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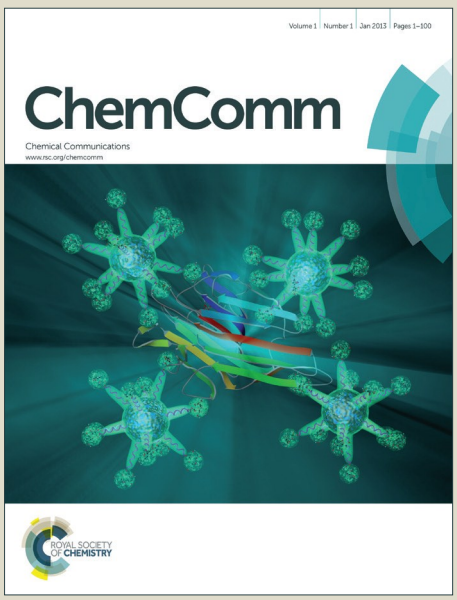

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FEATURE ARTICLE

Glucose-sensitive polymer nanoparticles for self-regulated drug delivery

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The glucose-sensitive drug delivery systems, which can continuously and automatically regulate drug release by the concentration of glucose, have attracted much interest in recent years. The self-regulated drug delivery platforms have potential application in diabetes treatment to reduce the intervention and improve the quality of life for patients. At present, there are three types of glucose-sensitive drug delivery systems respectively based on glucose oxidase (GOD), concanavalin A (Con A), and phenylboronic acid (PBA). This review covers the recent advances in GOD, Con A, or PBA-mediated glucose-sensitive nanoscale drug delivery systems, and provides their major challenges and opportunities.

1. Introduction

Diabetes mellitus is a chronic disease, which is one of the three major diseases endangering human health in addition to cancer and cardiovascular disease. The body of diabetic is unable to regulate the blood glucose concentration within normal physiological levels, resulting in a series of complications, such as cardiovascular disease, retinopathy, nephropathy, *etc*.[1] The total number of diabetics, which is predicted to be about 366 million all over the world in 2030 by the World Health Organization (WHO), increases sharply.[2] Therefore, the treatment of diabetes is imminent. The frequent injection of exogenous insulin is necessary to control the level of blood glucose, while it causes inevitable physical and mental pains, and greatly reduces the life quality of patients. The non-invasive/non-injective routes, such as oral,[3,4] nasal,[5,6] transdermal,[7–9] and pulmonary insulin delivery systems,[10,11] have been attracting more and more interest recently. However, the characteristics of insulin molecule, such as high-molecular weight, poor fat-solubility, and easy deactivation, make the bioavailability of insulin very low after the non-invasive/non-injectable administrations, limiting their widespread use for the treatment of diabetes. All of these provoke a smart insulin administration. The smart insulin administration can not only avoid the great mental and physical pains caused by the inconvenient and conventional injection of insulin, but also maintain the high insulin bioavailability.

Recently, the stimuli-responsive materials, called "intelligent" polymers, have attracted much attention because of their rapid responses to environmental stimuli, including light,[12] magnetic field,[13] temperature,[14] pH,[15] ionic strength,[16] *etc*. The smart responses of polymers to the physical and/or chemical environmental stimuli promise various types of stimuli-responsive and self-regulated systems, which are applied in various fields, such as drug delivery,[17,18] gene therapy,[19,20] and biosensors[21,22]. Among them, the glucose-sensitive self-regulated drug delivery systems for the treatment of diabetic mellitus are one typical example of stimuli-responsive systems. The glucose-sensitive platforms aim to achieve the automatic and continuous insulin release in response to the elevated level of blood glucose with minimal patient intervention and improved diabetic patient's quality of life. The glucose-sensitive drug delivery systems can adjust the insulin dosage in real-time depending on the diabetic patient's unexpected fluctuations of blood glucose. Glucose-sensitive self-regulated drug delivery systems can release insulin at basal release rates under normal blood glucose level while at bolus insulin release under hyperglycaemic conditions when the administrations of subcutaneous injection or implants are given. Therefore, the glucose-sensitive drug delivery systems like artificial pancreas can mimic the biofeedback systems with the control of blood concentration to normal level. The smart glucose-sensitive drug delivery systems are expected to be a promising therapy approach to replace the frequent insulin injection.[23]

To develop the glucose-sensitive self-regulated drug delivery systems, a common strategy is based on the incorporation of glucose oxidase (GOD) as a sensing section with pH-responsive polymer materials.[24–26] GOD consumes glucose to gluconic acid that will grant the pH change of microenvironment, cause the swelling or shrinking of the GOD-incorporated carriers, and then result in the release of preloaded drug in a relatively high level of glucose.[27] Concanavalin A (Con A), a well-investigated plant lectin protein, which possesses specific binding capacity for glucose, mannose, and polysaccharide, is also used as the glucose sensing section for fabricating glucose-sensitive platforms.[28–30] Phenylboronic acid (PBA) and its derivatives, known to reversibly form cyclic boronic ester with *cis*-diol compounds, also have great potential application for the self-regulated drug delivery.[31,32] In summary, this article reviews the recent developments in glucose-sensitive nanoscale

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platforms based on GOD, Con A, or PBA for self-regulated drug delivery (Fig. 1).

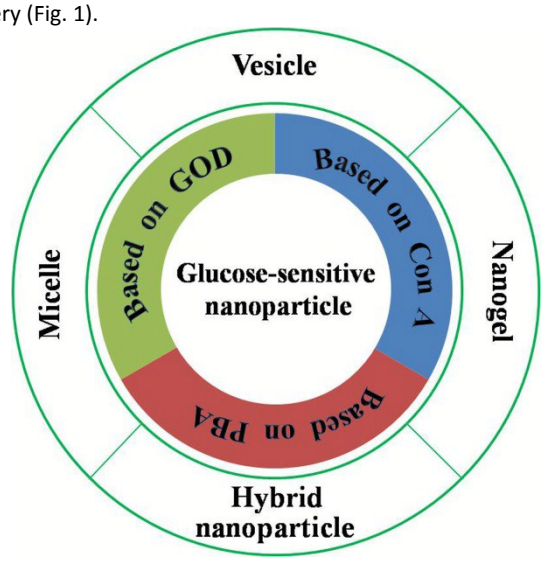

Fig. 1 Glucose-sensitive self-regulated drug delivery platforms.

2. GOD-mediated nanoparticles

Recently, the employment of GOD in glucose-sensitive drug delivery systems has been largely investigated for controllably self-regulated drug delivery. GOD is a homo-dimer composed of two identical 80 kDa subunits and two non-covalently bound flavin adenine dinucleotides complexes. As aforementioned, GOD converts glucose to gluconic acid, which endows the pH-sensitive GOD-incorporated materials with glucose-sensitive properties and results in the swelling or shrinking of carriers due to the pH change of microenvironment. In detail, GOD catalyzes the glucose metabolized to gluconolactone with simultaneous production of hydrogen peroxide (H_2O_2), and then the gluconolactone is rapidly hydrolyzed to gluconic acid in aqueous environment. The reactions are listed in Equations (1) and (2).

$$\text{D-glucose} + O_2 \xrightarrow{\text{GOD}} \text{D-gluconolactone} + H_2O_2 \quad (1)$$

$$\text{D-gluconolactone} + H_2O \longrightarrow \text{D-gluconic acid} \quad (2)$$

Table 1 GOD-mediated nanoparticles

Matrix	Nanoparticle	Activity compared to native GOD	Model drug	Diameter (nm)	Status	Preparation	Ref.
P(NIPAM-*co*-MAA-*co*-ODA)	EPC liposomes	20 – 50%	Calcein	EPC liposome: 180; DOPE/CHEMS liposome: 323.7	*In vitro* release	The pH-sensitive liposome was embedded in GOD-immobilized alginate bead, and the ratio of EPC/GOD/alginate in the bead was 7.8 : 1.0 : 140.4.	42
P(NIPAM-*co*-MAA-*co*-ODA); HmGOD	EPC and DOPE liposomes	—	Calcein	EPC liposome: 300 – 350 (DLS); DOPE liposome: 450 – 500 (DLS)	*In vitro* release triggered by pH and glucose	GOD was hydrophobically modified with a palmitic acid ester resulting in HmGOD, then HmGOD and NIPAM copolymers were incorporated in EPC or DOPE liposome.	43
Polym-GOD	EPC or DPPC liposome incorporating Polym-GOD	40% at pH 5.0	Calcein	EPC liposome: 202.1 (DLS); DPPC liposome: 280.8 (DLS)	*In vitro* release triggered by pH and glucose	P(NIPAM-*co*-MAA-*co*-ODA) was conjugated to GOD resulting in Polym-GOD, and then Polym-GOD was incorporated in EPC or DPPC liposome.	44
MCM-41	MSN-anchor-RB)@GOD	52.5%	RhB	100 (TEM)	*In vitro* release	The external surface of MCM-41 was first functionalized with D-(+)-glucosamine, an effective inhibitor of GOD. The pore of MCM-41 was loaded with RhB with GOD as the capping agent.	49
MCM-41; CD-GOD	CD-GOD-capped MSN	—	Ruthenium dye: $[Ru(bpy)_3]Cl_2$	100 (TEM)	*In vitro* release triggered by pH and glucose	MCM-41, where the external surface was functionalized with 3-iodopropyltrimethoxysilane, was reacted with benzimidazole, resulting in a solid functionalized with 1-propyl-1-*H*-benzimidazole groups. Then the solid was capped with β-CD-modified glucose oxidase (CD-GOD) through the formation of inclusion complexes between CDs and the propylbenzimidazole group anchored to the solid.	50

— Not available. DLS: Dynamic light scattering measurement. TEM: Transmission electron microscopy assessment.

As shown in Equations (1) and (2), H_2O_2 is produced when glucose is oxidized to gluconic acid, and the high concentration of H_2O_2 will prevent the reaction and inhibit the production of gluconic acid. Therefore, in the glucose-sensitive drug delivery systems based on GOD as a catalyst, which can catalyze the decomposition of H_2O_2, must be co-immobilized with GOD on the matrix to reduce the concentration of H_2O_2. Catalase (CAT), one important catalyst, can decompose H_2O_2 and produce oxygen molecule that can be further used to oxidize glucose to gluconic acid under the catalysis of GOD.[33] In addition, some other chemicals such as hemoglobin

(Hb) also can catalyze the reduction of H_2O_2 due to its peroxidase activity.[27,34] GOD must be immobilized on pH-sensitive materials, which exhibit triggered swelling or shrinking due to the presence of gluconic acid. Given GOD is a protein with high molecule weight, hydrogels, microcapsules, and multilayer films are commonly used to immobilize GOD generally.[35–40] However, the GOD-immobilized nanoscale platforms used as glucose-sensitive drug nanocarriers are relatively fewer.[41]

2.1. GOD-incorporated vesicles

GOD-incorporated vesicles used for glucose-sensitive carriers must be modified by pH-sensitive materials, and the common form is liposome. These liposomes are usually composed of physiological lipids, for instance, phospholipids, which endow the liposomes with favourable biocompatibility. The principle of glucose-sensitive liposome is based on the acidification induced by gluconic acid resulted from the enzymatic reaction of GOD under the presence of glucose. The liposomal membranes will take a contracted form due to the presence of gluconic acid. At the same time, a mechanical stress can be applied to liposomal membranes, resulting in an extensive drug release from liposomes. In that case, by modifying the surface of pH-sensitive liposomes with GOD, the glucose-sensitive liposomes could be obtained (Table 1).

The egg phosphatidylcholine (EPC) liposomes incorporating GOD are usually used as glucose-sensitive nanocarriers. The glucose-sensitive EPC liposome bearing a copolymer of *N*-isopropylacrylamide, methacrylic acid, and octadecylacrylate (P(NIPAM-*co*-MAA-*co*-ODA)) was embedded in GOD-immobilized alginate bead.[42] With calcein as a model drug, the EPC liposome with GOD immobilized in alginate bead exhibited the glucose-sensitive drug release. However, the release of calcein from EPC liposome without GOD co-contained in alginate bead almost was independent of glucose concentration, which further confirmed that the reaction of GOD with glucose is responsible for the glucose-triggered release.

To obtain the great glucose-sensitivity of liposomes, GOD was modified to improve its hydrophobicity before incorporated in liposomes. Kim *et al.* prepared the hydrophobically modified glucose oxidase (HmGOD), which was modified with a palmitic acid.[43] HmGOD and P(NIPAM-*co*-MAA-*co*-ODA) were incorporated into both EPC and dioleoylphos-phatidylethanolamine (DOPE) liposomes. Furthermore, the research group conjugated GOD to the copolymer of P(NIPAM-*co*-MAA-*co*-ODA) covalently, marking as Polym-GOD.[44] Subsequently, they prepared EPC and dipalmitoylphosphatidylcholine (DPPC) liposomes incorporating the Polym-GOD conjugate. The maximum enzymatic activity of Polym-GOD was about 40% of that of native GOD at pH 5.0, which acted as a sensor for glucose, endowing the liposome with glucose-sensitive drug release profile.

2.2. Hybrid nanoparticles based on GOD

Silicon and its oxides with high biocompatibility and easy surface functionalization are widely used as biomaterials for drug delivery and tissue engineering.[45,46] Mesoporous silica materials with the incorporation of stimuli-responsive polymers or biomolecules have attracted intense interest in stimuli-responsive drug delivery due to the biocompatible and modifiable properties.[47,48]

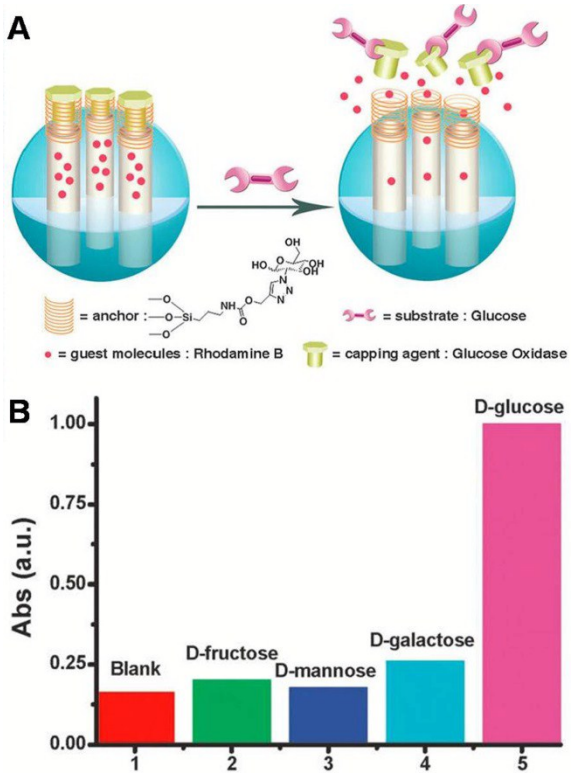

Fig. 2 (A) Schematic illustration of enzyme inhibition mechanism-triggered release of guest molecule from the pore of functionalized mesoporous silica material; (B) The selectivity profiles of (MSN-anchor-RB)@GOD for different saccharides in 30.0 μL of PBS (glucose: 1.0 mM, others: 10.0 mM).[49]

As a typical example, Chen and coworkers reported the GOD-gated mesoporous silica nanoparticles (MSN) as controlled glucose-responsive drug release system.[49] The design strategy of the glucose-sensitive platform was shown in Fig. 2A. In this system, the external surface of mesoporous silica material MCM-41 was functionalized with D-(+)-glucosamine resulting in MSN-anchor. D-(+)-glucosamine was an effective inhibitor of GOD. Rhodamine B (RhB), a model molecule, was loaded into the pore of MSN-anchor using GOD as capping agent and target product, obtaining (MSN-anchor-RB)@GOD. As shown in Fig. 2B, the *in vitro* release profiles revealed that RhB could be released from the nanocontainer triggered by glucose with higher selectivity over other monosaccharide, which had great potential as self-regulated drug release system.

Cyclodextrins (CDs), known as complexing agents, can interact with guest molecules to form noncovalent inclusion complexes, which are helpful in the applications for drug delivery. Using β-CD-modified glucose oxidase (CD-GOD) as the capping agent and MSN as inorganic scaffold, Aznar and coworkers studied the glucose-triggered release from the new gated mesoporous silica nanodevice.[50] On the pore outlet of MSN, there was propylbenzimidazole unit, which could form inclusion complex with CD, resulting in a new gated nanodevice with CD-GOD as a capping agent. The glucose-triggered uncapping was shown in Fig. 3A. In glucose solution, the CD-GOD oxidized glucose to gluconic acid, resulting in the protonation of benzimidazole group. Therefore, the capping CD-GOD of MSN displaced, and the preloaded dye was

released. Fig. 3B and 3C showed the excellent glucose-induced release profiles, which endowed the nanoparticle with potential for glucose-sensitive drug delivery or glucose determination.

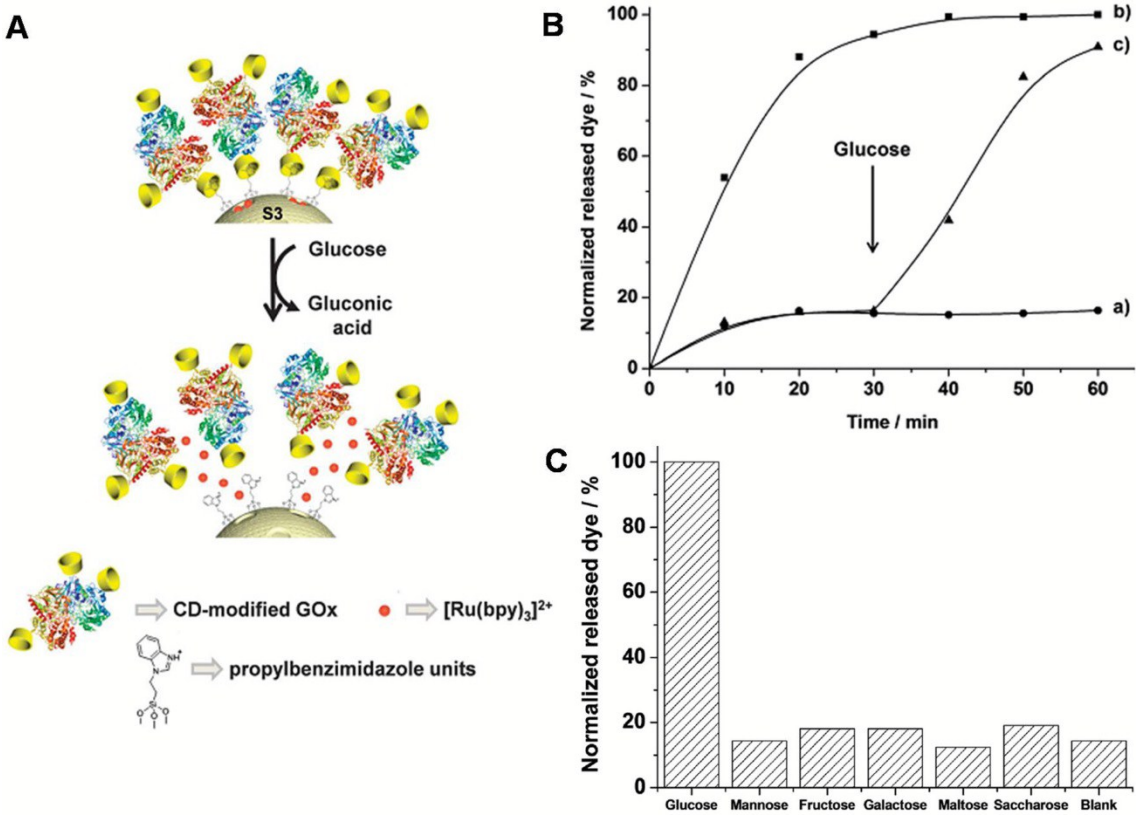

Fig. 3 (A) Schematic illustration of glucose-triggered release of mesoporous silica nanoparticle capped by β-CD-modified glucose oxidase; (B) Release profile of $[Ru(bpy)_3]Cl_2$ from MSN at pH 7.5: a) in the absence of glucose, b) in the presence of glucose, and c) with glucose addition at 30 min; (C) Dye release from 1 mg of MSN in the presence of different analysts (1×10^{-3} mol L^{-1}).[50]

Furthermore, Pingarrón *et al.* reported a smart delivery system, in which the cargo delivery from the capped MSN was controlled by an integrated enzyme-based "control unit".[26] The system consisted of Janus-type nanoparticle, which has opposing Au and mesoporous silica faces. The mesoporous silica face was functionalized with a pH-responsive β-CD-based supramolecular nanovalve. The "control unit" Au nanoparticle was selected as the scaffold and immobilized by two effectors, *i.e.*, glucose oxidase and esterase, with high enzyme loading due to the large surface area of Au nanoparticle (Fig. 4). The GOD and esterase enzyme catalyzed the oxidation of D-glucose and hydrolysis of ethyl butyrate, resulting in gluconic acid and butyric acid, respectively. Both catalytic reactions resulted in a reduction in the pH of the incubation solution, causing the dethreading of the inclusion complex between benzimidazole moieties and β-CD with the controlled cargo release. The Janus enzyme-controlled capped nanodevice behaved as an enzymatic logic or operator, which could be used for *in vitro* release and in-cell controlled delivery. The smart nanodevice was the first report for on-command release controlled by biochemical logical operations. Although the glucose-sensitive drug delivery systems based on GOD have been widely researched, the disadvantages of using enzyme reactions as glucose-sensitive delivery systems, such as limited pH and temperature ranges, and possible bioactivity loss during the preparation of carriers, restrict the potential application in self-regulated drug release.[51] In addition, due to the scale and the biological characteristics of GOD, the GOD-immobilized nanocarriers for glucose-sensitive drug delivery are relatively fewer.[52] How to maintain the activity of GOD and the repeated glucose-sensitivity in the process of preparation are the challenges of GOD-based glucose-sensitive drug delivery systems. On the basis of the solution of all these problems, the clinical applications of GOD-based glucose-sensitive drug delivery systems in diabetic treatment maybe a possibility in future.

3. Con A-incorporated nanoparticles

Con A, a lectin protein found in jack beans, is well known to contain four identical binding sites to glucose, mannose, and polysaccharide, and so on. The property makes Con A-modified system a promising candidate for glucose-sensitive drug delivery.[53–56] For Con A-based systems, the mechanism for glucose-sensitive drug release is as follows: Con A is entrapped or immobilized in the matrices, which are glycopolymers, polysaccharides, or materials with glycosylated moieties. Insulin or other model drugs are loaded into the matrixes during or after the formation of three-dimensional (3D) structures due to the identical binding between Con A and saccharide. When glucose is added, Con A quickly competitively binds with glucose to replace the saccharide moieties on the materials, resulting in the broken of original 3D structure and drug release. With the increase of glucose

concentration in the medium, more glucose binds with Con A and more drug is released, endowing Con A-modified materials with potential application as glucose-sensitive drug delivery systems.[57,58] Of course, the glucose-sensitive nanoparticles based on Con A have rarely been studied compared to hydrogels, microgels, and microparticles that have macro 3D structures.[59–65] However, nanoparticles-based Con A holds great potential for glucose-sensitive drug delivery. Wu and coworkers reported a glucose-sensitive polymer nanogel, which was made from the chemically crosslinked Con A-interpenetrated network of poly(*N*-isopropylacrylamide) (PNIPAM).[66] The nanogel was prepared by free radical precipitation copolymerization of NIPAM and MBAAm using APS/TEMED as an initiating system (Fig. 5). The semi-interpenetrating-structured nanogel could undergo a reversible and rapid volume and phase transition in response to the glucose concentration at physiological pH and temperature. More importantly, the nanogel with good stability could modulate the *in vitro* delivery of pre-loaded insulin as a function of medium glucose concentration.

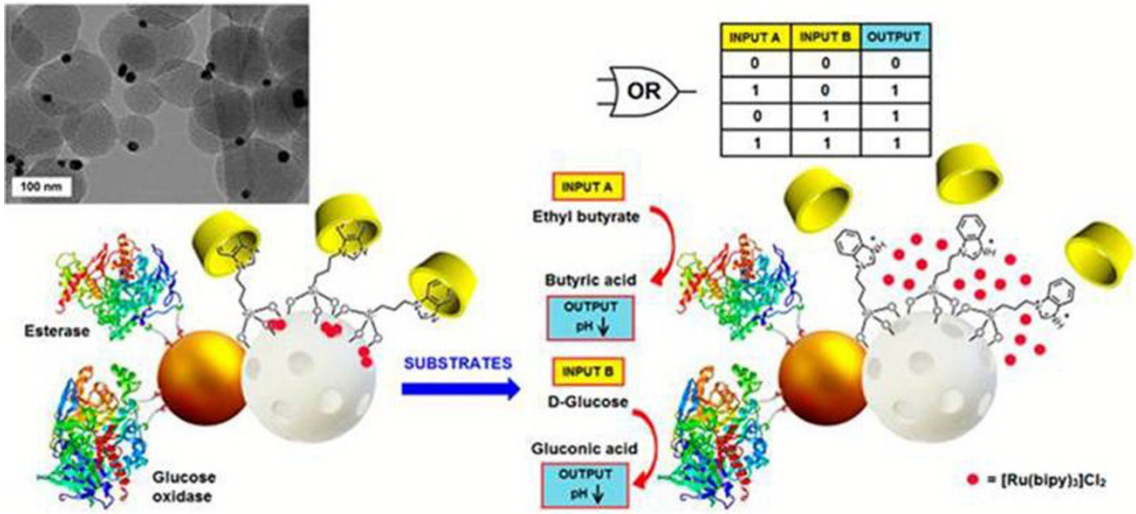

Fig. 4 Performance of the Janus-based nanodevice for smart delivery systems controlled by integrated enzyme-based biocomputing ensembles.[26]

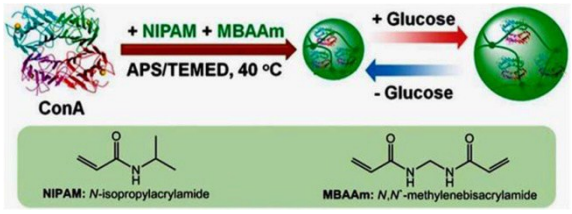

Fig. 5 Schematic illustration of synthesis of glucose-responsive nanogel based on Con A and chemical structures of key components.[66]

Mesoporous silica also can be used in Con A-based glucose-sensitive delivery. Du and coworkers prepared the Con A-gated mannose-functionalized mesoporous silica nanocontainer for the glucose- and pH-responsive release of cargo.[67] The MSN was functionalized with the mannose ligand at the optimized surface density. And the tight Con A nanogate was then constructed using multivalent carbohydrate-protein interaction to encapsulate the cargo within the pore. Because the isoelectric point of Con A is *ca.* 4.5 – 5.5, the cargo could be released triggered by an acidic environment, such as, in tumor cells and inflammatory tissue. In addition, the protein nanogate could be opened by competitive binding of glucose at high concentrations, which would have potential application for diabetes therapy. The Con A-gated MSN delivery system is promising for *in vivo* application of site-specific drug release for the treatment of diabetes and cancer.

Even though the studies of Con A-incorporated nanoparticles for glucose-sensitive drug delivery are rarely compared to microcosmic and grant dimension carriers, Con A also has potential application for fabricating glucose-sensitive platforms. However, the instability and biotoxicity of Con A must be premeditated when designing the glucose-sensitive Con A-based nanoscale platforms.[68]

4. PBA-regulated nanoparticles

Although the glucose-sensitive drug delivery systems based on GOD and Con A are highly specific, the immunogenicity, biotoxicity, and instability of GOD and Con A as protein-based components limit their application in glucose-sensitive drug delivery.[51,69]. In contrast, the glucose-sensitive formulations with PBA as the sensitive agent have received great interest as glucose-sensitive drug delivery platforms recently as shown in Table 2. PBA and its derivatives can reversibly form a cyclic boronic ester with *cis*-diol compounds, indicating their application in glucose-sensitive drug delivery.[52,70–72] PBA-functionalized polymers are synthetic materials with better stability and long-term storability in comparison to GOD and Con A.[73,74] In aqueous solution, the PBA moiety has neutral trigonal-planar form and negatively charged tetrahedral boronate form, and between them there is an equilibrium.[75] When the pH of the solution is below the pK_a of PBA (*i.e.*, 8.2 – 8.6), most of PBA moieties are neutral and relative hydrophobic, while when the pH of the solution is above the pK_a of PBA, most of PBA moieties are relative hydrophilic due to the negative charge.[76] Despite that two kinds of complexes with diols can be formed, only the hydrophilic and negatively charged tetrahedral state exhibits the stable cyclic

boronic ester with *cis*-diol compounds. It makes the equilibrium shift to the hydrophilic and negatively charged form for improving the hydrophilicity of PBA functionalized materials.[77,78] The increase of the hydrophilicity of PBA-functionalized materials induces the swelling of nanoparticles and subsequent release of the payload. Glucose bearing *cis*-diol group is well-documented to form stable glucose-PBA complex at neutral or alkaline pH, endowing the PBA-functionalized materials with great potential for glucose-sensitive drug delivery *via* the formation of hydrophilic glucose-PBA complexes.[79,80]

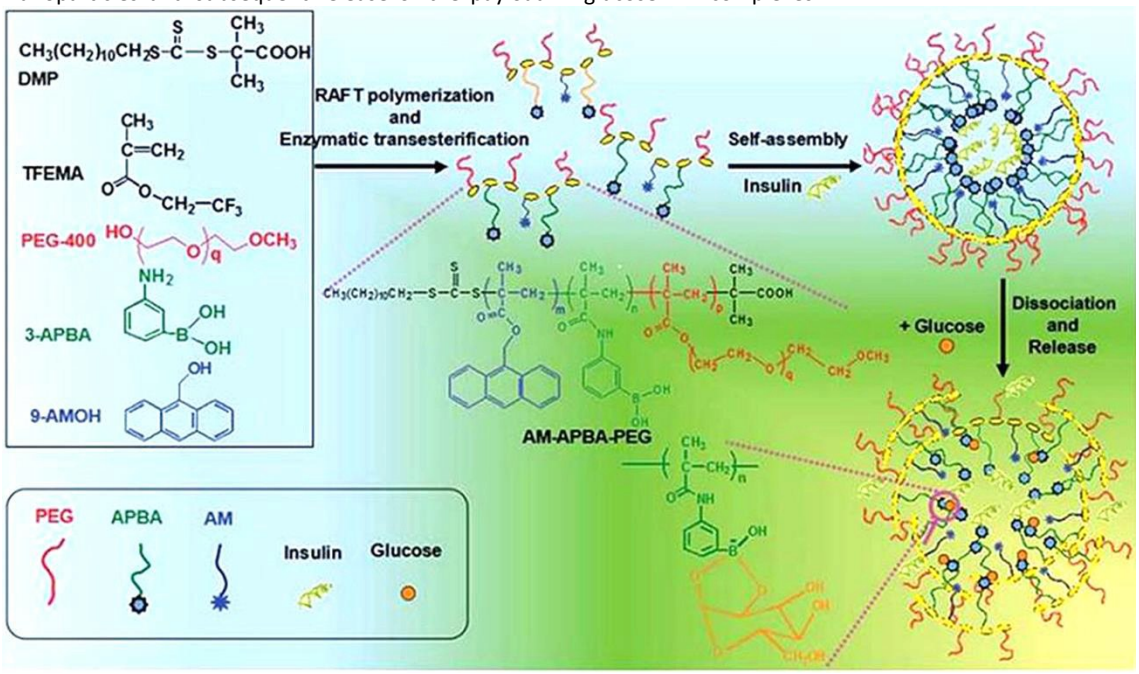

Fig. 6 Schematic of preparation of AM-APBA-PEG copolymer with glucose-responsive and fluorescence properties *via* a combination of RAFT polymerization and an enzymatic transesterification method for controllable release of insulin.[84]

4.1. Micelles with PBA

Micelles are one kind of the effective PBA-based nanosized platforms for glucose-sensitive drug delivery. PBA-functionalized amphiphilic copolymer self-assembles into micelle in solution with hydrophobic micellar core acting as the reservoir of drugs and hydrophilic PEG shell interfacing the biological media. The micelles promote the circulation stability of payload. Recently, the glucose-sensitive micelles based on PBA and its derivatives have much interest due to the easier preparation, longer circulation stability, and faster sensitivity to glucose. As typical instances, the PBA-functionalized polymers synthesized by reversible addition-fragmentation chain transfer (RAFT) polymerization could self-assemble into polymer micelles with glucose-sensitivity.[81–83]

Jiang *et al.* prepared AM-APBA-PEG copolymer *via* a one-pot combination of RAFT polymerization and chemoenzymatic transesterification for the first time.[84] The copolymer self-assembled into micelle with glucose-responsive and fluoresce properties. As shown in Fig. 6, in the structure of AM-APBA-PEG, the introduction of 9-AMOH endowed the micelle with fluorescence, which has potential cell imaging application. In addition, 3-APBA endowed the micelle with great glucose-sensitivity, which could be used for controlled insulin release.

Jiang *et al.* also prepared MePEGA-*b*-(PNBA-*co*-PAAPBA) copolymer micelle with UV light and glucose-sensitive profiles through RAFT polymerization of 3-acrylamidephenylboronic acid (AAPBA) and 2-nitrobenzyl acrylate (NBA) using poly(methoxypolyethylene glycol acryl-amide) (MePEGA) as a macroinitiator.[85] Under UV light irradiation, 98% of loaded insulin was released after 30 min. The reason maybe that hydrophobic PNBA converted into hydrophilic poly(acryl acid) under UV light irradiation due to the detachment of 2-nitrobenzaldehyde from PNBA with the wreck of the micelle (Fig. 7). More importantly, in glucose solution the glucose-boronate complex enhanced the hydrophilicity of the micelle, which endowed the polymer micelle with glucose-induced insulin release profile.

Moreover, a novel type of amphiphilic block copolymer with phenylboronate ester as a leaving group in the hydrophobic block was designed and synthesized as a nanocarrier to successfully realize glucose-responsiveness at neutral pH.[86] Yang *et al.* fabricated the amphiphilic block copolymer of poly(ethylene glycol)-*block*-poly((2-phenylboronic esters-1,3-dioxane-5-ethyl) methylacrylate) (MPEG5000-*b*-PBDEMA) *via* atom transfer radical polymerization (ATRP) using MPEG5000-Br as a macroinitiator.[87] The block copolymer self-assembles into micellar aggregate, which can be used as a glucose-responsive vesicle containing phenylborate ester. The transition of the polymer polarity from amphiphilic to double hydrophilic attributing to the leaving of phenylboronate ester endowed the polymer micelle with glucose-triggered insulin release. The scheme of the glucose-sensitivity was shown in Fig. 8.

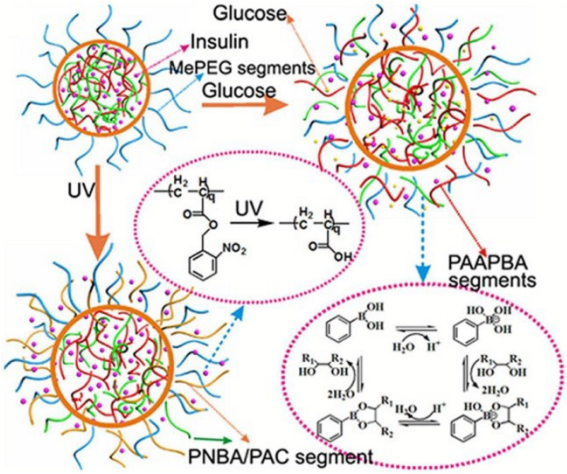

Fig. 7 Schematic illustration of evolution of micelles under different conditions.[85]

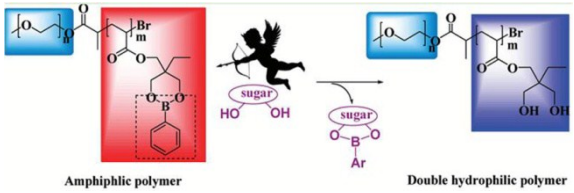

Fig. 8 Schematic illustration of glucose-sensitivity of micelle.[87]

Table 2 PBA-mediated nanoparticles

Matrix	Nanoparticle	Model drug	Diameter (*D*) or hydrodynamic radius (R_h) (nm)	LC (wt.%) and EE (wt.%)	Status	Preparation	Ref.
AM-APBA-PEG	Micelle	Insulin	D_h: 70 – 90 (TEM); 68 (DLS)	LC: 18.5	CLSM; Methyl thiazolyl tetrazolium (MTT) assay; CD spectroscopy; *In vitro* release	AM-APBA-PEG copolymer was prepared by a combination of RAFT polymerization and chemoenzymatic transesterification using an enzymatic catalyst to catalyze the transesterification between 2,2,2-trifluoroethyl methacrylate monomer (TFEMA) and primary alcohols of 9-anthracene methanol (9-AMOH), hydrophilic polyethylene glycol (PEG400), and amino-phenyl boronic acid (3-APBA), and then *S'*-1-dodecyl-S''-(*α,α''*-dimethyl-*α''*-acetic acid) trithiocarbonate (DMP) were used as a RAFT agent and a surfactant to promote the microemulsion RAFT polymerization.	84
MePEGA-*b*-(PNBA-*co*-PAAPBA)	Micelle	Insulin	D_h: 80 – 120 (TEM); 119 (DLS); 192.1 (with insulin-loaded, DLS)	LC: 25.6	MTT assay; Stability study; *In vitro* release	Poly(methoxypolyethylene glycol acrylamide)-*block*-(poly (2-nitrobenzyl acrylate)-*co*-poly(3-acrylamide phenylboronic acid)) (MePEGA-*block*-(PNBA-*co*-PAAPBA)) was synthesized *via* RAFT polymerization of MePEGA-macroinitiator, NBA, APBA, and BCA.	85
MPEG-*b*-PpBDEMA	Micelle	Nile red; FITC-insulin	D_h: 30 (TEM); 90 (DLS)	—	*In vitro* release	The polymer was fabricated *via* ATRP of monomer containing pinacolphenylboronate using poly(ethylene glycol)-Br as a macroinitiator.	86
MPEG5000-*b*-PPBDEMA	Micelle	FITC-insulin	D_h: *ca.* 10 (TEM); 18.0 – 35.4 (DLS)	EE: 13 – 40	*In vitro* release *In vitro* cytotoxicity; CD spectroscopy	Using MPEG5000-Br as a macroinitiator, poly(ethylene glycol)-*block*-poly((2-phenylboronic esters-1,3-dioxane-5-ethyl) methylacrylate) (MPEG5000-*b*-PPBDEMA) was fabricated *via* ATRP with the feeding ratio of PBDEMA monomer to MPEG5000-Br as 100 to 1.	87
PEG-*b*-(PAA-*co*-PAAPBA)	Micelle	Insulin	D_h: 50 (TEM); 77.8 (DLS); 157 (with insulin-loaded, DLS)	LC: 29	*In vitro* release	PEG-*b*-(PAA-*co*-PAAPBA) was synthesized by modified PEG-*b*-PAA, which was prepared by hydrolyzing PEG-*b*-PtBA with APBA.	92
P(PBA)-*g*-P(PEG)	Micelle	5-Flucytosine	—	—	Interaction between P(PBA)-*g*-P(PEG) and biomacromolecule; *In vitro* release	The amphiphilic copolymer of P(PBA)-*g*-P(PEG) was synthesized by copolymerization of 4-vinylphenylboronicacid (PBA) and poly(ethyleneglycol) methyl ether methacrylate (PEGMA).	93
mPEG-*b*-P(GA-*c*	Polypep	Insulin	R_h: 74 – 133 (DLS);	LC: 17.8 –	MTT assay; *In vitro*	mPEG-*b*-P(GA-*co*-GPBA) was synthesized by modifying	95

o-GPBA)	tide micelle		D_h: 60 (TEM); *ca.* 100 (with insulin-loaded, TEM)	18.1; EE: 71.3 – 72.4	release; Alternant release ability; CD spectroscopy	monomethoxy poly(ethylene glycol)-*block*-poly(L-glutamic acid) (mPEG-*b*-PGA) with APBA.	
PEG-*b*-P(Asp-*co*-AspPBA); PNIPAM-*b*-P(Asp-*co*-AspPBA)	Complex polymer micelle	FITC-insulin	D_h: 90 – 120 (DLS)	—	MTT assay; *In vitro* release; Repeated on-off release; Insulin protection against tryptic degradation	PEG-*b*-P(Asp-*co*-AspPBA) was synthesized by modification of poly(ethylene glycol)-*block*-poly(aspartic acid) (PEG-*b*-PAsp) with APBA. PNIPAM-*b*-P(Asp-*co*-AspPBA) was prepared by modification of poly(N-isopropylacrylamide)-*block*-poly(aspartic acid) (PNIPAM-*b*-PAsp) with APBA.	96
p(GAMA-*r*-AAPBA); CS-NAC	Nanocapsule	Insulin	D_h: *ca.* 110 (TEM)	LC: 18.3 – 27.6; EE: 61.8 – 78.3	*In vitro* release studies; Cell viability	Using chitosan-*N*-acetyl-L-cysteine conjugate (CS-NAC) and glycopolymer poly(D-gluconamidoethyl methacrylate-*r*-3-acrylamidophenylboronic acid) p(GAMA-r-AAPBA) as the alternant multilayered polyelectrolyte hybrid shell, the nanocapsules were fabricated *via* lay-by-lay (LbL) self-assembly after etching the amino functionalized SiO_2 sphere by NH_4F/HF.	98
p(AAPBA-*b*-AGA); p(AAPBA-*r*-AGA)	Nanoparticle	Insulin	D_h: 83 – 140 (DLS) D_h: 119 – 220 (with insulin-loaded, DLS)	LC: 7.5 – 12.9; EE: 50.1 – 64.9	*In vitro* release studies; Cell viability	Block copolymer of p(AAPBA-*b*-AGA) was prepared by RAFT copolymerization using homopolymer of poly(3-acrylamidophenylboronic acid) (pAAPBA) as macroRAFT agent and 2-(acrylamido) glucopyranose (AGA) as monomer. The random copolymers of p(AAPBA-*r*-AGA) were synthesized by RAFT polymerization with different molar ratios of AAPBA to AGA.	100
P(AAPBA-*b*-GAMA)	Nanoparticle	Insulin	D_h: 129 – 220 nm (DLS)	LC: 9.9 – 11.6; EE: 53.2 – 63.8	*In vitro* release; MTT assay; Alternant release study; CD spectroscopy	P(AAPBA-*b*-GAMA) was synthesized by RAFT copolymerization at [GAMA] : [pAAPBA macroRAFT] : [AIBN] = 50 : 1 : 1, where GAMA was D-gluconamidoethyl methacrylate, and macroRAFT agent pAAPBA was poly(3-acrylamidophenylboronic acid).	101
PEG_{45}-*b*-P(Asp-*co*-AspGA); PEG_{114}-*b*-P(Asp-*co*-AspPBA)	Vesicle	Vancomycin	D_h: 60.3 (DLS); 40 – 60 (TEM)	LC: 38.2; EE: 48.3	*In vitro* release	The polymer vesicle was fabricated based on the complexation between glucosamine (GA)-containing block copolymer poly(ethylene glycol)-*block*-poly(aspartic acid-*co*-aspart-glucosamine) (PEG_{45}-*b*-P(Asp-*co*-AspGA)) and PEG_{114}-*b*-P(Asp-*co*-AspPBA) *via* a template of α-CD/PEG inclusion complex.	102
PEG-*b*-P(Asp-*co*-AspGA); PNIPAM-*b*-P(Asp-*co*-AspPBA)	Vesicle	FITC-insulin	D_h: 266 – 377 (DLS)	—	*In vitro* release; Glucose-triggered on-off release	PEG-*b*-P(Asp-*co*-AspGA) was synthesized by partial modification of PEG-*b*-PAsp with glucosamine. Poly(*N*-isopropylacrylamide)-*block*-poly(aspartic acid) (PNIPAM-*b*-PAsp) was obtained by the deprotection of poly(*N*-isopropylacrylamide)-*block*-poly(β-benzyl-L-aspartate) (PNIPAM-*b*-PBLA).	103
glycol chitosan; sodium alginate; PGGA	Nanogel	Insulin; FITC-insulin	D_h: 700 (DLS); 767.9 (with insulin-loaded, DLS)	EE: 71 ± 3.5	Cell viability; Hemolysis assay; *In vitro* release; *In vivo* release	GC/SA-PGGA double-layered nanogel was prepared by anisotropic gelation method and electrostatic interaction between glycol chitosan (CS) and sodium alginate-poly(L-glutmate-*co*-*N*-3-L-glutamylphenylboronic acid) (SA-PGGA).	110
mPEG-*b*-P(BLG-*co*-(PLG-*g*-Glu)); adipoylamidophenylboronic acid	Nanogel	Insulin	D_h: 65 (TEM); 74.1 (with insulin-loaded, TEM)	LC: 9.5; EE: 47.5	MTT assay; Hemolysis assay; *In vitro* release; CD spectroscopy	A novel kind of nanogel was prepared by the ROP of BLG NCA and PLG NCA using mPEG-NH_2 as a macroinitiator followed by clicking azido-modified glucose to the PLG unit and a subsequent cross-linking with adipoylamidophenylboronic acid.	111

PEGDA; mPEGA; AAPBA	Nanogel	Alizarin red S (ARS); Insulin	R_h: 107 ± 3.0 (DLS); D_h: 80 ± 4.0 (TEM)	LC: 9.5; EE : 47.5	*In vitro* release; MTT assay; Lactate dehydrogenase assay	The nanogel was prepared through one-pot thiol-ene copolymerization of pentaerythritoltetra (3-mercaptopropionate) (QT), poly(ethylene glycol) diacrylate (PEGDA), methoxyl poly(ethyleneglycol) acrylate (mPEGA) and *N*-acryloyl-3-aminophenylboronic acid (AAPBA).	112
P(NIPAM); dextran; AAPBA	Nanogel	Insulin	D_h: 82.3 – 141.2 (DLS)	LC: 16.2% EE : 80.6%	Cell viability; Reversible glucose sensitivity; *In vitro* insulin release; *In vivo* study	An injectable glucose-sensitive nanogel was prepared by the one-pot method with poly(*N*-isopropylacrylamide) (P(NIPAM)), poly(3-acrylamidophenylboronic acid) (AAPBA) using maleic acid–dextran as a cross-linker.	113
BA-MSN	MSN	FITC-G-Ins; cAMP	—	cAMP: 27 μmol g^{-1} (HPLC); FITC-G-Ins: 64 μmol g^{-1} (HPLC)	*In vitro* FITC-G-Ins release; *In vitro* cAMP release; Cell viability and proliferation profiles	4-Carboxyphenylboronic acid, *N*-hydroxysuccinimide, and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride were introduced to AP-MSN in DMSO to yield the boronic acid-functionalized MSN material (BA-MSN)	116
P(AA-AGA); MSN; EPBA	Hybrid MSN	Rd6G	D_h: 100 (TEM); Shell thickness: 8 (TEM)	—	TGA; cytotoxicity; *In vitro* release induced by acid and glucose	The poly(acrylic acid) incorporated on MSN was glycosylated with glucosamine to obtain P(AA-AGA). And then the P(AA-AGA) chain was cross-linked through the formation of boronate ester between 4,4-(ethylenedicarbamoyl)-phenylboronic acid (EPBA) and the hydroxyl groups of P(AA-AGA) obtaining the hybrid MSN.	117
C-βCD; MSN	CD-PBA-MSN	Propidium iodide (PI) dye	D_h: 100 (TEM)	—	*In vitro* release induced by acid and different sugar; Synergistic release triggered by acid and glucose	Phenylboronic acid stalk was firstly grafted onto the platform of MSN, and then cross-linked by catechol-containing β-CDs (C-βCD) through the formation of boronate ester obtaining CD-PBA-MSN nanocontainer.	120
MPS-MSN; PNIPAM; Dex-Ma; AAPBA	MSN	Insulin	D_h: 265.0 ± 2.5 (DLS); Shell thickness: 34.9 ± 1.3 (TEM)	LC: 11.3 – 15.0; EE: 81.5 – 92.7	*In vitro* release; Cell viability; CD spectroscopy	Monodisperse MSN@p(NIPAM-*co*-AAPBA-*co*-Dex-Ma) nanoparticle was synthesized in the presence of 3-(methacryloxy) porpyltrimethoxysilane-modified MSN (MPS-MSN) nanoparticle as seed by the polymerization of NIPAM, AAPBA, and Dex-Ma with APS as initiator in water.	121
magnetic mesoporous silica (MMS); Dextran	MMS-dextran; FA-MMS-dextran	Tolbutamide; camptothecin	D_h: 190 (DLS)	—	Drug release study; Targeted and glucose-responsive cellular delivery of drug; MTT assay	Magnetic mesoporous silica (MMS) including γ-Fe_2O_3 was functionalized with phenylboronic acid and folate, and then gated by dextran obtaining MMS-dextran and FA-MMS-dextran nanoparticle, which could be used for advanced drug delivery for diabetes and cancer.	122
p(VPBA-DMAEA)	Hybrid nanogel	FITC-insulin	D_h: *ca.* 172 (TEM)	LC: 33.1 – 38.3	*In vitro* release; *In vitro* cytotoxicity	Multifunctional hybrid nanogel was prepared by free-radical precipitation polymerization of the monomers to form a glucose responsive gel shell of a poly(4-vinylphenylboronic acid-*co*-2-(dimethylamino) ethyl acrylate) p(VPBA-DMAEA) copolymer on the Ag nanoparticle template. The glucose-sensitive and fluorescent components can be integrated into a single nano-object.	123

— Not available.

In PBA-based glucose-sensitive polymers, acrylate monomer was widely used due to the easy modifications.[88–91] The core-shell micelle was also prepared by the self-assembly of synthesized poly(ethylene glycol)-*block*-poly(acrylic acid-*co*-acrylamidophenylboronic acid) (PEG-*b*-(PAA-*co*-PAAPBA)).[92] PEG-*b*-(PAA-*co*-PAAPBA) was synthesized by the partial modification of PEG-*b*-PAA with 3-aminophenylboronic acid (APBA). The core was hydrophobic and composed of PAAPBA, whereas the shell was hydrophilic and composed of PEG. In aqueous solution at pH 7.4, the disaggregation of core-shell structure as it was exposed to

glucose endowed the micelle with good glucose-sensitivity. Also, an amphiphilic graft copolymer of poly(phenylboronicacid)-*graft*-poly(ethylene glycol) (P(PBA)-*g*-P(PEG)) could self-assemble into stable monodisperse micelle above its critical micelle concentration (CMC) or critical micelle temperature (CMT).[93] P(PBA)-*g*-P(PEG) was synthesized by copolymerization of 4-vinylphenylboronic acid and poly(ethylene glycol) methyl ether methacrylate. The glucose and thermo dual-responsive properties endowed the micelles with glucose-triggered drug release behavior. Li and coworkers synthesized the amphiphilic poly(acrylic acid-*co*-acrylamidophenylboronic acid)-*block*-poly(2-acryloxyethylgalactose)-*block*-poly(acrylic acid-*co*-acrylamidophenylboronic acid) (((PAA-*co*-PAAPBA)-*b*-)$_2$PAEG) copolymer, which also self-assembled into micelle.[94] The micelles exhibited pH-responsive property and showed a degree of sensitivity to glucose at pH 7.4. In addition, the pH- and glucose-sensitive glycopolymer micelle based on PBA had good cytocompatibility.

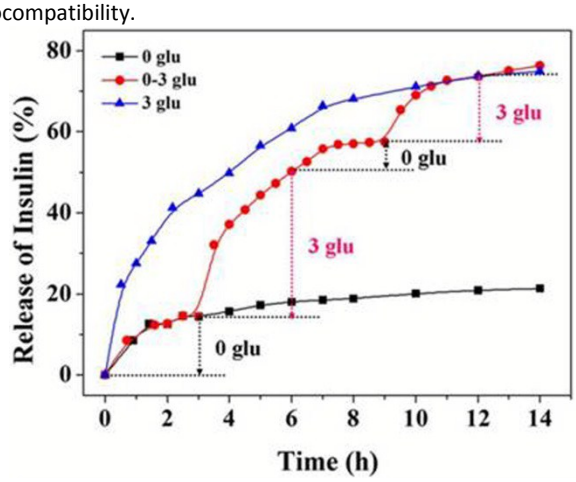

Fig. 9 Glucose-sensitive insulin release from insulin-loaded PGP-95 micelle in PB with alternant glucose concentrations at pH 7.4, 37 °C. The markers of 0 glu and 3 glu represented the cumulative insulin release in PB with 0 and 3.0 mg mL^{-1} glucose, respectively. The marker of 0-3 glu represented the cumulative insulin release in PB with alternant 0 or 3.0 mg mL^{-1} glucose.[95]

Despite PAA-based PBA-containing copolymers exhibit great biocompatibility and are proverbially used as glucose-sensitive drug delivery carriers, the non-degradability is unfavourable for blood clearance after drug delivery and limits their clinical application. The glucose-sensitive copolymers with improved biocompatibility and degradability for self-regulated drug release have attracted more interest. Chen and coworker reported a PBA-functionalized block copolymer, methoxy poly(ethylene glycol)-*block*-poly(L-glutamic acid-*co*-*N*-3-L-glutamylamidophenylboronic acid) (mPEG-*b*-P(GA-*co*-GPBA)), which self-assembled into micelles in phosphate buffer (PB).[95] Poly(L-glutamic acid) (PGA), due to their pH-responsive property (pK_a = *ca.* 4.1), downregulated the pK_a of PBA and endowed the micelle with excellent glucose-sensitivity at physiological pH (pH 7.4). In addition, owing to the presence of PGA, the micelle could swell in acidic or alkaline medium, while shrink at physiological pH. The property endowed micelle with advantageous capability for capture drug in physiological condition by changing the solution pH. The *in vitro* release profiles revealed that the release of insulin from micelles could be triggered by glucose. In detail, less amount of insulin was released under healthy blood glucose level (*i.e.*, 1.0 mg mL^{-1} glucose), while quick release occurred under diabetic blood glucose level (above 2.0 mg mL^{-1} glucose). The excellent glucose-triggered release was further confirmed by the alternant release assay (Fig. 9).

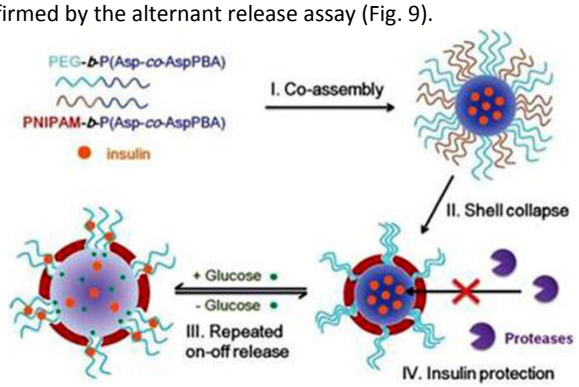

Fig. 10 Schematic illustration of glucose-responsive complex polymer micelle self-assembled from two diblock copolymers for repeated on-off release and insulin protection under physiological conditions.[96]

In addition, Shi and coworkers reported a glucose-responsive complex polymer micelle through the self-assembly of two types of diblock copolymers, poly(ethylene glycol)-*block*-poly(aspartic acid-*co*-aspartamidophenylboronic acid) (PEG-*b*-P(Asp-*co*-AspPBA)) and poly(*N*-isopropylacrylamide)-*block*-poly(aspartic acid-*co*-aspartamidophenylboronic acid) (PNIPAM-*b*-P(Asp-*co*-AspPBA)).[96] By controlling the weight ratio between PNIPAM and PEG (W_{PNIPAM}/W_{PEG} = 6 : 4), the block copolymer form complex micelle with a novel core-shell-corona structure (Fig. 10). Owing to the presence of PBA, the complex micelle exhibited high glucose-sensitivity with repeated on-off release profiles due to a continuous PNIPAM shell around the glucose-responsive core. In addition, the continuous PNIPAM shell of the complex micelle could provide effective insulin protection against protease degradation. Both on-off regulation and insulin protection make the biocompatible glucose-responsive complex polymer micelle a promising approach for diabetes treatment.

4.2. Vesicles based on PBA

While most examples of PBA-based nanoparticles are polymer-based micelles, vesicles based on PBA for glucose-sensitive controlled drug release are also studied.[97,98] Polymer vesicles with bilayer spherical structure are also obtained by self-assembly of amphiphilic polymers. However, the hydrophobicity of amphiphilic polymers used for vesicles is higher than that of polymers to form micelles. Polymers with intermediate levels of hydrophobicity, that is about 40 – 80% by weight of the polymer molecule consisting of hydrophobic moieties, favouring the formation of vesicles.[99] However, Polymers with low levels of hydrophobicity form micelles easily. Polymer vesicles enhance the drug loading capacity with high drug bioactivity protected by the bilayer membrane.

Li and coworkers prepared glucose-responsive vehicles through block or random amphiphilic PBA-based glycopolymers.[100] The block and random glycopolymers were synthesized by RAFT polymerization using AAPBA and 2-(acrylamido) glucopyranose (AGA) monomers with different molar ratios. Both glycopolymers self-assembled into nanoaggregates with stable spherical morphology (Fig. 11). Even though the block and random glycopolymers had different structures, the nanoparticles of them had glucose-triggered insulin release profiles. In addition, the random glycopolymer nanoparticles possessed more apparent glucose-responsive insulin release than that of block glycopolymer nanoparticles, indicating that the glycopolymer structure plays an important role in the self-assembly and glucose-sensitive behaviors of the nanoparticles.

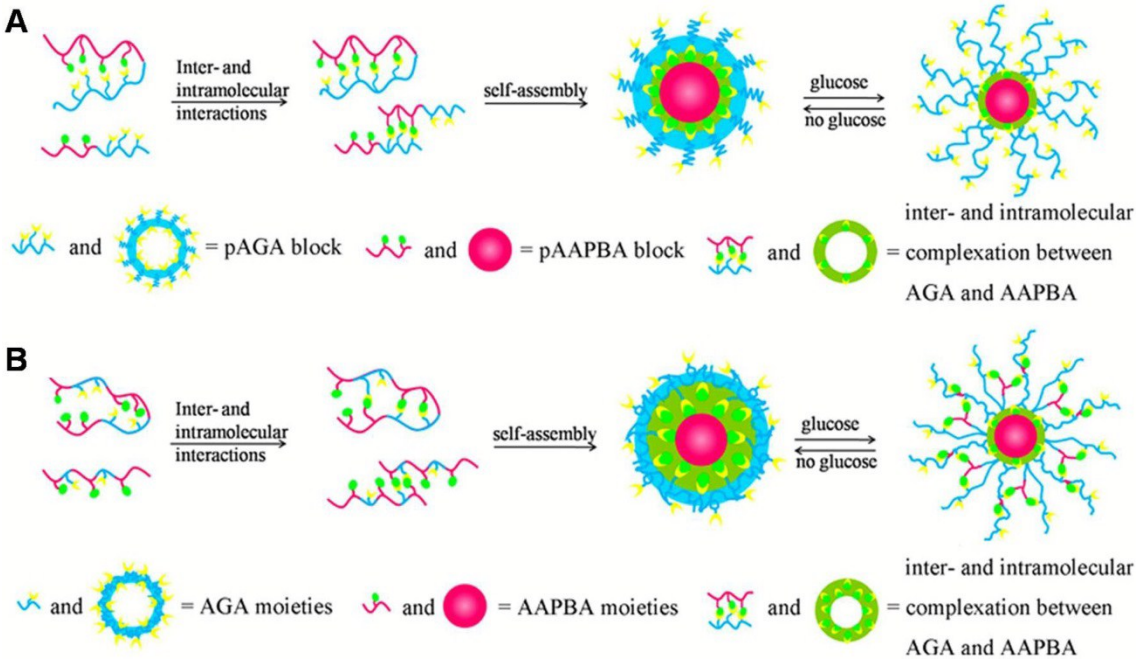

Fig. 11 Schematic illustration of the self-assembly of block (A) and random (B) glycopolymers into nanoparticles in solution without or with glucose.[100]

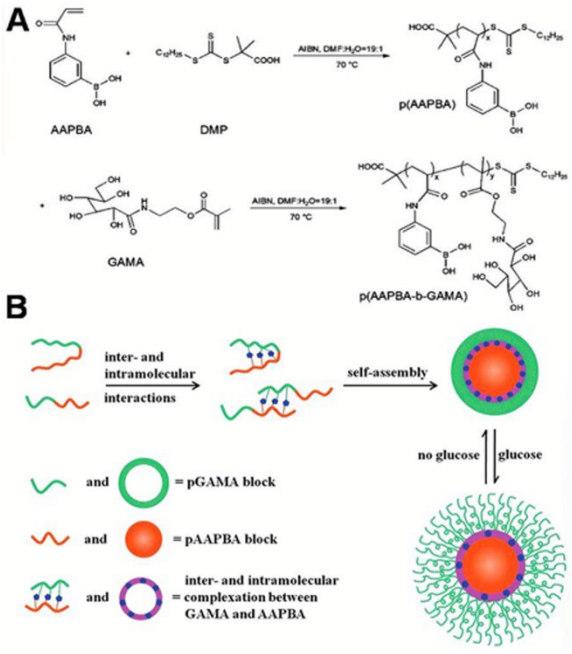

Fig. 12 (A) Synthesis of p(AAPBA-*b*-GAMA); (B) Schematic representation of formation of P(AAPBA-*b*-GAMA) nanoparticle.[101]

An amphiphilic block glycopolymer poly(D-gluconamidoethyl methacrylate-*block*-3-acrylamidophenylboronic acid) (P(AAPBA-*b*-GAMA)) based on PBA and carbohydrate was synthesized by Li and coworkers (Fig. 12A).[101] Based on the cross-linking between the diol groups of carbohydrates and PBA, the glycopolymers self-assembled into nanoparticles with a hydrophilic PGAMA corona and a hydrophobic PAAPBA core (Fig. 12B). The glucose-sensitive PBA-diol-crosslinked carrier could control insulin release responding to the glucose levels in the blood, which avoids glucose fluctuations, and subsequently decreases the occurrence and development of complications. The smart drug delivery systems may have potential applications in the treatment of diabetes.

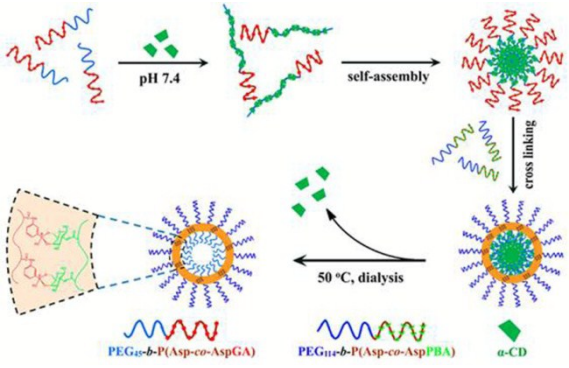

Fig. 13 Schematic illustration for fabrication of polymer vesicle using a α-CD/PEG inclusion complex-templated strategy.[102]

Shi and coworkers fabricated polymer vesicles based on the complexation between glucosamine (GA)-containing block copolymer of poly(ethylene glycol)-*block*-poly(aspartic acid-*co*-aspart-glucosamine) (PEG_{45}-*b*-P(Asp-*co*-AspGA)) and PEG_{114}-*b*-P(Asp-*co*-AspPBA) *via* a template of α-CD (α-CD)/PEG inclusion complex.[102] As shown in Fig. 13, when α-CD was added, PEG_{45}-*b*-P(Asp-*co*-AspGA) self-formed into core-shell micelle due to the formation of insoluble α-CD/PEG inclusion complex. After the addition of PBA-containing copolymer PEG_{114}-*b*-P(Asp-*co*-AspPBA), the micelle further transformed into the core-shell-corona one. In the core-shell-corona micelle, the insoluble α-CD/PEG_{45} inclusion complex was the core, while the cross-linked P(Asp-*co*-AspGA)/P(Asp-*co*-AspPBA) *via* formation of GA/PBA cycloborate was the shell and PEG_{114} was the corona, respectively. After removing α-CD, the novel polymer vesicles was obtained with PEG as both inner and outer coronas, and cross-linked P(Asp-*co*-AspGA)/P(Asp-*co*-AspPBA) as wall. Vancomycin, a model drug, was loaded into the polymer vesicles with high entrapment efficiency (EE) and loading capacity (LC), and the sugar-triggered drug release was successfully realized.

In addition, the same group prepared the polymer vesicles through a template of thermo-sensitive micelle and the preparation method was as follows.[103] The thermo-sensitive PBA-containing block copolymer of PNIPAM-*b*-P(Asp-*co*-AspPBA) self-assembled into core-shell micelle at the temperature above the lower critical solution temperature (LCST) of PNIPAM. Then PEG-*b*-P(Asp-*co*-AspGA) was added into the micelles, resulting in core-shell-corona complex micelle. Polymer vesicle was obtained simply by storing the core-shell-corona complex micelle below the LCST of PNIPAM. In the vesicles, the swollen PNIPAM, a cross-linked P(Asp-*co*-AspPBA)/P(Asp-*co*-AspGA), and PEG were the core, vesicular membrane, and corona, respectively. Also the polymer vesicles had good glucose-sensitivity.

The glucose-sensitive vesicles based on PBA are also prepared by the complexation of PBA in poly(3-methacrylamido phenylboronic acid) (PMAPBA) and glucose moiety in dextran.[104] In addition, PMAPBA/chitosan nanoparticles are obtained by the coordinating interaction between PBA in PMAPBA and amino group in chitosan.[105] PBA-grafted chitosan used for glucose-sensitive vehicle for controlled insulin release was also be studied.[106] Moreover, organoboron copolymers, which were synthesized by the ring-opening polymerization (ROP) of boronic acid-installed cyclic carbonate first time using a poly(ethylene glycol) (PEG) macroinitiator, also could self-assemble into spherical nanoparticles or vesicle-like aggregates depending on the hydrophilic/hydrophobic ratio of the polymer.[107]

4.3. PBA-functionalized nanogels

Even though micelles and vesicles are proverbially used as the glucose-sensitive drug delivery carriers, micelles and vesicles obtained by self-assembly of amphiphilic polymers lack long-term stabilities. Polymer micelle will disaggregate when the concentration of the polymers below CMC. This concentration-dependent instability limits the use of micelle as drug delivery platform. Also the structure of polymer vesicles depends on the preparation and application conditions. In contrast, the nanogels with cross-linked structure are more stable and exhibit reversible swelling/shrinking changes, endowing them with repeated glucose-sensitivity. Therefore, the glucose-sensitive nanogels have promising potential application in glucose-sensitive drug delivery owing to the structure integrity.

Several groups reported the synthesis of glucose-sensitive PBA-functionalized nanogels. Using two-step colloidal template polymerization, Zha and coworkers prepared hollow nanogel, which was composed of poly(*N*-isopropylacrylamide) and poly(*N*-phenylboronic acid acrylamide).[108] The nanogel had interpenetrating polymer network and morphological structure of inner cavity with both temperature- and glucose-responsive properties. Polymer nanogel was also prepared by one-pot copolymerization of polyethylene glycol methylacrylate (PEGMEM) and AAPBA using *N,N*-methylene-*bis*-acrylamide (MBA) as cross-linking agent.[109]

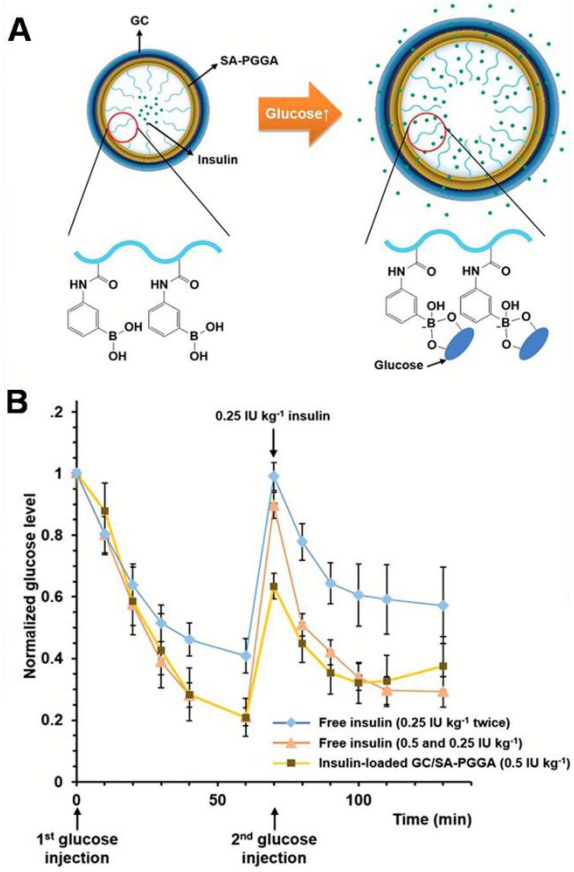

Fig. 14 (A) Schematic illustration of controlled insulin release from glucose-sensitive GC/SA-PGGA double-layer nanogel by complexation between PBA derivative and glucose; (B) Normalized blood glucose levels in mice by the administration of free insulin twice (0.25 IU kg^{-1}), free insulin (0.5 and 0.25 IU kg^{-1}), and insulin-loaded GC/SA-PGGA (0.5 IU kg^{-1}).[110]

Although the PAA-based nanogels possess good biocompatibility, the non-degradability of the glucose-sensitive nanocarriers limits their clinical application. Biocompatible and degradable materials with easy clearance from blood and circulation or metabolism in cells have received a great attention in the drug delivery field. Kim *et al.* designed a glycol chitosan (GC)/sodium alginate (SA)-poly(L-glutmate-*co*-*N*-3-L-glutamylphenylboronic acid) (PGGA) graft copolymer (*i.e.*, GC/SA-PGGA) bilayer nanogel.[110] GC/SA-PGGA

double-layer nanogel was prepared by an isotropic gelation method and electrostatic interaction between GC and SA-PGGA (Fig. 14A). When glucose was added, the binding between the glucose molecule and boronic acid group on PGGA endowed the PGGA chain with enhanced hydrophilicity. The improved hydrophilicity induced the swelling of the bilayer nanogel and the consequent release of insulin. More importantly, the controlled insulin release capability of GC/SA-PGGA nanogel *in vivo* was also confirmed in mouse study. Glucose was administered to mice to raise their blood glucose level to diabetic glucose range, and then the mice were administrated of free insulin or insulin-loaded GC/SA-PGGA nanogel. The insulin-loaded GC/SA-PGGA double layered nanogel exhibited controlled release of the encapsulated insulin at high glucose level *in vivo*, and maintain low glucose level for almost 3 h. Additionally, as shown in Fig. 14B, the insulin-loaded nanogel exhibited a similar blood glucose reduction effect as that of free insulin treatment with reduced injection number. The glucose-recognition insulin release profile endowed the nanogel with promising application in self-regulated insulin delivery.

Chen and coworkers designed a polypeptide nanogel by crosslinking glycopolypeptides poly(ethylene glycol)-*block*-poly-(*γ*-benzyl-L-glutamate-*co*-(*γ*-propargyl-L-glutamate-*graft*-glucose) (mPEG-*b*-P(BLG-*co*-(PLG-*g*-Glu))) using adipoylamidophenylboronic acid.[111] With insulin as a model drug, the drug release from the nanogel possessed excellent glucose-sensitivity, which was triggered by the presence of glucose through a competitive binding mechanism with the conjugated glucose. In addition, MTT and hemolysis assays confirmed the good cytocompatibility and hemocompatibility of the nanogel. Using a simple method, the same group reported a facile one-pot synthesis of glucose-sensitive nanogel *via* thiol-ene click chemistry for self-regulated drug delivery.[112] The nanogel with disulfide cross-linked core and PEG shell was prepared by a one-pot thiol-ene copolymerization of pentaerythritoltetra (3-mercaptopropionate) (QT), poly(ethylene glycol) diacrylate (PEGDA), poly(ethylene glycol) acrylate (mPEGA), and AAPBA (Fig. 15). PBA embedded in nanogel endowed the nanogel with remarkable glucose-sensitivity. Using ARS and insulin as model drugs, the *in vitro* release results revealed that the release of drug from nanogel was highly glucose concentration dependent, *i.e.*, a higher release rate and more amount of drug released were achieved by increasing the glucose concentration in PBS.

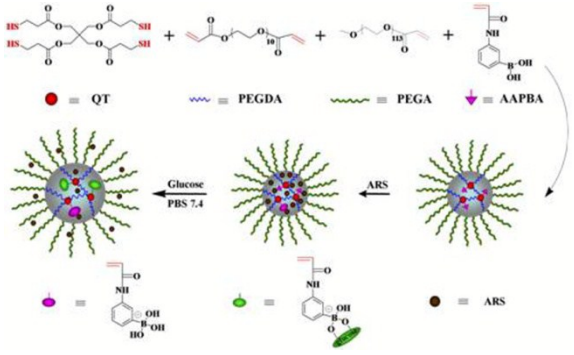

Fig. 15 Structure of nanogel and glucose-sensitive behavior of ARS-loaded nanogel in PBS at pH 7.4.[112]

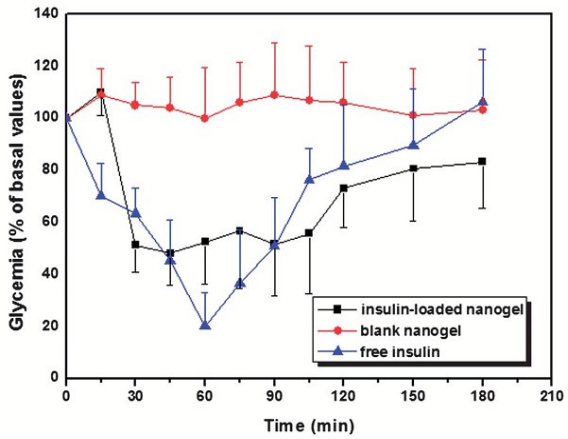

Fig. 16 Profiles of glycaemia after a subcutaneous administration of free insulin (2.0 IU kg^{-1}), insulin-loaded nanogel (4 IU kg^{-1}), or blank nanogel in fed diabetic rats. Before the injections, glycaemia was 426 ± 13 mg mL^{-1}.[113]

An injectable nanogel, with interpenetrating polymer networks of poly(*N*-isopropylacrylamide), dextran, and poly(3-acrylamidophenylboronic acid) (P(NIPAM-Dex-PBA)), presented better dispersion and glucose-sensitivity under physiological conditions.[113] The glucose-sensitive insulin release profiles were related to the dextran contents. More insulin was released from the nanogel with high dextran content in medium with glucose concentration of 2.0 mg mL^{-1}. In addition, the considerable hypoglycaemic effect of the insulin-loaded nanogel was also studied. As shown in Fig. 16, *in vivo* experiments demonstrated that the blood glucose level of diabetic rats treated with the insulin-loaded nanogel was reduced to 51% of the baseline level for almost 2 hours. Compared with free insulin, the insulin-loaded nanogel kept stable blood glucose level without remarkable fluctuation of blood sugar. The insulin-loaded nanogel with prolonged and stable blood glucose reduction effect provides a possibility to use as glucose-sensitive platform for self-regulated insulin delivery.

4.4. PBA-incorporated hybrid nanoparticles

PBA-functionalized hybrid nanoparticles are also used as glucose-sensitive drug nanocarriers.[114,115] MSN, with large capacity for drug loading, functionalized surface, and high biocompatibility, has been extensively explored as a promising candidate as drug nanocarrier. Drugs are usually protected by caps on the pore of MSN after being loaded. The closed pores are opened when the caps are displaced, following by drug release. MSN-based double-drug delivery system for glucose-responsive release of both gluconic acid-modified insulin (G-Ins) and cyclic adenosine monophosphate (cAMP) was designed, which can active the Ca^{2+} channels of pancreas beta cells and hence stimulated insulin secretion.[116] In detail, G-Ins was immobilized on the exterior surface of PBA-functionalized MSN, serving as caps to encapsulate cAMP molecules inside MSN. The release of both G-Ins and cAMP could be triggered by glucose. It was demonstrated that the nanodevice served as an efficient glucose-sensitive insulin-release system, benefited from its good biocompatibility and cellular uptake properties.

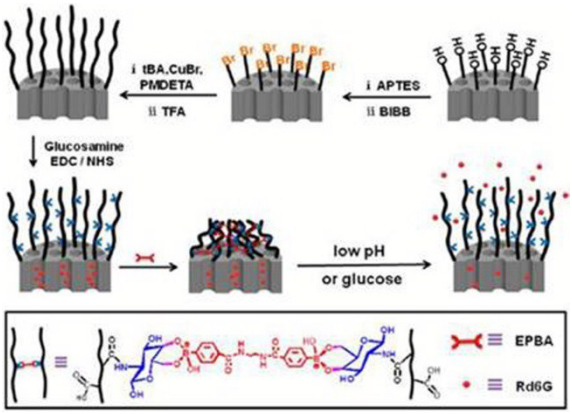

Fig. 17 Schematic representations of preparation of cross-linked MSN-PAA-AGA and dual-responsive drug release behavior.[117]

Also using MSN, Liu *et al.* designed novel pH and glucose-sensitive hybrid nanoparticle of MSN-PAA-AGA based on the cross-linked polymer network-capped MSN.[117] They prepared PAA brush on MSN and subsequently modified partially by glucosamine. As shown in Fig. 17, MSN-PAA-AGA was cross-linked through the formation of boronate ester between hydroxyl groups of glucosamine in the polymer brush on MSN and 4,4-(ethylenedicarbamoyl)-phenylboronic acid (EPBA). Rd6G, a model drug, was loaded into the MSN-PAA-AGA nanogated ensemble and the release could be triggered by glucose. The glucose-induced drug release was attributed to the competitive binding of glucose molecule to the EPBA comparing with glycosyl agent in polymer brush. At the same time, the destruction of cross-linking resulted in the accelerated drug release. In addition, the release of Rd6G was accelerated in acid condition because that the complexation between EPBA and glycosylation in polymer brush could be cleaved under mild acid condition with the release of cargo molecules.

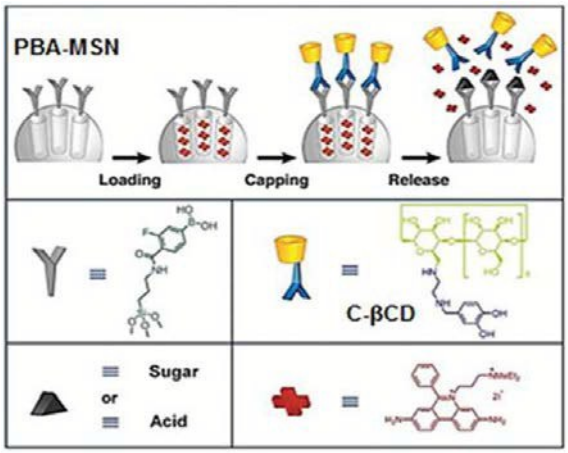

Fig. 18 Schematic illustration of structure and dual-responsive cargo release process of CD-PBA-MSN.[120]

CDs with good modifiability have been greatly used in the PBA-based glucose-sensitive drug delivery system.[118,119] Also using competitive binding mechanisms, a sugar and pH dual-responsive controlled release system with incorporated CD was developed.[120] PBA stalk was firstly grafted onto the platform of MSN, and then cross-linked by catechol-containing β-CD (C-βCD) through formation of boronate ester obtaining CD-PBA-MSN nanocontainer (Fig. 18). The cargo release from CD-PBA-MSN could be triggered by different sugar solutions. Fructose and glucose induced faster release of the cargo from the nanopores than maltose and sucrose depending on the corresponding sugar-PBA-MSN complex binding constant with competitive binding mechanism. In addition, the release of cargo entrapped in CD-PBA-MSN was pH-dependent, resulting from the disassociation between C-βCD and PBA. Furthermore, the combination of glucose and acid provided a synergistic effect on the disassociation process with multiple cargo release rather than a simply additive release.

Li and coworkers reported a pH-gated and glucose-sensitive nanoparticle based on worm-like mesoporous silica for controlled insulin release.[121] It had a MSN core and cross-linked or non-cross-linked polymer shell, bearing AAPBA and NIPAM as sensor moieties. The hybrid nanoparticles displayed obviously thermo- and pH-gated glucose sensitivity. Furthermore, the cross-linked shell with dextran-maleic acid as a macromolecular cross-linker enabled insulin to release more persistently compared with the non-cross-linked shell.

Furthermore, Jana and coworkers designed a dextran-gated multifunctional mesoporous nanoparticle, which was used for glucose-responsive and targeted drug delivery.[122] In this drug delivery system, magnetic mesoporous silica including γ-Fe_2O_3 was functionalized with PBA and folate obtaining MMS-PBA and FA-MMS-PBA, respectively. Dextran was used as a gate to close the outside of the pores after drug loading inside the pores of MMS-PBA and FA-MMS-PBA, obtaining MMS-dextran and FA-MMS-dextran nanoparticles, respectively (Fig. 19). Tolbutamide and camptothecin as representative therapeutic agents of type II diabetes and cancer were loaded into two kinds of nanoparticles. Glucose could induce significant tolbutamide/camptothecin release with successful open of pore surface by replacing dextran in glucose solution. In addition, the MMS-dextran nanoparticle could target pancreatic beta cells, while FA-MMS-dextran nanoparticle could target specific cancer cells depending on bulk glucose concentration. The dextran-gated multifunctional mesoporous nanoparticles have advanced drug delivery applications for diabetes and cancer with more efficient therapy.

Except γ-Fe_2O_3 nanoparticles, Ag nanoparticles are also used in glucose-sensitive drug delivery. Inorganic-organic core-shell-structured hybrid nanogels were made of Ag nanoparticle cores (10 ± 3 nm) covered by a copolymer gel shell of poly(4-vinylphenylboronic acid-*co*-2-(dimethyl amino)ethyl acrylate) (P(VPBA-*co*-DMAEA)) (Fig. 20).[123] The multifunctional nanocarrier combining both optical glucose detection and self-regulated insulin release firstly appeared in the literature. The smart hybrid nanogel exhibited glucose-sensitive volume phase transition due to the introduction of glucose sensitive P(VPBA-DMAEA) gel shell. The small-sized Ag nanoparticle core could provide the hybrid nanogel with strong fluorescence. The fluorescence intensity of Ag nanoparticle core could be manipulated by the physicochemical environment, which was modified by the glucose-induced

swelling/shrinking of the gel shell. When glucose level changed, the nanogel converted the disruptions in homeostasis of glucose level into optical signals and modulated the release of preloaded insulin. The smart hybrid nanogel shows a new proof-of-concept for the treatment of diabetes that exploits the properties from each building block. In addition, the multifunctional nano-object hastens the development of more efficacious systems toward a good control toward diabetic.

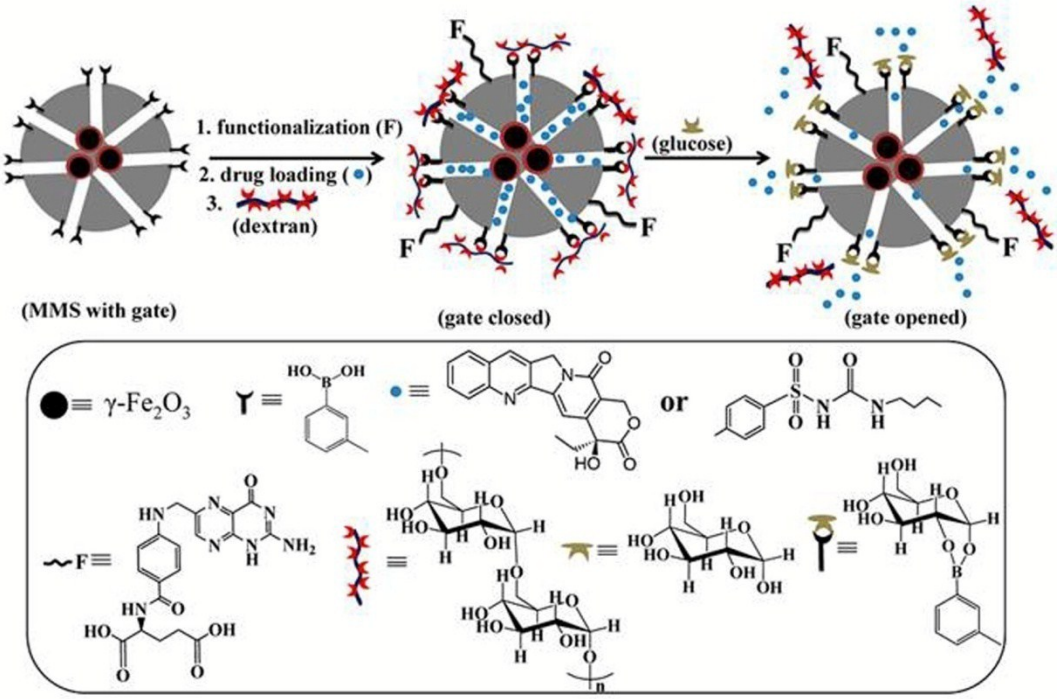

Fig. 19 Preparation of dextran-gated multifunctional mesoporous silica nanoparticle and mechanism of glucose-sensitive drug release.[122]

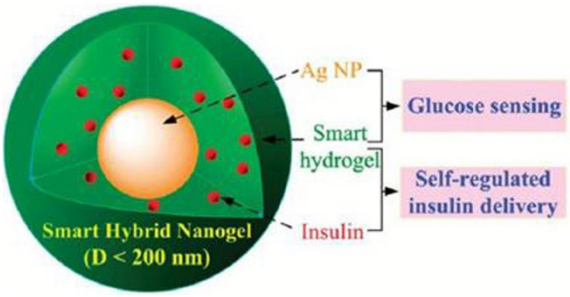

Fig. 20 Schematic illustration of optical glucose detection and self-regulated insulin delivery at physiological condition of smart hybrid nanogel.[123]

PBA and derivatives have more promising applications in the design of glucose-sensitive nanoparticles with greater stability, longer term storability, and lower cytotoxicity compared to GOD- and Con A-based nanoparticles.[33, 124] However, the high pK_a of PBA is a major obstacle limiting the practical application of glucose-sensitive drug delivery in the physiological conditions.[125, 126] How to reduce the pK_a of PBA derivatives to increase the affinity at lower pH conditions with excellent glucose-triggered drug release profiles in physiological environments is one urgent problem in the design of glucose-sensitive system.

5. Conclusions and outlooks

The glucose-sensitive drug delivery systems, which can continuously and automatically release payload in response to the elevated level of blood glucose, have attracted much attention recently. Moreover, the smart platforms become the focus of research to reduce the intervention toward patient and improve their quality of life.

Recently, a series of advances in glucose-sensitive nanoparticles based on GOD, Con A, or PBA have been made. Polymer micelles have much interest as nanosized platform for glucose-sensitive drug delivery. The core-shell nanostructure endows polymer micelles with excellent properties, such as enhanced stability, long circulation time in the blood, higher safety, *etc*.[127] Even though the studies of glucose-sensitive polymer micelles are only in *in vitro* drug release stage, the platform is one potential carrier for self-regulated drug delivery in clinic. Polymer vesicles could be formed by high hydrophobic amphiphilic polymers with complicated technologies, which is different from the relatively simple self-assembly of polymer micelles. Importantly, polymer vesicles provide larger inner volumes for hydrophilic drug encapsulation with enhanced drug loading content. Compared with micelles and vesicles, nanogels are more stable when injected subcutaneously due to the cross-linked structure. The repeated on-off drug releases, which are triggered by glucose concentration resulting from the reversible swelling/shrinking, and the structure integrity endow the glucose-sensitive nanogels with promising potential application in self-regulated drug delivery. Glucose-sensitive hybrid nanoparticles, which are mostly mesoporous silica nanoparticles (MSN), have created intense interest in the area of self-regulated drug delivery systems.

MSN-based glucose-sensitive drug delivery systems have significant advantages, such as tailorable mesoporous structure, large pore volume, large capacity, modifying properties, *etc.*[128] All of these glucose-sensitive polymer nanoparticles based on GOD, Con A, or PBA have more promising applications in self-regulated drug delivery and maybe approved for clinical diabetic therapy in the future.

Although there is considerable progress in self-regulated drug release, some challenges and limitations still restrict the development. Of course, the opportunities are always accompanied by challenges.

(1) A major challenge for the development of glucose-sensitive drug delivery systems is to remain the activity of glucose-sensitive moieties in physiological conditions with allow for the continuous glucose-sensitivity. Although the activity of GOD is preserved during the preparation of carriers, GOD is not well for continuous sensing of glucose due to the attenuation of enzymatic reaction under numerous reaction products. It restricts the potential application in self-regulated drug release. Con A, a lectin protein, is also instable during the fabrication of glucose-sensitive platforms, which limits its application in glucose-triggered drug delivery systems. PBA and its derivatives, which have better stability and long term storability than GOD and Con A , as the glucose-sensitive agent have received great interest as glucose-sensitive drug delivery recently. However, the pK_a of PBA (*i.e.*, 8.2 − 8.6) is higher than physiological pH (pH 7.4), and how to adjust the value of its pK_a to 7.4 with excellent glucose-sensitivity is a great challenge.

(2) Biocompatibility and biodegradability without long-term side effect of the polymer matrices used in the self-regulated drug delivery system is a challenge. The medical treatment for diabetes is a long process, so it needs the safe of matrices, non-toxicity, and friendly to the body for *in vivo* application. However, most of the materials used in the currently studied glucose-sensitive drug delivery platforms are not biodegradable even though excellent biocompatible. Therefore, the great biodegradable and biocompatible materials should be considered for designing glucose-sensitive insulin delivery systems.

(3) The selectivity of glucose-sensitivity for the carriers with rapid and numerous release of drug under the diabetic blood glucose level, while few under the healthy blood glucose level is another challenge. The prandial blood glucose level in the healthy human body is below 1.5 mg mL^{-1}, while the prandial blood glucose concentration for diabetics is above 2.0 mg mL^{-1}, and the maximum detectable blood glucose concentration of the body is even 4.0 mg mL^{-1}. Thus, the glucose-sensitivity of the drug delivery system should be conformed when the glucose concentrations equal to or above that in diabetic patients. However, most studies on the glucose-sensitivity of the matrix were at the glucose concentration much higher than the diabetic maximum blood glucose level. Except that, the high sensitivity that the carriers can timely and rapidly adjust the drug release on-demand of the body with the fluctuations of the diabetic blood glucose concentrations also should be considered.

(4) Another challenge for glucose-sensitive drug delivery system is to preserve the bioactivity of released drug (*e.g.*, insulin). The dose control of drug delivery is very important for the hypoglycemic effect. Therefore, in the preparation of the drug-loaded matrix and the drug release process, the payload must maintain the original bioactivity. To better investigate the drug delivery triggered by glucose, the entrapment capacity and entrapment efficiency of payload must be controlled strictly.

Glucose-sensitive polymer nanoparticles for self-regulated drug delivery could provide better control of blood level, which could deliver an accurate dose of drug (*e.g.*, insulin), mimicking the physiologic regulation of normally functioning pancreas. Great efforts must be devoted to promote the clinical application of glucose-sensitive self-regulated drug delivery systems based on GOD, Con A, or PBA. Although there are some challenges in glucose-sensitive drug delivery needing great efforts to overcome, it is believed that glucose-sensitive drug delivery system will be promoted under continuous efforts of researchers. Through ingenious design combining multidisciplinary, the glucose-sensitive self-regulated drug delivery platforms based on biodegradable and biocompatible materials with excellent glucose-triggered drug release under physiological conditions will migrate from laboratory to clinical application in the near future.

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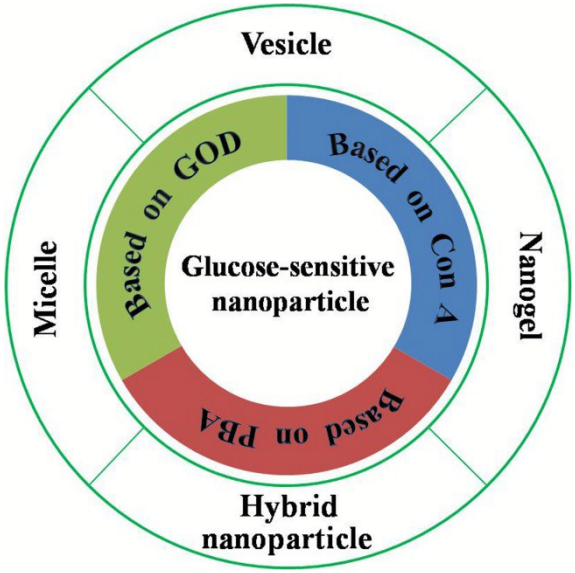
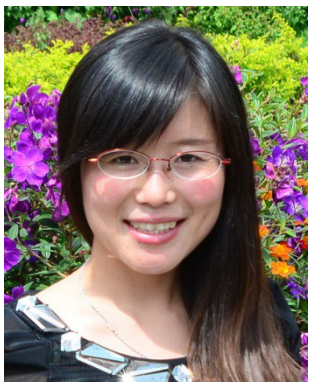
Colour graphic



Text

The glucose-sensitive polymer nanoparticles based on glucose oxidase, concanavalin A, or phenylboronic acid for self-regulated drug delivery have been reviewed.

Photographs and biographies



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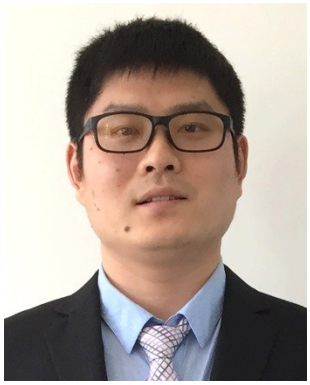

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