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Review Article

Recent developments in blood glucose sensors

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ABSTRACT

Diabetes has recently become a leading cause of death worldwide. To date, although there is no means to cure or prevent diabetes, appropriate medication and blood sugar monitoring can enhance treatment efficiency, alleviate the symptoms, and diminish the complications of the condition. This review article deals with current growth areas in the market for blood glucose sensors and possible future alternatives, which are generally considered to be the point sample test and the continuous glucose monitor (CGM). Most glucose sensors are enzyme-based, whereas others are enzyme-free. The former class is sensitive and some products are extensively employed for daily self-sensing and in hospital environments as reliable diagnostic tools. The latter class, particularly the boronic acid fluorescent sensor, is facile and extremely promising. Practicality demands that all types of sensors offer accuracy, specificity, and real-time detection.

1. Introduction

Since Emil Fischer established the monumental theory of supramolecular chemistry on interactions between substrate molecules and specific enzymes, molecule recognition is of particular interest to numerous scientists [1]. Molecular recognition based on the lock-and-key principal occurs in biological systems such as enzyme–substrate interactions, antigen evoking antibody [2–5], and sugar binding to lectin [6–9]. Following development of the first two-dimensional structure of crown ether for a specific metal ion by Pedersen, Cram, and Lehn [10], the possibility of synthetic receptors that mimic important biological activities was demonstrated. Particularly, saccharide recognition attracts the attention of biochemists and medicinal chemists not only because saccharides are involved in cell–cell interactions within biological organisms but also because saccharide sensing offers promise for clinical diagnostic applications such as blood sugar level, pathogens, and cancer [11–18].

2. Saccharides and their importance

Carbohydrates, the most abundant organic form of material on the earth, which form biological building blocks and dietary components, are classified as single sugars (monosaccharides) and their polymers, namely oligosaccharides and polysaccharides [19–21].

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Monosaccharides are generally the simplest and most basic of carbohydrates, serving both as energy fuels and fundamental constituents of living organisms. For example, five-carbon sugars exist in information carriers, such as deoxyribose in DNA and ribose in RNA; moreover, the best-known six-carbon sugars include D-glucose, also known as either grape sugar or blood sugar; D-fructose, fruit sugar; and D-galactose, which forms milk sugar when combined with glucose. The D series of sugars are thus designated based on the observation that most natural monosaccharides have the same configuration at C-5 as D-glyceraldehyde. In aqueous solution, the isomeric structures of glucose molecules display equilibrium. In neutral solution, glucose exhibits the linear open-chained form in <0.1% of molecules. Most of these molecules exist as a more stable cyclic hemiacetal with a six-membered pyran ring and thus are termed the pyranose (Fig. 1).

In humans, D-glucose is vital for its role in metabolic homeostasis; it acts as an energy source in living systems and maintains human bodily functioning when consumed or through the formation of other essential saccharides via biosynthesis. When taken up by human cells, glucose can be either broken down (glycolysis) to yield energy, converted into other metabolites in the form of metabolic intermediates, or polymerized to form cellulose and starch through biosynthesis to function properly. In the human body, besides existing in free form, glucose can covalently link to lipids (glycolipids) and proteins (glycoproteins) and other biological molecules as glycoconjugates, which are crucial building components of cell membranes and are mainly involved in the mechanism of intercellular recognition [22].

Monosaccharides can also join other sugars via glycosidic bonds through the sequential reaction of their anomeric hydroxyl groups with the hydroxyl groups of other sugars, together with the elimination of water, resulting in a yield of oligosaccharides or polysaccharides. The simplest and most biologically important oligosaccharides are disaccharides. Three naturally abundant disaccharides are maltose, lactose, and sucrose. The glycosidic linkages of these three disaccharides are formed stereospecifically by enzymes; therefore, only one of the possible configurations (α or β) occurs and, like all glycosides, its mutarotation is not permitted. Maltose, which occurs mainly in malt, comprises two D-glucose units joined with an α(1→4) bond via a condensation reaction. Lactose, the most important sugar in mammalian milk, is the combination of D-galactose and D-glucose. Sucrose, also named table sugar, consists of D-glucose and D-fructose. Oligosaccharides also form glycoconjugates with proteins and lipids, some of which are important in cell biology. Additionally, taking advantage of their biological effects, complex oligosaccharides and their analogs are widely applied in pharmaceuticals. For example, the first oligosaccharide analog used as a chemotherapeutic agent was streptomycin, a bactericidal aminoglycoside antibiotic isolated in 1943, and also the first cure for tuberculosis. Acarbose, an antidiabetic drug used to treat type II diabetic mellitus by inhibiting α-glucosidase, localized in the brush border of intestinal epithelium, is also an oligosaccharide derivative comprising two glucose moieties with a rare sugar unit. Cyclic oligosaccharides such as cyclodextrins, obtainable by partial hydrolysis of starch, which bear a hydrophilic exterior and hydrophobic interior, can form host–guest complexes and be applied in drug delivery systems (Fig. 2) [21]. Cyclodextrins also have numerous applications in foods, pharmaceuticals, chemicals, and agriculture.

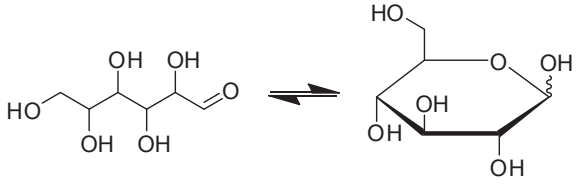


Fig. 1 – Linear and cyclic form of D-glucose.

Polysaccharides, macromolecules comprising numerous monosaccharide moieties, are ubiquitous in nature. They are frequently classified into three classes according to function: structural polysaccharides, water-binding polysaccharides, and reserve polysaccharides. Polysaccharides are important biological polymers and possess great structural diversity.

3. Glucose-related disease: diabetes

Various saccharides-related diseases are common in clinical practice, including disorders of carbohydrate metabolism, such as lactose intolerance, Andersen's disease, Pompe disease (acid maltase deficiency) [23,24], obesity, hypoglycemia, hyperactivity (mostly in children), and most important of all, diabetes [25–27].

Diabetes is a chronic disease that has devastating human, social, and economic consequences. According to the World Health Organization (WHO) and the International Diabetes Federation, its worldwide prevalence is projected to double over the next couple of decades, from 347 million people in 2005 to 700 million people in 2030. Notably, >80% of diabetic patients live in low- and middle-income countries [25,28].

Diabetes can be divided into three main types. Type I diabetes is insulin-dependent; it was previously called insulin-dependent diabetes mellitus or juvenile diabetes. It is caused by deficient insulin production within the body and typically manifests among the youth. Daily replacement of insulin becomes indispensable for those with the condition. Type II diabetes is noninsulin-dependent and is caused by insulin resistance, a condition in which the target organs develop a failure to properly respond to insulin. Type II diabetes is termed adult-onset diabetes and makes up >95% of all cases. Gestational diabetes occurs when pregnant women, usually without a previous history of diabetes, develop a high blood glucose level. Women with gestational diabetes typically have a high risk of eventually developing type II diabetes.

Although diabetes is not actually caused by saccharides, it is one of the most notorious saccharide-related diseases. This is because body cells cannot digest glucose from blood themselves. To maintain blood sugar concentration following ingesting carbohydrate, the body requires insulin, produced and released from the B- (or β-) cells of the pancreas, to transport glucose into cells for subsequent metabolism. The result of inefficient insulin production or secretion is an excessive rise in blood glucose, even spilling into the urine.

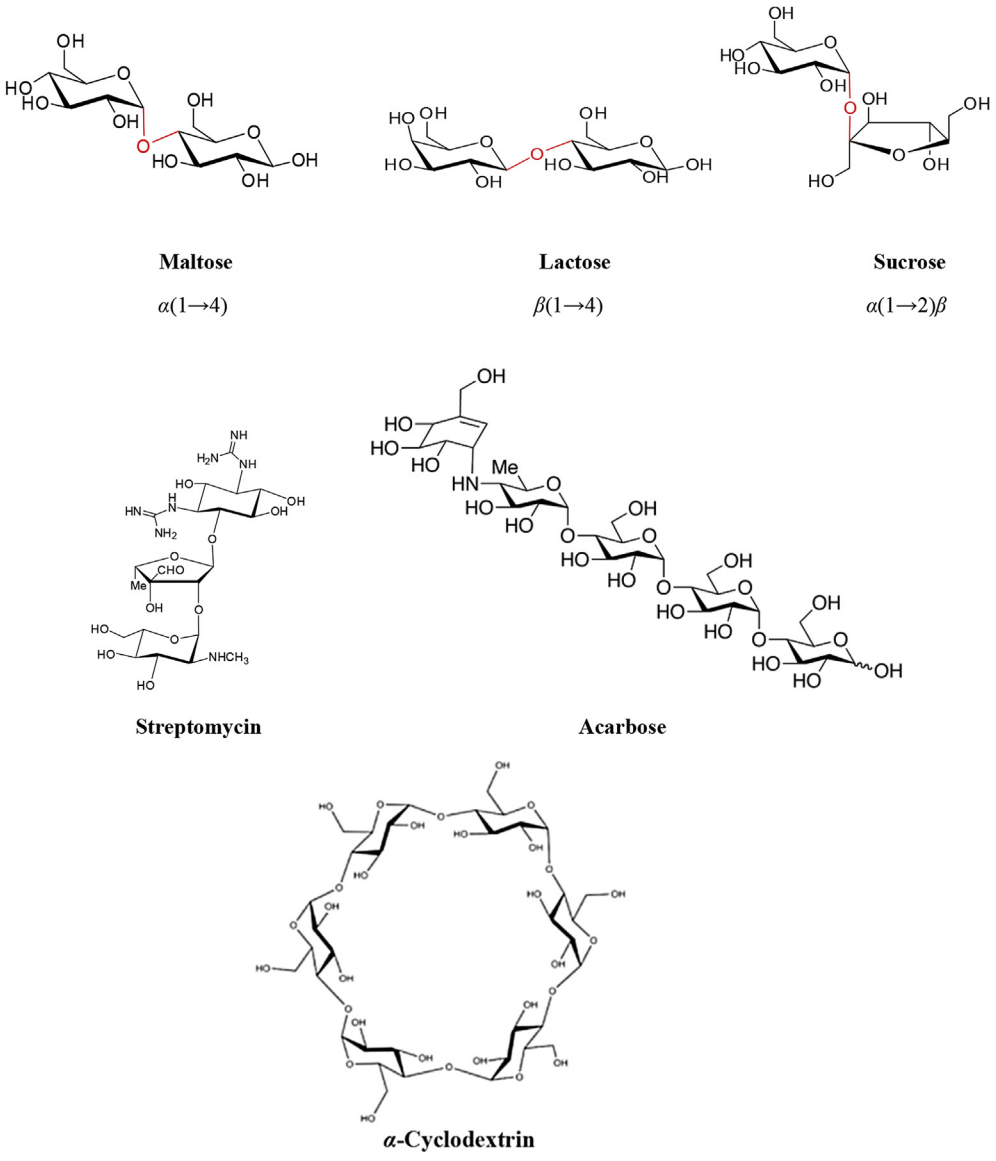


Fig. 2 – Common oligosaccharides and their analogs.

Seven million people develop diabetes annually. The WHO has also warned that the number of deaths from diabetes is expected to increase by >50% over the next decade. Nowadays, one person dies from diabetes every 10 seconds. Diabetes has become an urgent global problem that requires serious action.

4. Glucose sensors

Despite the lack of any known cure for diabetes, we have managed to improve treatment efficiency to alleviate its symptoms and diminish its complications through appropriate medication and blood sugar monitoring, to improve treatment decisions and glucose control. Glucose sensor systems are classified into two groups based on duration of measurement method and time: the point sample test and the continuous glucose monitor (CGM) (Table 1) [29]. Most glucose sensors are enzyme-based, whereas others are enzyme-free.

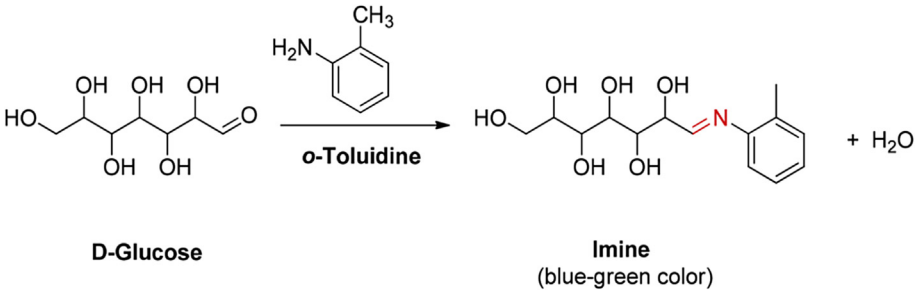
4.1. *Point sample test*

The earliest method for glucose detection was based on the formation of a Schiff base (imine) between aldehydes and aromatic amines. The reaction of the aldehyde group on glucose with 2-methylaniline (o-toluidine) forms a stable blue/green color imine (an anil). The resulting imine displays a maximum absorption (λ_{max}) in the visible region of the spectrum at 625 nm (Scheme 1). The glucose concentration is proportional to the absorption intensity. The glucose concentration in the test sample can be obtained based on the plot of a standard curve. The main weakness of this method is its lack of selectivity owing to aldehyde being the common functional group in numerous sugars and consequent prevalence of false-positive results. Fortunately, glucose is the principal saccharide in the blood; other monosaccharides and disaccharides are present only in very low concentrations.

By exploiting glucose oxidase as an enzyme specific to β-D-glucose, an enzyme-based assay was introduced to assess

Table 1 – Technologies under development for glucose sensors [29].

Glucose sensor	Point sample	Urine dipstick	
		Finger prick glucometer	
	Continuous	Invasive	Subcutaneous amperometric electrodes, microdialysis, intravenous implantable devices, and micropores/microneedles
		Noninvasive	Transdermal: reverse iontophoresis, sonophoresis, etc
			Optical: fluorescence, infrared spectroscopy, Raman spectroscopy, etc



Scheme 1 – Reaction of D-glucose and o-toluidine.

glucose levels. Molecular oxygen, O_2, when catalyzed by glucose oxidase, readily oxidizes β-D-glucose to D-gluconic acid, while it is reduced to hydrogen peroxide (H_2O_2). The generated H_2O_2 can then further oxidize o-toluidine to form a colored product with a concentration proportional to that of H_2O_2 and hence to that of glucose. Based on this concept, several commercial test kits have been employed as routine diagnostic tools, including those utilizing chemical strips, and those used to test blood and urine glucose levels by sampling specimens directly into the strip followed by visual reading of the color charts (Scheme 2).

In 1971, Clemens developed the Ames Reflectance Meter (ARM), a device to detect reflected light and automatically assess strip color change, using a standard strip for calibration. The ARM was also the first blood glucose monitor patent filed in the USA for point-of-care test devices for diabetes patients [29].

Existing point sample tests require patients to draw blood with a lancet several times daily. Such discrete tests are unsuited for use while sleeping or driving, and moreover hyper- or hypoglycemia events are unlikely during sampling.

4.2. CGM

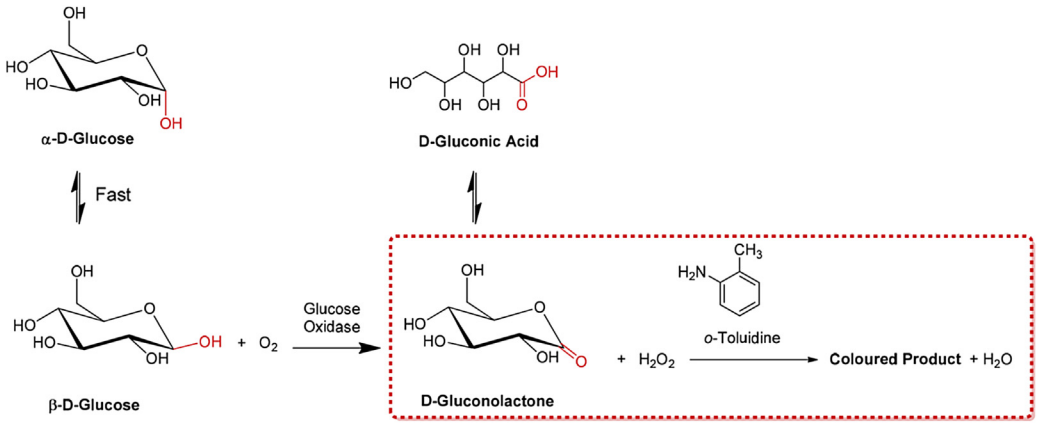
Investigations have demonstrated that intensive glycemic control to maintain blood sugar levels as near normal (*euglycemia*) as possible can diminish complications of diabetes and improve quality of life, stimulating the launch of numerous investigations on CGMs. CGM systems employ a tiny sensor inserted beneath the skin and remain in place for a period of time to assess glucose levels in tissue fluid. CGM systems should provide data on glucose levels, particularly the tendency, magnitude, frequency, period, and changes of fluctuations in real-time to alarm patients should rapid changes in glucose levels occur in the blood, particularly while sleeping or exercising. Numerous technologies are involved in CGM investigations, and they can be classified as invasive and noninvasive (Table 1).

4.2.1. *Invasive continuous glucose sensors*

In 1954, the first oxygen electrode, known as the "Clark electrode", was invented by the American biochemist Leland C. Clark, also considered the "Father of Biosensors" [30]. To monitor oxygen signals and calibrate the oxygen electrode, Clark used glucose and a glucose-specific enzyme, glucose oxidase, to remove oxygen by reducing it to H_2O_2. This process found the decrease of oxygen to be proportional to the concentration of glucose in the solution. Eventually, Clark realized that this simple device could be used to measure oxygen/glucose in water, blood, and other solutions. Most modern glucose sensors used daily by millions of diabetics are based on Clark's concept.

Invasive continuous glucose sensor research involves four technologies: subcutaneous amperometric electrodes, microdialysis, intravenous implantable devices, and micropores/microneedles. To date, only subcutaneous and microdialysis studies have yielded commercial products. Subcutaneous needle-type sensors adapt protected technologies, and immobilize enzyme and mediator onto a polymer membrane and electrode surface. Glucose oxidase serves as the catalyst to convert glucose to gluconolactone. Reduction–oxidation reactions can generate a concentration-dependent current or voltage to be measured by electrochemistry (Fig. 3) [29,31].

In 1990, the Medtronic MiniMed (Northridge, CA, USA) introduced the Continuous Glucose Monitor System (CGMS), the first CGM approved by the US Food and Drug Administration (FDA). The CGMS allows 3-day continuous glucose monitoring and data recording, where blood glucose measurement records can be processed and analyzed retrospectively. Current Medtronic products are the Guardian REAL-Time and MiniMed Paradigm Real-Time (glucose monitor combined with insulin pump). In 2006, the first real-time continuous glucose monitoring system, DexCom-7, was approved by the FDA and in 2007 its lifetime was extended from 3 days to 7 days. The latest CGMS model to follow this FreeStyle Navigator achieved 5 days of continuous glucose monitoring and was approved by the FDA in 2008 (Table 2) [32–34].



Scheme 2 – Oxidation of D-glucose catalyzed by glucose oxidase.

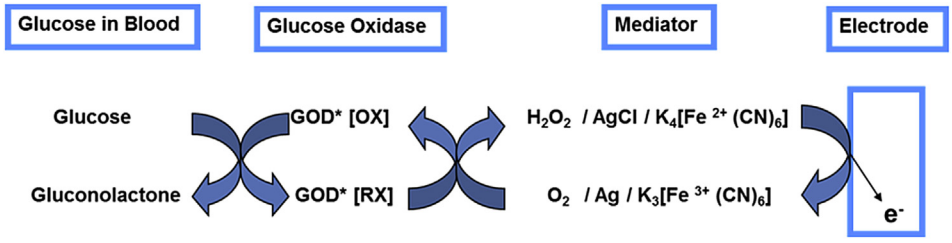


Fig. 3 – Enzyme-based electrode with glucose oxidase and mediators [29,31].

Microdialysis probes, which are valuable adjunctive tools for glucose trend analyses, use a subcutaneous inserted hollow fiber combined with a semipermeable membrane filter. The membrane is permeable to glucose and other small molecules. Meanwhile, the fiber is perfused with isotonic fluid, glucose in the interstitial fluid diffuses into the fiber, and the fluid is then pumped to an enzyme-based electrode. The glucose concentration depends on the equilibrium of the interstitial fluid. A common weakness of this technology is membrane blockage owing to biofouling. GlucoDay (Menarini Diagnostics, Firenze, Italy), marketed in 2002, is the only commercial product approved in Europe [32].

Consequently, the first generation of invasive CGMs are all enzyme-based sensors and require calibration using the finger-prick blood sensor. Future improvement in invasive CGMs will undoubtedly focus on accuracy, reliability, cost, and lifetime.

4.2.2. *Noninvasive continuous glucose sensors*

The availability of home-use glucometers has significantly improved quality of life for diabetes sufferers; however, such monitors require a new strip for each test, as well as a blood draw from the finger pricks, with the latter causing pain and inconvenience. To overcome the short lifetime and calibration needs of the invasive continuous glucose system, and to increase patient compliance, noninvasive continuous glucose sensors represent an obvious solution. Numerous technologies pursued as noninvasive sensor systems can be classified as transdermal and optical sensors [33,34].

4.2.2.1. *Transdermal sensors.* GlucoWatch (Cygnus Inc., Redwood City, CA, USA), a transdermal noninvasive continuous glucose sensor approved by the FDA in 2001, is worn on the wrist like a watch and does not require drawing blood. GlucoWatch employs reverse iontophoresis. A patented hydrogel pad is located between the skin and an electrode. A small

Table 2 – Comparison of current market CGMS devices [33,34].

Brand	Guardian Real-Time	MiniMed 530G with Enlite	Dexcon G4 Platinum	FreeStyle
Company	Medtronic	Medtronic	Dexcom	Abbott
FDA approved date	2006	2007	2007	2008
Sensor life (d)	3	6	7	5
Sensor style	Insertion under skin	Insertion under skin	Insertion under skin	Insertion under skin
Startup initialization time (h)	2	2	2	10
Calibration (Y/N) with finger-stick test	Y, 2 h after insertion, and the first 6 h, then every 12 h	Y, 2 h after insertion, and the first 6 h, then every 12 h	Y, every 12 h	Y, approximately 1, 2, 10, 24, and 72 h after insertion

CGMS = continuous glucose monitor system; FDA = Food and Drug Administration.

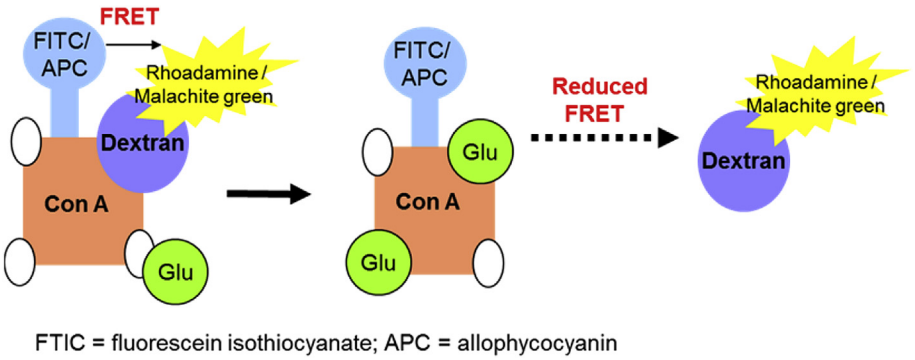


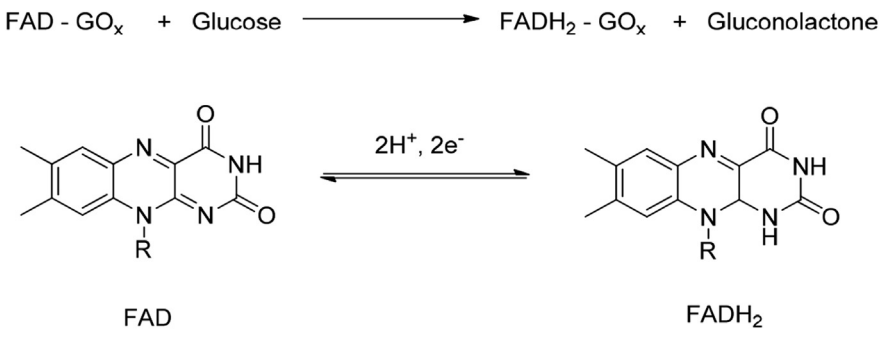
Fig. 4 – Principle of fluorescence resonance energy transfer (FRET) from Concanavalin A (Con A) to dextran by adding glucose [36].

current from the electrode passes through the hydrogel and draws out interstitial fluid from the skin to the iontophoretic electrode. The glucose concentration in the sampling fluid is 1000 times lower than that of interstitial fluid below the skin (the concentration of glucose in the interstitial fluid can sometimes be 100 times greater than the oxygen concentration) and is detected using the glucose oxidase catalytic system. Low glucose concentration means oxygen supply ceases to be a limitation for glucose oxidase. Additionally, the skin filters off large molecules, reducing biofouling and electrochemically active fouling. However, the extended warm-up time, difficult operation, need for calibration, and most importantly, skin irritation, are all disadvantages of this technology. Consequently, GlucoWatch was withdrawn from the market after 2008.

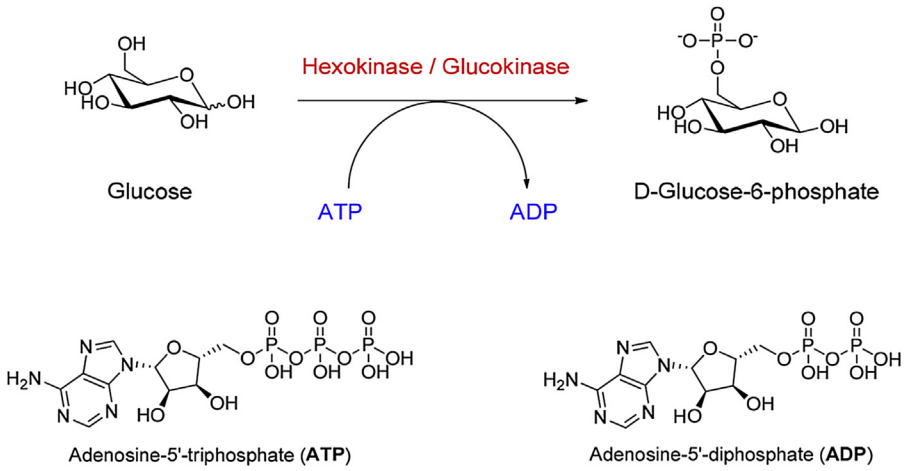
Compared to transdermal technology, alternative optical technology offers more investigative options, including polarimetry, Raman spectroscopy, scattering/occlusion spectroscopy, (near) infrared spectroscopy, fluorescence, photoacoustic spectroscopy, optical coherence tomography, etc. To date, the medical market lacks a product for optical continuous glucose monitoring. However, owing to the prevalence of diabetes, optical technology has attracted increasing scientific attention. Among all types of glucose sensors, fluorescence is considered the most promising technology for creating the ideal glucose sensor.

4.2.2.2. *Optical sensors: fluorescence-based glucose sensors.* Fluorescence is a specific type of photoluminescence. When a molecule with a rigid structure absorbs light energy from the ground state to an excited state, it returns to the ground state by emission of light, at a lower energy level than that at which it absorbed light, from different singlet states and is known as fluorescence. Fluorescence-based technology possesses numerous advantages over the conventional ultraviolet-visible spectrophotometry used in sensing. Fluorescence spectrophotometry is extremely sensitive and causes only trivial damage to the host. Fluorescence can be measured not only by its intensity but also its lifetime (generally $<10^{-5}$ s). Fluorescence spectrophotometry also offers information on biomolecule structure and environment and how biomolecules respond and change in healthy versus diseased states [35].

The Concanavalin A (Con A) sensor developed in 1984 was the first fluorescence-based glucose sensor. Con A is a plant lectin (carbohydrate-binding protein) and a homotetramer, with each possessing a specific glucose binding site. Con A can be labeled using a fluorophore (fluorescein isothiocyanate or allophycocyanin, as the fluorescent donor) and immobilized to fine, hollow fibers. Dextran, another polysaccharide, is also labeled with a fluorophore (rodamine or malachite green, as the fluorescent receptor) in the fiber. Glucose and dextran are competing ligands of Con A in the fiber system. The combination of dextran with Con A causes fluorescence resonance energy transfer (FRET) from the fluorescence donor to the fluorescent receptor. Addition of further glucose replaces more dextran, and consequently a corresponding decrease in FRET (Fig. 4) [29,36].



Scheme 3 – Reaction of glucose oxidation with flavin adenine dinucleotide–glucose oxidase (FAD-GOx) and reversible oxidation of FAD [22].



Scheme 4 – D-Glucose catalyzed by hexokinase forms D-glucose-6-phosphate.

Glucose oxidase can also bind to fluorophores such as fluorescein, enabling energy transfer from intrinsic flavin adenine dinucleotide fluorescence of glucose oxidase to the extrinsic fluorophore. In this system, glucose concentration is not proportional to the fluorescence intensity, but rather to the time between the addition and the fluorescence change (Scheme 3) [22].

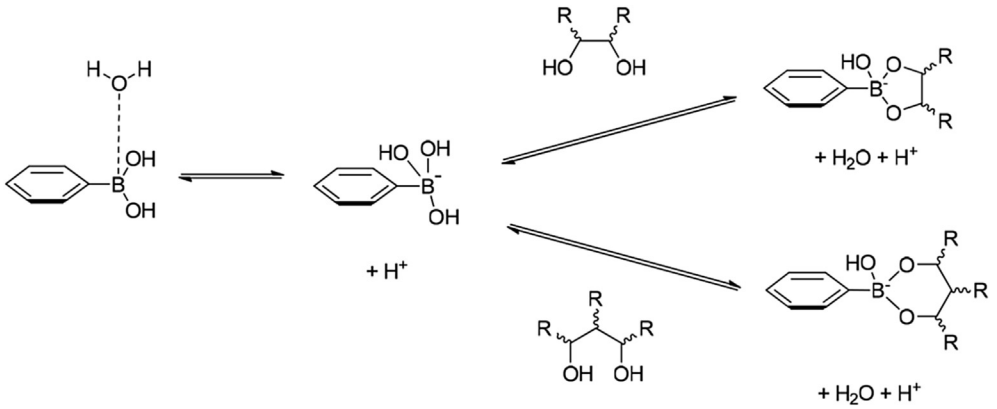
D-Glucose can be subjected to phosphorylation, catalyzed by a hexokinase (glucokinase), to D-glucose-6-phosphate coupling with the hydrolysis of adenosine-5′-triphosphate (ATP). Hexokinase from yeast usually exists as a dimer and has intrinsic fluorescence that is quenched following adding glucose. However, hexokinase is temperature-unstable, which limits its application (Scheme 4) [22].

4.3. *Newcomers: enzyme-free boronic acid-based glucose sensors*

The above mentioned glucose sensors on the current medical diagnosis market are mostly enzyme-based sensors, such as glucose oxidase or glucose dehydrogenase, and rely on electrochemical analytical measurement. However, the good sensitivity of enzyme-based glucose sensors is counteracted by instabilities due to numerous other factors such as environmental temperature and pH. The biological foil can also cause sensor instability and false alarms, as well as missed blood glucose readings [37]. Numerous efforts have been made on the development of enzyme-less or enzyme-free glucose sensors involving nanostructured electrodes to oxidize glucose directly on the surface. However, chloride fouling following a long detection period remains problematic [38–44]. Another alternative method for enzyme-free glucose sensors is synthetic boronic acid-based receptors [31,45].

A boronic acid is a substituted boric acid containing a carbon (C)–boron (B) bond that belongs to the larger class of organoboranes and serves as a Lewis acid capable of reacting with Lewis bases, such as *cis*-1,2-diol and *cis*-1,3-diols or amino acids, to form reversible covalent complexes of five- and six-membered cyclic boronate esters. During the last decade, numerous boronic acid-based fluorescent sensors have developed as saccharide sensors and some specific *bis*-boronic acid sensors even reveal high selectivity for D-glucose (Scheme 5) [35,46,47].

Boronic acid–sugar recognition can be explained by the nitrogen (N)–B interaction and the photoinduced energy transfer (PET) mechanism [31]. The N–B interaction is sometimes considered a hydrogen bond-like interaction. However, in protic solvent systems, solvent insertion can occur in N–B interaction to generate a zwitterionic species. Moreover, in protic media, the N–B interaction can better be described by



Scheme 5 – Interaction of phenylboronic with 1,2- and 1,3-diols to form cyclic boronate esters [46].

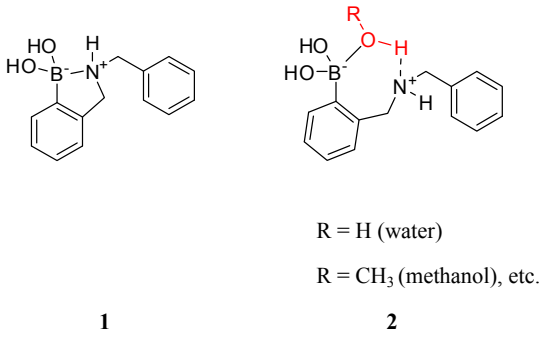


Fig. 5 – The nitrogen–boron interaction in boronate esters (1) (not solvent-inserted) and (2) (solvent-inserted).

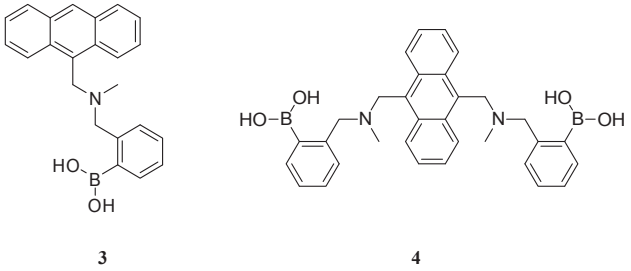


Fig. 6 – Structures of *N*-methyl-*o*-(aminomethyl) phenylboronic acid (3) and *bis*-boronic acid (4).

solvent-inserted (2) instead of (1) (Fig. 5). Although the N–B interaction in protic solvent systems is indirect, it remains an important effect in sensory system design and application [48].

Regarding the N–B interaction, the PET mechanism was introduced to the design of boronic acid fluorescent sensors. Initially, it was proposed that a reduction of boronic acid pK_a via the N–B interaction facilitates binding of the saccharides and boronic acid at physiological pH 7.4. Later, when a 1,2- or 1,3-diol binds with a boronic acid, it rapidly but reversibly forms a cyclic boronate ester, increasing the Lewis acidity of boron, as well as the N–B interaction. Given these advantages, the N–B interaction can help modulate the neighboring fluorophore and create a fluorescence *off–on* response in the sensory system.

The first fluorescence PET sensor was described by James et al [49] in 1994 and has recently experienced strong growth. Notably, the anthracene-based *N*-methyl-*o*-(aminomethyl) phenylboronic acid (3) was selective for increase of D-fructose and fluorescent intensity on addition of saccharides. The

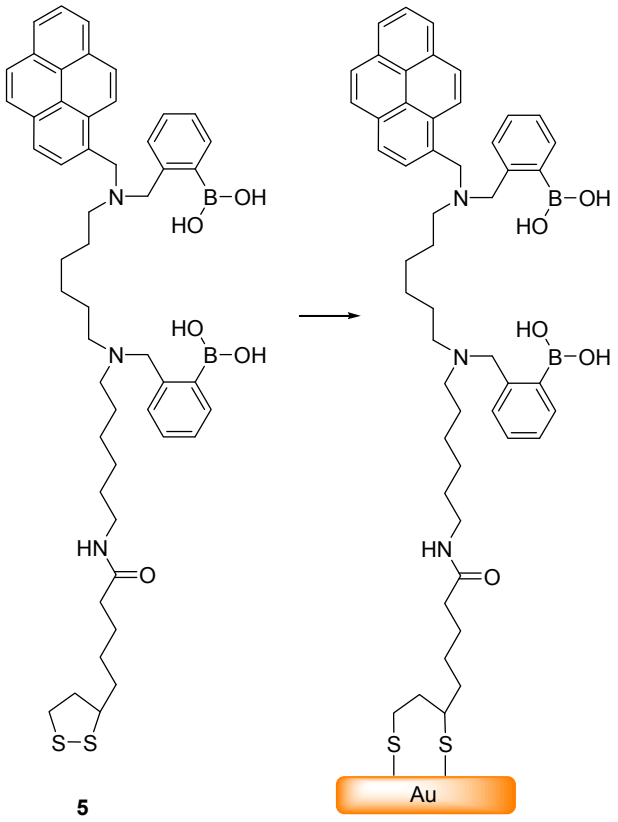


Fig. 8 – Gold electrode surfaced functionalized with a pyrene-based *bis*-boronic acid [37,51].

selectivity for D-glucose can be improved by introducing a second boronic acid, for example, (4), to the system (Fig. 6) [50].

A *fluorophore-spacer-receptor* model can clearly describe the fluorescence off-on mechanism of the PET sensor (Fig. 7) [50]. In this model, in the neutral boronic acid state (sugar-free), the electrons (in most cases from the nitrogen) can be internally transferred to the fluorophore and cause fluorescence quenching to create the sensor *off* spate. Once the boronic acid binds with a sugar, the increased Lewis acidity of the boronate attracts the electron from nitrogen, then binds with the boron atom and creates a sensor *on* state, which enhances fluorescent intensity.

Besides fluorescence analysis, electrochemical impedance spectroscopy and surface plasmon resonance were also administered in boronic acid-based glucose sensors (Fig. 8) [37,51].

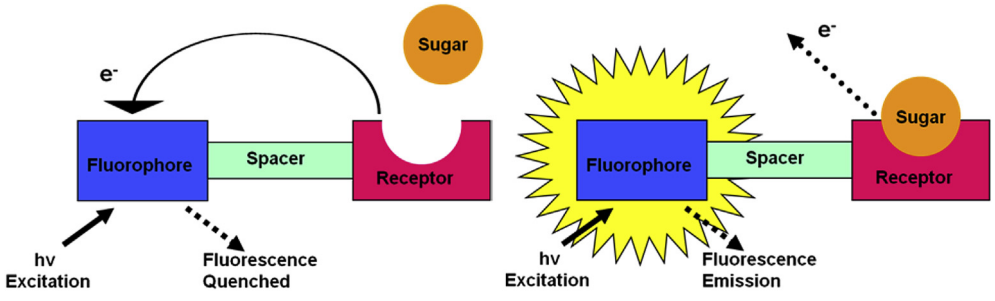


Fig. 7 – Schematic representation of the Fluorophore-Spacer-Receptor design assembly for fluorescence photoinduced energy transfer (PET) sensory system [50].

The glucose sensing contact lens is another breakthrough in the application of boronic acid sensors [52]. These contact lenses using acrylamide copolymer hydrogel with phenylboronic acid incorporate new monosaccharide fluorescent signaling boronic acid-containing probes and enable the measurement of lachrymal glucose concentration [53]. When the boronic acid copolymer binds with glucose, the interference fringes swell and alter the color of the light reflected by the holographic element of the contact lens. This color change occurs proportionally to the glucose concentration. The probe technology can employ fluorescence, fluorescence lifetime, colorimetric, or polarization-based methods.

Despite extensive research on enzyme-free glucose sensors, the clinical market has no commercial products. Meanwhile, improvements in biocompatible sol-gel, potential fluorescence lifetime tests, the application of quantum dots for size-dependent fluorescence emission, and the design of highly selective boronic acid derivatives are expected to continue.

5. Conclusion

Given demand from the growing global population of diabetics, the development of blood glucose control and monitoring technology has achieved significant progress over the past decade. This review summarized current growth areas in blood glucose sensors, ranging from invasive to noninvasive devices. Compared with point of sample tests, CGMS offers diabetes patients a means of real-time measurement of blood glucose level together with alarms of blood glucose events, thus improving their quality of life. However, limitations of sensor lifetime and the accuracy of CGMS still require constant calibration against point of sample tests. Boronic acid derivatives offer promising alternatives as enzyme-free-based glucose sensors, although many such applications remain immature.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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