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Review—Electrochemistry and Other Emerging Technologies for Continuous Glucose Monitoring Devices

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Diabetes leads to chronic microvascular complications for the heart, kidney, and eyes due to uncontrolled glycemic fluctuations. Self-monitoring blood glucose meters can only provide a snapshot of glucose level and are incapable of capturing the granular glucose fluctuations over the 24 h in day. The clinical research has indicated that random blood glucose fluctuations can lead to organ damage. In pursuit of better glucose management, Continuous Glucose Monitoring (CGM) is emerging as a popular alternative owing to its ability to detect instantaneous changes in glucose levels and to alert the users of impending hypo- or hyperglycemic events. In the last decade, several CGM devices have been launched in the market based on different glucose sensing chemistries and techniques. More research is still needed to come up with novel bio sensing concepts to make CGM low cost and highly accurate. Here, we elaborate the CGM techniques such as electrochemical, optical, reverse iontophoresis, microdialysis, and impedance spectroscopy. We emphasize on the widely used electrochemical CGMs with a focus on sensor design and biocompatibility. We also provide an outlook for the future technologies, highlighting the need for innovative materials, possibility of integrating with the Internet of Things (IoT) for real-time e-health monitoring.
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Diabetes is a chronic metabolic disorder in which a patient cannot produce (Type 1) or efficiently use (Type 2) insulin hormone. One death in every 6th second is due to diabetes worldwide and every year more than 7 million people develop diabetes. With this trend, the worldwide incidence of diabetes is expected to reach 552 million by 2030. Generally, diabetic patients experience abnormal oscillation of glucose levels in the body. If glucose is not managed appropriately, over time, diabetes can lead to severe complications which include high blood pressure, strokes, retinal damage, neuropathies, kidney failure, skin ulcers, and cardiovascular diseases. A constant monitoring of the glucose level and adjusted insulin therapy or medications are the only lifesaving solutions for it.

Traditionally, patients have been monitoring their glucose via an invasive finger-prick method, where a patient's finger is punctured with a small lancet followed by analyzing blood glucose levels with a "home glucose monitor or a self-monitoring blood glucose meter (SMBG) (Fig. 1a)." Since home glucose testing meters started to be marketed in the late 1970s, commercial glucose test kits have revolutionized diabetes management.[1] Since then, the glucose sensor market has seen tremendous progress accounting for almost 85% of the world market for biosensors.[2,3] In 2021, the global market for blood glucose monitoring devices had a value of 11.71 billion[4] and it is estimated to reach USD 27.2 billion by 2026. This growing demand for glucose sensors has motivated the scientific community to provide innovative glucose sensing products. As a result, more than six thousand research papers have been published on glucose sensors from 2011 to 2021 (PubMed search, terms "glucose" and "sensor"). Similarly, a search by keyword "glucose monitoring" in Google patent shows more than 100,000 patents filed in a span of four years (2018–2022) and the major contributors are Abbott, Dexcom, and Medtronic.[5]

Presently, over 40 different glucose test kits are commercially available on market. Despite their benefits, SMBG suffers from a few major drawbacks: (i) inconvenience to patients due to regular pricking, and (ii) the time intervals between the finger prick measurements cannot provide the complete glucose dynamics of the patient. Thus, it is possible that in the non-measured interval, the patient is unaware of his or her glycemic fluctuations leading to fatal complications. To circumvent these problems, the idea of an analytical device featuring a continuous measurement of in vivo glucose is contemplated. In this direction, in the last two decades, the Continuous Glucose Monitoring (CGM) device, attached with the body to provide glucose readings every 1–5 min along with glucose trends and alarm for hypo and hyperglycemic condition, has been significantly helpful for effective diabetic management (Fig. 1b). Ideally, such CGMs can also be linked with an insulin pump, which allows the monitor to automatically adjust delivery in response to any rapid changes in glucose, leading to an artificial pancreas.

The first commercial CGM was available in 2004, almost three decades after the launch of SMBG. This indicates the potential challenges associated with the CGM project. Progress in this area would be strongly accelerated by the availability of a review describing the present status of their sensing platform, especially commercially available CGM systems. In this paper, we have emphasized to review (1) Various CGM sensors available in the market, (2) Evolution of these sensors over the years, (3) The sensing chemistries being used in these CGMs. In addition, special focus has been devoted to the history and evolution of subcutaneously implantable electro-chemical CGMs. The strategies and perspectives summarized here will provide practical guidance for an increasing number of researchers to explore next-generation CGMs, and the methodology explained may also be beneficial to develop other sensing systems. In the last section, we have also discussed the future direction for CGM systems.

Glucose Sensors: (Journey from Point Test to CGM)

The origin of modern-day portable glucose sensors is all linked to the fundamental discoveries on sensing technology developed between the years 1950–1980. The conventional glucose sensors were divided into two parts: (i) analytical reaction chemistry, and (ii) a detection system to capture the reaction product and indicate the quantified glucose. For analytical chemistry, most of the sensors relied on the enzymatic reaction between Glucose and Glucose oxidase (GOx) whereas the product of the reaction is detected using either reflectance photometry or electrochemical technology (Fig. 2). Typically, the glucose strip is impregnated with GOx. When in contact with blood, GOx catalyzes the oxidation of glucose to produce Gluconic acid and H_2O_2 in presence of O_2. Most early days glucose sensors quantified the H_2O_2 concentration, which is directly proportional to the level of glucose in the blood.

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ABBOTT Exhibit 2025, Page 1 of 19
Dexcom, Inc. v. Abbott Diabetes Care Inc.
IPR2023-01251

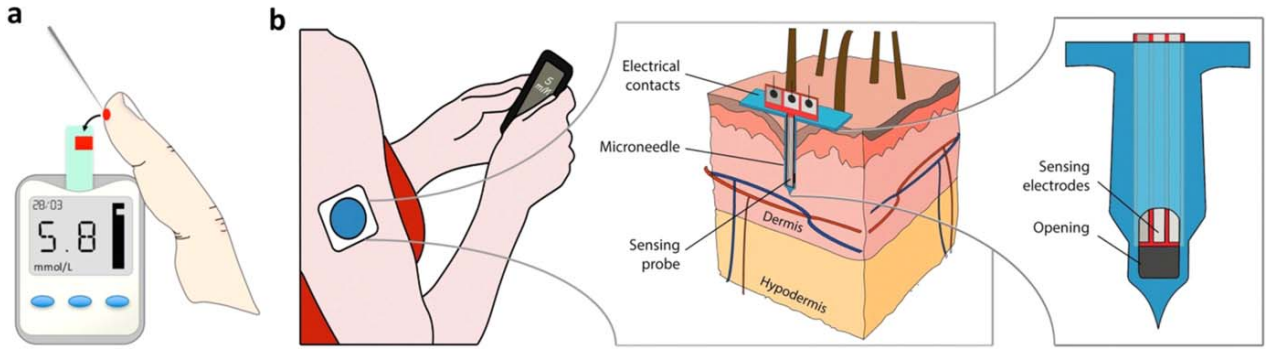

Figure 1. (a) Finger pricking device. Lancet needle; Blood sample on test-strip; Glucose meter displaying glucose concentration in mmol l^{-1}. Adapted from[6] (b) Continuous glucose monitor. Adapted from Ref. 7.

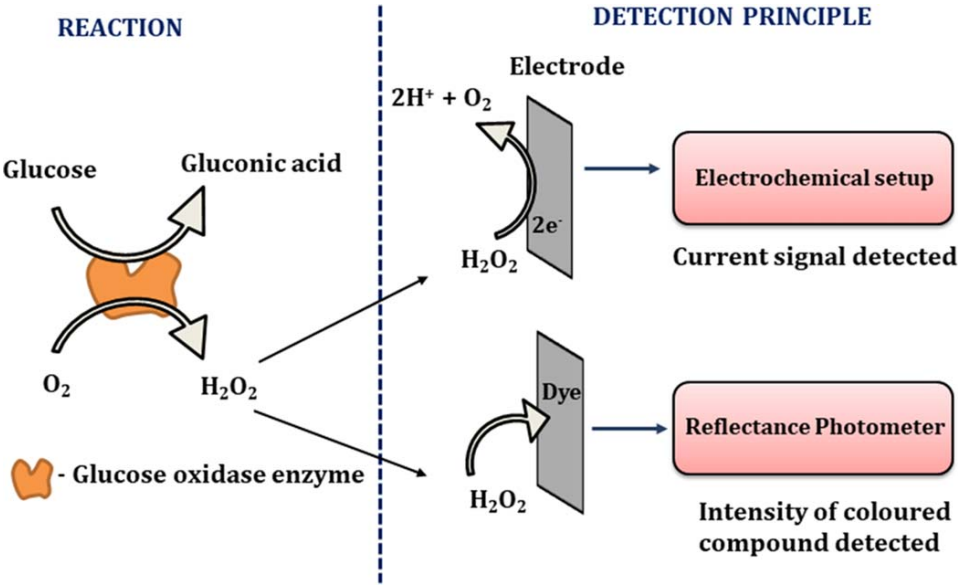

Figure 2. Glucose sensors based on the principle of reflectance photometry and electrochemical technology.

In the reflectance photometry method, the strip is also embedded with a dye which when reacts with H_2O_2, resulting in a colored compound. The intensity of the produced color is then measured using a reflectance photometer which is proportional to the concentration of the H_2O_2. Similarly, in electrochemical technology, quantification of H_2O_2 is obtained using electrical current generated during a reaction. In this method, H_2O_2 is forced to oxidize by applying a potential and an electrochemical setup detects the flow of electrons. The number of electrons detected is directly proportional to the concentration of the H_2O_2. The principle of the electrochemical sensor will be described further (see section CGM Devices Based on Electrochemical Approaches).

By employing the above fundamental sensing mechanism, several home glucose meters are developed. The foremost attempt in this direction was made in 1957, when Joachim Kohn in Miles-Ames laboratory developed a "dip and read" reagent strip, Clinistix.[8] In Clinistix, he used a stiff filter paper embedded with GOx, peroxidase, and the dye orthotolidine. In a redox coupled reaction, glucose oxidase transform glucose to gluconic acid and, in the presence of oxygen, formed H_2O_2. Then H_2O_2 is catalyzed by peroxidase for the oxidation of orthotolidine to a blue-colored chromogen. The generated color was then matched to a color chart to assess the blood glucose level. The above setup was further improved by Ernie Adams in 1965, when he developed Dextrostix, a paper reagent strip that used the glucose oxidase/H_2O_2 reaction but with an outer semipermeable membrane that trapped red blood cells but allowed soluble glucose to pass through to react with the dry reagents. Based on a similar concept, the German company Boehringer Mannheim also developed a blood glucose strip named Chemstrip bG.

These visually monitored strips were widely used by health professionals during the 1965–1970s. However, the color-based visual detection was later realized to be inconsistent and inaccurate because the color was susceptible to fade and dependent on the ambient lighting condition. To encounter this problem, during the early-1970s, Ames laboratory continued its research with the help of Anton Clemens which resulted in a reflectance photometry-based blood glucose sensor.[9] It was known as "Ames Reflectance Meter (ARM)" and considered to be the first-ever blood glucose meter. Based on a similar concept, few other first-generation products were launched such as the Eyetone blood glucose meter by Japanese company Kyoto-Daiichi (1972)[10] and Reflomat by Boehringer Mannheim (1974). Until this time, a blood glucose meter was exclusively used by health professionals only. By the late 1970s, the idea of a handheld blood glucose monitoring system (BGMS) was sought. To achieve this, more efforts were paid towards making the meters smaller in size, user-friendly design, improved meter reliability, and capacity to handle less sampling volume. As a result, next generations of blood glucose meters based on reflectance photometry were developed which include Glucochek (1980) and

ABBOTT Exhibit 2025, Page 2 of 19
Dexcom, Inc. v. Abbott Diabetes Care Inc.
IPR2023-01251

Glucoscan (1983) by Lifescan, Glucometer (1981) by Ames, Reflocheck (1982), and AccuChek (1984) by Boehringer Mannheim became available and reached the hand of diabetics for their personal use.[11]

While pioneering work by Anton Clemens at Ames in the early-1970s laid the platform for the entire modern-day glucose meters which are based on reflectance photometry, a breakthrough discovery by Clarke and Lyons in 1962 gave birth to the electrochemical glucose sensors.[12] They demonstrated that Glucose/GOx/Gluconic acid/O_2/H_2O_2 redox reaction generates current proportional to the glucose concentration that can be detected by an amperometric sensor. Based on Clark's technology, Yellow Springs Instrument Company developed their first blood glucose analyzer in 1975. However, this analyzer was desktop-based and designed particularly to be used in clinical laboratories. The first portable home blood glucose meter using electrochemical approach was ExacTech, which was launched in 1987 by MediSense.[13] Later Medisense was acquired by Abbott which continued developing electrochemical blood glucose meters.

There was no doubt that the arrival of BGMS for home use in the 1980s revolutionized diabetes management. BGMS created a huge impact on the life of millions of patients who otherwise relied only on health professionals for their routine blood sugar checkups. Subsequently, around this time, the idea of a miniaturized artificial pancreas was contemplated. The concept could only become reality if we monitor the glucose continuously and combine it with an insulin pump for the automatic yet accurate delivery of insulin according to the glucose level. It did not take too long to develop the insulin pump. In 1983, MiniMed introduced their first insulin pump MiniMed 502. However, developing a wearable and portable continuous glucose monitoring (CGM) sensor was challenging. This is mainly due to the unavailability of the practical tool for in vivo study. In 1982, Shichiri et al. made the first and most important attempt towards developing a needle-type CGM sensor and tested it in pancreatectomised dogs.[14] However, the development of reliable CGM sensors for a human had remained as a challenge. During 1980–2000, more effort was dedicated to developing CGM for humans. In 1999 first commercial FDA-approved CGM sensors were launched by Medtronic which could run for 3 d. Since then, several CGMs, with improved functionality, have been introduced commercially for personal use. In the next section, we will discuss some of these CGMs and their evolution with a special focus on their sensing chemistry.

Continuous Glucose Monitoring Sensors

The CGM device consists of 3 basic components: a minimally invasive or non-invasive glucose sensor, the transmitter, and the receiver or display (see Fig. 3). The sensor is designed to collect the glucose information in the fluid just under the skin (interstitial fluid) and send a reading. Then the transmitter retrieves the sensor reading and communicates with the receiver for displaying the collected glucose reading. Out of these, the sensor is the main unit that contains an analytical method to detect glucose and is responsible for the accuracy and lifetime of the CGM. The analytical technique and the corresponding sensing platform play a huge role in determining the success and acceptability of a commercial CGM.

Several analytical techniques have been reported for sensing glucose in the past few decades (Fig. 4), these include (i) electrochemical (enzymatic, and non-enzymatic); (ii) Optical (near-infrared absorption, mid-infrared absorption, Raman spectroscopy, photoacoustic spectroscopy, radio wave spectroscopy, fluorescence, optical coherence tomography, surface plasmon resonance, and optical polarimetry); (iii) transdermal (impedance spectroscopy, reverse iontophoresis, sonophoresis, and ultrasound; (iv) thermal (metabolic heat confirmation, and thermal emission spectroscopy).[18–20] However, among these only a few glucose sensing technologies have found themselves successfully integrated into commercial CGM. The most widely used CGM devices are based on electrochemical sensors, although reverse Iontophoresis and optical detection have also been employed. In the next section, we have categorized the commercial CGMs based on their analytical technique, explained the respective sensing principle, and described the product developments along with their sensing chemistries. The accuracy of these commercial CGMs is expressed as MARD (Mean Absolute Relative Difference) with reference to the gold standard for glucose measurement (Yellow Springs Instrument, YSI). To note, the lower the MARD value higher is the accuracy of the sensor.

Blood Glucose vs Interstitial Glucose

To date, all commercial CGMs have sensors inserted into subcutaneous tissue. So, they do not measure blood glucose directly but measure glucose concentration in interstitial fluid (ISF). The blood distributes glucose throughout the body, while ISF supplies glucose to cells. Glucose in blood plasma diffuses across the capillary endothelium and reaches ISF. The ISF glucose concentration depends on several factors such as rate of glucose diffusion into ISF, rate of glucose uptake by cells, blood flow in the given area, and capillary permeability.[21] The changes in blood glucose and ISF glucose are correlated, but these changes occur with a delay. This physiologic lag time has been reported to vary from 5 to 15 min. Depending on glucose levels and the trend of glucose change, the magnitude of lag time can vary. The altered capillary wall structure in diabetic patients can also increase the diffusion barrier and add to physiologic lag time. At times, this can lead to wrong interpretation of readings leading to inaccurate clinical decisions.[22,23] To account for this issue, most of the CGMs require finger-stick calibration against blood glucose values.[24–26] Hence, many device manufacturers advise always confirming CGM readings with blood glucose readings, before any acute therapeutic decision.[27]

CGM devices based on electrochemical approaches.— Biosensors based on electrochemical approach have revolutionized biomedical and healthcare applications. This is primarily because

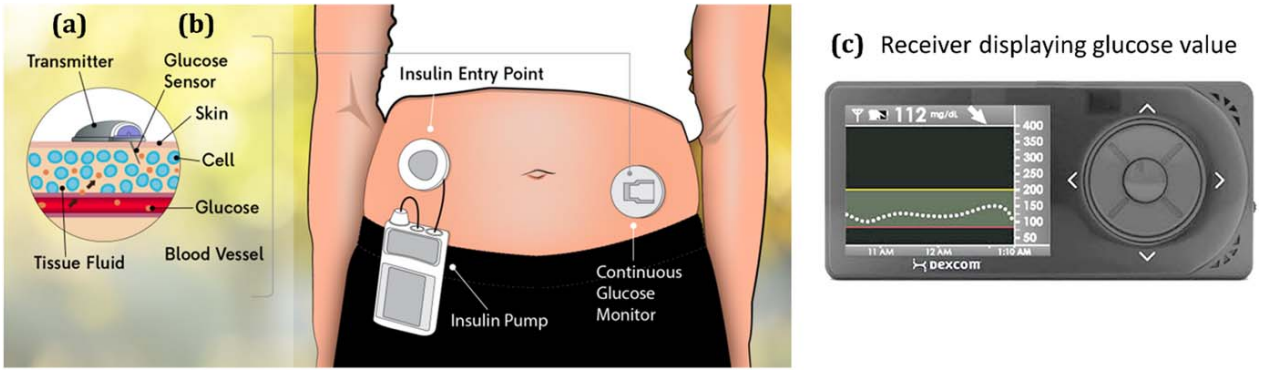

Figure 3. A CGM system consists of (a) a transmitter, (b) a glucose sensor, and (c) a receiver or display. Adapted from Refs. 15–17.

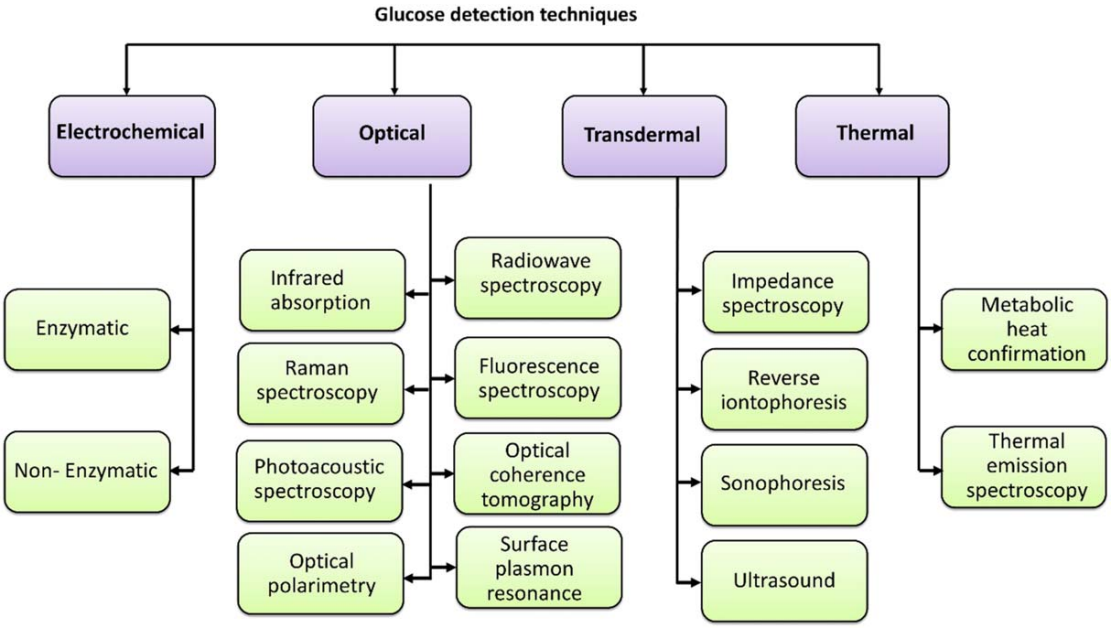

Figure 4. Glucose detection techniques classification chart.

electrochemical sensors can skip the external sample preparation unlike other techniques and whole blood can be directly analyzed.[28–31] They have a shorter response time, are highly user friendly, and utilize a small volume of the sample thus enabling them as an ideal candidate for real-time in-vivo monitoring of biological molecules.[32] In addition, the simplicity and flexibility of preparation, scalable production process with low cost, and the possibility of automation and miniaturization have made the electrochemical sensors attractive.[33,34] Several concepts have been developed based on different electrochemical techniques, these include cyclic voltammetry, chrono-potentiometry, chrono-amperometry, and impedance spectroscopy.[31,35–38]

Principle of electrochemical sensing.—It is based on the mechanism of measuring the flow of current resulting from the oxidation reaction at one electrode (conducting surface) and a reduction reaction at another electrode. In electrochemical glucose sensors, a similar oxidation-reduction is carried out by Glucose/GOx system. In a chemical reaction, glucose transfers its two electrons to the FAD site of GOx and gets oxidized to gluconic acid. The reduced FAD site is then re-oxidized by the dissolved O_2 in the blood. Because of this, O_2 is reduced to H_2O_2. Since H_2O_2 is an electroactive compound, an external potential (voltage) applied causes oxidation of H_2O_2 at the electrode to produce current.[39] The magnitude of the current produced from H_2O_2 is proportional to the concentration of glucose in the blood that reacts in the first place with GOx. This way of sensing glucose via the production of H_2O_2 is called first-generation glucose sensors (Fig. 5a). Here, O_2 acts as a mediator in tunneling the electron from GOx to the electrode surface, and the potential required to reduce it is called as "redox potential" of the mediator. The redox potential must be applied with reference to a known standard electrode system. Therefore, all CGM sensors are equipped with Ag/AgCl as the reference electrode. Typically, most CGM devices are "three-electrode" sensors which consist of (i) a working electrode where Glucose/GOx/ O_2/H_2O_2 exchange electrons, (ii) a counter electrode that helps in completing the circuit, and (iii) an Ag/AgCl reference electrode. In some of the sensors, the reference and counter electrode are combined into one electrode and known as "two-electrode" sensors.

All 1st-generation sensors face a major problem- the enzyme requires dissolved O_2 in the sample to react with glucose. That means, at low O_2 concentration; the reaction becomes virtually independent of the glucose. The aim should be to have an enzyme reaction limited by glucose concentration and not oxygen concentration. To address this issue, all first-generation sensors must find a way to either supply an excess of O_2 at the GOx membrane or dilute the glucose concentration at par with dissolved O_2. The dilution method is used in the YSI glucose meter and still now is considered as the gold standard. However, this practice is complex to integrate with a CGM. Therefore, many commercial CGMs have come up with a proprietary diffusion barrier membrane on top of the GOx to allow an excess of O_2 diffusion than glucose such that the O_2 deficit problem can be avoided.

Alternatively, in second-generation sensors, the role of O_2 is replaced by using an exogenous redox mediator to react with the enzyme (Fig. 5b). Since the mediator is added externally, its concentration can be sufficiently higher than O_2 (thus eliminates the dependence on O_2 concentration).[41] However, the challenge of using an exogenous mediator is that they needed to be attached to the enzyme as well as the electrode. Therefore, a method must be used to immobilize the mediator and enzyme onto the working electrode. This factor is very crucial for CGM sensors, because without proper immobilization, the sensing chemistry may wash away over time from the electrode leading to failure of the sensor. Several immobilization techniques are proposed which include adsorption, covalent binding, cross-linking, and entrapment.[42] Despite it, developing a second-generation glucose sensor that can be used in vivo for continuous monitoring has been challenging.

In third-generation sensors, electrons can directly communicate between the enzyme and the conducing electrode without requiring any mediator (Fig. 5c). The fourth-generation sensors are enzyme independent and rely on metal nanoparticles for the oxidation (Fig. 5d). Both the 3rd and 4th generation sensors are in the incipient stage and require extensive study before they can be used commercially. Presently, all commercially available electrochemical CGM systems are either the first- or the second-generation sensors. These are described in the next section.

Medtronic (MiniMed).—**Product development:** In the 1980s, MiniMed's main focus was to make insulin pump to help diabetics. In that pursuit, they developed two models named MiniMed 502, and MiniMed 506 in the years 1983 and 1992 respectively. Their vision

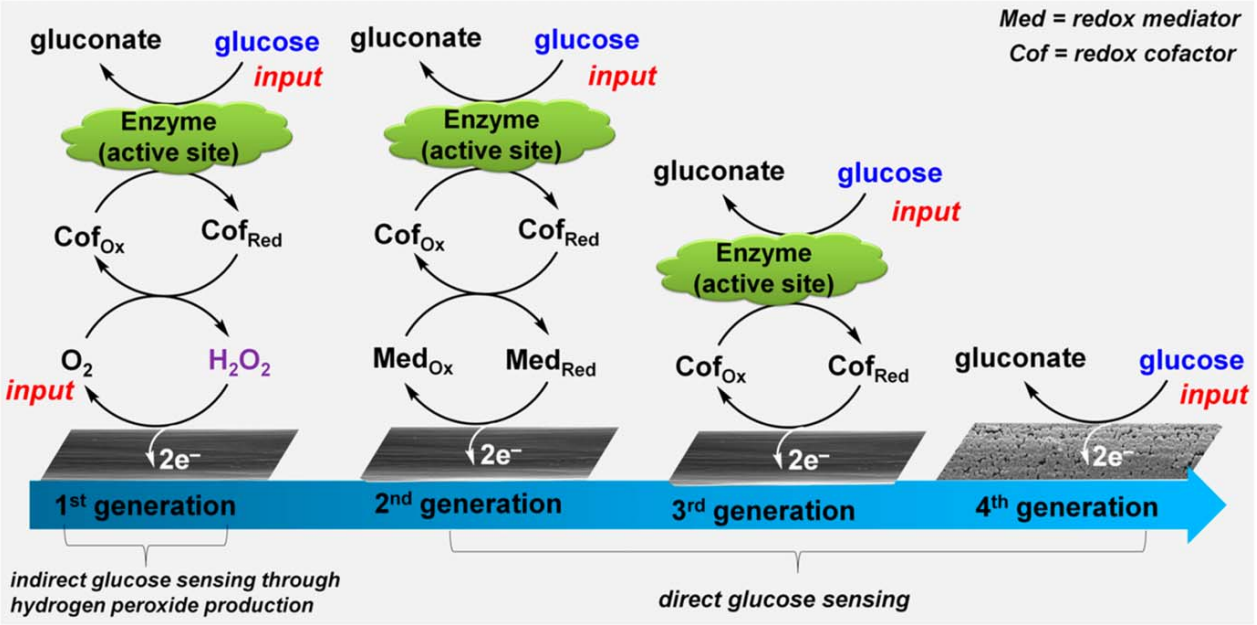

Figure 5. Different generations of the electrochemical glucose sensor. Adapted from Ref. 40.

was to develop a "close-loop" insulin delivery system. To achieve this, they wanted to make a CGM system. Around this time, Dr John Mastrototaro, who earlier worked for Lilly on their glucose sensors, joined MiniMed to work on their CGM project. In 1996, MiniMed prepared their first CGM sensors for the human trial. This led to their first FDA-approved CGM device in 1999 followed by the market launch in 2000 (See Table I for the timeline of Medtronic's event). In 2001, Medtronic acquired MiniMed and continued focusing on improving their CGM devices. The first device was a subcutaneous sensor that could collect interstitial glucose levels every 5 min and was reliable for up to 3 d. However, the device had no display to provide real-time glucose values to the patient; instead, the data was stored in the memory and the information could only be extracted to a computer at the doctor's office. In 2003, the company launched the second product "MiniMed CGMS Gold" which was the same as the earlier model except it could store data for up to 14 d. The first CGM which displayed glucose value in real-time and allowed the patient to manage diabetes was 'MiniMed Guardian RT-System in 2005.

In 2007, Medtronic developed a CGM system that was integrated with an insulin pump (Paradigm Real-Time). The system was called "Guardian Real-Time" and was also equipped with an alarm for indicating dangerously high or low sugar. In 2008, Medtronic launched a CGM system called "iPro" which used wireless technology to retrieve data from the device. It was a "blinded" CGM system and designed specially to aid healthcare professionals. In 2011, Medtronic released a new glucose sensor named "Enlite Sensor" which had a 31% accuracy improvement than its previous generation along with an easier insertion and removal feature. The sensor could perform for up to 6 d and used in the CGM system "iPro2" in 2011. later on, the Enlite sensor was further used in MiniMed 530G (in 2013 for patients outside the USA) and MiniMed 640G (in 2015 for the USA) CGM system. These devices were further integrated with an auto-controlled insulin delivery pump and proposed as the first FDA-approved artificial pancreas.

In 2017, MiniMed 670G CGM system became available which came with Medtronic's most advanced glucose sensor "Guardian Sensor 3" with an accuracy improvement of ~20% from the previous generation. The sensor performance was extended up to 7 d. Medtronic's newest product is Guardian Connect CGM System which was released in 2018. It used the same glucose sensor as the previous model but integrated with upgraded software which can predict possible high or low glucose events up to 60 min in advance.[43–47]

Design of sensor: Medtronic CGM sensor is a three-electrode system based on a first-generation sensor that uses O_2 to react with GOx. It means the sensor must find a way to solve the O_2 deficit problem at the GOx surface. To solve this, Medtronic developed a proprietary glucose limiting membrane comprised of polyurea polyurethane polymer which enhances the O_2 diffusion while limiting the glucose permeability. Figure 6a shows the image of a minimally invasive subcutaneous Medtronic CGM sensor. To present the construction of this sensor, a cross-sectional view of it is displayed in Fig. 6b.

It can be seen that the sensor consists of several layers. These are arranged from bottom to top as follows: (1) The first and bottom layer is called base which is a ceramic or polymer having thickness <30 μm. Typically the ceramic is Al_2O_3; (2) the second layer is comprised of three electrodes as working, counter, and reference. While Platinum black is preferred as a working and counter electrode, other conducting materials such as Palladium, Gold, and carbon can also be used. The reference electrode is Ag/AgCl. The electrodes will sense the electrons generated by the enzyme catalyzed reaction to produce current. Often the electrode surface is modified such that it can become reactive to bind with the upper layer;[50] (3) The third layer is an interference rejection membrane, which is used to inhibit the diffusion of interfering species such as acetaminophen, ascorbic acid, and uric acid. The membrane is comprised of primary amine polymers cross-linked with methacrylate polymers. An example would be a mixture of poly 2-hydroxyethyl methacrylate, poly-l-lysine, and cellulose acetate.[49] In some membrane, polyvinyl alcohol (PVA) polymers cross-linked by an acid crosslinker has also been used.[51] The thickness of this membrane is around 200 nm.

(4) The fourth layer is the analyte sensing layer which is comprised of a glucose-sensing enzyme, a matrix protein in which enzyme is immobilized by an amine cross-linking reagent. For example, the enzyme GOx is combined with matrix protein Bovine serum albumin or human serum albumin that is either sprayed, spin-coated, or brushed on Pt black electrode and cross-linked together with glutaraldehyde by chemical vapor deposition to achieve a layer thickness <1 μm.[49] In recent sensors, the use of glutaraldehyde has been avoided owing to its toxicity. Instead, a highly controllable UV-cross linker is used to cross-link with UV

ABBOTT Exhibit 2025, Page 5 of 19
Dexcom, Inc. v. Abbott Diabetes Care Inc.
IPR2023-01251

Table I. Timeline of CGM devices from Medtronic MiniMed.

Year	Product Development	Comment	Sensor Life (days)
1999	MiniMed was approved by FDA	5 min frequency, but no display	3
2003	MiniMed CGMS Gold launched	14 d data stored, still no display	
2005	MiniMed Guardian RT-System	First display with glucose value indication for patient	3
2007	Guardian Real-Time with Guardian Sensor	CGM attached with insulin pump. (15%-17% MARD)	
2008	MiniMed iPro	Blinded system for health professionals	3
2011	Enlite Sensor launched	13% MARD	6
2011	MiniMed iPro2	Enlite Sensor integrated with CGM	6
2013	MiniMed 530G with Enlite Sensor (First FDA-Approved Artificial Pancreas)	Auto-controlled insulin delivery	6
2015	MiniMed 640G CGM		6
2017	MiniMed 670G CGM with Guardian Sensor 3	World's First Hybrid Closed Loop system. (8.7% MARD)	7
2018	Guardian™ Connect CGM System (with the latest algorithms)	Can alert high or low glucose events up to 60 min in advance	7

ABBOTT Exhibit 2025, Page 6 of 19
Dexcom, Inc. v. Abbott Diabetes Care Inc.
IPR2023-01251

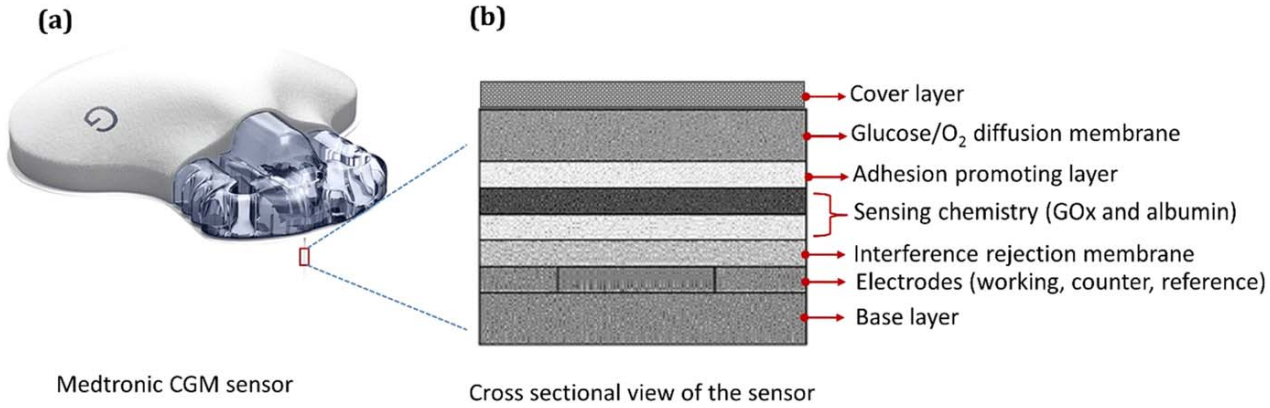

Figure 6. Medtronic CGM Sensor (a) Guardian Sensor 3. Adapted from Ref. 48, (b) Cross-section of the sensor showing different layers used in it. Adapted from Ref. 49.

polymerizable polymer matrix.[52] Alternately, GOx can also be cross-linked with PVA; [53](5) The fifth layer is an adhesion-promoting layer that is required to facilitate the bonding between analyte sensing layer (below) to glucose diffusion membrane (above). Typically, the adhesion-promoting layer consists of a silane coupling reagent such as poly dimethyl siloxane or y-aminopropyltrimethoxysilane.[54,55] Recently, high-density amine layers (e.g. poly-l-lysine polymers) have also been proposed as a promising adhering agent. However, this is only tested with pigs and human trials are yet to be published.[53]

(6) The sixth layer is an analyte diffusion membrane which is the most crucial for evaluating the sensor performance in the 1st-gen sensor. The membrane is specifically designed for high O_2 and low glucose diffusion. The differential diffusion is achieved by an amphiphilic membrane. While the hydrophobic moieties favor O_2 permeability, the hydrophilic moieties promote glucose diffusion. The ratio of hydrophobic to hydrophilic moieties is tailored to obtain the desired permeability of O_2/glucose. Medtronics' patent reveals that the membrane is a polyurea polyurethane polymer formed from the blended mixture of diisocyanate, a hydrophilic diol or diamine, a short-chain aliphatic diol, and a siloxane polymer (Fig. 7a). A representative formulation would be a mixture of hexamethylene diisocyanate, polyethylene glycol, diethylene glycol, and amino-propyl-terminated siloxane. While, the siloxane and short-chain diol permeate O_2 and block glucose, the long-chain diol enables glucose diffusion.[56,57] Earliest Medtronic's CGM sensor used this membrane. However, the glucose permeability of polyurea polyurethane polymer is observed to be decreasing by 3%/ °C with an increase in temperature from 22 °C–40 °C. To address this issue, an additional second polymer, branched acrylate, was used which could increase the glucose permeability by 3%/ °C with an increase in temperature from 22 °C–40 °C. When the linear polyurea polyurethane polymer is blended with branched acrylate, the temperature effect canceled out and resulted in a membrane whose permeability is independent of temperature change.[49,55] The branched acrylate is formed from the mixture of a methyl acrylate, a hydroxyethyl acrylate, a siloxane acrylate, an amino acrylate, and Poly (ethylene oxide)-acrylate[55] (Fig. 7b). Moreover, branched acrylate is highly permeable to glucose. Thus, the proportion of polyurea polyurethane and branched acrylate must be tailored appropriately to get the desired maximum O_2 and minimum glucose diffusion at the subcutaneous environment; (7) The topmost layer is an electrically insulating protective cover layer. It is a non-toxic biocompatible polymer such as silicone compounds, polyimides, epoxy acrylate copolymers, or solder masks. An example of a cover layer polymer would be polydimethyl siloxane. It is ensured that the cover layer is perforated enough to permeate the analytes for reacting with the sensing layer.[54]

Dexcom.—**Product development:** Dexcom's CGM technology can be traced back to the famous discovery in 1967 by Dr Stuart Updike on electrochemical detection of glucose by immobilized glucose oxidase electrode sensor.[58] The sensor was compact and was efficient enough to analyze plasma glucose without separating from the blood. For accurate measurement, the assay required excessive oxygen diffusion over glucose in the sample. Meanwhile, Dr Updike realized that the sensor can be further utilized for continuous in vivo glucose monitoring. In 1979, his team successfully developed a bedside continuous blood glucose monitor which used an automatic blood collecting system combined with an enzyme-immobilized sensor to measure the glucose concentration every 150 sec.[59,60] However, the device needed repeated blood dilution to avoid oxygen depletion, making it impractical for patients to wear or transport. In the 1980s, Dr Updike envisioned making a fully implantable long-term CGM sensor that can measure tissue glucose directly. With this goal, he founded the company Markwell Medical and in 1987 filed a patent for a glucose assay that could measure glucose without the need for dilution. Here, they solved the oxygen depletion problem by attaching a semipermeable membrane on electrode which was capable of permeating more oxygen than glucose. This improved sensor was then implanted in rats and dog which performed up to 3 months with mixed results. In 1999, Markwell Medical was renamed as Dexcom which continued its effort towards commercializing the long-term implantable CGM sensor. In that pursuit, they attempted human trials and found that the implant packaging was not leak-proof which subsequently led to compromised sensor performance in vivo. Because the implantable sensor did not perform as satisfactorily as it was expected, Dexcom later focused exclusively on developing minimally invasive subcutaneous CGM sensor.

In 2006 Dexcom received the FDA approval to sell their first subcutaneous glucose sensor as a short-term CGM system STS (See Table II for the timeline of Dexcom's CGM system). The sensor could detect interstitial glucose levels every 5 min and display the reading on a dedicated receiver in real-time. It had a lifespan of up to 3 d with MARD value of 26%. Subsequently, in 2007 they launched their second CGM system as SEVEN, which had a longer lifespan of up to 7 d. The sensor accuracy was found to be improved with MARD of 17%. Both these systems were prescribed for adjunctive use along with blood glucose strips for diabetes treatment. Frequent calibration was required every 12 h. In 2009, Dexcom commercialized the SEVEN Plus, which came with displayable glucose trend arrows. This safety feature helped patients to know which way their glucose level was directed and at what pace. Following this, Dexcom introduced the G4 Platinum in 2012, featuring a 7-day sensor with a MARD of 13%. A Bluetooth receiver was incorporated into this system to enhance the feature. In 2015, Dexcom released the G5 Mobile equipped with a 7-day sensor and achieving a MARD of 9%. The data can be directly sent to a mobile device without the need for any dedicated receiver. Dexcom's latest CGM device is G6 which was introduced in 2017, featuring a glucose sensor that could last up

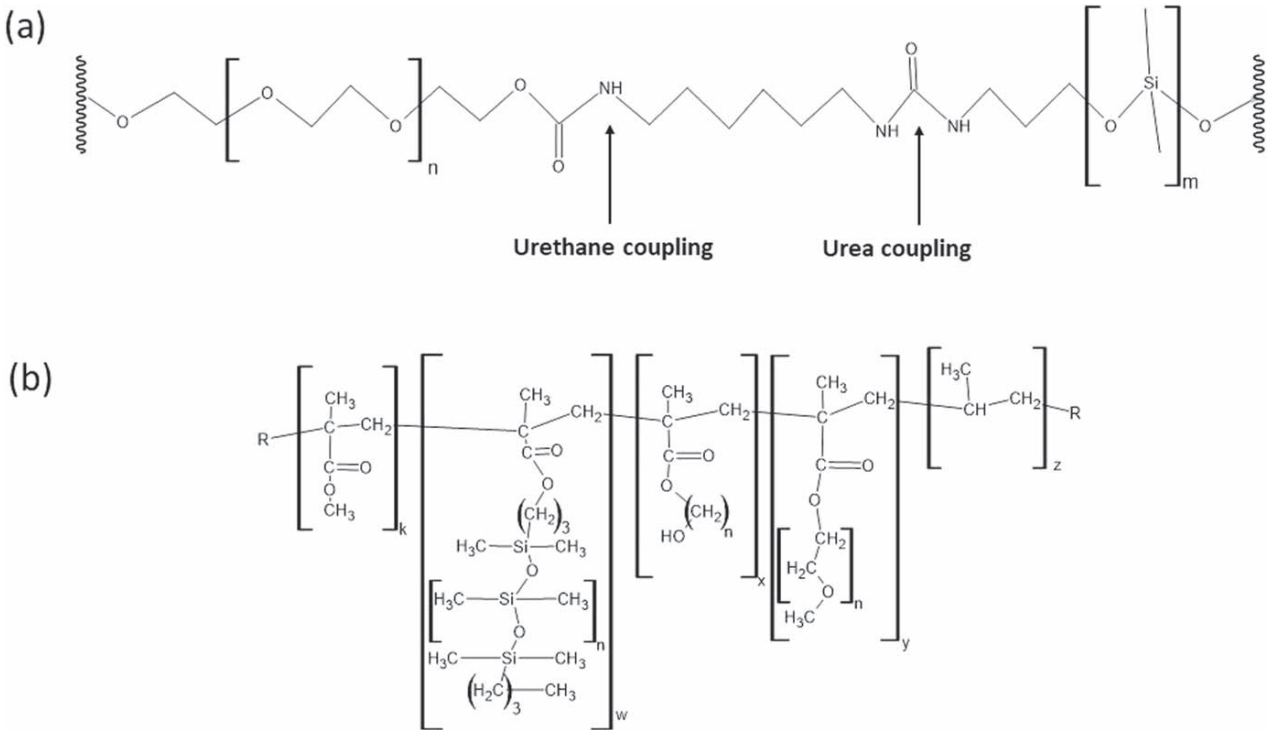

Figure 7. The diffusion membrane comprises of the mixture of (a) polyurea polyurethane polymer, and (b) branched acrylate.

Table II. Timeline of CGM devices from DEXCOM.

Year	Product Development	Comment	Sensor life (days)
2006	STS 3-Day	MARD 26%	3
2007	SEVEN	MARD 17%	7
2009	SEVEN Plus	MARD 16%	7
2012	G4 Platinum	MARD 13%	7
2015	G5 Mobile	MARD 9%	7
2018	G6	MARD 9%	10

to 10 d. The main improvement of the G6 was that it needn't require calibration, yet ensured the same accuracy as previous generations of the sensor.[61] Figure 8 shows the CGM systems developed by Dexcom.

Design of sensor: Dexcom CGM sensor is a two-electrode system and based on a first-generation glucose sensor. Dexcom's patented diffusion control membrane technology helps to counter the oxygen-deficient problem faced by this sensor. Figure 9a shows the cutaway image of a minimally invasive subcutaneous Medtronic CGM sensor. A cross-sectional view of the sensor displaying its construction is shown in Fig. 9b.

It can be seen that the sensor consists of several constituents in layers. These include: (1) Electrodes- The sensor has a working electrode with a helically wound counter/reference electrode (Fig. 9a). Each electrode is formed from a fine wire. While the working electrode can be Platinum/gold/carbon, the reference/counter electrode is Ag/AgCl. (2) Insulator- A non-conductive polymer coating is applied between the electrodes to create the required insulation. Typically, pyrelene produced by the vapor deposition or polymerization of para-xylylene is used as an insulator. Some part of the electrode surface remains uncoated for allowing the electrochemical reaction to happen at the electroactive surface. To create this uncoated part, a portion of the working and reference electrode is masked with a grit material before depositing the insulator. The subsequent stripping of the mask resulted in the exposed radial electroactive window for the reaction. (3) Electrolyte domain- Adjacent to the electroactive surface, an electrolyte domain is configured to facilitate the transport of ions in the aqueous environment at the electrode surface. It includes a buffer solution containing soluble chloride salt, such as normal saline. The solution also protects the sensor against the pH gradient resulted from the electrochemical activity.

(4) Interference Domain: It is purposed to inhibit the permeation of interferents such as acetaminophen, ascorbic acid, bilirubin, cholesterol, creatinine, dopamine, ephedrine, ibuprofen, L - dopa, methyldopa, salicylate, tetracycline, tolazamide, tolbutamide, triglycerides, and uric acid into the electrochemically reactive surface.[64] To trap these ionic interferents, a biocompatible layer comprised of water-soluble polycations and polyanion is used. Some examples of polycations are polyamine acids (poly-L-lysine, poly-arginine, poly-histidine), polysaccharides (chitosan, polyallylamine gluconolactone), and poly aminostyrene. Similarly, the polyanions include polymer those containing malic acid or fumaric acid in their backbone. In some embodiments, the polyanionic polymer is a biocompatible water-soluble polyanionic polymer, alginate, carrageenan, pectin, xanthan, hyaluronic acid, heparin, carboxymethyl cellulose.[65] Besides, the interference layer may also include a catalyst such as peroxidase for catalyzing a reaction that can remove interferents.[66]

(5) Enzyme domain- It consists of an immobilized glucose oxidase layer to catalyze glucose and enable its detection by an electrochemical redox reaction at the electroactive surface. Typically, the enzyme is mixed with an aqueous dispersion of colloidal polyurethane polymer and immobilize in it.[65] In addition, enzyme mutarotase is also impregnated in the enzyme domain to maintain the α D-glucose: β D-glucose equilibrium in the system. Mutarotase counters the effect of compounds such as calcium which otherwise attempt to shift the glucose equilibrium in the body leading to the error in glucose sensors relying on glucose oxidase.[64]

(6) Diffusion resistance domain- It is a polymer membrane that is designed to differentially regulate the diffusion of oxygen and

Figure 8. Dexcom CGM systems. Adapted from Refs. 62, 63.

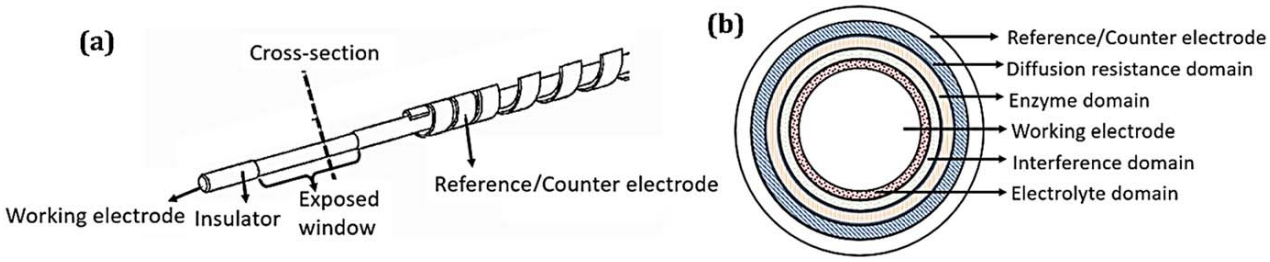

Figure 9. Dexcom CGM Sensor. (a) Expanded cutaway view of the distal portion of a sensor, (b) Cross-sectional view of the sensor marked with line c showing an exposed electroactive surface of a working electrode surrounded by a membrane system. Adapted from Ref. 64.

glucose to the enzyme domain of the sensor. Generally, the membrane is amphiphilic and the hydrophilic domain is dispersed throughout a hydrophobic matrix to permeate high O_2 and enable overcoming the oxygen deficit problem faced by the 1st generation of glucose sensor. The hydrophobic matrix is composed of either one or a mixture of the following polymers such as polyurethane, polyether urethane urea, polyesters, polyamides polysiloxane, polycarbosiloxanes. Similarly, the hydrophilic domain can include polyvinyl alcohol, poly (ethylene glycol), polyacrylamide, acetates, polyethylene oxide, polymethyl acrylate, or polyvinylpyrrolidone.[66,67] For example, one hydrophilic-hydrophobic copolymer formulation would be a polyurethane polymer consisting of 20% polyethylene oxide.[64] Another exemplary combination can be a mixture of silicon polycarbonate-urethane hydrophobic matrix polymer and polyvinylpyrrolidone hydrophilic polymer. Moreover, silicon or fluorocarbon-based material has also been used to enhance the oxygen solubility of the diffusion resistance domain.[68] Cross-linking agents such as carbodiimide, glutaraldehyde, isocyanate, acrylates, or ethylene glycol diglycidyl ether are further used to induce cross-linking between the added polymers during formulation.[65] The membrane thickness is between 2–5 μm.

(7) Bioprotective or biointerface domain- It is the topmost layer of the sensor configured to interface with biological fluid and modifies the host's tissue response when implanted in the body such that the sensor can have an enhanced life span. A porous material containing surface-active end groups such as silicon, florin, sulfonate, zwitterionic groups are typically used to block the charged species at the sensor's surface, hence help to reduce the sensor's break-in-time.[67,69,70] Some examples of porous materials include biostable polytetrafluoroethylene, silicone, PP, PVC, PVDF, and PMMA.[64] The porosity of the membrane plays two main roles: (i) it provides a place for ingrowth of tissue in vivo, (ii) store bioactive agents in the pores that diffuse out of the membrane to the surrounding sensor-tissue interface and prevent biofouling.[71,72] The bioactive agents that are incorporated in the polymers are a mixture of anticoagulant, antiseptic or disinfectant, antimicrobial (antifungal and antibiotic), anti-inflammatory and immunosuppressive agent, and vascularization agent with angiogenic properties. These agents can be mixed with the polymer before curing enabling a homogeneous distribution throughout the membrane of the sensor.[65,66,73]

Abbott.—**Product development:** Abbott's CGM technology can be traced back to the 1990s when Dr Adam Heller at the University of Texas developed a 2nd generation glucose sensor using a redox polymer-based wired-enzyme technology. The sensing chemistry used an exogenous mediator (e.g. a mediator other than H_2O_2) to react with the redox center of the enzyme and did not require oxygen. The mediator and enzyme are chemically functionalized in a polymer. The resultant redox polymer could then react with glucose and exchange electrons. Subsequently, this exchange of electrons is relayed through one mediator to another in the polymer until it reaches the electrode surface.[74] Owing to this connective shuttling of electrons from the enzyme's redox center to the electrode, the method is called wired enzyme technology. The team demonstrated the successful integration of this technology to a subcutaneously implanted glucose sensor.[75] Subsequently, in 1996, Dr Adam Heller and his son Ephraim Heller licensed this redox polymer technology and co-founded the company TheraSense intending to develop a CGM device.

Along the way of developing a subcutaneously implanted CGM sensor, in 2000, TheraSense also developed a glucose monitor FreeStyle™ for use with single-use test strips employing the same wired-enzyme technology. It would painlessly measure blood glucose concentration outside the body. The disposable test strip required just 300 nL of blood which was at least 10 times less than the volume required by other existing glucose sensors of that time.[76]

ABBOTT Exhibit 2025, Page 9 of 19
Dexcom, Inc. v. Abbott Diabetes Care Inc.
IPR2023-01251

TheraSense glucose test strip business became very successful and generated revenue for further continuing their research on implantable CGM sensors. In 2004, TheraSense was acquired by Abbott laboratory and became the core of Abbott Diabetes Care Inc.[77]

Abbott's first subcutaneous continuous glucose monitoring system was FreeStyle Navigator (Fig. 10a) which was approved by the FDA in 2007 but only as an adjunctive device. The system featured a glucose sensor that could be used up to 5-days with a MARD of 12.8%. The system can display real-time glucose values and is equipped with an alarm for hypo- and hyperglycemic conditions.[78] However, glucose levels cannot be recorded during the first 10 h of sensor insertion and frequent calibrations with blood-requiring-single-use strips are required after 10, 12, 24, and 72 h of sensor insertion with blood glucose tests.[79] In 2011, Abbott launched FreeStyle Navigator II, which reduced the warm-up time from 10 h to 1 h. Calibration after 1, 2, 10, 24, and 72 h is still required for accurate functioning. Subsequently, FreeStyle Libre (Fig. 10b) was launched in Europe in 2014 having a sensor lifetime up to 14 d and MARD of 11.4%. It is the first CGM system that is factory calibrated and no longer requires the use of fingerstick calibration. The device comes with a scanner reader which requires a user-initiated scan over the sensor patch for displaying the glucose readings and its trends for the past 8 h. Therefore, FreeStyle Libre is also called a flash or intermittent CGM system. Besides, it is the only CGM device in the market with no interference from acetaminophen. However, it does not have any alarm for hypo- or hyper-glycemia.

In 2016, a similar device was also commercialized in the U.S. labeled as FreeStyle Libre Pro. This system could provide a complete glycemic profile of patients up to 14 d and the glucose reading is blinded to the patients and was intended for use by healthcare professionals only for the analysis. For personal use, Abbott introduced the FreeStyle Libre Flash Glucose Monitoring system and received U.S. FDA approval in 2018.[82] Besides, it is featured to display on-demand glucose concentration values to the patient. FreeStyle Libre systems are approved only for patients aged 18 years or older. Recently, FreeStyle Libre 2 has cleared FDA approval in 2020 and is available to adults as well as children above 4 years of age. The sensor can be worn up to 14 d with MARD of 9.3%. Besides the elimination of fingerstick calibrations, the Libre 2 system has an alarm feature for a hypo-or hyperglycemic condition which was unavailable in earlier versions of Libre. Table III shows the timeline for different CGM devices of Abbott.

Design of sensor: Abbott's CGM sensor is a three-electrode system and uses an osmium-based complex as a mediator to shuttle electrons from glucose oxidase to electrode (Fig. 12). Thus, it does not face the oxygen-deficient problem as is the case with 1st generation of glucose sensors.

Figure 11a shows the image of an Abbot's subcutaneous CGM sensor. The schematic of the sensor labelled with various components is depicted in Fig. 11b. It consists of a working and a counter electrode fabricated with carbon and an Ag/AgCl reference electrode. The portion of the sensor that goes into subcutaneous tissue has a length of 5 mm, width 0.6 mm, and thickness of 0.25 mm.[83] The sensor tip penetrates the skin surface and comes in contact with interstitial fluid containing the glucose molecule. The enlarged and cutaway view of the sensor insertion tip is shown in Fig. 11c.

The working electrode is further coated with a wired enzyme sensing layer. The layer is a polymer hydrogel and primarily responsible for the sensing of glucose. The gel is formed by the crosslinking of enzyme glucose oxidase and a high molecular weight redox polymer. A key proprietary of Abbott's CGM sensor is their redox polymer technology. The redox polymer has three components: (i) a polymeric backbone such as poly(4-vinylpyridine) or poly(N-vinylimidazole); (iii) a cross-linker such as poly(ethylene glycol) diglycidyl ether or N,N-diglycidyl-4-glycidyloxyaniline; and (iii) a transition metal complex as the electron mediator. Although osmium complexes are primarily preferred owing to their low electrode potential, other metals such as iron, cobalt, ruthenium, or vanadium can also be used.[85] An appropriate example of a redox polymer is shown in Fig. 12a, where poly(4-vinylpyridine) is cross-linked with osmium complex by cross-linking agent poly(ethylene glycol) diglycidyl. Moreover, the sensing layer gel has a thickness of 2 μm and a mass of 300 ng. The redox polymer, glucose oxidase, and cross-linkers are present in the weight ratio of 35:40:25.[83]

The gel is very effective in wiring the electrons produced by the reaction of glucose and glucose oxidase to the working electrode via one or more osmium (2+/3+) complex-based redox-polymer mediators. A schematic of the wired enzyme sensing layer showing its various components as well as the path of electron flow is illustrated in Fig. 12b. The electrochemical sensing of glucose is achieved as follows. First, glucose at the interstitial fluid reduces the enzyme's FAD centers to $FADH_2$. Second, $FADH_2$ gets re-oxidized by reducing Os^{3+} to Os^{2+} present in the redox polymer. Finally, Os^{2+} is oxidized back to Os^{3+} at the electrode surface at an applied potential, resulting in a current. The current produced by the oxidation reaction is directly proportional to the glucose concentration in the sample. Nevertheless, the electron transport within redox polymer is due to the collision between oxidized and reduced redox centers tethered to polymer backbone.[87] The electron transfer rate within the polymer is determined by the extent of crosslinking, and length and flexibility of tether between redox center and polymer. The long and flexible tethers are favored to achieve the higher electron transfer rates.[84] Importantly, the degree of cross-linking has to be optimized in the polymer. Otherwise, the excessive cross-linking can result in reduced electron transfer rate, whereas insufficient crosslinking can swell the polymer leading to leaching of sensing chemistry.[85]

Typically Abbott's CGM sensor operates at low redox potential (+0.04 V vs Ag/AgCl) owing to the excellent design of their redox polymer. The redox potential is dependent on the type of ligands used in the transition metal complexes. Examples of some metal

Figure 10. Freestyle Navigator (a), FreeStyle Libre CGM systems (b). Adapted from Refs. 80, 81.

Table III. Timeline of CGM devices from Abbott.

Year	Development	Features/Comments	Sensor Lifetime (days)
2007	FreeStyle Navigator	10 h warm-up time (MARD 12.8%)	5
2011	FreeStyle Navigator II	1 h warm-up time (MARD 12.3%)	5
2014	FreeStyle Libre (bloodless)	(MARD 11.4%)	14
2016	FreeStyle Libre Pro	Professional CGM (MARD 11.4%)	14
2018	FreeStyle Libre Flash	—	14
2020	FreeStyle Libre 2	(MARD 9.3%)	14

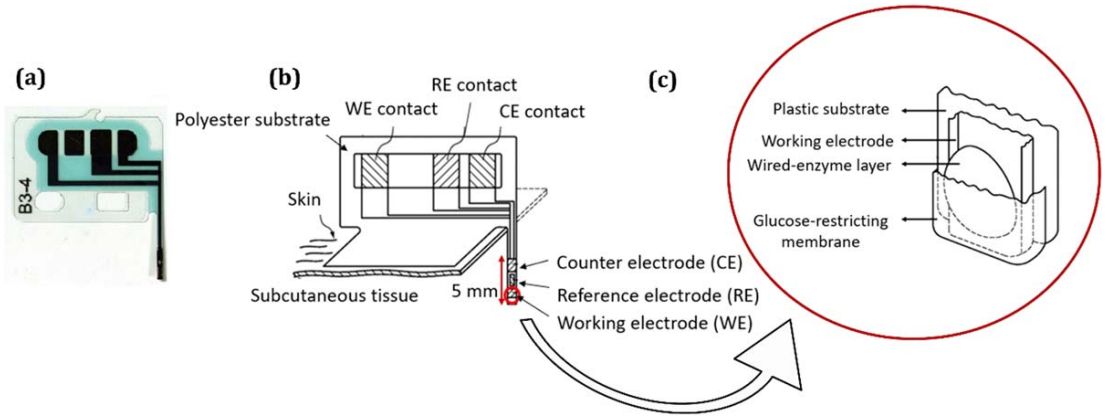

Figure 11. (a) Fully fabricated sensor. Reprinted with permission from Ref. 84. Copyright {2010} American Chemical Society; (b) Schematic of FreeStyle Navigator sensor; (c) Schematic of different layers present on encircled portion of sensor in (b). Adapted from Ref. 83.

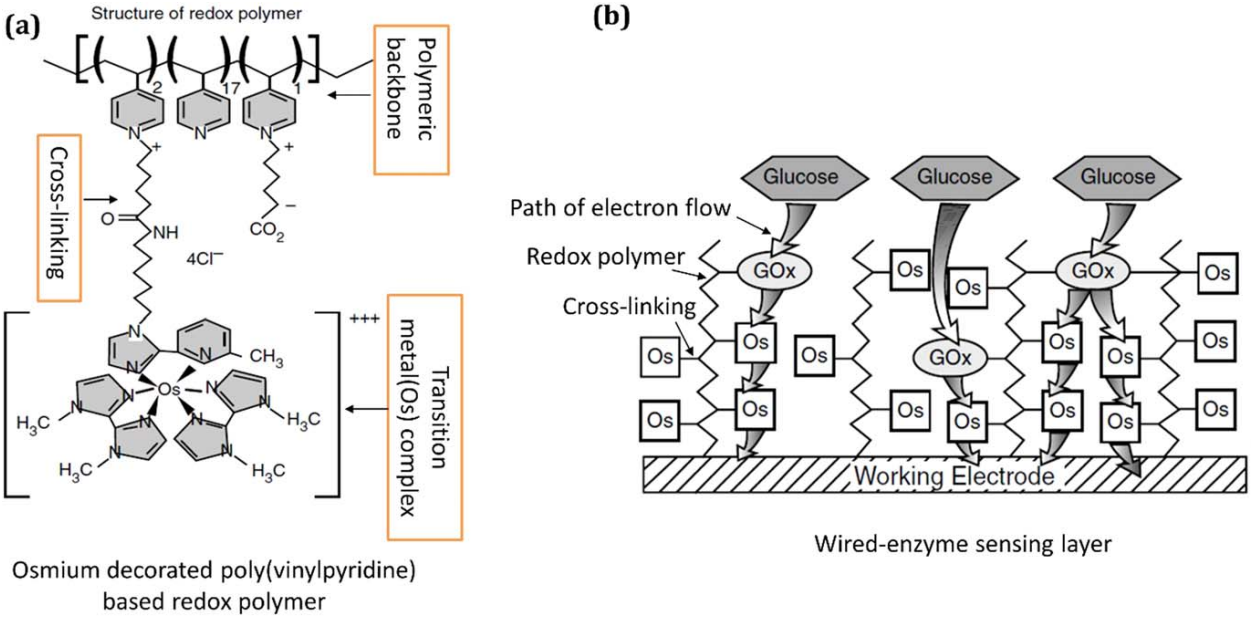

Figure 12. (a) Redox polymer in Abbott FreeStyle Navigator CGM, (b) Schematic of enzyme immobilized within redox polymer with arrows indicating electron transfer from glucose to the working electrode via enzyme and mediator. Adapted from Ref. 86.

complexes along with their redox potential are shown in Table IV. The low redox potential of the mediator is particularly advantageous for minimizing the interference of other electroactive species present in the sensing solution. Hence, it eliminates the requirement for a complex interfering rejection membrane, unlike 1st generation sensor.

Above the sensing layer, a glucose-restricting membrane is disposed to reduce the glucose transport rate to the electrochemically active region around the working electrode. The membrane is hydrophilic and 50 μm thick. It consists of poly(vinylpyridine-co-styrene) copolymer cross-linked by an epoxide cross-linker.[83] The membrane is further modified with hydrophilic moieties as poly

ABBOTT Exhibit 2025, Page 11 of 19
Dexcom, Inc. v. Abbott Diabetes Care Inc.
IPR2023-01251

Table IV. Redox potential varying with different transition metal complexes (For the chemical structure of the complexes, the reader can refer to Ref. 83).

Sr No.	Complex name	Redox Potential (mV)
1.	[Os(1,1′-dimethyl-2,2′-biimidazole)$_2$(4-dimethylamino-2,2′-bipyridine)]Cl_3	−110
2.	[Os(1,1′-dimethyl-2,2′-biimidazole) $_2$ (4-methylamino-2,2′-bipyridine)] Cl_3	−100
3.	[Os(1,1′-dimethyl-2,2′-biimidazole) $_2$ (4-bromo2,2′-bipyridine)]Cl_3	128
4.	[Os(1,1′-dimethyl-2,2′-biimidazole) $_2$ (4-di(2-methoxyethyl)amino- 2,2′-bipyridine)]Cl_3	−86
5.	[Os(1,1′-dimethyl-2,2′-biimidazole) $_2$ (4-di(3-methoxypropyl)amino- 2,2′-bipyridine)]Cl_3	−97
6.	[Os(1,1′-dimethyl-2,2′-biimidazole) $_2$ (4-diethylamino-2,2′-bipyridine)] Cl_3	−120
7.	[Os(1,1′-dimethyl-2,2′-biimidazole) $_2$ (4-methoxypyridine)$_2$] Cl_3	−125
8.	[Os(1,1′-dimethyl-2,2′-biimidazole) $_2$ (4-(N-(4-carboxy)piperidino)− 2,2′-bipyridine)]Cl_3	−60
9.	[Os(1,1′-dimethyl-2,2′-biimidazole) $_2$ (1-methyl-2-(pyridyl)imidazole]Cl_3	−74
10.	[Os(1,1′-dimethyl-2,2′-biimidazole) $_2$ (1-methyl-2-(6-methylpyrid-2-yl)imidazole]Cl_3	−97
11.	[Os(1,1′-dimethyl-2,2′-biimidazole) $_2$ (1-(6-aminohexyl)−2–6-methylpyrid-2-yl)imidazole]Cl_3	−81
12.	[Os(3, 3′-dimethyl-2,2′-biimidazole)$_3$]Cl_3	−230

(ethylene glycol), polyhydroxyl, or hydroxyl modifiers to provide a biocompatible surface required for the subcutaneous part of the sensor.[88,89]

Other subcutaneous electrochemical CGM development.—Recently, Medtrum has developed A6 TouchCare and S7 EasySense CGM system after receiving the CE mark in 2014. While the former can be used for 7 d,[90] the latter is operational for up to 14 d.[91] The device comprised of three components: a tiny flexible transcutaneous glucose oxidase-based electrochemical glucose sensor, a wireless transmitter, and a mobile device for display the glucose value. The sensor measures the glucose level in interstitial fluid and provides a reading every 2 minutes.[92,93] The sensor has claimed accuracy with MARD of 9%.[90] However, the system requires calibration every 12 h.

POCTech CT-100 CGM system launched by Zhejiang POCTech Co. Ltd and has earned its CE certification in 2016 and waiting for their FDA approval. The glucose sensor used here is based on electrochemical detection of hydrogen peroxide resulting from the enzymatic oxidation of glucose and glucose oxidase. The sensor uses a four-electrode system having platinum as working and Ag/AgCl as the reference electrode. The fourth electrode is a blank electrode and employed for measuring the signal from interfering species such that they can be considered while evaluating the pure glucose value. The flexible sensor subcutaneous sensor has a life span7-day with MARD 0f 10.22%.[94,95]

Gradually, more companies have embarked on developing subcutaneous electrochemical CGM realizing their significance and importance. In 2019, Waveform Technology, formerly known as AgaMatrix, was granted CE approval to commercialize their cascade CGM system. It has a 14-day subcutaneous glucose oxidase-based electrochemical sensor combined with a square transmitter for sending real-time glucose readings wirelessly to a mobile app. It also requires calibration every 24 h. The MARD of the sensor is observed to be 11% when compared with Dexcom G5 CGM.[96,97] Moreover, Infinovo has also created a CGM system namely, Glunovo i3. The device provides glucose value every 3 min and can be worn for up to 14 d. The product has received the CE mark in 2019 and is expected to launch in the market soon.[98]

CGM based on microdialysis approach.—**Working principle:** Microdialysis is a continuous sample collection technique that employs a diffusion-based separation method for the collection of tissue fluid. When this approach of sample collection is combined with a glucose sensor, a continuous glucose monitoring device can be hypothesized. It has the advantage of measuring glucose in interstitial fluid or blood without the sensor being in direct contact with blood or tissue; hence overcomes the problems associated with sensor stability and biocompatibility. The main component in this technique is the subcutaneously inserted semi-permeable hollow membrane fiber as shown in Fig. 13. The membrane is permeable only to small molecules such as glucose. In a microdialysis probe, glucose-less solution (perfusate) isotonic to interstitial fluid is pumped into the hollow fiber. The resultant osmotic force drives the diffusion of glucose from the interstitial fluid into the membrane fiber. Gradually, the diffused glucose within the inner lumen of the fiber reaches equilibrium with the glucose in the interstitial fluid. Then, the glucose collected inside the membrane fiber is pumped

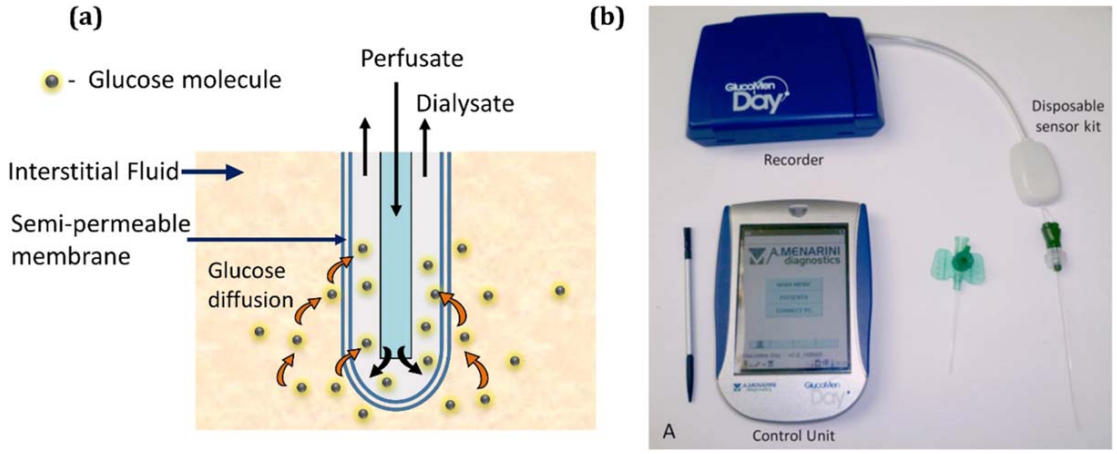

Figure 13. (a) Schematic representation of a microdialysis probe. (b) Image of GlucoMen Day CGM with disposable sensor kits. Adapted from Ref. 100.

(dialysate) to a glucose sensor attached with the microdialysis sampling probe for the detection.[99]

Product development: GlucoDay device by Menarini Diagnostics used microdialysis technique for the collection of interstitial fluid and combined with electrochemical glucose sensor.[101] It is the first microdialysis-based system available in the market to obtain CE marking in 2002. The device can provide continuous glucose information for up to 2 d. GlucoDay consists of a subcutaneously-inserted microdialysis probe coupled with a 1st generation electrochemical glucose sensor. The microdialysis probe is made of regenerated cellulose and can be sterilized using ethylene oxide gas.[99] The sensor consists of a two-electrode system, where Platinum wire and Ag/AgCl are used as working and reference respectively. On the working area, a glucose oxidase layer is present which is immobilized in nylon net via crosslinking with glutaraldehyde. The topmost layer is a glucose flux modulating membrane comprising cellulose acetate and polycarbonate.[79,102]

Menarini Diagnostics also developed the GlucoMen Day CGM system. This system is more compact, lesser electrochemical interference, a wider linear response range, and a more effective signal processing algorithm than GlucoDay.[103] It used a second-generation glucose sensor and functional for up to 4 d. The subcutaneous microdialysis probe uses a polyethersulfone/polyvinylpyrrolidone copolymer.[100] The key novelty of this sensor is its working electrode which is screen-printed carbon modified with a Prussian blue mediator. This allowed the reduction of H_2O_2 at a low working potential of-20 mV vs Ag/AgCl reference, thus minimizing the unwanted electrochemical interference.[104] NAFION is used as a component for the glucose flux modulating membrane.[100]

CGM based on optical approach.—Working principle: Several CGMs based on optical detection techniques are being researched with the expectation of a longer sensor lifetime, better sensitivity, and reagent-free measurement. These include spectroscopic technologies such as near-infrared, mid-infrared, Raman, and photoacoustic methods.[19,105,106] The detection of glucose is based on the interaction of light with glucose. However, CGMs based on these techniques are mostly in their early research stage and yet to be commercially realized. In contrast, recently optical detection based on fluorescence spectroscopy has finally emerged as a potential solution towards developing a commercial CGM system. It does not measure the fluorescence of glucose directly; instead, they measure the signal from an exogenous fluorophore that can reversibly interact with glucose (Fig. 14a). That means, a fluorophore molecule is introduced in the body that is designed to form complex selectively with glucose, and the interaction results in fluorescence. The fluorescence signal is directly proportional to the glucose concentration. Some examples of biocompatible fluorophores are concanavalin A and boronic acid derivatives. Additionally, the method will also require a UV-visible light source to excite the fluorophore molecule and the light should not interfere with the fluorescence of other fluorophores in the body.[105]

Product development: The first commercial CGM system based on optical detection is Eversense, which was launched by Senseonics after receiving the CE mark in 2016 and FDA approval in 2018. It is a fluorescence-based CGM with an implantable sensor that is surgically inserted by the physician under the skin for the detection of glucose in the interstitial fluid (Fig. 14b). After the insertion, a rechargeable and removable transmitter that powers the sensor wirelessly is attached to the skin over the sensor (Fig. 14c).[109] The transmitter converts the sensor's optical glucose signal to a displayable glucose concentration, which is then transmitted to the mobile device to display the glucose value. The sensor requires a 24-hour warm-up phase before the first reading and afterward provides glucose value every 5 minutes.[107] The sensor can be worn up to 90 d with a MARD of 11.1%.[109]

The sensor in the Eversense CGM system is cylindrical and has a dimension of 3.5 mm × 18.3 mm (Fig. 14b). The sensor's fluorescence detection system consists of a biocompatible hydrogel containing a fluorescent indicator molecule, a light-emitting diode (LED) to excite the fluorescent indicator and two photodiodes that measure the fluorescent signal after the binding of glucose to indicator hydrogel. The optical system and core electronics are placed inside biocompatible poly polymethylmethacrylate (PMMA) encasement.[110] The outside of the encasement is grafted with hydroxyethylmethacrylate based-hydrogel containing boronic acid derivative as fluorescence indicator.[105,111] As the interstitial fluid penetrates through the porous matrix of polymer hydrogel, the glucose molecule reversibly binds to boronic-acid derivatives. LED light inside the sensor case excites the indicator molecules that fluoresce when binds to glucose. That means, higher the glucose concentration, the more will be the fluorescence intensity. The resultant fluorescence signal is detected by the photodiodes. Furthermore, the anti-inflammatory response against the implanted sensor is reduced by the release of an anti-inflammatory drug, dexamethasone acetate (DXA), coated on a silicone collar attached to the sensor.[111] This helps in achieving sensor accuracy over a longer period. The system, however, requires fingerstick blood glucose calibration twice per day.[112] To date, this is the only commercially available CGM system based on optical detection of glucose.

Likewise, Profusa is another company that is currently developing a CGM system based on optical sensing of glucose. The system has a micro hydrogel (250 μm x 3 mm) sensor embedded with fluorescence light-emitting molecules that continuously detect the presence of glucose. The sensor is implanted under the skin and the output fluorescence signal from the sensor is detected by a non-invasive optical reader attached on the outside of the skin. Although the company claimed a 2-year lifespan of the sensor, the clinical data is yet to be published.[113]

CGM based on transdermal reverse iontophoresis approach.—Working principle: Reverse iontophoresis is a transdermal needleless technique that uses a small electric current to extract both charged and uncharged polar biomolecules across the intact skin. It employs two major transport mechanisms such as electromigration and electroosmosis to collect glucose in interstitial fluid.[114,115] While electromigration is responsible for the movement of ions across the skin by the direct influence of the electric field, electroosmosis is the major mechanism to transport neutral molecules such as glucose in

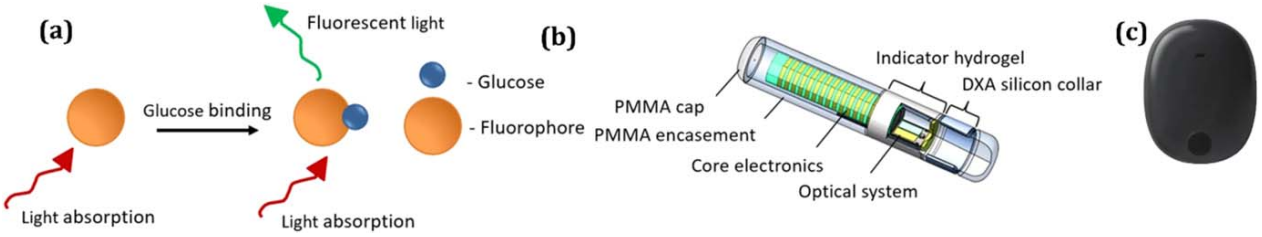

Figure 14. (a) Glucose sensing through fluorescent labeling. Interaction with glucose and fluorophore results in fluorescence, and when glucose is absent fluorescence is suppressed. (b) Eversense subcutaneous 90-day implantable optical CGM sensor. Adapted from Ref. 107, (c) Removable smart transmitter worn over skin. Adapted from Ref. 108.

the interstitial fluid. Typically, an anode and cathode are placed on the skin surface and a low current is applied between these electrodes. This induces the flow of sodium (Na^+) and chloride (Cl^-) ions under the skin towards the cathode and anode respectively. At physiological pH of 7.4, the skin is negatively charged and hence attracts more positive ions (Na^+) than negative ions (Cl^-).[19,116] This gradient of ions at electrodes results in an electroosmotic flow of interstitial fluid with dissolved neutral molecules such as glucose towards the cathode. The extracted glucose is collected into a reservoir near the cathode which is further substantially diluted before quantification by an externally attached electrochemical glucose sensor. The illustration of the reverse Iontophoresis technique is shown in Fig. 15.

Product development: GlucoWatch Biographer, a wrist-watch device by Cygnus, was the first transdermal non-invasive glucose monitor approved by the FDA in 2001. The device contains a single-use disposable component, the AutoSensor, which remains in contact with the skin-side of the biographer. It comprises iontophoresis electrodes, glucose-sensing electrodes, hydrogel pads, and adhesives for skin attachment. The hydrogel contains glucose oxidase and also serves as the reservoir for the glucose collected from the skin.[119] When the device is worn it extracts glucose from the interstitial fluid through the skin by applying an electric current of 300 μA and stores them in the hydrogel.[91,115] The extracted glucose then reacts with the enzyme glucose oxidase present in the hydrogel to form H_2O_2 and subsequently detected by an electrochemical glucose sensor. The sensor consists of a screen-printed platinum/carbon composite layer as the working electrode, screen-printed Ag and Ag/AgCl layers as a reference, and a counter electrode. The counter electrode used for the glucose sensor also serves as the iontophoresis electrode.[120]

GlucoWatch gave 3 readings per hour for 12 h after a 3-hour warm-up period and a single blood glucose measurement for calibration. The next-generation device, GlucoWatch G2 biographer, could provide 6 readings per hour for duration of 13 h with a warm-up time reduced to 2 h. Since the device extracted a very small amount of glucose for sensing, it solved the oxygen deficiency problem faced by peroxide-based sensors. Further, it eliminated the interference from ascorbate and urate which migrated towards anode.[119] The transdermal sampling further helped in filtering off large molecules by the skin, thus did not require any other permselective complex membrane.[120] Despite their advantages, the device had several major problems such as poor accuracy especially during sweating, long warm-up time, and skin irritation due to the flow of mild current.[116] As a consequence of the incessant problems, the device was finally retracted from the market in 2008. However, the concept of reverse Iontophoresis iontophoresis stayed on and the research continued.

Recently, Nemaura Medical has developed the SugarBeat CGM system which is also based on reverse iontophoresis. The device received the CE mark in 2019 and presently waiting for FDA approval. It uses a patch-type sensor that is worn on the upper arm along with a rechargeable transmitter in conjunction with a mobile app to display glucose reading every 5 min after a warm-up period of 25 min. The sensor promises to be functional for up to 24 h with a MARD of 13.7%. However, the peer-review publication is yet to be noted.[121]

***CGM based on transdermal impedance spectroscopy approach.*—Working principle:** Impedance spectroscopy (Dielectric spectroscopy) is a non-invasive glucose monitoring approach that doesn't require any sensing chemistries for glucose detection. Rather, it relies on the concept that variation in electrolytes such as sodium (Na^+) and potassium (K^+) ions in the body fluid is proportional to the variation in glucose centration, thus implying a direct correlation between the both. Thus, measuring the electrolyte concentration of the body fluid using impedance spectroscopy by applying a small current on the skin should indirectly measure the glucose concentration.[20,122]

Product development: Pendra, a non-invasive impedance spectroscopy-based-CGM device, was introduced in 2000 by Pendragon Medical. The device generates an electromagnetic field across the surface of the skin with a frequency ranging from 1 MHz to 200 MHz. Although glucose does not cause a change in impedance in this frequency range, sodium and potassium fluxes in response to glucose fluctuations can induce a change in conductivity across membranes which the device measures a change in impedance.[123] The induced impedance change is detected and displayed as glucose value.

Pendra received CE approval in 2003. However, a post-marketing validation study showed poor accuracy of the device and consequently, Pendra was withdrawn from the market in 2005.[124] Ascensia is another company that is also working on an electrochemical impedance spectroscopy-enabled continuous glucose monitoring system and peer-review results are pending.[125,126] However, changes in temperature, moisture content and any factors that affect microvascular circulation or electrolyte balance can affect the impedance measurements. In addition, the method does not address

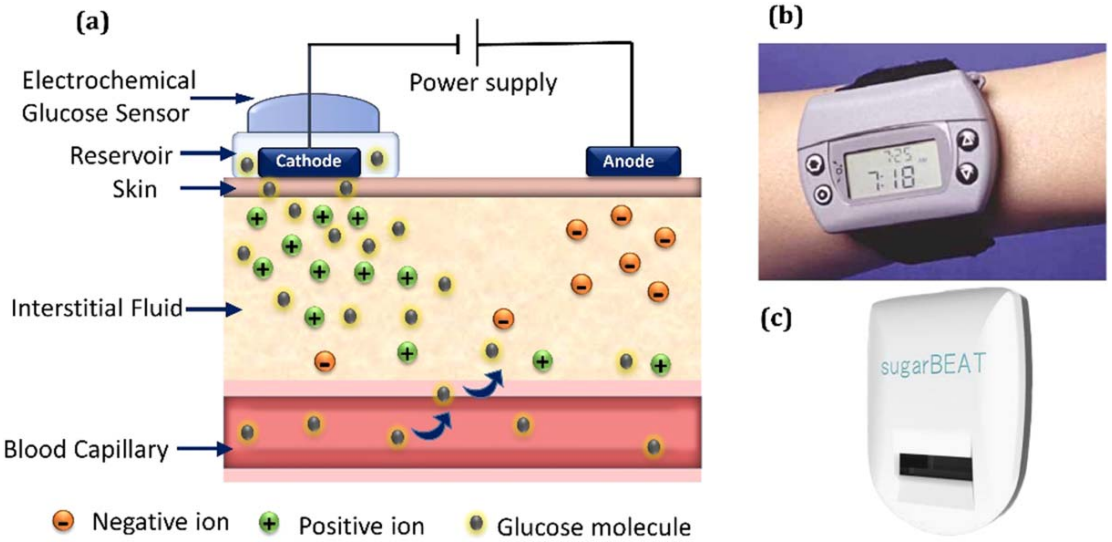

Figure 15. (a) Schematic showing extraction of the glucose by reverse Iontophoresis, (b) Photograph of the GlucoWatch biographer. Reprinted with permission from Ref. 117. (c) SugarBeat CGM system developed by Nemaura Medical.[118]

the interference from other molecules in the glucose-sensing by the variation of the concentration of sodium and potassium ions in the electrolyte. Further study on these factors is necessary for improving the accuracy of the sensors.[122]

Stability and lifetime of the CGM sensors.—The sensor lifetime of approved commercial electrochemical CGM systems is limited to 6–14 d. For example, Dexcom SEVEN Plus and G4 Platinum sensors could be used for 7 d while the G6 system has a 10-day wear period. Medtronic's Guardian REAL-Time and Guardian Sensor 3 have a life of 6−7 d.[127–129] While Abbott's FreeStyle Navigator II can be used up to 5 d, the FreeStyle Libre sensor could be used for two weeks.[130] Recently launched, Eversense CGM, an optical fluorescence-based implantable CGM by Senseonics, has a claimed lifetime of 180 d.[131] Menarini's GlucoDay and GlucoMen Day CGM systems based on microdialysis technique have sensors with a lifetime of 2 and 4 d respectively. GlucoWatch Biographer, CGM based on reverse iontophoresis, had a sensor that could be used for 13 h.[79] Pendra, an impedance-based CGM system, had a lifetime of 90 d however their stability is found to be compromised over time.[132] Among all these commercial CGMs, Pendra and Glucowatch were retracted from the market due to reliability issues.[124,133]

Conclusions

Grand challenges.—The idea of the CGM system seeded in the 1980s has now culminated into reality and is expected to improve significantly in the foreseeable future. For better day-to-day diabetes management and full filling the growing demands globally, the ideal CGM system should have a sensor that is (1) free of pain and discomfort while integrating the sensor, (2) stable, accurate, and reliable (3) long sensor lifetime, and (4) low-cost. Developing such a commercially viable sensor can be a life-changing factor worldwide. In the last two decades, multiple innovative attempts have been made in this pursuit.

Pain-free method.—Non-invasive approaches such as reverse iontophoresis and impedance spectroscopy are theoretically known for pain-free continuous glucose sensing. Despite the initially promising clinical data, the sensor suffers from low sensitivity and accuracy in real-world use, impacting user acceptance. To improve its accuracy, the sensor must find a way to increase the signal-to-noise ratio by minimizing the interference resulting from the body. In that case, failures from Cygnus's Glucowatch and Pendragon Medical's Pendra CGM system are expected to provide the corrective measure required for the success of upcoming non-invasive CGM products by Nemaura and Ascensia.

The advent of microneedle technology in the last decade has drastically reduced the size of the minimally invasive needle to such an extent that they have become virtually non-invasive and painless. Microneedles are either used as glucose sensing probes or as an interstitial fluid collector. Either way, they are integrated with electrodes and immobilized glucose sensing chemistry to catalyze the GOx/Glucose reaction.[134] Using this technology, Biolinq (San Diego, CA, USA) has recently introduced a 7-day wearable CGM patch and awaiting FDA approval.[135] While PKVitality is close to commercializing their product K'Watch,[20] Caura (London, UK), and Sano (San Francisco, CA, USA) are also in-line to launch their microneedle-based CGM devices.[136]

Long sensor lifetime.—Recently, the fluorescence-based optical sensor has been at the forefront to address the short-lifespan issue of the CGM sensor. While Eversense from Senseonics claims for 90 d of sensor life, Profusa is in process of developing a sensor that can be worn for up to 2 years. However, both these sensors are required to be implanted by medical professionals under the skin for the whole period of sensor life. That means, the sensor attachment is invasive and prone to exhibit foreign body response, practically may lead to inconvenience for many users. Hence, it will be research worthy to develop the next generation of optical sensors that can monitor glucose despite attaching outside of the body.

Futuristic Sweat, Saliva, and Tear glucose sensor.—Besides interstitial glucose, novel ideas have emerged to measure glucose continuously using biofluids such as sweat, saliva, and tear. For example, the possibility of a fully integrated warble patch type glucose sensor combining with electro-osmotic sweat extraction method has been demonstrated (Figs. 16a–16b).[137–139] Similarly, wearable oral cavity sensor comprising Pt/Ag/AgCl (Fig. 16c) or Prussian blue electrode system (Fig. 16d) immobilized with enzyme glucose oxidase for monitoring saliva glucose has also been shown.[140,141] A considerable progress in tear glucose-sensing technology is achieved by Dutch company NovioSense. They have developed a minimally-invasive spring-like micro-electrochemical sensor that is wearable under the lower eyelid to provide glucose information continuously (Figs. 16e–16f). The CGM device has shown promising clinical results upon comparison with Abbott FreeStyle Libre and Dexcom G4 over a 4.5 h experiment.[142] Unfortunately, most of these innovative methods are in their incipient stage and much work to be done before they are clinically reliable and commercially viable.

Challenges in electrochemical sensor.—While the quest for the ideal CGM system continues leading to many alternative possibilities, presently minimally invasive subcutaneous electrochemical

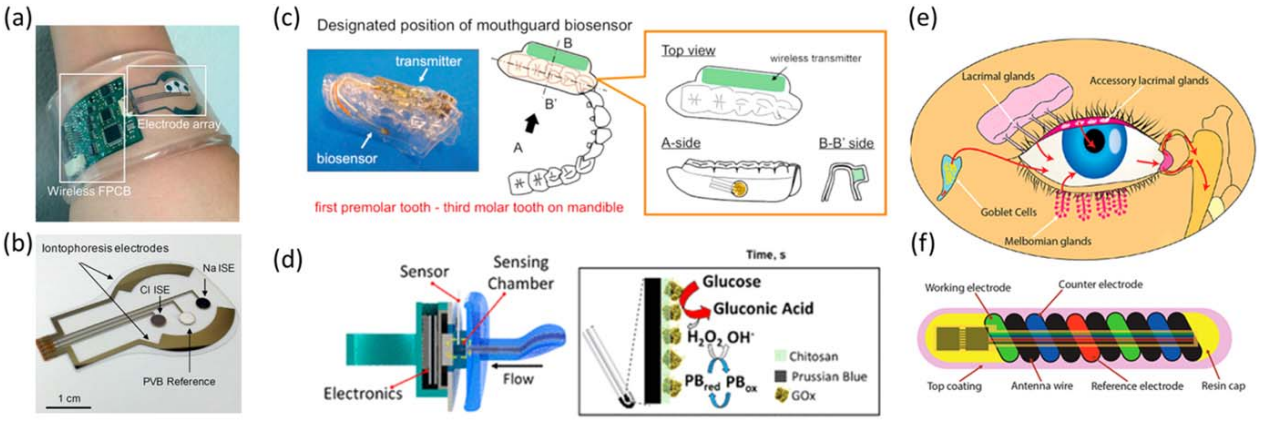

Figure 16. (a)–(b) Wearable sweat sensor adapted from Ref. 137, (c) Wearable oral sensor for saliva glucose detection adapted from Ref. 140, (d) Mouthguard-based sensor. Reprinted with permission from Ref. 141. Copyright {2019} American Chemical Society. (e) NovioSense electrochemical tear glucose sensor, with (f) design showing the electronic components adapted from Ref. 142.

CGM sensor is the market leader and unlikely to be replaced for a while. This is because, in the last decade, these sensors have addressed several key challenges. The size and weight of the CGM device have narrowed. The MARD of the sensor has drastically reduced from >20% in their early launch to <10% in 2021. The sensor life has been extended from 3 d to 14 d, while the user interface has also improved. The next immediate goal should be to reduce the MARD value below 5%. To enhance the sensor accuracy and stability, the focus must gradually shift towards incorporating the 2nd-gen or 3rd-gen glucose sensor in the CGM system. This will obviate the need for an additional complex membrane system to counter the oxygen-deficit problem in the 1st-gen sensor, which is often responsible for limiting the sensor performance. Nonetheless, if the 2nd-gen sensor is employed, an innovative immobilization strategy has to be developed such that the sensing chemistry containing external mediator remain stable for extended operation. Likewise, the sensor lifetime can be increased up to 30 d or more. To achieve this, one can take inspiration from optical CGM sensors owing to their longer sensor life (<90 d), and emphasize how to translate the understanding from optical sensing chemistry to an electrochemical detection system. Moreover, the ideal CGM sensor should be free from fingerstick calibration. For this, a possible solution would be to measure interstitial Na^+ along with glucose by the subcutaneous electrochemical sensor. The Na^+ concentration in interstitial fluid is approximately constant over time.[114,143] Hence, it can be potentially employed as an excellent internal standard for co-relating the blood and interstitial glucose without requiring any blood samples for calibration.[144]

Alternative approaches.—Few CGM systems were withdrawn from the market while many promising technologies didn't even reach the market due to irritation during usage, painful sampling, difficult handling, and inexplicable presentation of data. From a user's point of view, an ideal CGM system needs to be painless, with less maintenance requirements, and provide data in an easily understandable way without interfering with daily activities. In pursuit of this, CGM systems such as teeth tattoos, skin tattoos, contact lenses, and watches can be implanted to troubleshoot skin irritation problems. To resolve the user friendliness issues, many companies have come up with smartphone applications that can represent glucose levels and trends graphically and can alert users of impending hypo- or hyper-glycemia. Moreover, most minimally invasive CGM sensors have a short lifespan of up to 1–2 weeks. The major challenge faced by these sensors is the foreign body reaction at the sensor invasion area, resulting in reduced sensor stability. Several biocompatible coatings combined with angiogenic or anti-inflammatory drugs have been proposed demonstrating the sensor life of up to 2 months. For example, the sensor with a Cultrex-coated membrane has shown stability for up to 4 weeks. However, these are still in the proof-of-concept stage and more studies are required before they can be fully utilized in the market. More on this topic is recently reviewed by Nery et al.[128]

Innovative materials for biosensor.—Recently, the implementation of innovative materials for novel biosensors has been an emerging research area. Ideal materials for biosensing need to have several requirements such as good conductivity, biocompatibility, stability in response to changing temperature, ionic strength and pH, selectivity towards analyte of interest, low cost and should be easily mass- produced.[145,146] Metallic and carbon-based nanomaterials, conductive polymers, and metal-organic frameworks have been found to enhance the performance of biosensors and hence have received special attention lately.[34,147] For example, Rahman et al. developed a low-potential amperometric glucose sensor by modifying electrodes with multi-walled carbon nanotube film and demonstrated stability for up to 5 weeks with a sensitivity of 12.1 μA/mM.[148] Fan et al. fabricated an enzyme-less glucose sensor based on Cu-Ag_2O nanowalls which showed high sensitivity to glucose (298.2 μA mM^{-1}) at a detection potential of 0.4 V and retained about 90% of its initial performance even after 30 d.[149] Similarly, Hocevar et al. presented a potentiometric glucose sensor using a nanometric film of electroactive polythiophene derivative. The sensor showed an excellent sensing performance due to the structure of the polymer which enables the activation of the hydroxyl group resulting in the oxidation of glucose molecules.[150]

Prospects of integration with IoT, AI, and cloud computing.—The integration of CGM systems with the Internet of Things (IoT) has the potential to design flexible and intelligent e-healthcare systems. Sensors combined with IoT that consists of wireless sensor networks, smart gateways, and the Cloud can provide an innovative ground for real-time health monitoring.[3,143,151] For example, the huge amount of information that is available from wearable devices increases the complexity of the decision-making process. On integration with IoT, the sensor signals can be monitored, recorded, and analyzed from any corner of the world. They can also provide intelligent alarms in response to critical changes in the target analyte thereby helping to control global problems. The utilization of Artificial Intelligence (AI) based algorithms in health monitoring systems have provided a way to analyze the complex set of clinical data and generate predictive outcomes as well as recommendations for therapy adjustments.[152–154] In addition, AI and Machine Learning technology can also be applied to sensing material and architecture. They are capable of theoretically predicting the performance and limitations of a sensor and providing solutions before going into experimental evaluations. It helps the scientific community to save time, resources, costs as well as workforce. Moreover, there is still a need for the development of advanced algorithms to process and analyze the recorded data and provide predictions that can go a long way in helping humanity.[3]

Outlook.—Over the coming years, the CGM platform will continue to improve its accuracy, precision, selectivity and stability, ease of operation, patient safety, and calibration simultaneously with advanced software and miniaturized hardware to make a huge impact in diabetes management. Concurrently, special attention must be devoted to making the device cost-effective such that it can address the current economic burden faced by diabetics, especially patients living in low- and middle-income categories. Meanwhile, healthcare teams are expected to continue to educate people through demonstrable clinical benefits for wider adoption of CGM technology. They can also communicate patient's product feedback to the manufacturing companies for sustained product quality. Finally, combining the continuously evolving next-generation of CGM devices with a closed-loop insulin delivery system, may fructify the vision of creating a fully automatic artificial pancreas in the near future.

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