

The Chemistry of Commercial Continuous Glucose Monitors

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Abstract

The analytical methodologies of the continuous glucose monitors (CGMs) commercialized to date are described. The devices include two noninvasive products: the GlucoWatch[®] (Cygnus, Redwood City, CA) G2 Biographer uses iontophoresis to obtain a sample and electrochemistry for glucose detection, and PENDRA[®] (Pendragon Medical Ltd., Zurich, Switzerland) utilizes impedance spectroscopy. Three minimally invasive systems employ subcutaneous amperometric sensors—Guardian REAL-Time (Medtronic MiniMed, Sylmar, CA), DexCom[™] STS[™]-7 (DexCom, San Diego, CA), and FreeStyle Navigator[®] (Abbott Diabetes Care, Alameda, CA). The GlucoDay[®] (A. Menarini I.F.R. S.r.l., Florence, Italy) collects a sample with a minimally invasive microdialysis fiber and measures the glucose electrochemically.

Introduction

AS A PRIMARY METABOLIC FUEL, the glucose molecule is intrinsically interesting, but the central role of glucose in the diagnosis and treatment of diabetes mellitus has made the detection and quantitation of glucose an enormous field of research for nearly a century. The work of Banting and Best in the early 20th century included not only the discovery of insulin but also the development of methods for the analysis of glucose in blood and urine that were necessary to demonstrate insulin's therapeutic action. As insulin therapy became the life-saving treatment for patients with diabetes, urine glucose tests evolved as a necessary management tool.

Improvements in insulin therapy have proceeded hand in hand with improvements in glucose testing. When researchers postulated the superiority of blood glucose measurement over urine tests for the control of insulin therapy, the fundamental technology for performing blood glucose tests outside of the lab was already available. Although the devices for measuring blood glucose used for that pioneering work are crude by today's standards, no breakthrough for the measurement of blood glucose at home was required to conduct the critical research. Subsequently, the need for more accurate and convenient blood glucose tests spawned what has become a multi-billion dollar industry devoted to the self-measurement of blood glucose. The combination of improved insulin therapies with improved blood glucose tests revolutionized the treatment of diabetes within 10 years.

Commercial possibilities for improved glucose testing have been the most significant stimulant for the continued research

and development in this field, and the work has continued at an accelerating pace. Development of the continuous glucose monitor (CGM) was initiated with the hope that this new glucose measurement tool would enable significant improvements in diabetes management. Although the possibility for therapeutic improvement was understood intuitively, no hard research could be conducted without a practical tool. Shichiri et al.¹ reported an in vivo glucose sensor in 1982, but the enormous technical challenges of developing a reliable glucose sensor for humans could not be overcome without considerable commercial investment. That investment has resulted in a number of commercially available products that report real-time glucose concentration in a near-continuous manner, and the research to incorporate these new tools into diabetes management is currently underway. It is highly probable that the improved information available from CGMs will again revolutionize the treatment of diabetes.

This review will be narrowly focused on the chemistry of the commercialized CGM products. More exhaustive reviews of the vast field of glucose biosensors have been published recently.²⁻⁵

Noninvasive Methods

*GlucoWatch[®] G2 Biographer
(Cygnus, Redwood City, CA)*

The GlucoWatch technology was developed by Cygnus and subsequently sold to Animas Technologies LLC, which is currently part of Johnson and Johnson. This product was approved by the Food and Drug Administration in 2001 as an

adjunct to finger stick testing, i.e., finger stick tests have the necessary accuracy for insulin therapy decision-making, but the additional information from GlucoWatch could be used to improve therapeutic decisions. The system includes a hydrogel pad placed on the skin covered by a watch-shaped meter. After a 3-h warm-up period and a finger stick glucose test for calibration, the GlucoWatch Biographer reports glucose results that are updated every 20 min. After 13 h the disposable pad and the site of the pad application are changed. A second-generation product, the GlucoWatch G2 Biographer, has a 2-h warm-up period and reports glucose every 10 min.

The GlucoWatch employs reverse iontophoresis whereby a small current applied to the skin brings subcutaneous fluid through the skin by the attraction of ions to an Ag/AgCl electrode pair. The fluid contains glucose proportional to the tissue glucose concentration below the skin.⁶ The fluid is collected in the hydrogel pad located between the skin and the iontophoresis electrode. A hydrogel pad described in a Cygnus patent application is a mixture of two hydrophilic polymers, polyethylene glycol (Fig. 1) and polyacrylic acid (Fig. 2), cross-linked by an electron beam.⁷ The electron beam forms radicals on the polymer backbones, and the radicals combine to form the cross-linking bonds.

The glucose is detected electrochemically through catalytic oxidation by the enzyme glucose oxidase (GOx) incorporated into the pad. The oxidation of glucose, shown in Figure 3,

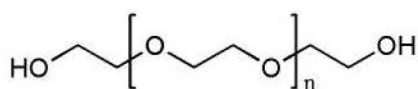


FIG. 1. Polyethylene glycol.

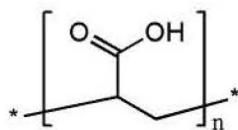


FIG. 2. Polyacrylic acid.

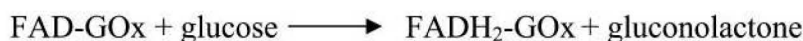


FIG. 3. Reaction of glucose with GOx.

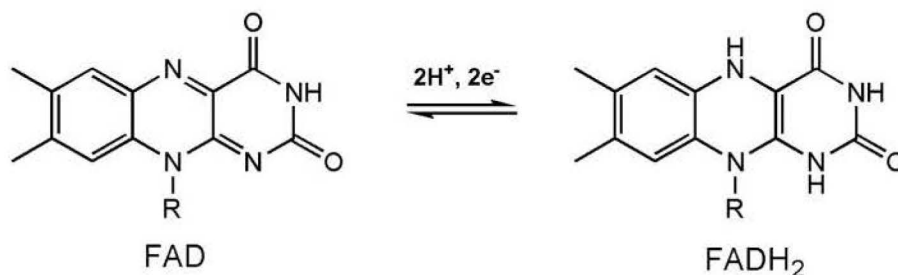


FIG. 4. Reversible oxidation of FAD.

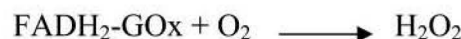


FIG. 5. Reaction of reduced GOx with oxygen.

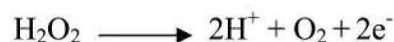


FIG. 6. Reaction of hydrogen peroxide on an electrode surface.

involves a transfer of two electrons from glucose to the flavin adenine dinucleotide (FAD) cofactor of GOx.

The flavin of FAD undergoes the reversible reaction shown in Figure 4.

The direct re-oxidation of FADH₂ on an anodic electrode to produce a measurable current is impractically slow because the cofactor is buried deep inside the enzyme, and efficient oxidation on the electrode surface requires physical contact. An enzyme electrode requires the action of a small molecule that can oxidize the enzyme cofactor and transfer the electrons to an electrode. GlucoWatch uses atmospheric oxygen/hydrogen peroxide (O₂/H₂O₂) as the redox pair to perform the electron transfer shown in Figures 5 and 6. The redox pair is referred to as the mediator.

The measurement cycle of the GlucoWatch includes a 3-min application of a 3 mA iontophoretic current followed by a 7-min cycle to completely oxidize the H₂O₂ at an applied potential of 0.42 V versus Ag/AgCl. This is followed by a second cycle on a second electrode; a running average of the integrated current from both electrodes produces a glucose value every 10 min.

The iontophoretic current disrupts the skin surface, and skin irritation proved to be a major drawback to this product. The GlucoWatch has been withdrawn from commercial distribution.

PENDRA® (Pendragon Medical Ltd., Zurich, Switzerland)

The PENDRA was CE approved and released in European markets in 2004 as an adjunct to finger stick blood glucose tests. There is no chemistry involved in the PENDRA device;

rather, a physiological process correlated to glucose concentration is interrogated by impedance spectroscopy at the skin surface.⁸ A small electromagnetic field generated by an AC current in the range of 1–200 MHz induces impedance changes within the skin and underlying tissues. The changes in impedance are related to sodium and potassium gradients, which are correlated to glucose concentration. Although initial evaluations of the device were promising,^{8,9} post-market evaluations indicated poor accuracy, and the device was withdrawn from commercial distribution.¹⁰ Clearly this device was not adequately evaluated before introduction, and this embodiment of impedance spectroscopy is not a reliable method for measuring glucose noninvasively.

Subcutaneous Amperometric Electrodes

General principles

An amperometric system measures the current flowing from an oxidation (electron-producing) reaction at a working electrode to a reduction (electron-consuming) reaction at a counter electrode. Glucose oxidation (Fig. 3) is the first step in the reaction sequence of the commercially available subcutaneous glucose sensors. As explained earlier, a mediator is then required to shuttle the electrons from GOx to the working electrode, and a potential (voltage) must be applied to the working electrode in order to oxidize the mediator. The magnitude of the potential is determined by the electrochemical properties, i.e., redox potential, of the mediator. A stable reference potential provided by a reference electrode is required to apply a defined voltage to the working electrode. In the commercially available subcutaneous glucose sensors, the reference electrode is Ag/AgCl. A typical configuration of the sensor includes three electrodes: a GOx working electrode, a counter electrode, and an Ag/AgCl reference electrode. A two-electrode configuration can be constructed if the reference and counter are combined into a single electrode, the counter/reference. In this configuration the reaction at the counter/reference electrode is the reduction of AgCl to Ag, and the amount of AgCl within the electrode must be sufficient to react for the lifetime of the sensor.

In electrochemical finger stick blood glucose test strips, the enzyme and mediator are typically applied to the working electrode as a solution and deposited by solvent evaporation. When blood is applied to the electrode, the enzyme and mediator redissolve, and the reactions of glucose and mediator occur. This method cannot be employed in the fabrication of implantable sensors because the enzyme and mediator would dissolve in the subcutaneous fluid and diffuse away from the electrode surface, making the electrode inoperable. A scheme must be devised to immobilize the enzyme and mediator onto the electrode surface.

There are a variety of techniques for immobilizing enzymes. Enzymes can be adsorbed onto insoluble particles with high surface areas such as finely divided carbon or silica gel. Enzymes can also be covalently linked to an insoluble polymer matrix or cross-linked to themselves, to another protein such as bovine serum albumin, or to a synthetic polymer to form an insoluble matrix. A polymer membrane with pore sizes too small to allow diffusion of the enzyme through the matrix has been employed to entrap enzymes, and a structure such as micelle can be used to encapsulate the enzyme. In all immobilization techniques, care must be taken

to minimize denaturing of the enzyme. In some of the sensors described in this review, the immobilization methods are proprietary and are protected as trade secrets.

An obvious choice of mediator is O_2/H_2O_2 , as was employed in the GlucoWatch (Figs. 5 and 6), because oxygen is available without requiring immobilization. There is a serious limitation, however, when this is the mediator for a subcutaneous sensor: the glucose concentration in interstitial fluid can be several hundred times greater than the oxygen concentration. A method must be devised to limit the glucose such that the available oxygen exceeds the glucose at the surface of the electrode. Alternatively, a mediator to act as a substitute for oxygen must be immobilized with the enzyme.

The first sensors for subcutaneous glucose measurement reported in the literature exhibited a persistent failure mode. Although a current proportional to glucose was observed initially, the current decayed over the course of several hours. This phenomenon, referred to as biofouling of the sensor, is caused by the foreign body response to an object introduced below the skin. For nearly a decade, biofouling stymied researchers until more biocompatible materials that overcame the foreign body response were discovered.

All of the commercial CGM systems reporting glucose in real time consist of a disposable subcutaneous sensor connected to a non-implanted transmitter that powers the sensor and sends sensor current data by radiofrequency to a handheld device that processes the raw data and displays the glucose results. The sensors are inserted by the patient and can be immediately replaced after the useful lifetime of the sensor.

Guardian REAL-Time (Medtronic MiniMed, Sylmar, CA)

MiniMed introduced the first commercial glucose sensor with Food and Drug Administration approval of the Continuous Glucose Monitoring System (CGMS[®]) in 1999 and product introduction in 2000. The system includes a 3-day sensor and the necessary hardware to record the sensor current data and blood glucose measurements used for sensor calibration. The recorded information is processed and analyzed retrospectively. It was not Food and Drug Administration approved to provide real-time glucose measurements, but the retrospective data analysis provides insights to improve insulin therapy.

In 2005 the Guardian RT, providing glucose measurements in real time, was Food and Drug Administration approved as an adjunct to blood glucose testing. The system includes a 3-day sensor that reports results at a 5-min interval and saves the data for retrospective analysis. A minimum of two blood glucose measurements per day are required for calibration. The current CGM product is the Guardian REAL-Time, which was launched in 2007. This product was integrated with an insulin pump, Paradigm[®] REAL-Time, and launched in 2006.

The Guardian sensor is a three-electrode device that uses immobilized GOx with O_2/H_2O_2 as the mediator (Figs. 3–6). A key proprietary technology of this sensor is a polymer membrane that limits the glucose flux to the enzyme while maximizing the oxygen availability.¹¹ An embodiment of the patented membrane polymer is composed of a diisocyanate, a

diamino silane, and a diol, which form a polyurethane polyurea polymer. An example would be hexamethylene diisocyanate (Fig. 7), an aminopropyl-terminated siloxane polymer (Fig. 8), and polyethylene glycol (Fig. 9) to form the polyurethane polyurea block copolymer (Fig. 10).

A block copolymer consists of "blocks" of a homogeneous polymer (identical monomer subunits) connected to "blocks" of a different homogeneous polymer. The hydrophobic siloxane is highly permeable to oxygen with negligible permeability to water and thus glucose, and the hydrophilic diol imparts water/glucose permeability. By altering the ratio of siloxane to diol, the membrane can be tuned to give optimum oxygen and glucose transport. A short chain diol or diamine can be added to the polymerization to adjust the structural properties of the polymer. This sophisticated polymer provides an elegant solution to the oxygen deficiency encountered in the subcutaneous environment.

DexCom™ STS™-7 (DexCom, Inc., San Diego, CA) continuous glucose monitoring system

The DexCom STS monitor was first approved as a 3-day subcutaneous sensor providing real-time data as an adjunct to finger stick blood glucose tests in 2006. In 2007 the sensor lifetime was extended to 7 days for the STS-7 continuous glucose monitoring system. Glucose is reported at 5-min intervals, and calibration with finger stick blood glucose tests is



FIG. 7. Hexamethylene diisocyanate.

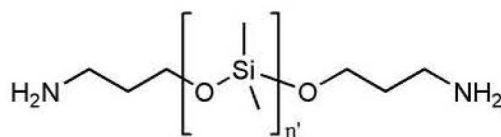


FIG. 8. Aminopropyl-terminated siloxane polymer.

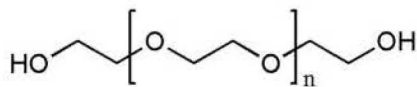


FIG. 9. Polyethylene glycol.

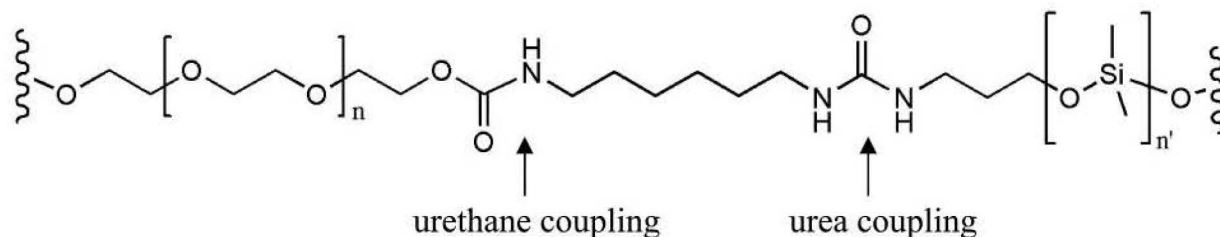


FIG. 10. Polyurethane polyurea block copolymer.

required every 12 h. The glucose data are also stored for retrospective analysis.

The STS sensor can trace its lineage through the careers of Stuart Updike and Mark Shults back to the earliest days of the enzyme electrode.^{12,13} The company's initial intent was to develop a long-term implanted glucose electrode, and much of the technology from this work was applicable when the product focus changed to a short-term subcutaneous sensor.

The STS sensor is a two-electrode device with a coiled Ag/AgCl wire serving as a counter/reference electrode. The working electrode uses immobilized GOx with O₂/H₂O₂ as the mediator (Figs. 3–6). A glucose barrier membrane, composed of a hydrophobic polyurethane and a hydrophilic polyurethane mixture, addresses the subcutaneous oxygen deficit. The hydrophobic polymer allows oxygen flux and blocks glucose, and the hydrophilic polymer enables glucose flux. The hydrophilic polymer is a block copolymer where the hydrophilic moiety is polyethylene glycol (Fig. 1) introduced into a polyurethane identical to the hydrophobic polymer.¹⁴ The structure of the polyurethane polymer is not disclosed. By varying the ratio of the two polymers the oxygen and glucose flux can be optimized, and rapid development of an optimum formulation is facilitated because the synthesis of a new polymer with optimum properties is not required. According to the patent,¹⁴ the identical polyurethane segments of the two polymers promote intimate mixing of the polymer chains, and under controlled processing conditions a highly homogeneous membrane can be produced. The membrane is tuned to a glucose permeability that generates the minimum accurately measurable current. In this manner, the required oxygen concentration and the hydrogen peroxide generated are minimized. Hydrogen peroxide is a strong oxidizing agent that can damage both the enzyme and the membrane. Keeping oxygen dependence and hydrogen peroxide formation to a minimum is particularly necessary for a long-term implantable device, but it also adds robustness to a short-lived sensor with less rigorous design parameters.

FreeStyle Navigator® (Abbott Diabetes Care, Alameda, CA) continuous glucose monitoring system

The FreeStyle Navigator continuous glucose monitoring system was approved as an adjunctive device in 2008. The three-electrode sensor is inserted for 5 days, but glucose is not reported for the first 10 h. Calibration with finger stick blood glucose tests is required after 10, 12, 24, and 72 h during the 120-h sensor lifetime. The glucose concentration is updated every minute and stored for retrospective analysis every 10 min.

GOx is immobilized on the working electrode, but an alternative mediator substituting for oxygen is also immobilized in a scheme referred to as a Wired Enzyme™. A vinyl pyridine polymer with pendant osmium complexes (Fig. 11) serves as the wire. A cross-linker (Fig. 12) connects exposed amines on the enzyme surface to the polymer backbone pyridyl groups by epoxy linkages (Fig. 13); it also cross-links polymer chains to form an insoluble hydrogel on the electrode surface.¹⁵ The flexible arm on the pendant osmium complex allows mediator access to the reduced FAD buried within the enzyme and facilitates efficient transfer of electrons

between the osmium complexes down the polymer chain to the electrode surface. An advantage of the wired enzyme is the osmium complex was designed to react at a relatively low potential, -0.2 V. At the 0.4 – 0.7 V required to reduce hydrogen peroxide, interference from the oxidation of endogenous substances such as uric acid or exogenous substances such as acetaminophen (Tylenol®, McNeil Laboratories, Fort Washington, PA) can be expected; these species do not react at -0.2 V.

Although the Wired Enzyme is not subject to the subcutaneous oxygen deficit, the enzyme concentration that can be

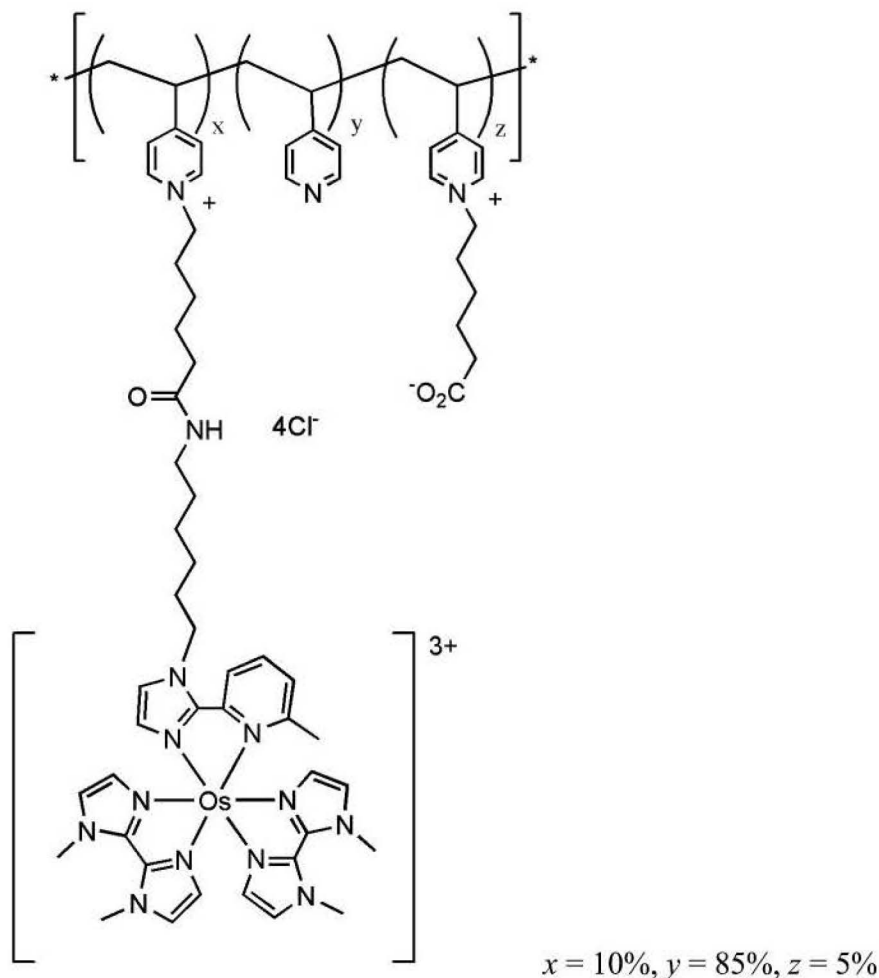


FIG. 11. Wired Enzyme electron conducting wire.

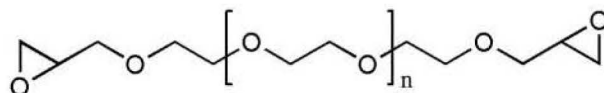


FIG. 12. Wired Enzyme cross-linker.

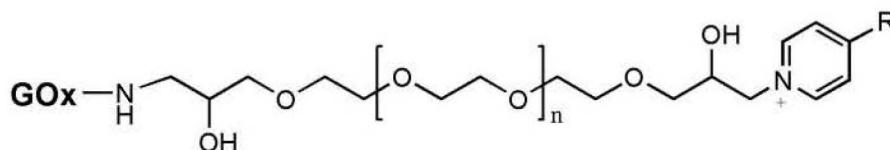


FIG. 13. Wired Enzyme epoxy linkages.

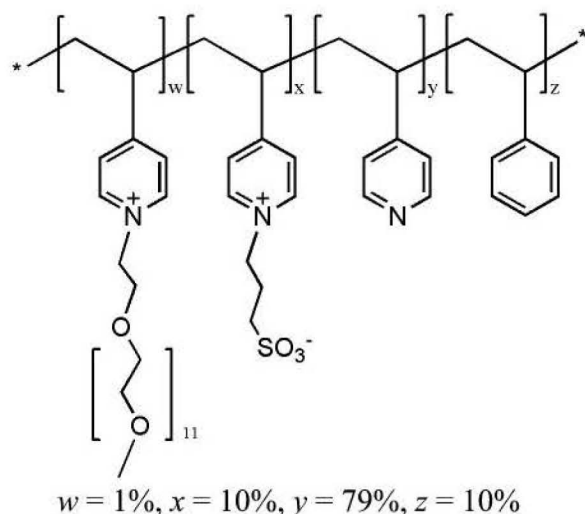


FIG. 14. Functionalized vinyl pyridine-styrene copolymer.

immobilized on the surface of an electrode is too low to accommodate the high physiological glucose concentrations; the enzyme is saturated at a very low glucose level. The FreeStyle Navigator continuous glucose monitoring system sensor has a vinyl pyridine-styrene copolymer (Fig. 14) with an epoxy cross-linker (Fig. 15) as a glucose limiting hydrogel membrane.¹⁶ The backbone copolymer provides the necessary barrier to glucose diffusion, but this polymer can be easily functionalized to impart additional desirable properties such as enhanced hydration and biocompatibility. A membrane composed of the cross-linked polymer backbone alone can take several hours to hydrate after insertion below the skin, but the functionalized polymer hydrates instantly. The membrane-coated sensor is highly biocompatible, exhibiting no encapsulation for at least 1 year when implanted in rabbit muscle. The cross-linking chemistry provides covalent binding between the glucose-sensing Wired Enzyme and the glucose-limiting membrane, an absolute barrier to delamination of the membranes.

The FreeStyle Navigator sensor chemistry is an excellent example of optimized molecular design. The desired properties are incorporated into the functional polymers and cross-linkers. Starting with a versatile vinyl pyridine backbone, specifically designed moieties can be grafted onto the backbone at optimum concentrations. Some of the electrochemical and structural properties of the hydrogels are modified by the choice and concentration of cross-linker.

Microdialysis Sensors

General principles

Microdialysis employs a semipermeable membrane filter in the form of a hollow fiber inserted subcutaneously. The membrane is permeable to glucose and other small molecules and impermeable to larger molecular species. An isotonic fluid containing no glucose is pumped through the membrane fiber, and the glucose in the interstitial fluid diffuses through the membrane into the fluid stream by osmotic forces. The glucose concentration in the pumped fluid will approach an equilibrium concentration equal to the glucose concentration

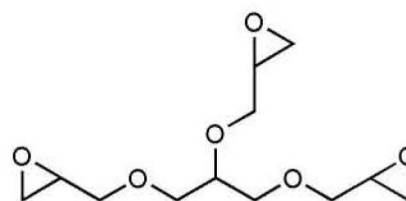


FIG. 15. Glucose-limiting membrane cross-linker.

in the interstitial fluid. The fluid flowing through the microdialysis membrane is pumped to a glucose detector. The detector can be exposed to atmospheric oxygen, eliminating the subcutaneous oxygen deficit in a GOx electrochemical sensor using O_2/H_2O_2 as the mediator. Another principal advantage of this method is the sensing element is outside the body where biofouling mechanisms cannot interfere with the measurements. Unfortunately, the foreign body response can block the flow of interstitial glucose through the membrane, and a biocompatible microdialysis membrane is a necessity. The plumbing between the microdialysis membrane and the glucose sensor introduces a time lag into the measurements. Although the lag can be minimized by maximizing the fluid flow rate, if the flow is too high there is not sufficient time to establish the glucose equilibrium between the pumped fluid and the interstitial fluid.

GlucoDay® (A. Menarini I.F.R. S.r.l., Florence, Italy)

Although there has been significant research into the microdialysis method, the GlucoDay is the only product that has been commercialized to date; the GlucoDay received the CE Mark and was introduced in 2002. It is approved for professional use for the retrospective analysis of glucose trends, although there is an available operating mode that displays real-time glucose results to the user. The microdialysis fiber is inserted by a medical professional and calibrated with a blood glucose test; glucose results are stored for retrospective analysis for 48 h, after which the fiber is removed.

Glucose is detected amperometrically with GOx and oxygen (Figs. 3–6), and the probe has been described in detail.¹⁷ A platinum electrode is covered with three membranes: a cellulose acetate membrane, an enzyme membrane, and a polycarbonate membrane. The cellulose acetate membrane (Fig. 16) allows diffusion of hydrogen peroxide while removing potential interference from ascorbic and uric acid. GOx is immobilized in the enzyme membrane by cross-linking with glutaraldehyde (Fig. 17), a classic method of enzyme immobilization. The polycarbonate membrane (Fig. 18) is glucose limiting in order to obtain a linear response to glucose. The dialysis membrane is regenerated cellulose (Fig. 19), and the membrane fiber is reinforced against collapse by a pair of twisted tungsten wires.

Future Developments

It is not surprising that the first commercial continuous monitors are enzyme electrodes that evolved from the first enzymatic methods employed for measuring glucose in the clinical lab. The development path was a continuation of a robust and well-understood analytical methodology. The early indications that the use of CGM can lead to improved

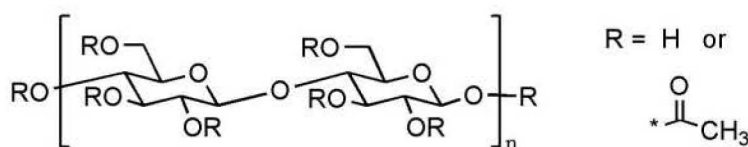


FIG. 16. Cellulose acetate.

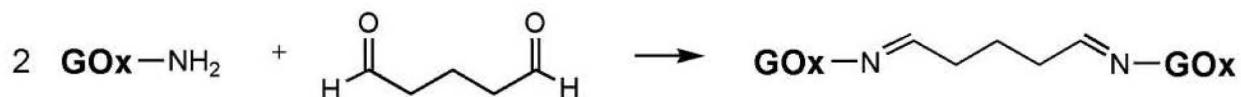


FIG. 17. Reaction of GOx with glutaraldehyde.

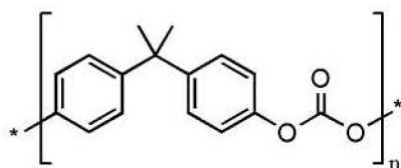


FIG. 18. Polycarbonate.

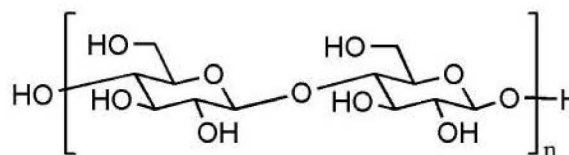


FIG. 19. Cellulose.

diabetes therapies will spur the continued refinement of these first-generation products.¹⁸

We can look forward to improvements in user interface with certainty. As the practical use of CGM for improving therapy is developed, there will be improvements in ease of use, and more useful and convenient presentations of the information will be developed. These improvements can occur with no fundamental change to the measurement technologies; the knowledge gained as the market matures will drive the desired improvements.

It is also very likely that improvements in the accuracy, reliability, and cost of the current technology will follow. Now that the fundamental measurement principle has been demonstrated, and as the market need is more firmly established, the process of incremental improvement is sure to continue. It will be many years and many ingenious adaptations before the ultimate limitations of the current technologies are overcome.

It is far less certain if any of the more esoteric measurement methods currently in the research phase will supplant today's technology. The photometric and electrochemical methods employed in finger stick products evolved from the methods developed previously for the clinical lab. But, blood glucose testing in the home and in the lab has a striking similarity: the test sample is removed from the patient and measured in vitro. Although semicontinuous glucose measurements are known in the clinical lab, to date they are simply frequent in vitro tests. The current CGM products perform the glucose measurement in vivo, and continuous glucose testing in vivo has not been performed in the clinical lab. The challenges that have never been previously encountered may best be overcome by measurement technologies that have never been exploited. The new challenges beg for new solutions, but only time will tell if a breakthrough technology can replace the established solutions of the past.

Author Disclosure Statement

G.M. is an employee of Abbott Diabetes Care.

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