937.
- [110] Sharmah B, Barman H, Uddin AN, Loring R, Kabir ME, Borah A, et al.: Surface-Functionalized Nanoceria: Dual Action in Diabetes Management Via Glucose-Responsive Insulin Delivery and Oxidative Stress Mitigation. *ACS Biomaterials Science & Engineering* 2024, 10:6397–6414.
- [111] Ji K, Wei X, Kahkoska AR, Zhang J, Zhang Y, Xu J, et al.: An Orally Administered Glucose-responsive Polymeric Complex for High-efficiency and Safe Delivery of Insulin in Mice and Pigs. *Nature Nanotechnology* 2024, 19:1880–1891.
- [112] Wang Y, Yu H, Wang L, Hu J, Feng J, Shen D, et al.: Microneedles with Two-Stage Glucose-Sensitive Controlled Release for Long-Term Insulin Delivery. *ACS Biomaterials Science & Engineering* 2023, 9:2534–2544.
- [113] Wu X, Li Z, Chen X-X, Fossey JS, James TD, Jiang YB: Selective Sensing of Saccharides Using Simple Boronic Acids and Their Aggregates. *Chemical Society Reviews* 2013, 42:8032.
- [114] Xiang Y, Xian S, Ollier RC, Yu S, Su B, Pramudya I, et al.: Diboronate Crosslinking: Introducing Glucose Specificity in Glucose-responsive Dynamic-covalent Networks. *Journal of Controlled Release* 2022, 348:601–611.
- [115] Xian S, VandenBerg MA, Xiang Y, Yu S, Webber MJ: Glucose-responsive Injectable Thermogels via Dynamic-covalent Cross-linking of Pluronic Micelles. *ACS Biomaterials Science & Engineering* 2022, 8:4873–4885.
- [116] Xian S, Xiang Y, Liu D, Fan B, Mitrová K, Ollier RC, et al.: Insulin–Dendrimer Nanocomplex for Multi-day Glucose-responsive Therapy in Mice and Swine. *Advanced Materials* 2024, 2308965.
- [117] Liu X, Li C, Lv J, Huang F, An Y, Shi L, et al.: Glucose and H_2O_2 Dual-Responsive Polymeric Micelles for the Self-Regulated Release of Insulin. *ACS Biomaterials Science & Engineering* 2020, 3:1598–1606.
- [118] Li X, Pennington J, Stobaugh JF, Schöneich C: Synthesis of Sulfonamide- and Sulfonyl-phenylboronic Acid-modified Silica Phases for Boronate Affinity Chromatography at Physiological pH. *Analytical Biochemistry* 2008, 372:227–236.
- [119] Zhang P, Ma Q, He D, Liu G, Tang D, Liu L, et al.: A New Glucose-Responsive Delivery System Based on Sulfonamide-Phenylboronic Acid for Subcutaneous Insulin Injection. *European Polymer Journal* 2021, 157:110648.
- [120] Wang X, Huo H, Xu C, Lin H, Wang Q, Yang J, et al.: A Sensitive Non-enzymatic Dual-conductive Biosensor for Continuous Glucose Monitoring. *Analytica Chimica Acta* 2023, 1279:341845.
- [121] Osuna V, Aparicio Martínez EP, Dominguez RB, Rios AV: A Review on the Advances in Nanomaterials for Electrochemical Non-enzymatic Glucose Sensors Working in Physiological Conditions. *Chemosensors* 2024, 12:159.
- [122] Tong M-Q, Luo L-Z, Xue P-P, Han YH, Wang LF, Zhuge DL, et al.: Glucose-responsive Hydrogel Enhances the Preventive Effect of Insulin and Liraglutide on Diabetic Nephropathy of Rats. *Acta Biomaterialia* 2021, 122:111–132.
- [123] Ma Q, Bian L, Zhao X, Tian X, Yin H, Wang Y, et al.: Novel Glucose-responsive Nanoparticles Based on p-hydroxyphenethyl Anisate and 3-acrylamidophenylboronic acid Reduce Blood Glucose and Ameliorate Diabetic Nephropathy. *Materials Today Bio* 2022, 13:100181.
- [124] Hua S, Zhang Y, Zhu Y, Fu X, Meng L, Zhao L, et al.: Tunicate Cellulose Nanocrystals Strengthened Injectable Stretchable Hydrogel as Multi-responsive Enhanced Antibacterial Wound Dressing for Promoting Diabetic Wound Healing. *Carbohydrate Polymers* 2024, 343:122426.
- [125] Zhang S, Ge G, Qin Y, Li W, Dong J, Mei J, et al.: Recent Advances in Responsive Hydrogels for Diabetic Wound Healing. *Materials Today Bio* 2023, 18:100508.
- [126] Wang R, He X, Su S, Bai J, Xiang Q, Liu H, et al.: Advances in Smart Biomaterials that Modulate the Bone Microenvironment to Promote Bone Defect Repair in Diabetes Mellitus. *Smart Materials in Medicine* 2024, 5:359–372.
- [127] Liu Z, Mao J, Li W, Xu C, Lao A, Shin A, et al.: Smart Glucose-responsive Hydrogel with ROS Scavenging and Homeostasis Regulating Properties for Diabetic Bone Regeneration. *Chemical Engineering Journal* 2024, 497:154433.
- [128] Gupta H, Bhandari D, Sharma A: Recent Trends in Oral Drug Delivery: A Review. *Recent Patents on Drug Delivery & Formulation* 2009, 3:162–173.
- [129] Kaur G, Arora M, Ravi Kumar MNV: Oral Drug Delivery Technologies—A Decade of Developments. *The Journal of Pharmacology and Experimental Therapeutics* 2019, 370:529–543.
- [130] Drabczyk A, Kudłacik-Kramarczyk S, Jamróży M, Krzan M: Biomaterials in Drug Delivery: Advancements in Cancer and Diverse Therapies—Review. *International Journal of Molecular Sciences* 2024, 25:3126.
- [131] Eldor R, Francis BH, Fleming A, Neutel J, Homer K, Kidron M, et al.: Oral Insulin (ORMD-0801) in Type 2 Diabetes Mellitus: A Dose-finding 12-weeks Randomized Placebo-controlled Study. *Diabetes Obesity Metabolism* 2023, 25:943–952.
- [132] Smith F, Sabri AH, Heppel M, Fonseca I, Chowdhury F, Cheung K, et al.: The Clinical and Translational Prospects of Microneedle Devices, with a Focus on Insulin Therapy for Diabetes Mellitus as a Case Study. *International Journal of Pharmaceutics* 2022, 628:122234.
- [133] Chen R, Liu E, Fang Y, Gao N, Zhang M, Zhang X, et al.: Naturally Sourced Amphiphilic Peptides as Paclitaxel Vehicles for Breast Cancer Treatment. *Biomaterials Advances* 2024, 159:213824.
- [134] Sikder A, Chaudhuri A, Mondal S, Singh NDP: Recent Advances on Stimuli-Responsive Combination Therapy Against Multidrug-resistant Bacteria and Biofilm. *ACS Applied Bio Materials* 2021, 4:4667–4683.
- [135] Knipe JM, Chen F, Peppas NA: Enzymatic Biodegradation of Hydrogels for Protein Delivery Targeted to the Small Intestine. *Biomacromolecules* 2015, 16:962–972.

- [136] Averill-Bates D: Reactive Oxygen Species and Cell Signaling. Review. *Biochimica et biophysica acta. Molecular Cell Research* 2024, 1871:119573.
- [137] Son Y, Cheong Y-K, Kim N-H, Chung HT, Kang DG, Pae HO: Mitogen-Activated Protein Kinases and Reactive Oxygen Species: How Can ROS Activate MAPK Pathways? *Journal of Signal Transduction* 2011, 2011:792639.
- [138] Wang X, Li S, Chen J, Liu L, Li F: Exogenous Alpha-Ketoglutaric Acid Alleviates the Rabbit Dermal Papilla Cell Oxidative Damage Caused by Hydrogen Peroxide Through the ERK/Nrf2 Signaling Pathway. *Antioxidants* 2025, 14:455.
- [139] Horowitz KM, Dorey A, Horowitz BZ: Severe Hypoglycemia and Hypothermia in Massive Metformin Overdose. *Clinical Toxicology* 2025, 63:357–359.
- [140] Jeremy T, George E, Cunliffe A: Hypoglycemia Secondary to Intentional Insulin Poisoning Managed With Intravenous Hydrocortisone. *JCEM Case Reports* 2025, 3:luaf041.
- [141] Chen W, Yu S, Webber B, DeWolf EL, Kilmer R, Xian S, et al.: Supramolecular Peptide Depots for Glucose-Responsive Glucagon Delivery. *Journal of Biomedical Materials Research Part A* 2025, 113:e37854.
- [142] D'souza AA, Shegokar R: Polyethylene Glycol (PEG): A Versatile Polymer for Pharmaceutical Applications. *Expert Opinion on Drug Delivery* 2016, 13:1257–1275.
- [143] Wang H, Wang Y, Yuan C, Xu X, Zhou W, Huang Y, et al.: Polyethylene glycol (PEG)-associated Immune Responses Triggered by Clinically Relevant Lipid Nanoparticles in Rats. *NPJ Vaccines* 2023, 8:169.
- [144] Aguado BA, Grim JC, Rosales AM, Watson-Capps JJ, Anseth KS: Engineering Precision Biomaterials for Personalized Medicine. *Science Translational Medicine* 2018, 10:eaam8645.
- [145] Wang B, Siahaan T, Soltero R: *Drug Delivery: Principles and Applications*. Hoboken, NJ: Wiley-Interscience; 2005.
- [146] Zamboni WC, Szebeni J, Kozlov SV, Lucas AT, Piscitelli JA, Dobrovolskaia MA, et al.: Animal Models for Analysis of Immunological Responses to Nanomaterials: Challenges and Considerations. *Advanced Drug Delivery Reviews* 2018, 136–137:82–96.
- [147] Shi D, Beasock D, Fessler A, Szebeni J, Ljubimova JY, Afonin KA, et al.: To PEGylate or Not to PEGylate: Immunological Properties of Nanomedicine's Most Popular Component, Polyethylene Glycol and Its Alternatives. *Advanced Drug Delivery Reviews* 2022, 180:114079.
- [148] Salthouse D, Novakovic K, Hilken CMU, Ferreira AM: Interplay Between Biomaterials and the Immune System: Challenges and Opportunities in Regenerative Medicine. *Acta Biomaterialia* 2023, 155:1–18.
- [149] Ju Y, Carreño JM, Simon V, Dawson K, Krammer F, Kent SJ: Impact of Anti-PEG Antibodies Induced by SARS-CoV-2 mRNA Vaccines. *Nature Reviews. Immunology* 2023, 23:135–136.
- [150] Guerrini G, Gioria S, Sauer AV, Lucchesi S, Montagnani F, Pastore G, et al.: Monitoring Anti-PEG Antibodies Level upon Repeated Lipid Nanoparticle-based COVID-19 Vaccine Administration. *International Journal of Molecular Sciences* 2022, 23:8838.
- [151] Mndlovu H, Kumar P, Du Toit LC, Choonara YE: A Review of Biomaterial Degradation Assessment Approaches Employed in the Biomedical Field. *NPJ Materials Degradation* 2024, 8:66.
- [152] Liu Y, Yang G, Jin S, Xu L, Zhao CX: Development of High-Drug-Loading Nanoparticles. *ChemPlusChem* 2020, 85:2143–2157.
- [153] Shen S, Wu Y, Liu Y, Wu D: High Drug-loading Nanomedicines: Progress, Current Status, and Prospects. *International Journal of Nanomedicine* 2017, 12:4085–4109.
- [154] Paliwal R, Babu RJ, Palakurthi S: Nanomedicine Scale-up Technologies: Feasibilities and Challenges. *AAPS PharmSciTech* 2014, 15:1527–1534.
- [155] Muthu MS, Wilson B: Challenges Posed by the Scale-up of Nanomedicines. *Nanomedicine* 2012, 7:307–309.
- [156] Herdiana Y, Wathoni N, Shamsuddin S, Muchtaridi M: Scale-up Polymeric-based Nanoparticles Drug Delivery Systems: Development and Challenges. *OpenNano* 2022, 7:100048.
- [157] Kantak MN, Bharate SS: Analysis of Clinical Trials on Biomaterial and Therapeutic Applications of Chitosan: A Review. *Carbohydrate Polymers* 2022, 278:118999.
- [158] Namiot ED, Sokolov AV, Chubarev VN, Tarasov VV, Schiöth HB: Nanoparticles in Clinical Trials: Analysis of Clinical Trials, FDA Approvals and Use for COVID-19 Vaccines. *International Journal of Molecular Sciences* 2023, 24:787.
- [159] Lele M, Kapur S, Hargett S, Sureshababu NM, Gaharwar AK: Global Trends in Clinical Trials Involving Engineered Biomaterials. *Science Advances* 2024, 10:eabq0997.
- [160] New RRC, Ramanujam S, Chaudhari V, Bogus M, Travers GN, Namjoshi G: Safety and Efficacy of an Oral Insulin (Capsulin) in Patients with Early-Stage Type 2 Diabetes: A Dose-Ranging Phase IIb Study. *Diabetes Obesity Metabolism* 2023, 25:953–960.
- [161] Alshammari MK, Ghazwani JA, Alsharari FO, Alotaibi SS, Alotaibi RF, Alsayahani AA, et al.: An Update on Microneedle in Insulin Delivery: Quality Attributes, Clinical Status and Challenges for Clinical Translation. *Journal of Drug Delivery Science and Technology* 2022, 75:103668.
- [162] Zhao J, Xu G, Yao X, Zhou H, Lyu B, Pei S, et al.: Microneedle-based Insulin Transdermal Delivery System: Current Status and Translation Challenges. *Drug Delivery and Translational Research* 2022, 12:2403–2427.
- [163] Richardson T, Kerr D: Skin-Related Complications of Insulin Therapy: Epidemiology and Emerging Management Strategies. *American Journal of Clinical Dermatology* 2003, 4:661–667.
- [164] Du B, Ren X, Wang X, Wen Y, Yang J, Li L: Four-in-one pH/glucose-responsive Engineered Hydrogel for Diabetes Wound Healing. *Nano Today* 2025, 62:102725.
- [165] Wang G, Liao W, Han F, Shi Y, Hu Z: Advanced Biomaterials for Diabetes Healthcare and Complication Therapy: A Review. *APL Materials* 2024, 12:110601.
- [166] United State Food and Drug Authority (USFDA). Nanotechnology Guidance Documents. FDA [https://www.fda.gov/science-research/nanotechnology-programs-fda/nanotechnology-guidance-documents] Accessed on date 3 October 2024.