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Review

Cyclodextrin Host–Guest Recognition in Glucose-Monitoring Sensors

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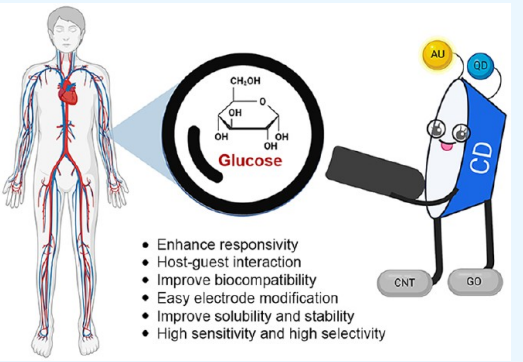
ABSTRACT: Diabetes mellitus is a prevalent chronic health condition that has caused millions of deaths worldwide. Monitoring blood glucose levels is crucial in diabetes management, aiding in clinical decision making and reducing the incidence of hypoglycemic episodes, thereby decreasing morbidity and mortality rates. Despite advancements in glucose monitoring (GM), the development of noninvasive, rapid, accurate, sensitive, selective, and stable systems for continuous monitoring remains a challenge. Addressing these challenges is critical to improving the clinical utility of GM technologies in diabetes management. In this concept, cyclodextrins (CDs) can be instrumental in the development of GM systems due to their high supramolecular recognition capabilities based on the host−guest interaction. The introduction of CDs into GM systems not only impacts the sensitivity, selectivity, and detection limit of the monitoring process but also improves biocompatibility and stability. These findings motivated the current review to provide a comprehensive summary of CD-based blood glucose sensors and their chemistry of glucose detection, efficiency, and accuracy. We categorize CD-based sensors into four groups based on their modification strategies, including CD-modified boronic acid, CD-modified mediators, CD-modified nanoparticles, and CD-modified functionalized polymers. These findings shed light on the potential of CD-based sensors as a promising tool for continuous GM in diabetes mellitus management.



1. INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder caused by the dysfunction of insulin secretion or insulin resistance, leading to abnormal glucose levels in the blood and potentially severe health complications. Insulin is a hormone responsible for regulating glucose levels in the body, and its deficiency or reduced effectiveness can cause hypoglycemia or hyperglycemia, respectively, which can result in serious medical problems such as tissue damage, kidney failure, blindness, and cardiovascular diseases.[1,2] Type 1 diabetes (T1D) is an autoimmune disorder characterized by a loss of β-cells in the pancreatic islets of Langerhans, leading to insulin deficiency and hyperglycemia.[3,4] Type 2 diabetes (T2D), on the other hand, is caused by a combination of insulin resistance and inadequate insulin secretion by pancreatic β-cells, resulting in high blood glucose levels.[4,5] Although there is no definitive cure for diabetes, lifelong monitoring of blood glucose levels is crucial for individuals with diabetes to manage their condition and prevent complications.[6−12] In recent years, there have been significant advancements in technologies related to glucose monitoring (GM). In the 1980s, blood glucose electrochemical self-testing devices were introduced, and by the 1990s, their widespread usage had led to considerable improvements in their determination capabilities.[13] These devices have undergone major enhancements in terms of speed, sample volume, sensing chemistries, mass production, miniaturization, connectivity to smartphones, accuracy, and precision.[11,12,14,15] Single-use glucose-monitoring sensors have limitations in providing comprehensive glucose level information, as they offer a one-time reading of glucose levels in the blood.[16,17] To address this limitation, continuous glucose-monitoring (CGM) systems have been developed, providing real-time glucose readings every few minutes, allowing for the detection of fluctuations and trends in glucose levels over time.[18−21] However, current CGM systems are still invasive and require frequent calibrations. Developing noninvasive CGM systems that are low cost, rapid, reliable, accurate,

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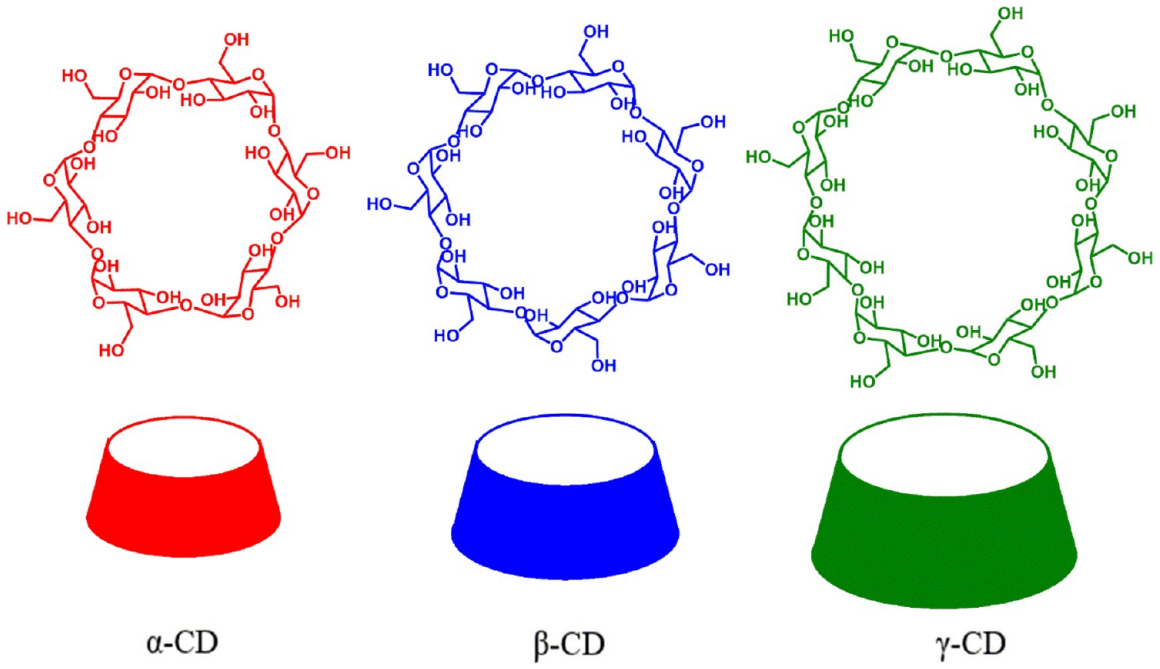

Figure 1. Chemical structures and cartoon representations of α-, β-, and γ-cyclodextrin.

sensitive, selective, and stable remains a challenge in diabetes management.[21] However, these methods are still in the development phase and require further research to validate their accuracy and reliability.

Glucose-monitoring (GM) technology has undergone significant advancements in three generations. The first-generation blood GM systems used neutral oxygen as the electron acceptor to measure the glucose concentration. Second-generation systems used artificial electron acceptors to prevent interference from other redox-stable species and commonly employed colorimetric or electrochemical systems to monitor reduced artificial electron acceptors. Third-generation systems directly transferred produced electrons to the electrode, minimizing errors from oxygen concentration variations in blood samples and removing toxic artificial electron mediators.[10] In these concerns, several quantitative methods have been developed for measuring glucose concentration in blood samples, including the colorimetric method,[22−25] optical sensors,[26,27] chemiluminescence,[28] attenuated total reflection-Fourier transform infrared,[29] high-performance liquid chromatography,[30] and electrochemical methods.[27,31−34] Among these, electrochemical and optical methods are the most commonly used for the quantitative analysis of glucose. These methods differ in the type of signal they measure, with photons detected by optical methods and electrons measured by electrochemical methods. Electrochemical sensors, such as voltammetry and amperometry, typically rely on enzymatic or nonenzymatic reactions to detect glucose.[33,35−37] Enzymatic-type glucose sensors employ a glucose-sensitive enzyme, such as glucose oxidase (GOx), anchored on the sensing electrode. This enzyme can reduce oxygen to H_2O_2 under amperometric monitoring. Non-enzymatic-type sensors, on the other hand, detect glucose via direct oxidation or reduction of glucose using the electrochemical sensing method with metal electrodes or nanoparticles (NPs). The optical methods for glucose measurement use light to detect changes in the concentration of glucose. This can include techniques such as absorption spectroscopy, fluorescence spectroscopy, luminescence, and Raman spectroscopy. The choice of method depends on factors such as the sensitivity, selectivity, and reliability required for the specific application. While optical methods have the potential for continuous glucose monitoring and are noninvasive, they suffer from certain limitations including high cost, complex design, and low accuracy. The electrochemical enzymatic or non-enzymatic glucose sensors, although commonly used, also have limitations such as insufficient stability, low selectivity, and the need for mediators to shuttle electrons to the electrode. Ensuring enzyme activity and resolving mass transport problems are also major challenges associated with electrochemical systems.[9,38,39] Thus, developing an efficient method for the ideal GM system remains a significant challenge.

Recent studies have sought to overcome the challenges associated with glucose monitoring by exploring the development and practical application of GM systems. This has led to a surge in literature reviews on this topic, providing valuable insights into the development and practical applications of GM systems.[7,10,12,19,20,38,40−42] For example, Zaidi and Shin provided an overview of recent progress in the development of electrochemical nanosensors for glucose sensing in 2016.[38] Lee et al. discussed the evolution of enzyme-based glucose biosensors from invasive to wearable devices in a 2018 review.[40] Teymourian et al. provided a comprehensive review of the recent developments in electrochemical glucose sensors for diabetes management from 2010 to 2020.[10] Furthermore, the use of molecular recognition via a host−guest strategy, specifically the use of cyclodextrins (CDs), has emerged as a promising approach for designing various sensing and biosensing systems.[43−45] CDs offer a unique platform for biosensing applications given their ability to serve as host molecules for various hydrophobic guests. This characteristic has enabled the development of numerous electrochemical and optical approaches for biosensors utilizing CDs.[1,46,47] Despite the extensive literature on GM systems based on CDs, there is still a lack of comprehensive reviews focusing on CD-based blood GM systems. Therefore, a comprehensive overview of

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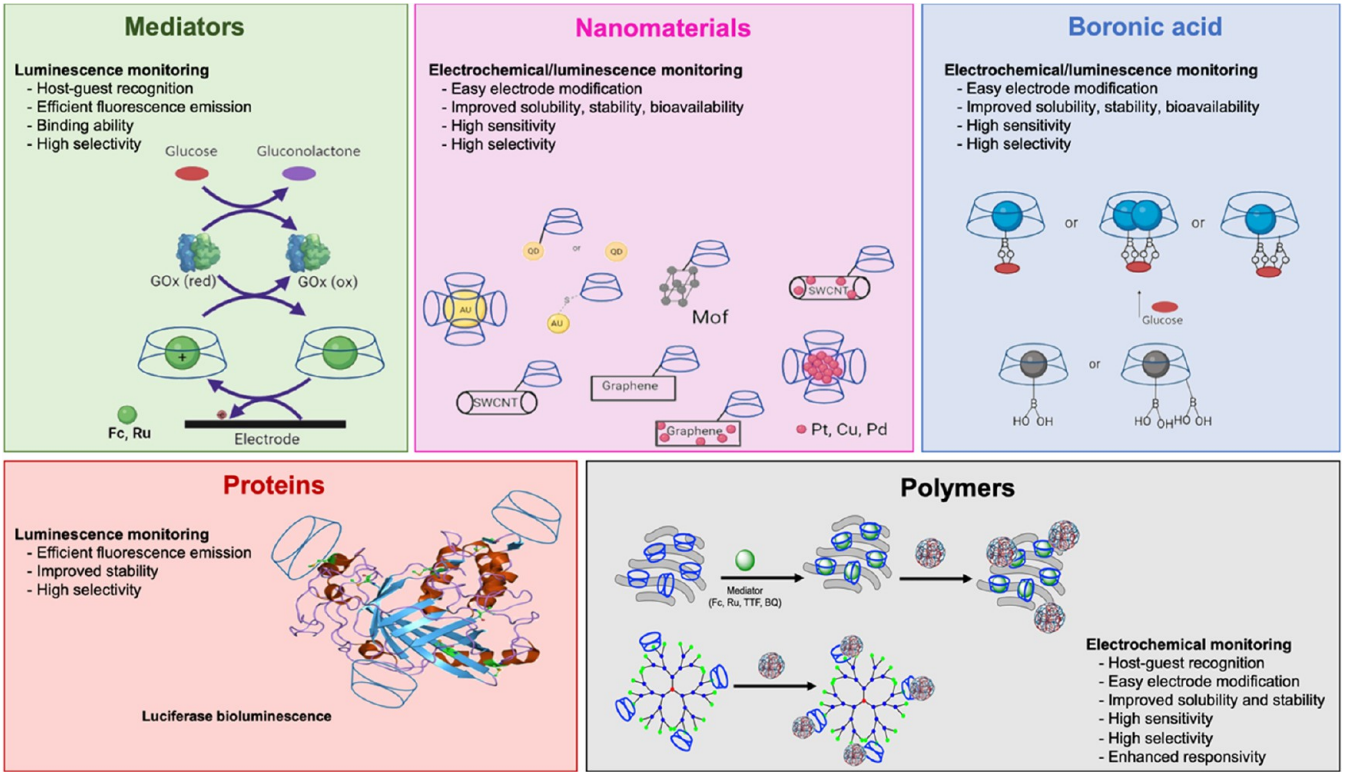

Figure 2. Various glucose-monitoring systems based on cyclodextrins.

CD-based GM systems is still needed. This review aims to fill this gap by presenting a comprehensive analysis of CD-based GM systems, outlining their significant applications and capabilities for developing innovative GM sensors. We believe that this review will provide valuable insights for the GM community, promoting the efficient development of CD-based systems for GM in clinical and marketing applications.

2. CYCLODEXTRIN-BASED GM SENSORS

CD, a cyclic oligosaccharide composed of several glucose molecules linked together by α-(1,4) glycosidic bonds, exhibits a toroidal configuration with a hydrophilic exterior and a hydrophobic internal cavity. The three most commonly used CDs are α-, β-, and γ-CDs, consisting of six, seven, and eight glucose units, respectively (Figure 1). CDs have garnered significant attention over the past few decades as a remarkable biobased material with diverse applications in various fields such as biomedical, biosensor, environmental, and food science.[48−60] Their unique ability to act as a host molecule for a variety of inorganic, organic, and biological molecules, permitting their stabilization and solubilization, makes CDs an attractive material for the development of functional materials.[61−65] CD-functionalized materials can make suitable interactions with an analyte and provide an excellent platform for diverse applications in biosensing.[66−70] These features make them ideal candidates for application in glucose sensor systems, which are the subject of this review.

In glucose-monitoring sensors, CDs are typically used as a part of the sensor's recognition element, which is responsible for either specifically binding to glucose molecules or encapsulating the glucose sensing agent. The presence of CDs in the recognition element facilitates the selective capture of glucose molecules from complex biological fluids. CDs, as bioactive materials, can significantly impact the selectivity, sensitivity, and limit of glucose detection in GM systems. In recent years, glucose-monitoring sensors have been developed with enhanced performance through the use of CDs combined with various sensing agents. These sensing agents fall under several categories including CD-modified boronic acids, CD-modified mediators, CD-modified nanoparticles, and CD-functionalized polymers. This review provides a thorough summary of published works that have explored the use of CDs in the design of GM systems. The review includes a schematic diagram in Figure 2 that outlines the role of CDs in different sensing methods, such as electrochemical and luminescence glucose sensing. Additionally, a comparison of glucose sensors that incorporate CDs is presented in Table 1. The table compares these sensors based on various parameters, including the detected medium, sensitivity, response time, linear response range, detection limit, detection techniques, and the role of CDs. The subsequent sections of this paper provide a detailed description of the works that have been reviewed along with their finding.

2.1. CD-Modified Boronic Acid. Boronic acid chemistry has gained significant attention in the development of glucose sensors.[71−74] Boronic acid, as a weak Lewis acid, forms stable boronate esters through interaction with *cis*-1,2-diols and -1,3-diols in an aqueous solution.[75,76] This allows for specific binding with the 1,2-diol groups present in glucose molecules, enabling glucose detection. This reaction that generates a stable boronate glucose complex is rapid and reversible. A major problem of boronic-acid-based probes is the lack of adequate selectivity during the detection process; hence, many efforts have been made to address this fundamental issue through ad-hoc chemical modifications. In this regard, researchers recently used the inclusion ability of CDs to design exclusive and unique host−guest interactions, to enhance the selectivity of boronic-acid-based glucose detection

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Table 1. Summary of Glucose Sensors Containing CDs, Including the Medium and pH of the Detection, the Applied Detection Techniques, and the Roles of CDs and the Electrodes' Sensitivity, Linear Range, Detection Limit, and Response Time[a]

CD-modified/functionalized		Sensor name	Medium; pH	Sensitivity ($\mu A \cdot mM^{-1}\ cm^{-2}$)	Linear range (mM)	Detection limit (μM)	Response time (s)	CD roles	Detection techniques	Ref
Boronic acid		α-CDP-GOx-BQ	PBS; pH 7.0	30.5 ± 0.5	NR	10	NR	Membrane for immobilization of GOx-BQ	Cyclic voltammetry	88
		α-CDP-GOx-TTF/GCE	PBS; pH 7.0	18.8 ± 0.8	NR	NR	NR	Membrane for immobilization of GOx-BQ	Cyclic voltammetry	88
		4-(4-(1-Pyrenyl)butoxy carbonylphenylboronic acid-β-CD	PBS; pH 7.5	NR	NR	NR	NR	Increasing fluorescence emission response	Fluorescence spectroscopy	77
		CPBA-β-CDGNP	Human blood serum	NR	1−20	1000	NR	Reducing and capping agent for the nanoparticle	UV−visible absorption	86
		β-CDV decorated with PBA-AD-ARS	7.4−10.1	NR	NR	NR	NR	Creating high local concentrations of PBA-AD for binding to ARS	Fluorescence spectroscopy	87
		BA-Azo−γ-CD complex		Na_2CO_3·HCl; pH 10	NR	NR	NR	NR	γ-CD can accommodate two BA-Azo probes and selectively encapsulate D-glucose	
		UV−vis spectra	80							
		C1-APB/3-PB-γ-CD complex	PBS; pH 8.5	NR	NR	NR	NR	(i) Improving the water solubility of C1-APB, (ii) enhancing the fluorescence emission of C1-APB in water, (iii) introducing the capability of selective recognition by using 3-NH_2−γ-CD complex	Fluorescence spectroscopy	82
		Stilbeneboronic acid (STDBA)-γ-CD	$NaHCO_3$-Na_2CO_3; pH 10.5	NR	NR	NR	NR	γ-CD can accommodate two STDBA probes and selectively encapsulate D-glucose	Fluorescence spectroscopy	83
		Phenylboronic acid/γ-CD complex	Na_2CO_3 buffer, pH 11.3	*NR*	*NR*	*NR*	*NR*	γ-CD can accommodate two probes and selectively encapsulate D-glucose	Fluorescence spectroscopy	79
		Anthracene−boronic acid fluorophore/γ-CD complex	PBS; pH 7.4	NR	NR	NR	NR	γ-CD can accommodate two probes and selectively encapsulate D-glucose	Fluorescence spectroscopy	81
β-CD-Rluc with PBA-Au NPs	Blood sample of diabetic rats	NR	0.001−0.1	1	NR	β-CD is used as a connector between the donor and receiver groups in BRET	Bioluminescence	28		
Mediator	Fc	DMFe-HP−β-CD complex/GOx enzyme/Pt electrode	Urine and juice samples	NR	0.02−0.5	20	120	β-CD was used to enclose DMFe into its hydrophobic cavity to form a water-soluble complex	Cyclic voltammetry	89
		DMFe−CD complex/GOx enzyme	PBS; pH 8.0	NR	0.9−6	100	NR	Membrane for immobilization of DMFe	HPLC system	30
		Fc−β-CD polymer/GOx & GAL enzymes/GCE	PBS; pH 7.0	NR	0.05−13.5	10000	NR	Membrane for immobilization of enzymes and ferrocene	Cyclic voltammetry	90
		Chamber-type microchips (CD-Fc complex)/GOx enzyme/Pt electrode	PBS; pH 7.0	NR	0.5−10	NR	60	Membrane for immobilization of enzyme and ferrocene	Cyclic voltammetry	91

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Table 1. continued

CD-modified/functionalized		Sensor name	Medium; pH	Sensitivity ($\mu A \cdot mM^{-1}\ cm^{-2}$)	Linear range (mM)	Detection limit (μM)	Response time (s)	CD roles	Detection techniques	Ref
		GNPs/CD-Fc/GOx enzyme/Pt electrode	PBS; pH 7.0	18.2	0.08−11.5	15	5	Membrane for immobilization of ferrocene	Cyclic voltammetry	92
	Ru	β-CDPA-GOx-(trans-[Ru^{III} (2,2′bpy)$_2$(OH_2)(OH)])/GOx enzyme/GCE	PBS; pH 7.0	0.4	>24	NR	NR	Membrane for immobilization of Ru complex	Cyclic voltammetry	93
		β-CDPA- ([(2,2′bpy)$_2$(OH)$Ru^{II-I}ORu^{III}$(OH)(2,2′bpy)$_2$]$^{4+}$)/GOx enzyme GCE	PBS; pH 7.0	3.2	>14	NR	NR	Membrane for immobilization of Ru complex	Cyclic voltammetry	93
		β-CDPA- ([([Ru^{II}(4,4′bpy)(NH3)$_5$]$^{2+}$)/GOx enzyme/GCE	PBS; pH 7.0	7.2	>4	NR	NR	Membrane for immobilization of Ru complex	Cyclic voltammetry	93
Nanoparticles	Gold	AuCM-β-CD/PCM-β-CD/GCE	NaOH solution	0.770	0.001−110	0.99	NR	Controlling the shape and size of AuNPs by the CMCDs self-assembly process to alter the nucleation and the growth of AuNPs	Amperometry	94
		UCPs-ConA-SH-β-CDs-Au	Buffer and human serum	NR	0.0004−0.01	0.043 in buffer; 0.065 in human serum	NR	The assay is based on the competition between CD and glucose toward ConA	Fluorescence spectroscopy	95
		β-CD-Pd@Au/TMB/GOx enzyme	PBS; pH 7.0	NR	0.02−2	9.28	NR	NR	UV−vis spectroscopy	96
	Platinum	GOx enzyme-PTy/SBCD/PtNP-modified BDD electrode	PBS; pH 7.0	NR	0−110	10	2	To form a permselective film against uric acid and ascorbic acid	Cyclic voltammetry	97
		PtCo−β-CD-IL/GCE	PBS; pH 7.4	13.7	0−20	100	NR	The film for immobilization of PtCo alloy NPs	Cyclic voltammetry	98
		GOx-AD/CD-PAMAM/PtNPs/Au electrode	PBS; pH 7.4	197	0.005−0.705	2.0	6	Membrane for immobilization of GOx	Cyclic voltammetry	99
		GOx-β-CD-o-PD/Pt−B/Au electrode	PB; pH 7.4	0.13	2.5−15	1420	NR	To form a permselective film against uric acid and ascorbic acid	Cyclic voltammetry	100
	Copper	β-CD-s in the presence of GOx enzyme and TMB	PBS; pH 6.0	NR	0.04−20	0.4	NR	Increasing the reaction rate by β-CD	Colorimetric analysis	101
	Quantum dots	β-CD-ZnS-QDs-3-HF	PBS; pH 7.4	NR	0.4−1.4	0.084	NR	Membrane for immobilization of 3-HF	FRET	102
		N,Fe-CQDs in the presence of GOx enzyme and TMB	PBS; pH 7.0	NR	0−60; 60−100	3	NR	Increasing the catalytic rate by β-CD	Colorimetric method	103
		QDs-ConA/β-CD-TRITC	PBS; pH 7.4	NR	0−27.75	NR	180−480	The assay is based on the competition between β-CD and glucose toward ConA	FRET	104
	Metal−organic framework	MOF-235/β-CD/GOx enzyme	Human serum	NR	0.01−3	0.01	NR	Catalytic role	Chemiluminescence	105
	Carbon nanotubes	SWCNTs/adamantine/β-CD AuNPs tagged with GOx enzyme/Pt electrode	PBS; pH 7.0	31.02	NR	NR	NR	Intermediate layer between adamantine and GOx	Cyclic voltammetry	106
		CNT-CDP/GOx enzyme−GCE	PBS; pH 5.6−7.8	21.6	0.004−3.23; 4.26−10.00	3.5	NR	The film for immobilization of CNT and GOx enzyme	Cyclic voltammetry	107
		Si_3N_4/SWCNT/pyrene-adamantane (dip-coat-	PBS; pH 7.0	14.4	$2 \times 10^{-4} - 1.6$	*NR*	20−37	The film for immobilization of adamantane and GOx enzyme	Cyclic voltammetry	108

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Table 1. continued

CD-modified/functionalized		Sensor name	Medium; pH	Sensitivity ($\mu A \cdot mM^{-1}\ cm^{-2}$)	Linear range (mM)	Detection limit (μM)	Response time (s)	CD roles	Detection techniques	Ref
		ing)/β-CD-GOx/Pt electrode								
		GOx/β-CD-SWCNTs/CTAB/GCE	PBS; pH 7	NR	1.87−12.87	484	NR	The film for immobilization of SWCNTs and GOx enzyme	Cyclic voltammetry	109
		SWCNT scaffolds/β-CD-GOx enzyme/Pt electrode	PBS; pH 7.0	3.0	NR	NR	5−30	NR	Amperometry	110
		Pt-MWCNTs/pyAd/β-CD-GOx	PBS; pH 7.0	1.41	5−110	NR	NR	Intermediate layer between adamantine and GOx enzyme	Cyclic voltammetry	111
		GCE/MWCNT/Fe_3O_4/PDA/β-CD-GOx	PBS; pH 7.4	115.74	1−26	1.55	NR	β-CD increases the immobilization and stability of GOx	Cyclic voltammetry	112
		GOx/β-CD/MWCNT/GCE	PBS; 7.0	35.44	0.05−1.15	0.27	NR	Provided more fixed sites for the adsorption of enzyme molecules	Cyclic voltammetry	113
		Fe_3O_4-CS−β-CD/MWCNTs/GOx/GCE	PBS; pH 7.0	23.59	0.04−1.04	19.30	NR	Intermediate layer between MWCNTs and GOx enzyme	Cyclic voltammetry	114
	Graphene	rGO/β-CD/GOx enzyme/GCE	PBS; pH 7.0	59.74 8.99	0.05−3.0 0.01−14.55	12.0 1.2	NR	Intermediate layer between rGO and GOx enzyme	Cyclic voltammetry Amperometry	115
		β-CD/rGO/GCE	NaOH solution	NR	0.001−8	0.4	NR	The film for immobilization of rGO	Cyclic voltammetry	116
		AuNPs and β-rGO/GCE	NaOH solution	327.79	0.01− 1.57	8	NR	β-CD used as capping agents	Cyclic voltammetry	117
		Au and rGO and β-CD/GCE		126.42	0.0985−2	2				
		AuNPs- β-CD-Gr/GCE	NaOH solution	NR	0.00004−3	≤0.01	NR	Acts as reducing agent and capping agent for the Au-Gr/AgGr	Cyclic voltammetry	36
		AuNPs-α-$Ni(OH)_2$/β-CD−rGO/GCE	NaOH solution	559.31 327.2	0.0025−0.1525 and 0.1525−2.0825	0.3	NR	β-CD prevents the reaggregation of rGO to improve their water solubility and dispersivity	Cyclic voltammetry	118
		GOx-β-CD/AgNPs@rGO/GCE	PBS; pH 7	2.01	0.305−5.805	101	6	β-CD is reducing rGO and AgNPs, and providing biocompatible microenvironment for immobilization of GOx enzyme	Cyclic voltammetry	39
		GOx-Fc-CD/AgNPs@rGO/GCE	PBS; pH 7	3.425	0.105−11.805	35	6			
Polymer	Hydrogel	PVA/β-CD/GOx enzyme/GCE	PBS; pH 7.4	7.58	1−5	514.1	NR	β-CD is providing biocompatible microenvironment for immobilization of GOx	Cyclic voltammetry	119
	Nanofiber	Cellulose/β-CD/GOx	PBS; pH 7.4	5.08	0−1	93.5	<3	β-CD acts as an electron shuttle mediator between electrode and GOx	Cyclic voltammetry	120
		PVA/BTCA/β-CD/GOx/AuNPs NF/Carbon electrode	PBS; pH 7.4	47.2	0−0.5	1×10^{-4}	<15	β-CD is providing biocompatible microenvironment for immobilization of GOx	Ccyclic voltammetry	121
	Microneedle	Pt-b/*o*-phenylenediamine/sulfonated-β-CD/GOx enzyme	PBS	0.00275	0.5−19.5	170	NR	NR	Amperometry	122
	Glyconano particles	Copolymer/GNPs/GOx-Ad/Pt electrode	PBS; pH 7.0	3.3 ± 0.2	0.084−72.1	84	NR	Intermediate layer between GNP and GOx-Ad	Voltammetry	123
		Copolymer/$(GNPs/GOx\text{-}Ad)_2$/Pt electrode		2.5 ± 0.2	0.068−100.6	68				
Sensing phase		GOx enzyme/α-CD sensing phase	pH 5.1	NR	1−50	NR	120	α-CD increases sensitivity	IR-ATR	29

[a]PBS: Phosphate-buffered saline. NR: not reported.

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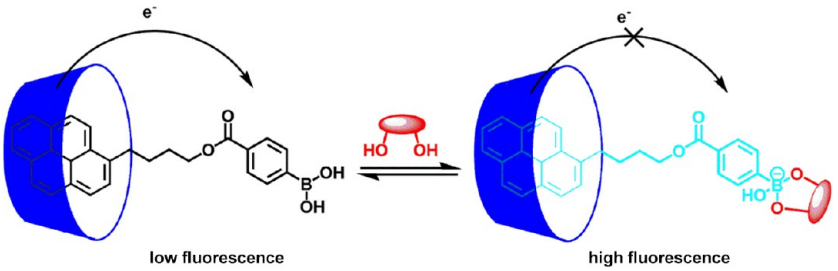

Figure 3. Schematic illustration of the boronic acid fluorophore/β-CD complex response mechanism for sugar binding.

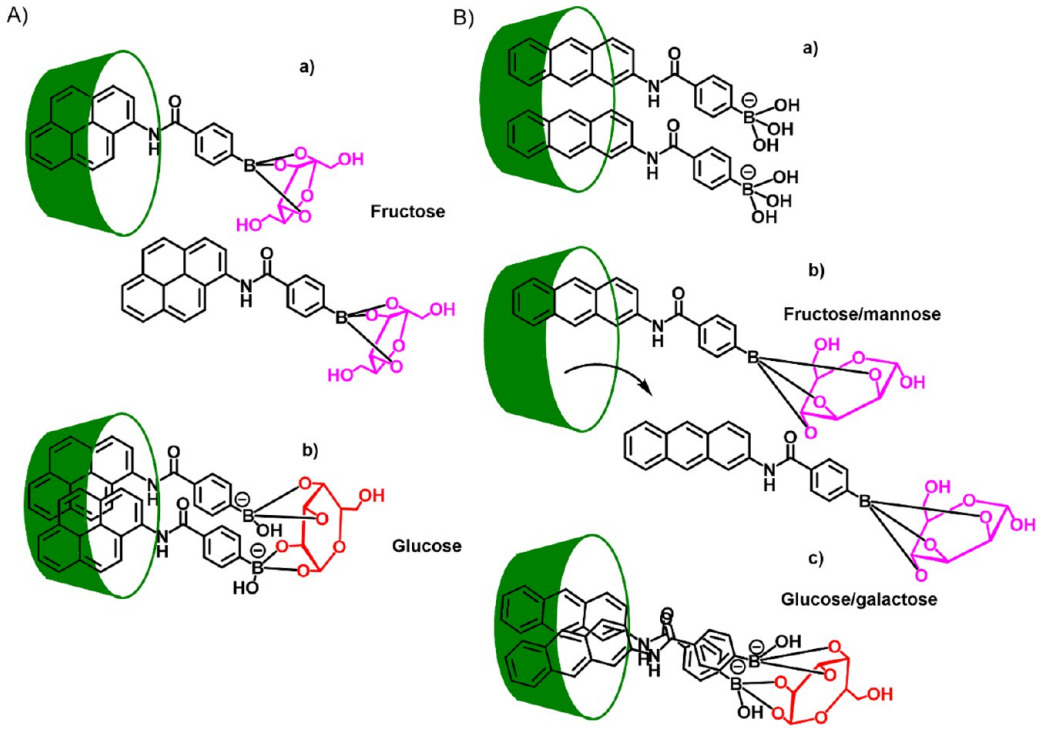

Figure 4. Proposed schematic illustration of (A) the structures of inclusion complexes of pyrene-based fluorescent probe/γ-CD with (a) fructose and (b) glucose and (B) structures of the inclusion complex of anthracene-based fluorescent probes (a) with/without sugar, (b) with fructose/mannose, and (c) with glucose/galactose.

systems, as summarized in Table 1. For example, Tong et al., in 2001, designed a complex of boronic acid fluorophore/β-CD and evaluated it as a sensor for the recognition of sugar in water.[77] The boronic acid bearing pyrene scaffold as a fluorescent signal transducer did not display light emission because of its accumulation in water containing DMSO and its self-quenching process. However, the fluorescence intensity turned on when the β-CD was present in this solution, and an inclusion complex of the boronic acid fluorophore was formed with β-CD. This complex showed a great fluorescence emission response over a sugar binding at pH 7.5. The selectivity and binding ability of the boronic acid bearing pyrene/β-CD complex for monosaccharides in water were: D-fructose $\gg$ L-arabinose > D-galactose > D-glucose. The observed trend is related to the phenylboronic acid binding selectivity. Therefore, the main mechanism in this contribution is the photoinduced electron transfer (PET) response that is revealed through the photochemical properties of the complex and studied by spectroscopic methods. This intramolecular PET response is initiated from the donor, pyrene, to the acid form of the acceptor, the phenylboronic acid derivative, in the inclusion complex; accordingly, sugar binding induced the proton dissociation of phenylboronic acid, inhibiting the PET system while enhancing the fluorescence intensity (Figure 3).

The above study found that the complex of boronic acid fluorophore/β-CD for sugar binding lacked selectivity for glucose. However, James et al. addressed this issue in their work by utilizing a diboronic acid compound for the selective detection of glucose. The diboronic acid compound was able to achieve this selective detection by recognizing the two 1,2-diol moieties of glucose through the two boronic acid moieties present in the compound.[78] In a similar way, γ-CD revealed an improvement in the selectivity of glucose binding by forming a 2:1 inclusion complex with a boronic acid fluorophore because of its larger cavity size compared to β-CD. In this regard, Hashimoto et al. designed a fluorescent probe based on the inclusion complex of γ-CD and pyrene- or anthracene-substituted phenylboronic acid to form a complex with sugars.[79] This study investigated the structural effects of selective glucose recognition in a DMSO−water mixture. The study used pyrene- and anthracene-type probes to observe the response of the system to different sugars. The pyrene-type probe showed no response to fructose and only one response in the presence of γ-CD and glucose. On the other hand, the

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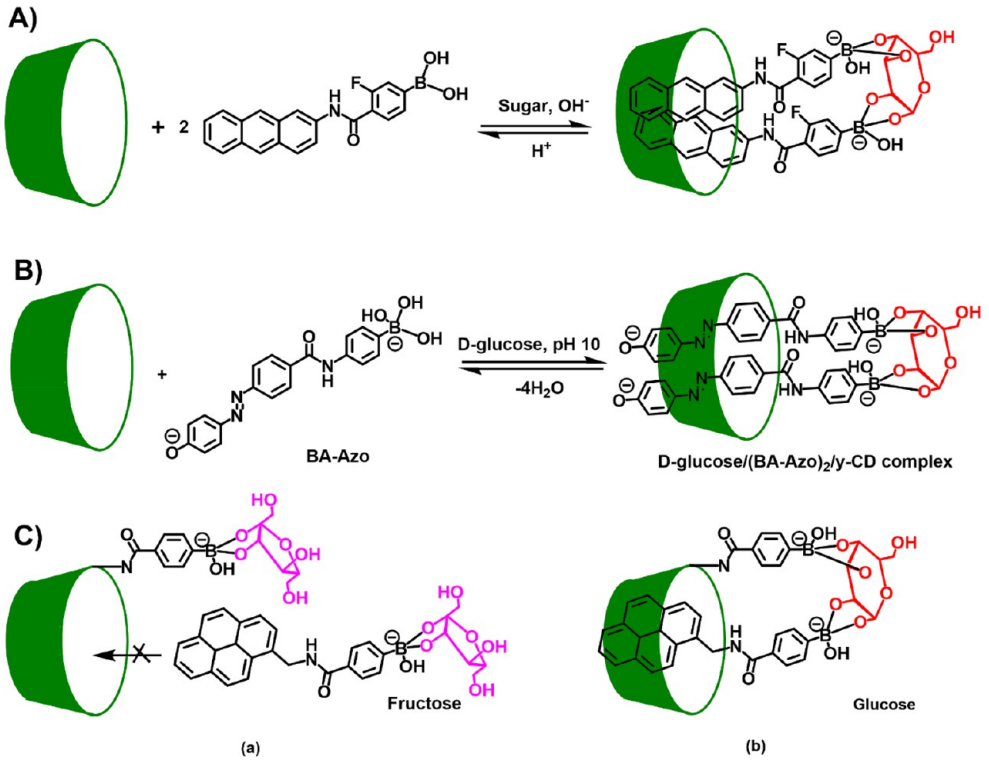

Figure 5. Proposed schematic illustration of (A) the formed 2:1 inclusion complex of BA-Azo/γ-CD in the presence of D-glucose, (B) the formed inclusion complexes of the 3-fluorophenylboronic-acid-based anthracene-type probe /γ-CD, and (C) the sugar recognition with the C1-APB/3-PB-γ-CD, (a) fructose, and (b) glucose.

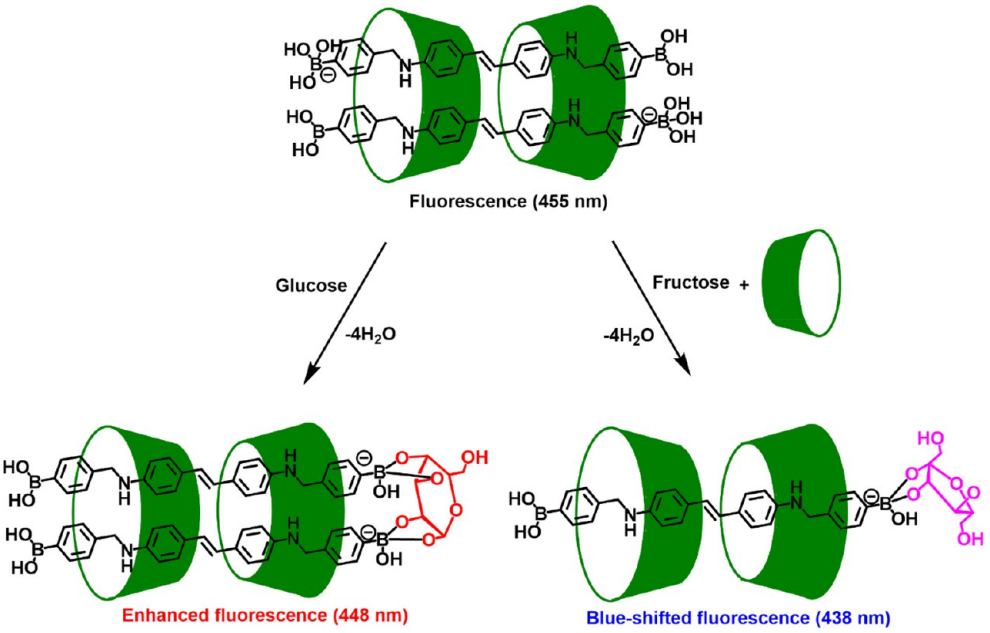

Figure 6. Proposed schematic illustration of the interaction of a 2:2 STDBA−γ-CD inclusion complex with fructose and glucose.

anthracene-type probe showed dimer fluorescence in the presence of both galactose and glucose, but not with fructose. These differences in responsivity were attributed to the interaction between the CD cavity and fluorescent site, as depicted in Figure 4. However, it should be noted that this sugar recognition mechanism was limited to alkaline pH conditions and therefore may not be suitable for glucose determination in biological or biorelated systems.[79]

Interestingly, in another work, the phenylboronic acid azoprobe (BA-Azo)/γ-CD complex with different spacers was prepared and used to evaluate the effect of the spacer types on the selectivity of biosensors for D-glucose recognition in water.[80] Similar to the previous examples, the sensor prepared from the formation of a 2:1 inclusion complex between azoprobes and γ-CD in the presence of D-glucose (Figure 5A) displayed that the specific spacer along with γ-CD greatly

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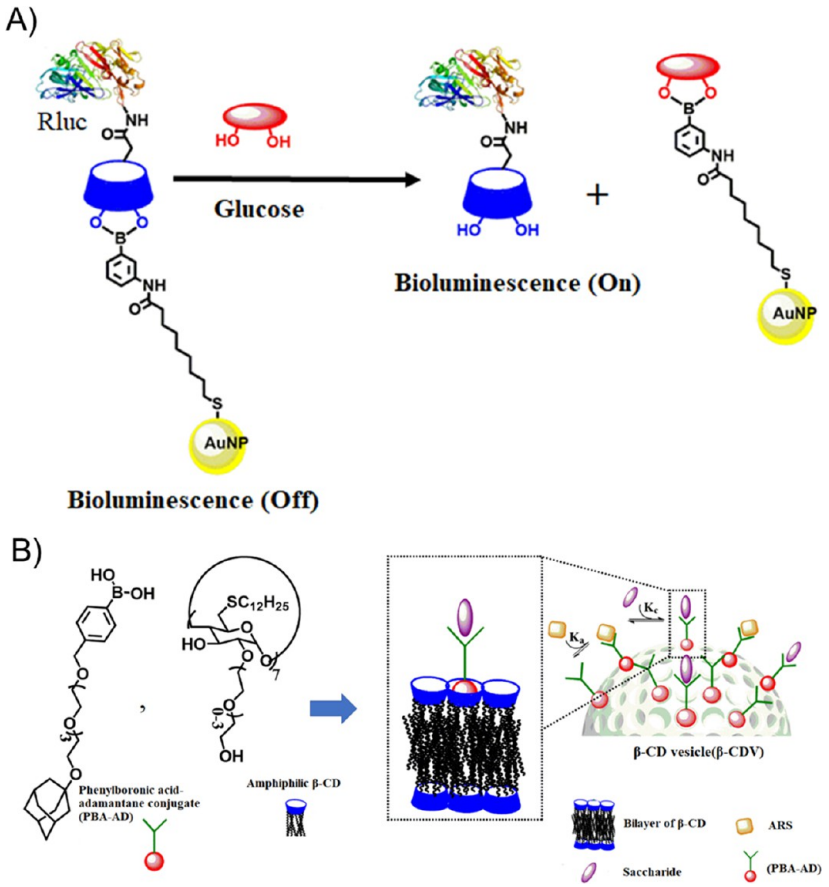

Figure 7. (A) Schematic representation of the glucose sensor based on bioluminescence quenching. (B) Schematic representation of the PBA-AD that is attached to the β-CD amphiphile (β-CDA) bilayer construction in aqueous solution via host−guest interactions and the competitive binding with ARS.

affected the D-glucose selectivity. The inclusion complex with different spacers, BA-Azo and B-Azo that do not have benzamide in their structure, revealed that only BA-Azo exhibited D-glucose selectivity in water at pH 10. To improve the GM system performance, Sugita et al. synthesized the 3-fluorophenylboronic-acid-based anthracene-type probe as a PET-type fluorescence glucose sensor to increase the Lewis acidity of the boronic acid moiety. In the proposed mechanism, the boronic acid moieties bind with glucose at physiological pH, and at the same time, an inclusion complex is formed when the fluorine groups are inserted into the γ-CD cavity (Figure 5B). The sensor generates fluorescent signals inside the cavity of γ-CD through the formation of the supramolecular 2:1 inclusion complex of a 3-fluorophenylboronic-acid-based anthracene-type probe with glucose in water.[81] In another study, the inclusion complex of a boronic acid fluorophore (C1-APB) with boronic-acid-functionalized γ-CD (3-PB-γ-CD) has been considered for improving the selectivity of glucose recognition in water.[82] Results showed that 3-PB-γ-CD enhanced the selectivity of glucose recognition in water through the formation of the stable inclusion complex with both a fluorophore and a boronate glucose complex (Figure 5C). The order of the response selectivity for the C1-APB/3-PB-γ-CD complex was glucose ≫ galactose and mannose > fructose at pH 8.5. Also, the pH-dependent fluorescent response revealed that a complex solution containing glucose and C1-APB/3-PB-γ-CD exhibited a higher intensity at physiological conditions at pH 8.5.

In another interesting research work, hydrophobic stilbeneboronic acid (STDBA) which can form an inclusion complex with the γ-CD cavity succeeded in demonstrating a sensitive and selective response toward glucose in water via a fluorescent 2:2 STDBA−γ-CD inclusion complex (Figure 6). In fact, this complex showed a higher affinity for glucose in comparison with fructose due to its specific recognition. The authors described that in artificial urine samples the prepared system could suitably detect glucose in the range of 0.1 to 10 mM without any other monosaccharide interferences.[83]

In recent research, Suzuki et al. presented a novel approach utilizing 1:2 stoichiometric inclusion complexes of γ-cyclodextrin with two molecules of fluorescent monoboronic-acid-based receptors for glucose recognition in water.[84] The resulting complexes exhibited strong selectivity and sensitivity toward D-glucose, with limits of detection of 1.1 and 1.8 μM for 1F/γ-CyD and 2N/γ-CyD, respectively. Additionally, the complexes demonstrated chiral-selective recognition of D-glucose, making them promising candidates for glucose sensing applications. In a separate study, the Tong research group developed a glucose-responsive bigel actuator for GM by employing a novel system with 3-acrylamidophenylboronic acid (AAPBA) as a glucose-sensing moiety.[85] The strategy utilized β-CD and ferrocene (Fc) portions in the guest and host gels to develop new bigel actuators capable of producing switches, artificial muscles, and remote controls. They fabricated a bigel strip using a polyacrylamide-based hydrogel functionalized with AAPBA and β-CD (AAPBA-CD) as the

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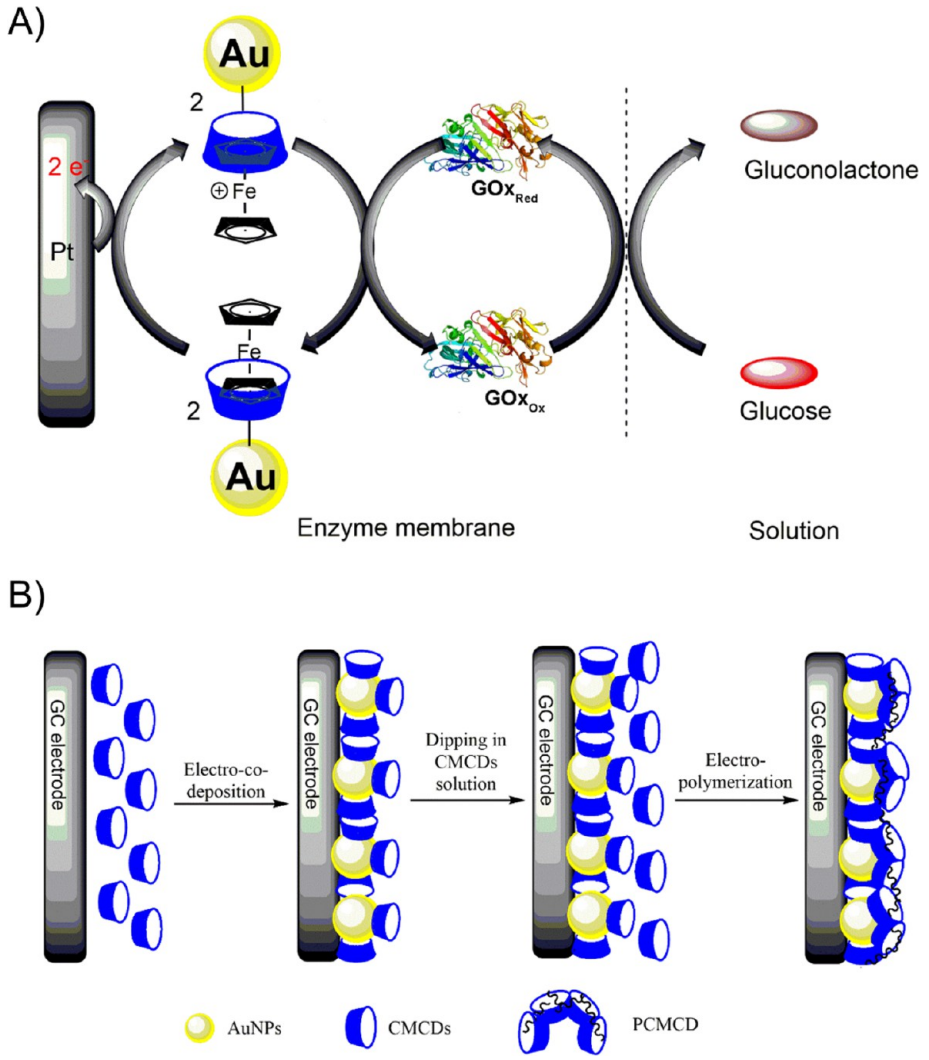

Figure 8. (A) Schematic representation of the glucose sensing mechanism for the modified platinum electrode surface by GNPs/CD-Fc/GOx. (B) The preparation of the Au-CMCD and Au-CMCD/PCMCD electrodes and current changes of the electrodes to (1) 0.1 mM glucose and 0.1 mM glucose in the presence of 0.1 mM (2) dopamine, (3) tyrosine, (4) guanine, (5) thymine, (6) folic acid, (7) glycerol, (8) ascorbic acid, (9) uric acid, (10) chloramphenicol, (11) fructose, (12) galactose, and (13) mannose, respectively.

host gel and a polyacrylamide-based hydrogel functionalized with ferrocene (PAM Fc) as the guest gel. Altering cross-linking and glucose concentration tuned the bending behavior of the bigel strip, demonstrating a large bending angle and fast bending ability that can serve as a glucose-sensing switch for GM. This work provides a systematic and efficient approach for the development of glucose-responsive bigel actuators.

Fluorescence-based detection methods require an external energy source, which can limit their application in in vivo genetic modification (GM) systems. Bioluminescent materials offer a promising alternative to overcome this drawback by providing responsiveness without the need for an external energy source. In 2020, Chen et al. developed a noninvasive and quick glucose nanobiosensor using bioluminescent proteins derived from invertebrates, marine vertebrates, or fireflies.[28] They functionalized luciferase bioluminescence protein (Rluc) with β-CD and covalently bonded it to AuNPs. β-CD facilitated the formation of a complex between Rluc and boronic acid functionalized AuNPs via a boronate complex. The presence of glucose restored the bioluminescence intensity of Rluc by replacing it with Rluc-β-CD. The sensor exhibited a detection limit of 1 μM for glucose measurement in the blood of diabetic rats, which was very close to the results obtained in an aqueous medium (Table 1). These findings demonstrate the potential of bioluminescent materials as an effective strategy for developing glucose biosensors for in vivo GM applications.

In continuing efforts for the construction of a new nonenzymatic glucose detection based on the green colorimetric method, Nair and Sreenivasan used an inclusion complex of β-CD stabilized AuNPs with 4-cyanophenylboronic acid (CPBA) to detect the glucose in aqueous solution.[86] Table 1 shows that the reported chemosensor has a suitable analytical response and could determine the glucose concentration in the range of 1−20 mM even in evaluating a real biological matrix, human blood serum. Indeed, β-CD can improve the low solubility of CPBA in aqueous media for the selective and sensitive colorimetric detection of glucose. In the presence of glucose, the plasmon absorption peak shifted, and an obvious color change was observed from red to blue. This phenomenon is due to the aggregation of the prepared chemosensor in the presence of glucose.

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The system based on self-assembled vesicles of the unilamellar bilayer of amphiphilic β-CD decorated with boronic acid was also evaluated as a glucose sensor (Figure 7B).[87] In this system, the heterobifunctional linker containing phenylboronic acid and adamantane (PBA-AD) which can act as a synthetic lectin formed an inclusion complex with adamantane β-CD at the surface of vesicles. The boronic-acid-based sensor prepared in this study employed alizarin red S (ARS) as a reporter molecule for glucose monitoring. ARS exhibited fluorescence emission when it was bound to PBA and was absorbed at 530 nm when it was free. ARS competed with saccharides, and in the presence of D-glucose or D-fructose, the ARS−PBA complex was disrupted, resulting in the release of ARS (i.e., a dye displacement assay). The results indicated that the system behavior was pH-dependent (pH 7.4−10.1), with a binding constant (K_c) in the range of 5−400 M^{-1} for glucose (Table 1) and a K_c ranging from 100 to 3000 M^{-1} for D-fructose.

2.2. CD-Modified Mediator. The performance of amperometric biosensors that utilize oxidase enzymes is reliant on their surface immobilization on electrodes. Due to the deep location of enzyme active sites within the protein, the electron transfer efficiency of redox enzymes is weak without a mediator. Immobilization of mediators within the electrode matrix has been found to notably enhance biosensor sensitivity.[124,125] Various mediators, such as ferrocene, its derivatives, ruthenium complexes, tetrathiafulvalene, and 1,4-benzoquinone, have been shown to be efficient electron transfers for glucose oxidase (GOx) enzymatic reactions.[40,126,127] However, mediator leakage is a significant problem due to the low molecular weight of the electrode substances. Covalent conjugation of mediators with polymers or various materials prior to surface immobilization on the electrode is a suitable approach to overcome this issue.[128] The production of inclusion complexes with cyclodextrins (CDs) can improve the efficacy of mediators such as ferrocene and its derivatives as well as enhance their stability. Several studies have been conducted to investigate the interactions of CD-modified mediator systems and their performance.

In 1993 and 1994, Groom et al. and Luong et al. used the DMFc/HP-β-CD complex for immobilization of the GOx to develop a homogeneous voltammetric biosensor system for glucose detection.[89,129−131] This complex was effective for glucose determination in beverage and food samples. In 1997, for online GM, a flow injection biosensor system was established during mammalian cell cultivation. In this work, immobilized GOx was employed with a water-soluble mediator DMFc/HP-β-CD inclusion complex to monitor glucose, which showed great stability and reproducibility.[30]

In 1998, an amperometric glucose biosensor was developed by immobilizing GOx in β-CD via cross-linking, followed by including Fc in the cavity of β-CD by a host−guest interaction.[90] The stability of the enzyme was significantly improved due to the water absorbability of the β-CD. Besides, this structure shortens the distance between the redox centers of GOx and Fc, an electron transfer mediator, and thus accelerates the electron transfer between the redox centers of the enzyme and electrode. Accordingly, the biosensor exhibited high sensitivity and a fast response to glucose. Chen and Diao described an amperometric glucose biosensor based on GOx and an inclusion complex of mono-6-thio-β-CD (SH-β-CD)/Fc immobilized on gold NPs (AuNPs/CD-Fc).[92] The GNPs/CD-Fc/GOx-modified electrode (Figure 8A) can diminish the leakage of Fc and enhance the stability and reproducibility of the GOx-based biosensors. Thus, the GNPs/CD-Fc/GOx biosensor demonstrated excellent stability, anti-interference ability, and a long natural lifespan, along with a low detection limit, high sensitivity, and relatively fast response time (5 s) within the linear range of glucose. The biosensor's performance was further enhanced by the inclusion complex of SH-β-CD/Fc as an artificial electron mediator, which facilitated electron transfer between GOx and the electrode, reducing the operating potential by 0.25 V and improving the sensitivity and selectivity for glucose. The effectiveness of the biosensor was validated through amperometric and cyclic voltammetry measurements, as summarized in Table 1.

In another study for the fabrication of the new GM system, Choi et al. developed an electrochemical glucose sensor using a CD-based self-assembled monolayer formed on a Au electrode as a molecular template. The α-CD was chosen due to its ability to fit glucose molecules into its cavity and compete well with the Fc mediator to form an insertion complex.[132] Forrow et al. demonstrated that both manganese and chromium half-sandwich complexes are efficient mediators for GOx and are comparable to Fc. The higher efficiency of these half-sandwich mediators is attributed to their relatively high stability in aqueous media and smaller molecular size in comparison to Fc, enabling them to penetrate the enzyme's active site. Moreover, the presence of a single π-ligand allows for effective interaction with the flavin cofactor. β-CD was found to form hydrophobic host−guest complexes with the half-sandwich mediator, permitting electrochemical analysis in aqueous media while protecting the electrode from fouling with the insoluble oxidized agent. The carbon electrodes incorporating GOx and a hydrophobic half-sandwich mediator exhibited excellent responses to glucose.[133]

In another work for designing glucose sensors, a "second-generation" amperometric glucose was fabricated as a highly permeable film constructed α-CD polymer (α-CDP). GOx was covalently immobilized on the membrane, but tetrathiafulvalene (TTF) or a 1,4-benzoquinone (BQ) mediator was incorporated by the host−guest interaction with α-CD sites. Then a simple one-step procedure was developed for surface casting of a membrane onto a substrate such as gold, glassy carbon, or a platinum disk. The performance of the prepared glucose sensor was favorably operated at a low potential bias. Results approved that the linear dynamic range and sensitivity of the sensor can be adjusted by incorporating the enzyme and/or mediator.[88] In another interesting research work, Kosela et al. used Ru/poly(pyridyl) complexes as non-physiological charge mediators of "second-generation" GM.[93] The membranes for the biosensors were fabricated through the direct casting of the anionic carboxymethylated β-CD polymer films onto glassy carbon (GC) or Pt disk electrodes. GOx was simultaneously immobilized by covalent bonding in the films. The Ru complexes were generated both by ion exchange at the carboxymethyl ion-exchange sites and by inclusion in the β-CD cavities. This complexation minimizes mediator leakage from the polymer matrix and eliminates the oxygen-dependent response in the solution. Besides, the employment of Ru complexes immobilized on carboxymethylated β-CD polymer films as a GM system gave some advantages in the sensor such as great sensitivities for a high linear range, lack of interference at their physiological concentrations (ascorbate, paracetamol, and urea), and response reversibility.

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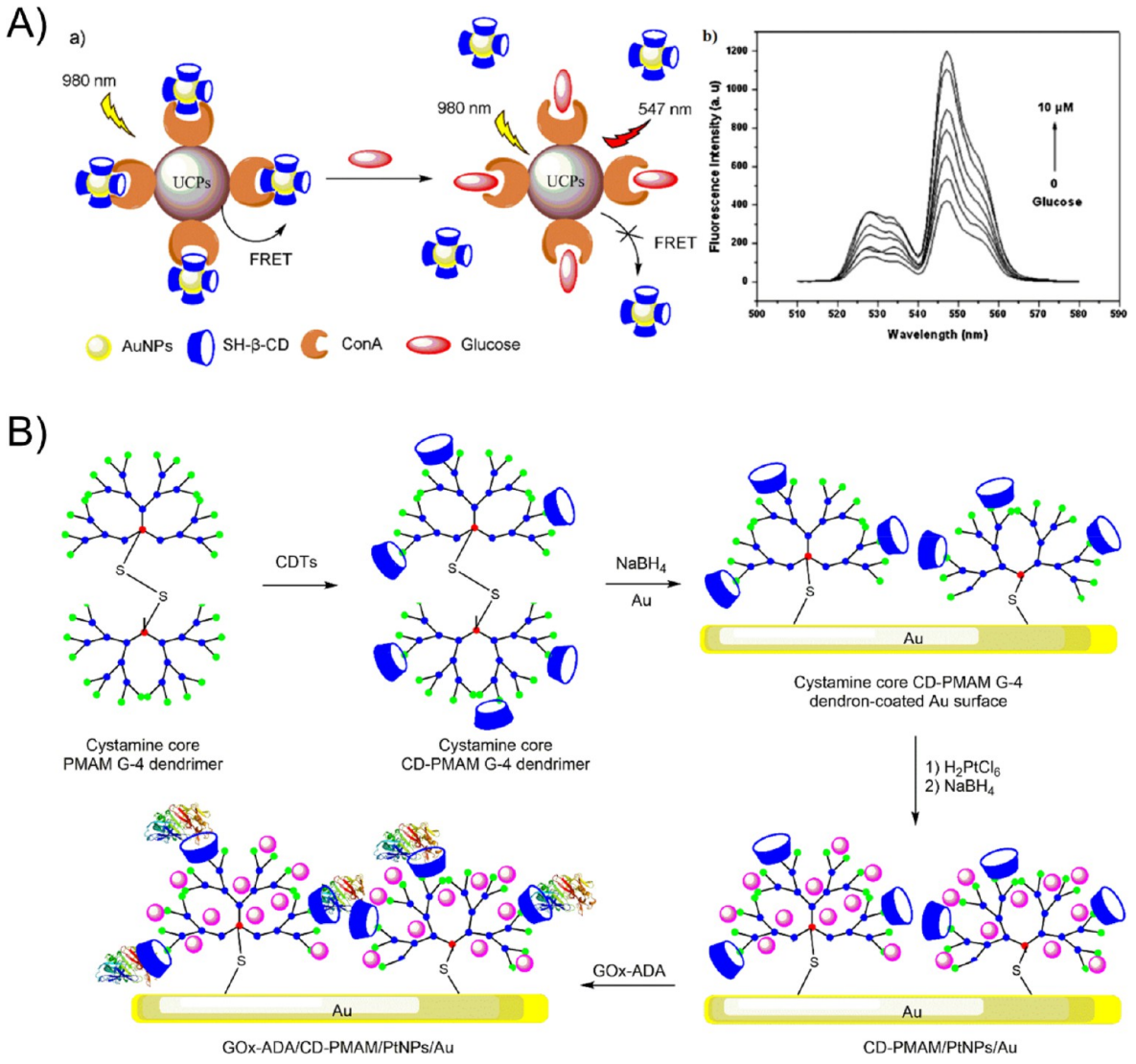

Figure 9. (A) Schematic illustration of the UC-FRET glucose biosensor mechanism. Reprinted with permission from ref 95. Copyright 2011 Elsevier. (B) Schematic illustration of the GOx-ADA/CD-PAMAM/PtNP/Au-based glucose biosensor electrode fabrication.

2.3. CD-Modified Nanomaterials. In recent years, there has been a growing interest in the use of nanomaterials to enhance detection capabilities.[134−136] This is due to their high surface area, which allows for greater enzyme immobilization and improved electron transfer rates between the active centers of enzymes and the surface. Nanomaterials such as metal NPs, 2D graphene, quantum dots (QDs), and metal−organic frameworks (MOFs) have been found to improve glucose detection, particularly in conjunction with glucose oxidase (GOx).[137] Furthermore, the use of advanced nanocomposites as electrode materials has shown promise in enhancing the synergistic effects of high surface area, conductivity, and catalytic activity. Numerous research studies have recently focused on nanocomposites based on cyclodextrins (CDs) for use in glucose-monitoring (GM) applications, which are summarized in Table 1. These studies suggest that CDs, as key materials, can effectively enhance the solubility, stability, and biocompatibility of nanomaterials. Additionally, CDs can improve the selectivity and sensitivity of nanobiosensors, making them highly useful in GM. This paper reviews and discusses the recent advances in the field of CD-modified and -functionalized nanomaterials as glucose biosensors, highlighting the productivity of CD-modified nanomaterials in GM (Figure 1 and Table 1).

2.3.1. Gold. Gold nanoparticles (AuNPs) have attracted significant attention in sensor fabrication due to their unique chemical and physical properties.[138] They have been widely used as nanoplatforms for sensing various analytes thanks to their ability to immobilize biomolecules while retaining their activities. However, the nonselective electrocatalysis of AuNPs leads to poor selectivity and efficiency. To address this issue, the modification of AuNPs with auxiliary agents has been proposed to enhance their electrochemical behaviors and selectivity. Cyclodextrins (CDs) have been utilized as auxiliary agents for modifying AuNPs in genetic modification (GM) detection, including electrochemical, fluorescence, and colorimetric monitoring (Figure 1). Hui et al. proposed a simple method to construct an electrochemical electrode based on AuNPs, carboxymethyl-β-CD (CMCD), and poly-(carboxymethyl-β-CD) (PCMCD).[94] The Au-CMCD/PCMCD electrode was utilized by a two-step electrochemical method, coelectrodeposition of CMCDs and AuNPs followed by electropolymerization of CMCDs (Figure 8B). The prepared electrode showed high sensitivity and higher

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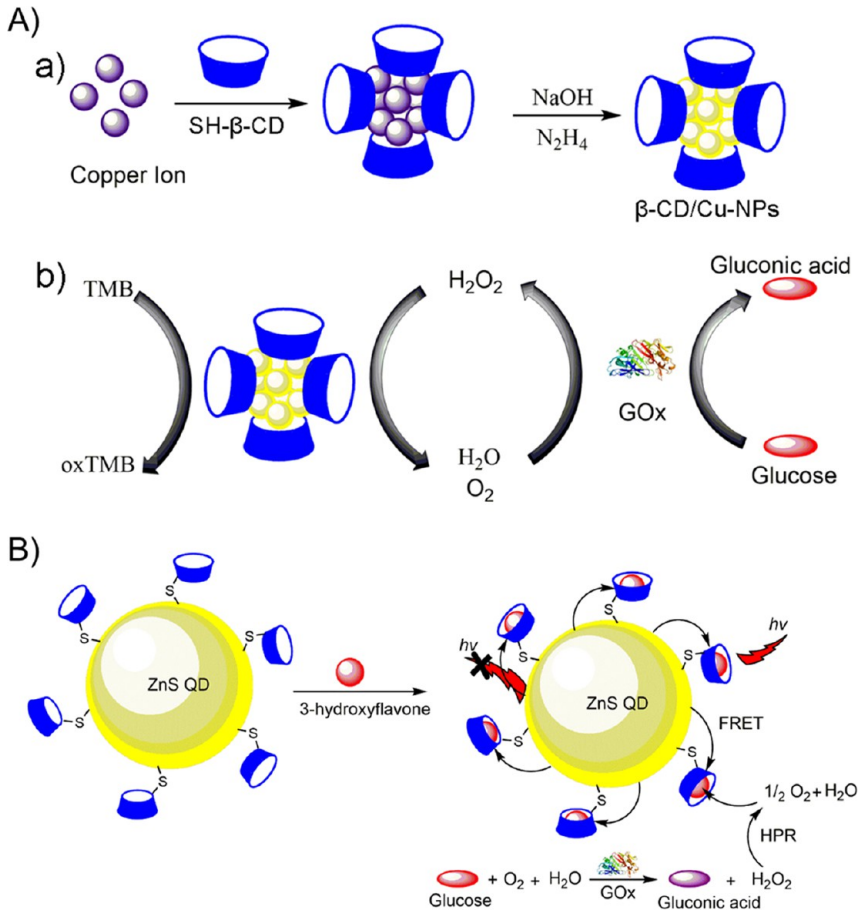

Figure 10. (A) (a) Schematic representation of the β-CD/CuNP synthesis and (b) colorimetric detection schematic for H_2O_2 and glucose. (B) Schematic representation of the GM mechanism by a fluorescent FRET system between 3-hydroxyflavone and β-CD/ZnS-QDs.

selectivity to glucose owing to the synergistic effect between Au-CMCD and PCMCD modified layers. The use of Au-CMCD/PCMCD has been shown to provide an extensive linear range and lower limit of detection for monitoring glucose under alkaline conditions (Table 1). This modification also demonstrated lower variations (~6.5%) in the presence of interfering species in glucose solutions compared to the Au-CMCD electrode (~28.2%).

SH-β-CD-functionalized AuNPs were used as the energy acceptor with upconverting phosphor (UCP, $NaYF_4$: Er, Yb) energy donors that were covalently labeled with Concanavalin A (ConA). This system has been developed as a glucose sensor based on upconverting fluorescence resonance energy transfer (UCFRET).[95] The combination between ConA and SH-β-CD/AuNPs results in quenching of the fluorescence of UCPs, which is due to the close proximity of the energy donor and acceptor. The structure of the UCPs-ConA-SH-β-CDs-Au biosensor was destroyed in the presence of glucose, and the energy donor was detached from the acceptor through adding competing glucose with SH-β-CD to the binding sites of ConA (Figure 9Aa). The fluorescence intensity of UCPs was altered, depending on the glucose concentration. The UC-FRET biosensor was also utilized to detect the amount of glucose in real human serum samples. Results indicated that the biosensor was directly capable of monitoring glucose without optical interference (Figure 9Ab).

2.3.2. Platinum. Platinum nanoparticles (PtNPs) have been extensively studied due to their exceptional electrocatalytic properties, which stem from their high surface area and energy.[139] As a result, several glucose sensors based on PtNPs have been developed.[140,141] However, these sensors have limitations in terms of selectivity, stability, sensitivity, and biocompatibility.[140,141] To address these concerns, the incorporation of CDs into these sensors could be an efficient way to improve their capability. Shang et al. modified a boron-doped diamond (BDD) electrode with CDs through electro-depositing PtNPs followed by a multipotential step deposition method to immobilize GOx.[97] The prepared stable enzymatic glucose biosensor showed a quick response with a low detection limit (Table 1). This is an interesting approach since the immobilization of enzymes can be controlled efficiently due to the contribution of film of poly(tyramine) and negatively charged sulfobutylether-β-CD (SBE-β-CD) that worked as an outstanding matrix polymer for the immobilization of the GOx with high selectivity, reproducibility, and stability. In another work, mediatorless glucose-oxidase-based amperometric glucose biosensors were prepared by surface modification of the Au with an inorganic−organic hybrid nanomaterial to stabilize PtNPs.[99] The rational strategy is based on the employment of a thiol-containing CD-modified polyamidoamine G4 dendron derivative (CD-PAMAM) as a stable and permeable surface-modifying agent for the electrode. β-CD moieties on the hyperbranched polymer not only acted as a molecular receptor for adamantane-modified enzymes (GOx-ADA) via the formation of host−guest supramolecular complexes but also can stabilize the PtNPs

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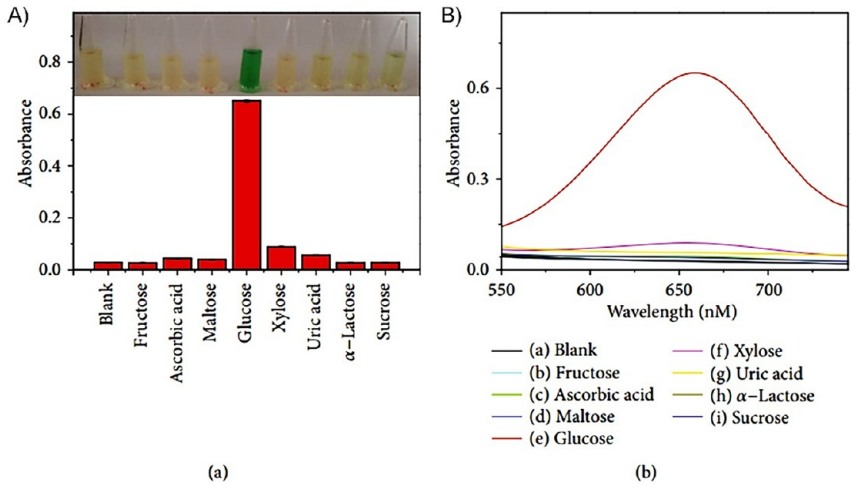

Figure 11. (A) Selectivity of N- and Fe-CQDs in the presence of different compounds and (B) the comparison of their absorbance intensity. Reprinted with permission from ref 103. Copyright © 2020. Yan Li et al. *Journal of Nanomaterials*.

(Figure 9B). The prepared inorganic−organic hybrid nanomaterial could catalyze the conversion of H_2O_2, accordingly constructing a third-generation GOx-based GM system.[99] The outcome showed that this glucose biosensor was highly selective, with a rapid electroanalytical responsivity, a low detection limit, and good sensitivity and stability.

Zhao et al. developed an inclusion complex film of PtCo alloy nanoparticles (NPs) and functionalized CD-ionic liquid (CD-IL) using the ultrasonic−electrodeposition method.[98] This film displayed excellent electrocatalytic performance for glucose oxidation in neutral solutions, without interference from other species, making it a promising candidate for nonenzymatic glucose monitoring (GM). The PtCo-CD-IL-modified electrode was also found to accurately detect glucose in urine and serum samples. In another study, Madden et al. utilized a two-step electrodeposition procedure to develop a microband biosensor that incorporated glucose oxidase onto a platinum-modified, gold microband electrode using an *o*-phenylenediamine and *β*-CD mixture.[100] The resulting enzymatic-based biosensor exhibited a linear response to glucose concentrations ranging from 2.5 to 15 mM in buffer-based solutions and was also effective in 30 μL volumes of fetal bovine serum. These studies demonstrate the potential of PtCo-CD-IL and microband biosensors for glucose monitoring in various environments. The electrochemical behavior of miniaturized electrodes on devices was also utilized in the studies, with electrochemical characterization performed at each step of the deposition process by cyclic voltammetry and electrochemical impedance spectroscopy.

2.3.3. Copper. Copper nanoparticles (CuNPs) have shown promise for biosensing applications due to their catalytic activity and electronic properties.[142] However, the preparation of highly stable and small CuNPs with the desired catalytic activity is challenging. To address this issue, nanocomposites with CDs have been developed. Zhong et al. utilized SH-*β*-CD as a template for synthesizing CuNPs and as a modulator to improve their peroxidase-like activity (Figure 10Aa).[101] *β*-CD was coated on CuNPs using hydrazine hydrate regent as a reductant, resulting in stable *β*-CD-coated CuNPs (*β*-CD/CuNPs) with an average diameter of 2 nm and strong fluorescence intensity. The prepared *β*-CD/CuNPs were used as a nonenzymatic photometric sensor for selective detection of glucose after the formation of H_2O_2 through glucose oxidase (Figure 10Ab). *β*-CD significantly improved the catalytic rate of CuNPs due to its cavity, which provided a template for substrate recognition and binding specificity similar to natural enzymes. Compared with natural enzymes, *β*-CD/CuNPs exhibited several advantages, such as low cost, ease of preparation, high activity, and good stability under severe conditions, making them a potential candidate for use as an enzymatic mimetic glucose sensor in clinical applications. Moreover, *β*-CD/CuNPs showed high specificity for glucose detection, as evidenced by a dramatic increase in absorbance, which could be observed by the naked eye.

2.3.4. Quantum Dots (QDs). Quantum dots (QDs), which are fluorescent semiconductor nanoparticles, have received significant attention in the sensor field due to their unique optical properties.[143] One of the ways to enhance their fluorescence efficiency is through fluorescence resonance energy transfer (FRET) between QDs as donors and chromophores as acceptors. This phenomenon has shown promising results in improving the response signals of the sensor for the detection of target molecules.[144] As a result, several glucose-monitoring systems based on QDs and the FRET mechanism have been developed.[145,146] However, determination of glucose via an environmentally friendly method still is a challenge. In this regard, Dong et al. used *β*-CD to develop fluorescent FRET probes with high stability, reproducibility, and sensitivity.[102] In this system, the natural pigment (3-hydroxyflavone) is also employed as an energy acceptor to interact with *β*-CD-functionalized ZnS quantum dots (*β*-CD/ZnS-QDs) as an energy donor. This phenomenon is followed by enclosing the 3-hydroxyflavone in the hydrophobic cavity of *β*-CD. Therefore, the fluorescence intensity of the pigment can be rapidly quenched in the probe by catalysis of the horseradish peroxide when glucose is oxidized by GOx to produce a small amount of hydrogen peroxide (Figure 10B). The results showed that the average spiking recoveries of glucose were from 102 to 113% with a standard deviation below 15% if the probe was used to determine glucose in human serum and urine samples (Table 1). Besides, the FRET probe showed a potential to detect glucose during an environmentally friendly process, so all components of this GM system were environmentally friendly and had low toxicity. This provided a new approach to the development of the fluorescent probe, which is selective and simple.

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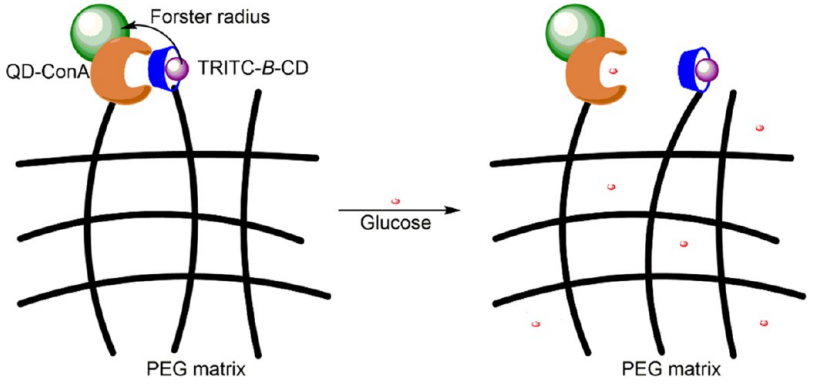

Figure 12. Illustration of a β-CD-based FRET glucose-monitoring system.

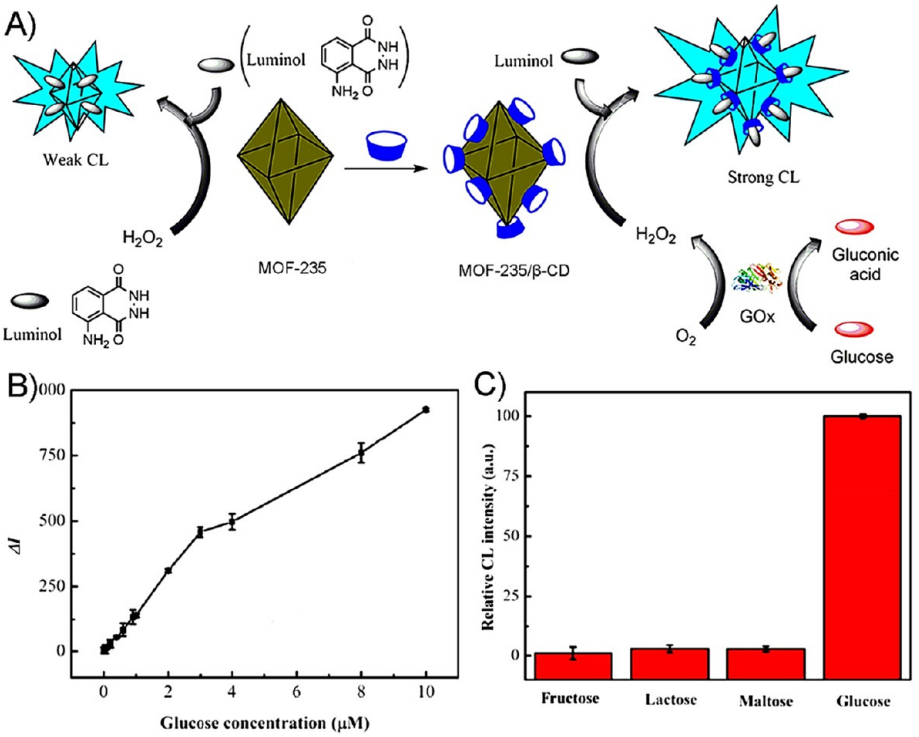

Figure 13. (A) Probable mechanism for chemiluminescence (CL) enhancement of the luminol–H_2O_2 system by MOF-235/β-CD hybrids. (B) The linear relationship between the concentration of glucose and net CL intensity under the optimized conditions. (C) Selectivity test for glucose detection by considering the relative CL intensity. Reprinted with permission from ref 105. Copyright 2018 Elsevier.

Li et al. synthesized N,Fe-codoped carbon quantum dots (N,Fe-CQDs) using β-CD, ferric chloride, and ethylenediamine through a convenient one-step green hydrothermal route.[103] The N,Fe-CQDs revealed higher catalytic activity in comparison with horseradish peroxidase (HRP), which produced an apparent color change in the presence of H_2O_2 for 3,3′,5,5′-tetramethylbenzidine. Therefore, efficient, sensitive, and selective colorimetric GM has been reported via the N,Fe-CQDs as simulated peroxidase to detect produced H_2O_2 as a result of glucose oxidation with GOx. Figure 11 illustrates the absorbance of the other compounds near the blank sample. Results revealed that this system has the desired selectivity for glucose with a 3.0 μM limit of detection (Table 1).

In another work, a family of disposable minimally invasive, fiber-optic sensors (SencilsTM, sensory cilia) developed based on QD-conjugated β-CDs can provide an in vivo GM possibility in a patient for several weeks. A transdermal optical fiber records a reliable spectroscopic determination of chemical reactions based on variations in FRET between fluorophores (QDs) conjugated to ConA (QDs-ConA) and tetramethylrhodamine isothiocyanate (TRITC)-labeled β-CD in a polymeric polyethylene glycol (PEG) matrix that conjugated to the end of the implantable fiber, QDs/β-CD/PEG. The mechanism of this system could be dependent on the good bioaffinity between Con A and different saccharides such as glucose and β-CD. On the other hand, β-CD-conjugated QDs are a reference FRET in this study, and replacement with glucose results in an alteration in the FRET (Figure 12). Developed optical fibers had all the desirable properties of medical devices, such as light weight, lower thickness, chemical stability, and biocompatibility. Besides, the fiber construction method is well organized and has attractive advantages for this application, for example, immunity to electromagnetic interference, low attenuation, high capacity, and intrinsic electrical isolation. In vitro studies revealed a precise and rapid correlation between the amount of glucose in saline at pH 7.4

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and two fluorescent emissions (response time: 180−480 s, Table 1). As well, the results of chronic animal implantation confirmed its good durability and biocompatibility for clinical applications.[104]

2.3.5. Metal−Organic Frameworks (MOFs). Metal−organic frameworks (MOFs) are a class of hybrid compounds formed through coordination bonding between metal ions and organic ligands.[147] MOFs have shown great potential as biosensors due to their remarkable chemiluminescence (CL) activity. However, the limited chemical stability of some MOFs in aqueous solutions has hindered their widespread application in CL analysis. To address this issue, researchers have explored the modification of MOFs with cyclodextrins (CDs). Mao et al. recently reported the development of stable MOF-235/β-CD hybrids through a simple coordination interaction between the hydroxyl groups of β-CD and unsaturated Fe(III) metal ions of MOF-235 (Figure 13A).[105] These hybrids showed higher catalytic activity than the H_2O_2-luminol system, resulting in over a 30-fold improvement in CL intensity. The synergistic interaction between MOF-235 and β-CD further enhanced catalytic activity. The MOF-235/β-CD hybrids were successfully employed for glucose determination in serum samples, demonstrating a low limit of detection, high sensitivity, and good reliability and stability (Table 1 and Figure 13C). This study highlights the potential of surface modification of MOFs with CDs for the development of efficient and stable biosensors.

2.3.6. Carbon Nanotubes (CNTs). Carbon nanotubes (CNTs) have garnered significant attention in the field of biosensing due to their potential in constructing three-dimensional (3D) nanostructured frameworks.[148,149] These 3D structures aim to improve biosensor sensitivity by increasing the density of the immobilized biomolecules. However, in biosensors utilizing CNTs, the accessibility to immobilized biomolecules is often limited due to the common preparation process. This process involves electropolymerization on CNT-modified electrodes with adsorbed coatings in the presence of biomolecules. As a result, there is a need to explore alternative approaches for immobilizing biomolecules on CNTs to overcome these limitations and enhance the performance of biosensors. To overcome this limitation, Holzinger et al. developed 3D frameworks based on single-walled carbon nanotubes (SWCNTs) by using adamantane/β-CD inclusion affinity.[106] First, they prepared a poly-(adamantane-pyrrole) film on the electrode surface via electropolymerization of the adamantane-pyrrole monomer, providing the moieties that can interact with β-CD to immobilize GOx. Then, the functionalization of SWCNT with poly(adamantane-pyrrole) generated the complexing ability to anchor GOx-modified β-CD. Besides, as the intermediate layer, AuNPs modified with β-CD were attached to the poly(adamantane-pyrrole)-functionalized SWCNT using this adamantane/β-CD inclusion affinity. Among these architectures, the β-CD-modified AuNPs as a linker for immobilizing GOx showed the highest sensitivity (31.02 mA M^{-1} cm^{-2}) and maximum current density (350 A cm^{-2}) (Table 1 and Figure 14). In conclusion, the immobilization of the proteins on the composition of SWCNT, polymer, and AuNPs through the adamantane/β-CD inclusion interactions provided a high specific surface area with outstanding availability.

Similarly, in 2010, a stable amperometric glucose biosensor was fabricated by dispersion of the CNTs in a mixed solution

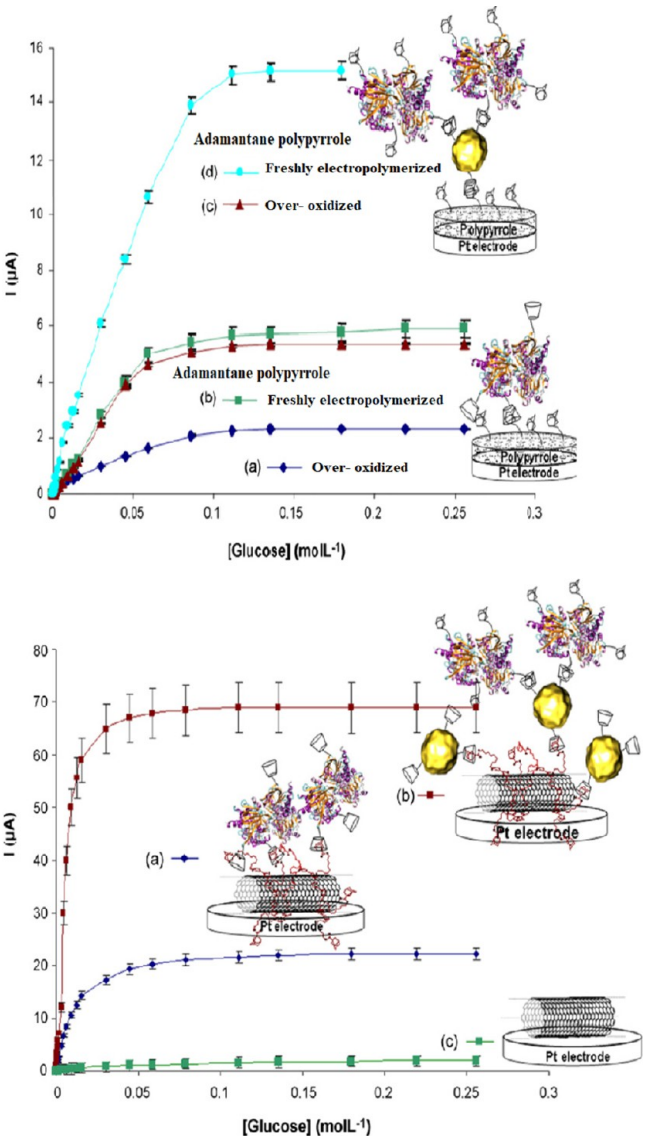

Figure 14. Structure of the prepared SWCNT electrodes and related standard calibration curves for glucose (applied potential of 0.7 V vs SCE, 0.1 M phosphate buffer, pH 7.0). Reprinted with permission from ref 106. Copyright 2009 Elsevier.

of β-CD, β-CD prepolymer (pre-β-CDP), followed by immobilization of GOx on the prepared β-CD/CNT composite film. In this system, β-CD not only can provide a large surface for loading of the mediator and enzyme but also maintain the bioactivity of immobilized GOx due to the biocompatibility of β-CD. The prepared glucose biosensor showed good sensitivity under a wide concentration range (Table 1). Moreover, the authors reported that the system could work without important variations in its sensitivity under a wide pH range (pH 5.6−7.8).[107] In another interesting research work, biological nanostructures based on host−guest interactions between β-CD-tagged GOx and poly(pyrene-adamantane)-functionalized SWCNTs were fabricated and deposited on platinum electrodes. This strategy allows the construction of the ultrathin films onto the SWCNT surface with exclusive contact to the underlying surface of the electrode. Table 1 shows that the constructed glucose biosensor exhibited a good linear response (2×10^{-10} − 0.16) with desired sensitivity (14.4 μA mM^{-1}).[108] A third-

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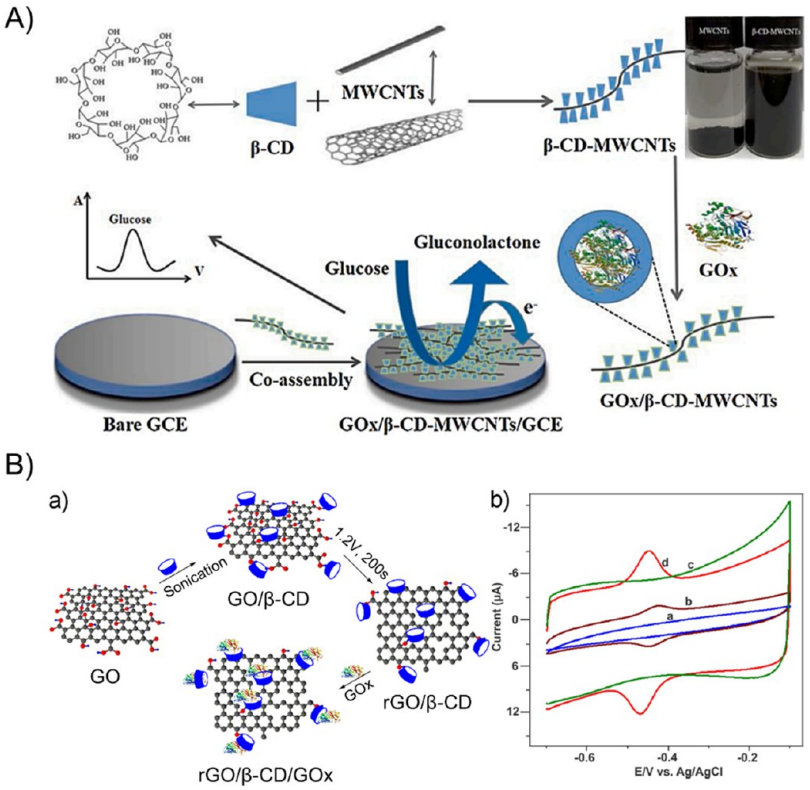

Figure 15. (A) Schematic illustration of the GOx/β-CD/MWCNTs/GCE fabrication. Reprinted with permission from ref 150. Copyright 2022 Elsevier. (B) Preparation of the rGO/CD composite as a glucose biosensor (a). The CV response of modified electrodes with blank CD (b-a), CD/GOx (b-b), rGO/CD (b-c), and rGO/CD/GOx (b-d) in the scanning range from −0.7 to 0 V. Reprinted with permission from ref115. Copyright 2015 Wiley-VCH.

generation glucose biosensor was also developed through immobilization of the GOx into covalently attached β-CD onto SWCNT (β-CD-SWCNTs)/cetyltrimethylammonium bromide (CTAB) composite film. This was utilized for the modification of a glassy carbon electrode (GCE) by a drop-casting method.[109] In this system, a direct electron transfer between the GOx and electrode was facilely attained due to the great electrical conductivity of CTAB and β-CD-SWCNTs. The developed glucose sensor exhibited good stability with a low detection limit and a wide linearity range (Table 1). Singh and co-workers also constructed 3D scaffolds with different pore sizes using SWCNTs and β-CD as sensor platforms. In this work, the glucose-based enzyme sensor was fabricated by immobilizing the biotinylated GOx (GOx-B) onto the 3D nanoscaffolds through the formation of a complex with pyrene-functionalized β-CD.[110] In the following research for the design and preparation of a new sensor for glucose detection, Kuznowicz and co-workers designed and constructed the novel β-CDs grafted onto magnetite/polydopamine (Fe_3O_4/PDA) thanks to the unique properties of magnetite, polydopamine, or β-CDs that enable the immobilization of enzyme. Then GO was immobilized on an Fe_3O_4/PDA/β-CD nanoplatform. Afterward, GC/MWCNT/Fe_3O_4/PDA/β-CD-Gox was developed. Results of glucose sensing showed a broad linear range (1−26 mM glucose), with sensitivity as high as 115.74 μA mM^{-1} cm^{-2}, and a limit of detection of 1.55 μM was achieved for GC/MWCNT/Fe_3O_4/PDA/β-CD-GOx. The fabricated long-term stable system showed excellent selectivity against uric acid, ascorbic acid, L-cysteine, and sugars, for example, maltose, saccharose, and fructose, which approve its suitability for sensing applications.[112] Glucose is the main portion that usually affects the honey taste. In view of this background, in 2022 a reproducible composite material of functionalized MWCNTs with β-CD (β-CD/MWCNTs) was fabricated, and then GOx was supported on it. The achieved GOx/β-CD/MWCNTs/GCE biosensor was used for glucose detection and determination of its concentration in honey. The schematic pathway of GOx/β-CD/MWCNTs/GCE construction for glucose sensing application is shown in Figure 15A. About 95.7% stability was observed after 2 weeks for the biosensor. Also, a linear response to the glucose concentration in the range of 50 μM∼1.15 mM, sensitivity of 32.28 μA mM^{-1} cm^{-2}, and the detection limit of 0.42 μM was obtained.[150]

2.3.7. Graphene. Graphene, a two-dimensional (2D) material consisting of a single layer of carbon atoms arranged in a chicken-wire pattern, has gained significant attention in various fields due to its exceptional properties.[45,151−154] It possesses impressive optical properties, mechanical strength, high electrical conductivity, and thermal conductivity. These unique properties have led to numerous applications including optoelectronics, energy storage, and sensing. In the field of biosensing, graphene has been utilized as an innovative electrode platform for glucose detection.[155] Reduced graphene oxide (rGO) has demonstrated superior electrochemical properties compared to other nanomaterials in many applications.[156,157] However, immobilizing redox proteins directly onto pure rGO is a challenging task due to the strong van der Waals forces between individual rGO sheets. This phenomenon presents significant obstacles in achieving a stable and efficient bioelectrochemical system, which is crucial for many applications in biosensors and bioelectronics. Therefore, various strategies have been developed to overcome this

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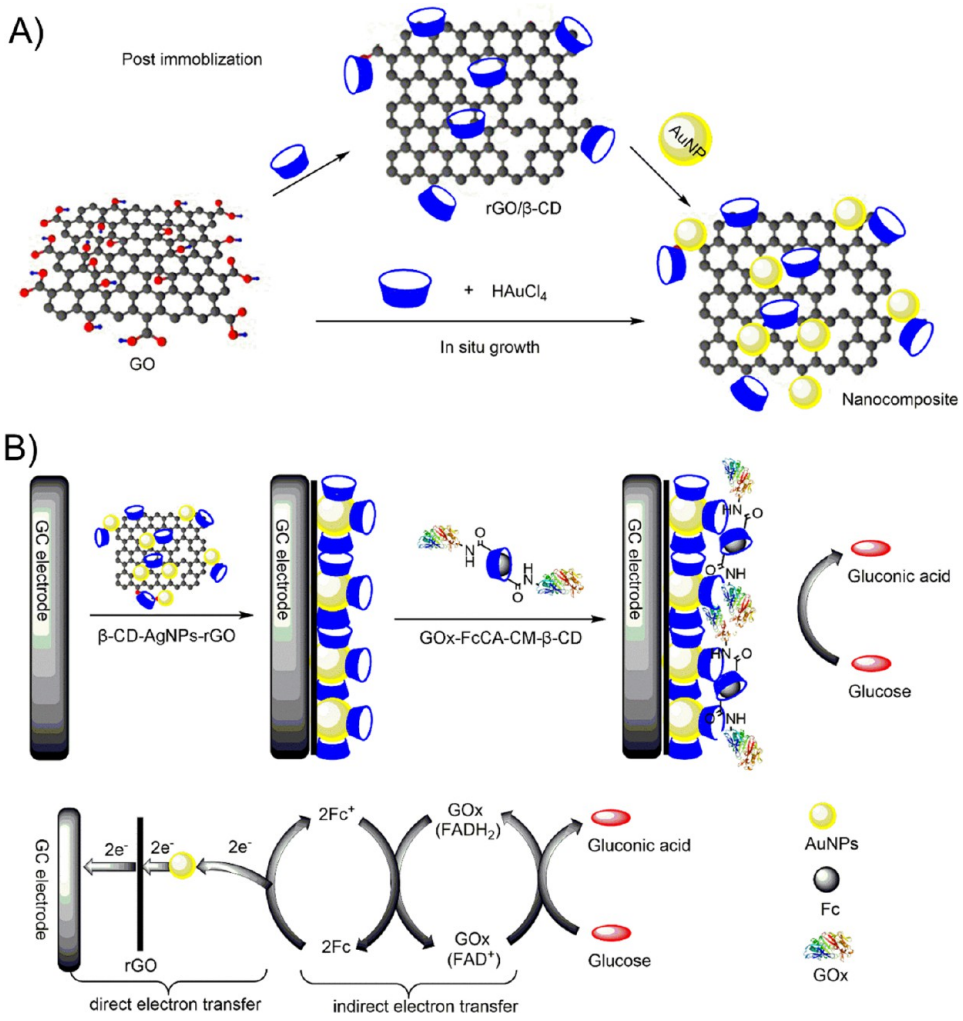

Figure 16. (A) Schematic represents the synthetic strategies of the graphene-based metal nanocomposite via in situ growth and post immobilization. (B) Schematic representation of the preparation procedure of β-CD-AgNPs-rGO, FcCA-CM-β-CD, GOx-FcCA-CM-β-CD, and GOxFcCD/AgNPs@rGO/GCE and a dual-path electron transfer mechanism for the modified electrochemical glucose biosensor.

problem, such as surface modification of rGO and the use of linker molecules to facilitate protein binding.[158,159] For this concern, Palanisamy et al. used β-CD to immobilize GOx on the rGO for developing a simple glucose biosensor (Figure 15Ba). The modified electrode with the rGO/β-CD composite exhibited a high heterogeneous electron transfer rate constant (3.8 s^{-1}) along with an extensive response to glucose and desired sensitivity (59.74 mA mM^{-1} cm^{-2}, Table 1). As seen in Figure 15Bb, the rGO/β-CD composite film improved the direct electrochemistry of GOx more than that of other modified electrodes. Based on the obtained results the authors proposed that the prepared rGO/CD composite has the potential to be employed for immobilizing other redox-active enzymes and used as electrode material.[115] Considering a crucial role of glucose detection in blood specimens and rGO chemistry, Wang et al., in 2018, investigated a simple wet chemical method for the functionalization of rGO with β-CD as a coating material onto the GCE.[116] Results presented a low limit of detection (0.4 μM) with a linear range from 1 μM to 8 mM. Moreover, the developed electrochemical glucose biosensor was successfully employed in blood specimens.

The graphene−metal nanocomposites are the new hybrid form of the GO that has been broadly investigated owing to their interesting synergistic effects. Despite some of the reviews discussing the various synthetic methods of graphene−metal nanocomposites such as in situ growth and post immobilization for the construction of these nanocomposites, their preparation is challenging due to the limited production and insolubility of graphene in most solvents. CDs make graphene more hydrophilic and can prevent aggregation by improving its water solubility.[66] Accordingly, CD-modified graphene could exist in the form of monolayers because of the larger specific surface area compared to unmodified graphene. This feature improves the loading capacity of the ether pre- or in situ synthesized metal NPs with specific size and shape and makes many catalytic sites in the glucose-sensing systems possible.[117,160]

Considering these aspects, Ma et al. utilized β-CD as the common functional reagent to synthesize two different graphene−metal nanocomposites through one-step in situ growth and postimmobilization methods, individually (Figure 16A).[117] Similarly, β-CD was used in another study to improve the dispersibility of rGO for nanocomposition with AuNPs. The aqueous suspension of β-CD-functionalized rGO produced a graphene-based gold nanocomposite on heating with chloroauric acid. In the synthesizing process, β-CD acted as the reductant material for Au(III) ions to generate AuNPs on the surface of rGO. The constructed nanocomposite

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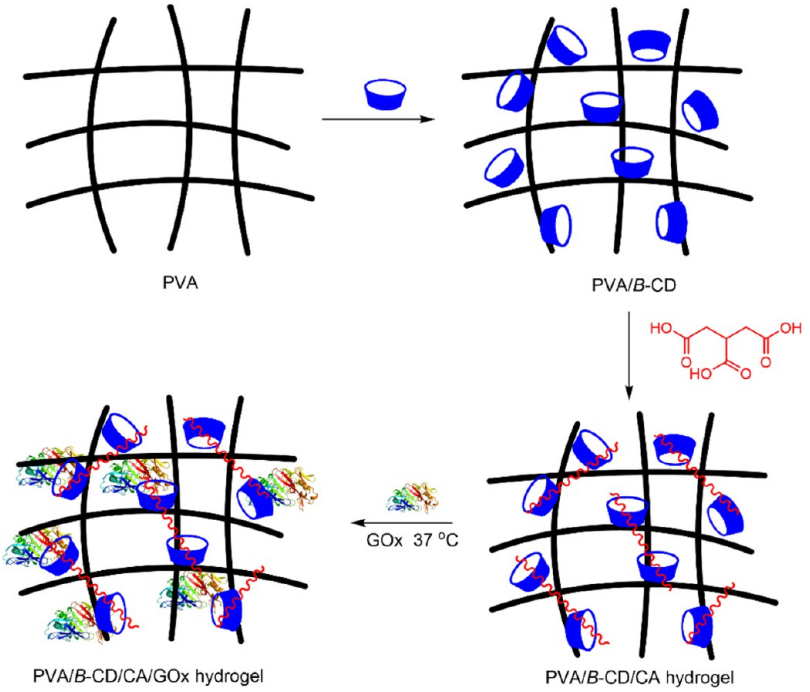

Figure 17. Schematic illustration of the preparation of the PVA/β-CD/CA/GOx hydrogel and its application on an epidermal patch with an iontophoresis mechanism.

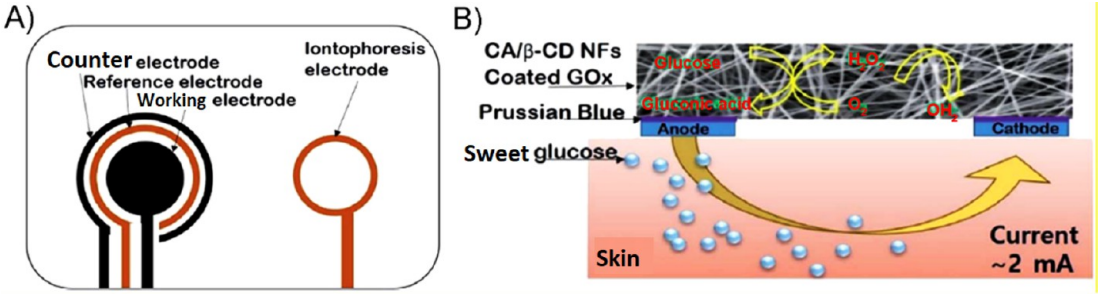

Figure 18. Schematic illustration of (A) the iontophoresis printable cellulose/β-CD/GOx NF electrode and (B) its iontophoresis mechanism on the epidermal glucose detection. Reprinted with permission from ref 120. Copyright 2019. Kyu Oh Kim et al. Royal Society of Chemistry.

showed great electrochemical sensing capability with the best detection limit achieved for glucose (10 nM, Table 1) in comparison with some of the other enzymatic or nonenzymatic electrodes reported in the literature. The prepared graphene-based metal nanocomposites revealed great performance in GM owing to the synergetic effects of the high catalytic activity and conductivity related to the metal components and graphene nanosheets, respectively.[36]

In an innovative method, a dual-path electron transfer mechanism was used to design a fast response glucose biosensor. In this regard, Qu et al. used ferrocenecarboxylic acid (FcCA) as the indirect mediator to transfer electrons from the embedded redox-active center of enzymatic reaction via the redox process.[39] Also, they employed conductive nanomaterials such as silver NPa (AgNPs) and rGO as direct mediators to provide fast electron transfer to the electrode (Figure 16B). In this system, β-CD played a key role since it works as a reducing agent for rGO and AgNPs and also provides a biocompatible microenvironment for the GOx. Simultaneously, carboxymethyl-β-cyclodextrin (CM-β-CD) could immobilize FcCA and Gox through an inclusion complex. This electrode indicates a fast electron transfer rate with a wide linear response range and a low detection limit (Table 1).

2.4. CD-Modified/-Functionalized Polymer Patch.

Polymer-based wearable sensors have shown significant promise as skin-adhesive electrochemical detecting devices for noninvasive glucose monitoring.[161,162] To be effective, these devices require polymer patches with high moisture-absorbing capacity, quick drying time, and high surface area, as well as strength in wet conditions, nontoxicity, and freedom from skin irritants.[161,162] While polymeric materials have demonstrated good mechanical properties, biocompatibility, and a high swelling degree, they lack appropriate selectivity for bioactive compounds. Therefore, enzyme immobilization remains a major challenge in hydrogel-based biosensing platforms. To overcome this limitation, in 2018, Kim et al. introduced the β-CD to the structure of the poly(vinyl alcohol) (PVA) patch using citric acid (CA) as a cross-linking agent.[119] Subsequently, they immobilized the GOx to a PVA/β-CD/CA hydrogel patch through the host−guest complexation with β-CD (Figure 17).[119] The prepared GOx-immobilized PVA/β-CD/CA hydrogel patch showed a long moisture retention time (about 4.5 h for complete drying at 37

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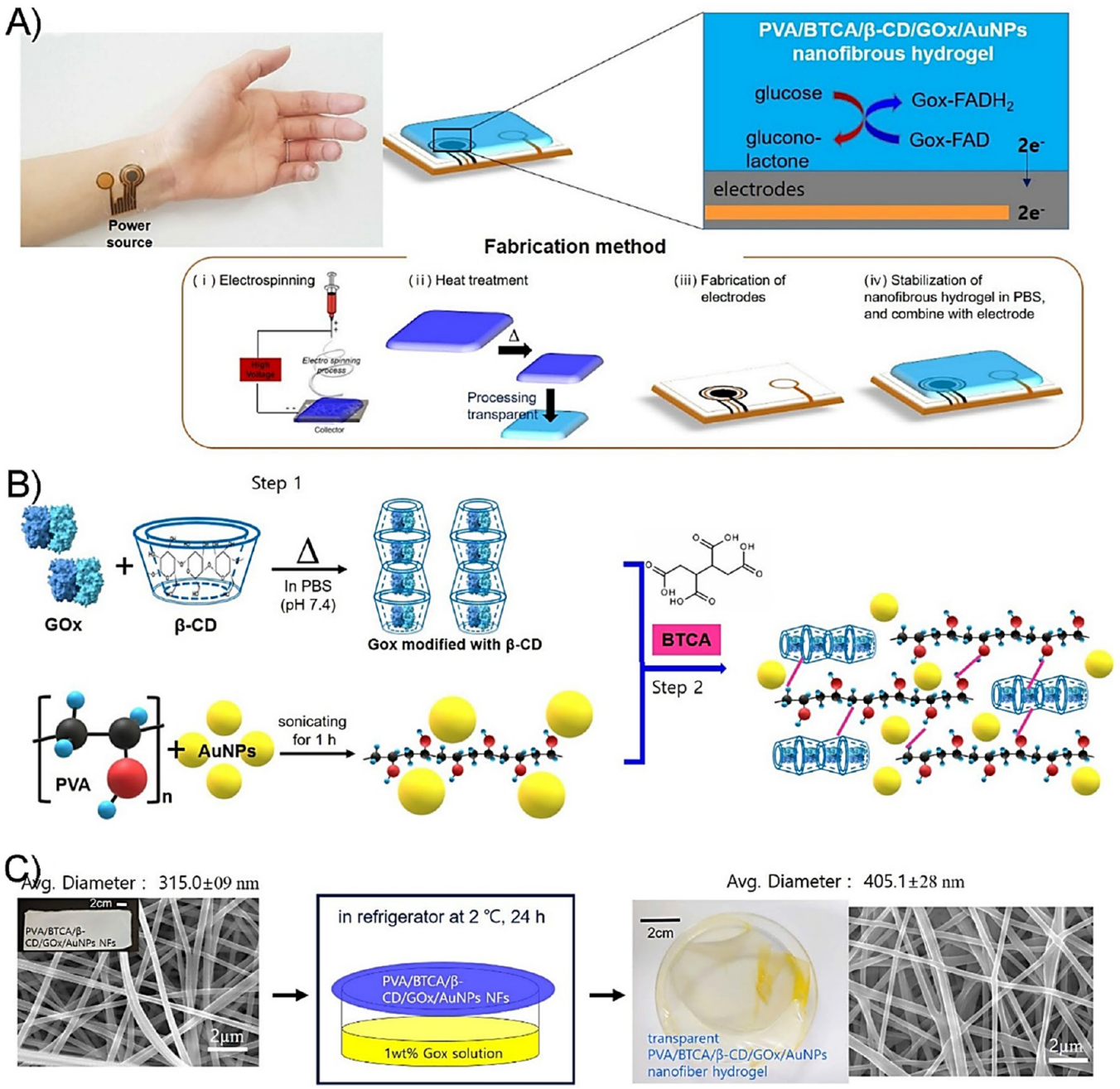

Figure 19. (A) Schematic of the patch-type glucose sensor employing PVA/BTCA/β-CD/GOx/AuNP NF hydrogels on electrodes and the mechanism of glucose sensing for the noninvasive real-time monitoring of glucose in sweat. (B) Schematic of the preparation of the PVA/BTCA/β-CD/GOx/AuNP complex dope solution for electrospinning. (C) Transparent PVA/BTCA/β-CD/GOx/AuNP nanofibrous hydrogel process (containing optical and SEM images). Reprinted with permission from ref 121. Copyright 2020. Gun Jin Kim et al., Pub Med.

°C), low solubility, and great water absorption (312%) properties. The three-electrode method is used with the prepared hydrogel, which is bound to the electrode by iontophoresis. Glucose as a substrate for GOx leads to a decrease in the concentration of the oxidized form of GOx on the electrode surface that restrains the electrocatalytic reaction and reduces the reduction current. This could be used for glucose sensing, as confirmed by the CV curves. A linear amperometric response with a low detection limit (5.1×10^{-10} μM) was observed for PVA/β-CD/CA/GOx hydrogel to detect the glucose in interstitial fluid (Table 1).

In another study, in 2019, Kim et al.[120] developed patch biosensors using an electrospun nanofiber (NF) for non-invasive continuous monitoring of glucose levels in interstitial fluid (ISF). NFs are known for their high interconnectivity with the skin and high porosity, making them a promising material for sensor devices. However, the main challenge for this type of platform is the shuttling of electrons between glucose oxidase (GOx) and the electrode. To overcome this challenge, the researchers constructed an NF patch sensor using cellulose/β-CD through the electrospinning method on the reverse iontophoresis electrode. The GOx was then immobilized on the patch surface using the physical absorption

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process. This approach allowed for the successful use of the NF patch sensor to monitor glucose levels continuously and noninvasively in IS (Figure 18a).[120] In this system, β-CD acts as an electron shuttle mediator between the electrode and GOx. Additionally, β-CD improves the stability of the enzyme and prevents its denaturation. The sensor showed a low detection limit (9.35×10^{-11}), a quick response time (<3 s), and a sufficient interference rejection (Table 1). The soft and stretchable/flexible features of the prepared cellulose/β-CD/GOx NF biosensor simplified uptake of a low concentration of glucose from the skin through high accuracy reverse iontophoresis for the noninvasive CGM (Figure 18b).

The electrospinning method was utilized to produce micro- and nanofiber (NF) hydrogels with a high porosity and specific surface area. Transparent poly(vinyl alcohol)/β-CD polymer NF hydrogels were used to contact reverse iontophoresis electrodes for monitoring interstitial fluid glucose levels, which were found to be around 1 mM.[121] By incorporating AuNPs, PVA/BTCA/β-CD/GOx containing NF hydrogels demonstrated rapid electron transfer and high permeability to biosubstrates, resulting in a PVA/BTCA/β-CD/GOx/AuNPs NF hydrogel patch with high sensitivity (47.2 μA mM^{-1}), a rapid response time (<15 s), and low sensing limit (0.01 mM) (Table 1). This work highlights the potential of the PVA/BTCA/β-CD/GOx/AuNPs NF hydrogel patch for measuring glucose concentration in human serum. The schematic of the patch-type glucose sensor by PVA/BTCA/β-CD/GOx/AuNPs NF hydrogels on electrodes, glucose-sensing mechanism, PVA/BTCA/β-CD/GOx/AuNPs complex dope solution fabrication for electrospinning, and transparent PVA/BTCA/β-CD/GOx/AuNPs NF hydrogel process is illustrated in Figure 19.

Polymer microneedle arrays are the other group of materials which are frequently evaluated as patch biosensors for potential GM in interstitial fluid.[163] Barrett et al. prepared a microneedle electrode array via the deposition method through the modification of the working electrode with a platinum layer and subsequent modification by immersion in sulfonated β-CD and *o*-phenylenediamine.[122] Then, GOx was immobilized on an *o*-phenylenediamine/sulfonated β-CD polymer matrix to generate a functional glucose-sensitive surface. The sensor array exhibited a linear response over 19.5 mM for glucose in the IF (Table 1). Interestingly, they reported that there was no disturbance with the presented interferants. Additionally, the cytotoxicity study revealed only minor detrimental effects due to the biocompatible features of β-CD.

In response to the increasing demand for GM systems, Buzzetti et al. developed glyconanoparticles (GNPs) using a carbohydrate-based polystyrene-*block*-β-CD copolymer as a building block.[123] The GNPs were firmly immobilized on electrochemically generated polymers, including poly(pyrrole-adamantane) and copolymer poly(pyrrole-adamantane)/poly(pyrrole-lactobionamide), through host−guest interactions between adamantane and β-CD. To evaluate the potential of GNPs for targeted anchoring of biological macromolecules, a glucose oxidase enzyme modified with adamantane groups (GOx-Ad) was used. The presence of immobilized GOx-Ad on a GNP coating was confirmed, and the bioelectrodes were tested for glucose detection. The analytical performance of bioelectrodes was compared, revealing better permeability of copolymers than of polymers and the possibility of creating two alternating layers of GNPs and GOx-Ad. The amperometric detection exhibited a wide linear range, indicating the potential for practical applications.

3. CONCLUSIONS: SUMMARY, PROSPECTIVE, AND CHALLENGES

Natural and modified cyclodextrins (CDs) have become a fascinating option for biomedicine due to their capacity to interact with various organic, inorganic, and biological molecules through host−guest inclusion complexes, electrostatic interactions, and hydrogen bonding. This ability makes them an excellent choice for improving the sensing capability of sensors, particularly in the composition of glucose-monitoring (GM) systems. The review of the currently reported techniques, summarized in this review, highlights that they include enhanced quality, safety, and efficiency, excellent cyto- and biocompatibility, as well as versatile capabilities.

CDs have proven to be effective stabilizers for mediators, enzymes, polymers, and nanoparticles (NPs) utilized in sensor structures. The interaction between CDs and these components has been shown to enhance the collection of analytes on the electrode surface, improving the electrochemical kinetics of glucose detection through amperometric techniques. This results in increased sensitivity, selectivity, and reproducibility of the sensors. Additionally, the use of CDs in the fabrication of glucose-monitoring sensors has the advantage of being low cost while still providing sufficient selectivity, high sensitivity, and flexibility in materials functionalization.

To summarize, the role of CDs in GM sensors to enhance or customize the glucose-sensing ability of boronic acid, mediators, nanoparticles, and polymer patches can be broadly categorized into three groups. First, they provide selectivity toward glucose over other interfering species, such as fructose and maltose. Second, they can increase the stability and lifetime of the sensor by protecting the immobilized enzyme from denaturation and degradation. Finally, they can improve the sensor sensitivity and response time by enhancing the mass transport of glucose to the electrode surface. In vitro studies have demonstrated the success of CD-based GM sensors. However, further research is needed to optimize these systems and conduct clinical validation studies to assess their accuracy and reliability in vivo. Future efforts should focus on interdisciplinary sciences and emerging techniques and materials to expand the scope of on-body GM systems. One of the major challenges in the development of prolonged continuous GM devices is their limited operational stability due to biofouling and a foreign body response. The potential of CD-based sensors in glucose monitoring is immense and could offer the possibility of more accurate and reliable continuous glucose measurement in clinical settings. Finally, this review provides a promising avenue for researchers in this field to develop innovative platforms based on CDs for clinical applications of GM devices, especially continuous GM systems.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATION

GM, Glucose monitoring; CDs, Cyclodextrins; DM, Diabetes mellitus; BG, Blood glucose; T1D, Type I diabetes; T2D, Type II diabetes; CGM, Continuous glucose monitoring; GOx, Glucose oxidase; HP-β-CD, 2-Hydroxypropyl-β-cyclodextrin; PET, Photoinduced electron transfer; BA-Azo, Phenylboronic acid azoprobe; PB-γ-CD, Boronic-acid-modified γ-CD; STDBA, Stilbeneboronic acid; Rluc, Luciferase bioluminescence protein; CPBA, 4-Cyanophenyl boronic acid; PBA-AD, Phenylboronic acid and adamantane; ARS, Alizarin red S; K_c, binding constant; β-CDA, β-Cyclodextrin amphiphiles; Fc, Ferrocene; TTF, Tetrathiafulvalene; BQ, 1,4-Denzoquinone; DMFe, 1,1′-Dimethylferrocene; SH-β-CD, Mono-6-thio-β-cyclodextrin; NPs, Nanoparticles; AuNPs/CD-Fc, Mono-6-thio-β-cyclodextrin/Fc immobilized on gold nanoparticles; α-CDP, α-Cyclodextrin polymer; β-CDPA, β-Cyclodextrin polymer films; GC, Glassy carbon; QDs, Quantum dots; MOFs, Metal−organic frameworks; AuNPs, Gold nanoparticles; CM-β-CD, Carboxymethyl-β-cyclodextrin; PCM-β-CD, Electropolymerization carboxymethyl-β-cyclodextrin; ConA, Concanavalin A; UCFRET, Upconverting fluorescence resonance energy transfer; β-CD-Pd@Au, β-Cyclodextrin-modified Pd@Au nanoparticles; TMB, 3,3′,5,5′-Tetramethylbenzidine; 4-AAP, 4-Amino antipyrine; TOPS, *N*-Ethyl-*N*-(3-sulfopropyl)-3-methyl-aniline sodium salt; DHBS, 3,5-Dichloro-2-hydroxy acid sodium; PtNPs, Platinum nanoparticles; BDD, Boron-doped diamond; SBE-β-CD, Sulfobutylether-β-cyclodextrin; CD-PAMAM, Cyclodextrin-modified polyamidoamine dendrimer; GOx-AD, Adamantane-modified enzymes; CD-IL, Cyclodextrin-ionic liquid; CuNPs, Copper nanoparticles; FRET, Fluorescence resonance energy transfer; N,Fe-CQDs, N,Fe-codoped carbon dots; HRP, Horseradish peroxidase; TRITC, Tetramethylrhodamine isothiocyanate; PEG, Polyethylene glycol; CL, Chemiluminescence; CNT, Carbon nanotubes; SWCNTs, Single-walled carbon nanotubes; pre-CDP, Cyclodextrin prepolymer; CTAB, Cetyltrimethylammonium bromide; Anti-CT, Anticholera toxin; GOx-B, Biotinylated GOx; rGO, Reduced graphene oxide; GCE, Glassy carbon electrode; $Ni(OH)_2$, Nickel hydroxide; FcCA, Ferrocenecarboxylic acid; AgNPs, Silver nanoparticles; PVA, Poly(vinyl alcohol); CA, Citric acid; NF, Nanofiber; ISF, Interstitial fluid; GAL, β-Galactosidase; 2,2′bpy, 2,2′-bipyridine; 4,4′bpy, 4,4′-bipyridine; Ru, Ruthenium; PCMCD, Poly(carboxymethyl-β-CD); UCPs, Upconverting phosphors; PTy, Poly(tyramine); SBCD, Sulfobutylether-cyclodextrin; *o*-PD, *o*-Phenylenediamine; Pt−B, Pt-Black; 3-HF, 3-Hydroxyflavone; MWCNTs, Multiwalled carbon nanotubes; CS, Chitosan; PyAd, Pyrene-adamantane; BTCA, 1,2,3,4-Butanetetracarboxylic acid; GNPs, Glyconanoparticles; IR-ATR, Infrared sensing system based on attenuated total reflection; β-CDV, β-Cyclodextrin vesicles; C1-APB, Boronic acid fluorophore; PB, Boronic acid; PBA, Phenylboronic acid; PAM, Polyacrylamide; AAPBA, 3-Acrylamidophenylboronic acid

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