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Bio-Techniques in Electrochemical Transducers: an Overview

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Abstract: Novelty in fabrication & designing of biosensors are being carried out at a high rate as these devices become increasingly popular in fields like environmental monitoring, bioterrorism, food analyses and most importantly in the area of health care and diagnostics. This rapidly expanding field has an annual growth rate of 65%, with major impetus from the health-care industry (30% of the world's total analytical market) supported with other analytical areas of food & environmental monitoring including defense needs. This context aims to highlight trends in practice for electrochemical biosensor design and construction. The availability and application of a vast range of polymers and copolymers associated with new sensing techniques have led to remarkable innovation in the design and construction of biosensors, significant improvements in sensor function and the emergence of new types of biosensor. Nevertheless, *in vivo* applications remain limited by functional deterioration due to surface fouling by biological components. However, use of new material and novelty in fabrication, raising hopes that the problems related to decreased functional of the bioanalytical layer be solved in time. *Copyright* © 2007 IFSA.

Keywords: Biosensor, Electrode, Electrochemical, Immobilization, Fabrication

1. Introduction

Most recently, biosensors as versatile analytical tools have been increasingly used for continuous monitoring of vial biochemical parameters in body fluids and to attain the analytical information in a faster manner. Potential applications continued to lie in clinical diagnostics, bioprocess, environmental monitoring and food and drug industries. Biosensors can also meet the need for continuous, real-time *in vivo* monitoring to replace the intermittent analytical techniques used in industrial and clinical

chemistry [1]. As low cost, portable, and simple-to-operate analytical tool, biosensors have had certain advantages over the conventional analytical instruments such as gas chromatographs. The systematic description of a biosensor should include five features [2]. These are (1) the detected or measured parameter, (2) the working principle of the transducer, (3) the physical and chemical/biochemical model, (4) the application and (5) the technology and materials for sensor fabrication. Many parameters have been suggested to characterize biosensors. Some are commonly used to evaluate the functional properties and quality of the sensor, such as sensitivity, stability and response time; while other parameters are related to the application rather than to sensor function, for example the biocompatibility of sensors for clinical monitoring. The first blood pO₂ electrode was introduced by Clark [3]. He described how to make electrochemical sensors more intelligent by adding "enzyme transducers as membrane enclosed sandwiches". This idea was commercially exploited in 1975 with the successful launch of the Yellow Springs Instrument Company's glucose analyzer based on the amperometric detection of hydrogen peroxide (H₂O₂) [4]. Since then, many biosensors have been developed to detect a wide range of biochemical parameters, using a number of approaches, each having a different degree of complexity and efficiency. Biosensors incorporating enzymes have been developed to measure concentrations of carbohydrates (glucose, galactose and fructose), proteins (cholesterol and creatinine), amino acids (glutamate) and metabolites (lactate, urea and oxalate oxidase) in blood and other body fluids and tissues. It is even possible to measure the concentrations of neurotransmitter molecules by means of a neuronal biosensor and the application of this technique is also studied in the actions of anesthetics [5-6]. A range of biologically active molecules, including antibodies and antigens has also been measured using immuno-sensors [7]. Recently, the most fascinating and prospective sensors include biosensors for the detection of DNA damage and mutation [8-9], and the identification of DNA sequences and hybridization [10] offers considerable promise in several medical fields. The reaction between the bioactive substance and the species (substrate) produces a product in the form of a biological or chemical substance, heat, light, or sound; then the transducer such as an electrode, semiconductor, thermistor, photometer, or sound detector changes the product of the reaction into usable data. Therefore, depending on the technique used transducers can be subdivided into the following four main types.

1. Electrochemical Transducers: (a) *Potentiometric*: These involve the measurement of the emf (potential) of a cell at zero current. The emf is proportional to the logarithm of the concentration of the substance being determined. (b) *Voltammetric*: An increasing (decreasing) potential is applied to the cell until oxidation (reduction) of the substance to be analyzed occurs and there is a sharp rise (fall) in the current to give a peak current. The height of the peak current is directly proportional to the concentration of the electroactive material. If the appropriate oxidation (reduction) potential is known, one may step the potential directly to that value and observe the current. This mode is known as *amperometric* (c) *Conductometric*: Most reactions involve a change in the composition of the solution. This will normally result in a change in the electrical conductivity of the solution, which can be measured electrically. (d) *FET-based sensors*: Miniaturization can sometimes be achieved by constructing one of the above types of electrochemical transducers on a silicon chip-based field-effect transistor. This method has mainly been used with potentiometric sensors, but could also be used with voltammetric or conductometric sensors.

2. Optical Transducers: These have taken a new lease of life with the development of fibre optics, thus allowing greater flexibility and miniaturization. The techniques used include absorption spectroscopy, fluorescence spectroscopy, and luminescence spectroscopy, internal reflection spectroscopy, surface plasmon spectroscopy and light scattering.

3. Piezo-electric Devices: These devices involve the generation of electric currents from a vibrating crystal. The frequency of vibration is affected by the mass of material adsorbed on its surface, which could be related to changes in a reaction. Surface acoustic wave devices are a related system.

4. Thermal Sensors: All chemical and biochemical processes involve the production or absorption of heat. This heat can be measured by sensitive thermistors and hence be related to the amount of substance to be analyzed.

The selectivity of the biosensor for the target analyte is mainly determined by the biorecognition element, while the sensitivity of biosensor is greatly influenced by the transducer. Most clinical applications have, so far, been restricted to academic studies and research laboratories rather than commercialized for routine clinical monitoring. The principal reason for this limitation is the poor biocompatibility of available materials which interferes with sensor function [11]. The selection of materials and fabrication techniques is crucial for adequate sensor function and the performance of a biosensor often ultimately depends upon these factors rather than upon the other factors mentioned above.

2. Materials

Materials used in electrochemical biosensors are classified as: (1) electrodes types and supporting substrates, (2) materials used for the immobilization of biological elements (3), membrane materials and biocompatibility and (4), biological recognition elements such as enzymes, antibodies, antigens, nucleic acids, mediators and cofactors.

2.1. Electrodes Types and Supporting Substrates

Metals and carbon are commonly used to prepare solid electrode systems and supporting substrates. Metals such as platinum, gold, silver and stainless steel have long been used for electrochemical electrodes due to their excellent electrical and mechanical properties. Carbon-based materials such as graphite, carbon black and carbon fiber are also used to construct the conductive phase. These materials have a high chemical inertness and provide a wide range of anode working potentials with low electrical resistivity. They also have a very pure crystal structure that provides low residual currents and a high signal-to-noise ratio [12]. Carbon fibers could be valuable in sensor construction and he showed how a parallel array consisting of a large number of carbon fibres, separated by insulators, can be prepared to obtain a very high signal-to-noise ratio [13]. More recently, a number of new mixed materials have appeared for the preparation of electrodes. A conducting composite formed by the combination of two, or more, dissimilar materials was introduced by [12]. Each material retains its original properties, while giving the composite distinct chemical, mechanical and physical properties that differ from those exhibited by the individual components. A carbon-polymer based composite is firstly prepared by dispersing powdered graphite in a polymer resin, such as epoxy, silicone, methacrylate, polyester or polyurethane. With the biological recognition element previously immobilized onto carbon particles, modifier, catalyst or mediator, the polymer composite is then mixed to form the integrated electrode unit. Using this method, an impure metal working electrode was prepared with the catalyst and enzyme adsorbed onto pyrolysedcobalt–tetramethoxy–phenylporphyrin(CoTM PP) [14]. From this basic pressed matrix tablet, it is possible to manufacture numerous electrodes with identical functional properties in terms of sensitivity, linearity and lifetime. Organic electro conductive polymers have aroused considerable interest in recent years. These materials can be used to prepare electrodes, or to provide a substrate for the immobilization of biological elements (see next section) simultaneously. A novel electrode was fabricated by the use of a flexible conductive polymer film of polypyrrole doped with poly anions and a microporous layer of platinum black [15]. Glucose sensors produced with this material provided a H₂O₂ oxidation current at a lower applied potential than conventional sensors.

2.2. Materials Used for the Immobilization of Biological Elements

Most of the materials traditionally used for this purpose are multifunctional agents such as glutaraldehyde and hexamethyl diisocyanate, which form crosslinks between biocatalytic species, or proteins. The process is known as coreticulation, since it creates complex matrices that make multi enzyme immobilization possible. Alternatively, non-conductive polymers, such as polyacrylamide and polyphenol, can be used to entrap elements physically. Organic conductive polymers provide advantages, including the formation of an appropriate environment for enzyme immobilization at the electrode and for its interaction with metallic and carbon conductors [16-17]. Therefore, electrical communication between the redox centre and the electrode surface is more efficient. These polymers can be deposited electrolytically from solution onto a conducting support to provide a three dimensional matrix for immobilized enzymes where reactants are converted to products. The polymers can be produced by a variety of chemical processes, including the Ziegler–Natta reaction for polyacetylene [18-19], the creation of an electrolyte solution e.g. poly (*p*-phenylene) [20], the coupling of organometallic components (polythiophene) [21] and the oxidation of monomers [22]. Redox polymer hydrogels entrap oxidoreductases efficiently and transfer electrons from enzymatic oxidation: reduction reactions through the gel to the conducting surface [23]. Gels based on networks of polyethylene glycol, diacrylate and vinylferrocene can be formed by illuminating a solution containing the comonomers and the ultraviolet photoinitiator, 2,2%-dimethoxy-2-phenylacetophenone at 365 nm, 20 W cm⁻². The enzyme can then be loaded by dissolving it in this mixture followed by exposure to light. Latex particles also provide suitable substrates for the controlled attachment of biomolecules in the recognition of analytes. Studies on the formation of two-dimensional latex assemblies covalently immobilized on conducting solid surfaces were performed [24]. Computer simulations illustrated the general properties of the 2-D latex assemblies and a real example of the composite, polystyrene: acrolein latex, on a quartz surface were presented.

2.3. Membrane Materials and Biocompatibility

Biosensors are usually covered with a thin membrane that has several functions, including diffusion control, reduction of interference and mechanical protection of the sensing probe. Commercially available polymers, such as polyvinyl chloride (PVC), polyethylene, polymethacrylate and polyurethane are commonly used for the preparation of these membranes due to their suitable physical and chemical properties. Biosensors with polymer membranes have been successfully applied in many fields such as the monitoring of food production, environmental pollution and pathological specimens. However, when biosensors are placed in a biological environment, numerous factors operate to affect their performance, the most significant ones being sensor surface interactions with proteins and cells [25]. Therefore, although biosensors have great potential for real-time clinical monitoring, the sensors so far constructed lack functional stability after implantation and sensor lifetime is usually restricted to several hours, or days [26]. Thus, functional stability is profoundly affected by the biocompatibility of the biosensor materials that are in contact with the biological medium. Attempts to improve the biocompatibility of artificial surfaces by bonding anticoagulants have not been very successful. For example, the surface treatment of membranes with heparin sulphate is commonly used to improve haemocompatibility, but when Smith and Sefton (1993) analyzed thrombin adsorption onto heparin treated polyvinyl alcohol and polyurethane, they observed that, whereas the rate of adsorption of thrombin was reduced by heparin coating, the final volume of thrombin desorbed remained similar [27]. Another problem is that the heparin tends to leach from the membrane surface into the surrounding medium. Materials with hydrogel-like properties are generally considered to favor biocompatibility. Water associates with the water-soluble polymers and the presence of water around the polymer hinders protein adsorption due to the energetically unfavorable displacement of water by protein and compression of the polymer upon the approach of protein. These factors have been described in terms of steric repulsion, van der Waals attraction, and hydrophobic interactive free

energies [28-29] by Jeon et al. (1991) and by Jeon and Andrade (1991). Surfaces grafted with water-soluble polymers have been developed using a number of techniques, including end-grafting [30] (Shoichet et al., 1994) and in situ polymerization by photo- or wet- chemistry, and by radio frequency glow discharge deposition [31]. An alternative to surface grafting is the adsorption of amphiphilic molecules onto hydrophobic polymers. Amphiphilic molecules can rearrange themselves on a surface in an attempt to maximize packing density and can be covalently immobilized on the surface to create a permanent adsorption layer [32]. Polyethylene glycol (PEG) has been used extensively to modify surfaces, so that protein adsorption and platelet interactions with the foreign surface are reduced [33]. The natural cell membrane is a self-assembled system and the extra-cellular matrix is a nano-structured system. Based upon these observations, amphiphilic, self assembled multilayers and nano-structured surface systems have been exploited in the production of liposomes modified with PEG. These surfaces suffer from significantly less protein adsorption and immune clearance mechanisms are reduced [34]. Chemical adsorption has been used to produce self-assembled monolayers on metals and ceramics. Alkanes terminated with thiols form densely packed monolayers, with the alkane chain oriented outwardly from the substrate surface. It is reported that protein adsorption could be virtually eliminated by alkane thiol terminated with oligoethylene glycol [35]. An optical biosensor chemically adsorbed with a monolayer of 16-mercaptohexadecan-1-ol has been produced to measure protein interactions with gold coated surfaces [36].

Surface modification of polymers has led to modest improvements in biocompatibility, but it is still not satisfactory for long-term in vivo applications, so there is an urgent need to design and develop new biocompatible materials. During the last two decades, several attempts have been made to do this by synthesizing new phospholipid copolymers based upon the principle of biological membrane mimicry. These copolymers have been successfully used as drug carriers as well as biosensor membranes. The basic philosophy behind this idea is due to Zwaal et al., (1977), who described the complex relationships between cell membrane structure and blood coagulation [37]. In vitro coagulation tests demonstrated that the inner surfaces of the plasma membrane of erythrocytes and platelets are highly procoagulant, but the outer surfaces are inactive. Liposomes having the same phospholipid composition as the outer surfaces of erythrocyte and platelet membranes were also inactive and did not reduce the time for recalcified plasma to clot. The simplest common feature of these non-reactive cellular and model membranes is the high content of electrically neutral phospholipids with phosphorylcholine head groups [38]. Consequently, the synthetic copolymer, poly (MPC-co-BMA) which contains head groups of 2-methacryloyloxyethyl phosphorylcholine (MPC) copolymerised with *n*-butylmethacrylate (BMA), also exhibits surface properties that are favourable for haemocompatibility. The surfaces are extremely hydrophilic and they contain large volumes of water [39]. During the construction of the membrane by liquid evaporation, the whole phospholipid molecule, which includes two fatty acid chains, undergoes significant rotation to minimize interface energy and this result in the orientation of the phosphorylcholine head group towards the side of the membrane that is exposed to air. The MPC moiety also has a strong affinity for natural phospholipids molecules in plasma, so a well organized natural lipid layer, biomembrane-like structure, forms on this surface during its exposure to plasma [40]. Protein adsorption is significantly reduced on poly (MPC-co-BMA) surfaces compared with other medical polymers [41] and the in vitro and in vivo performance of biosensors is significantly improved when poly(MPC-co-BMA) is coated onto the sensor surface [42-44]. These membranes might simulate natural membranes functionally as well as structurally the natural phospholipids may be continuously replenished in a continuous process of erosion and repair [45].

2.4. Biological Recognition Elements

Improvements in interface design have frequently been directed at the incorporation of active molecules, including enzymes such as glucose oxidase [4] and lactate oxidase [46], mediators, such as

Ferrocene (h²-bis-cyclopentadienyliron) and its derivatives [47], cofactors based on nicotinamide adenine dinucleotide (NADH_ and NADP_ [48], catalysts [49], antibodies and antigens [50]. Studies on the use of biosensors for gene detection are relatively recent and still uncommon. Deoxyribonucleic acid (DNA) has recently been suggested as a biological recognition element for such biosensors [51-52]. The unique nucleotide base structure of DNA provides the basis of the technique which allows single stranded DNA (ssDNA) to be used to identify other ssDNA molecules with the complementary bases [53]. Therefore, nucleic acid hybridisation is the underlying operating principle of DNA biosensors. During the last decade, there have been many advances in DNA biosensor technology and most work has focused on electrochemical, piezoelectric and optical transducers. Attempts to develop an electrochemical DNA biosensor have been made by several groups [54-55]. In these sensors, an ssDNA strand is covalently bound to the surface of an electrode. Hybridization of the immobilized sequence with its dissolved complement forms the double strand that can be detected using a DNA-specific redox-active metal: polypyridine complex. Damaged segments of DNA can also be detected by measuring changes in the redox signals of base residues in DNA immobilized on carbon electrodes. Covalently closed circular DNA can be attached to an electrode surface to obtain a sensor that detects a single break in the DNA sugar-phosphate backbone, or for the detection of agents leaving the DNA backbone such as hydroxyl radicals, ionizing radiation or nucleases [56]. DNA sensing protocols, based on different modes of nucleic acid interaction have been reviewed [57] by Wang et al. (1997). The review describes recent efforts to couple nucleic acid recognition layers to electrochemical transducers. Peptide nucleic acids (PNAs) have been found to exhibit unique and efficient hybridization properties that may offer significant advantages for sequence-specific recognition compared to their DNA counterparts. The advantages include higher sensitivity and specificity, faster hybridization at room temperature and minimal dependence upon ionic strength. The use of PNA incorporated with a Co (phen) (3) (3+) redox indicator on a carbon electrode for the detection of sequence specific DNA has been discussed [58].

3. Designing of Biosensors

Design and construction technology and material science are intimately linked in biosensor development. Therefore, discussions of biosensor design and fabrication should always involve the selection of materials. An electrochemical biosensor usually consists of a transducer such as a pair of electrodes or FET, an interface layer incorporating the biological recognition molecules and a protective coating. Sensor design, including materials, size and shape and methods of construction, are largely dependent upon the principle of operation of the transducer, the parameters to be detected and the working environment. Traditional electrode systems for measurements of the concentrations of ions in liquids and dissolved gas partial pressures contain only a working electrode (usually a noble metal wire) and an electrically stable reference electrode, such as Ag: AgCl, though a counter electrode is sometimes included. A simple electrical, or chemical, modification may sometimes improve specific electrode properties. For example, repeated potential cycling of 0.3 mm diameter carbon rods in 0.1 M potassium hexacyan ferrate improved the stability of glucose sensors for up to 6.5 days [59]. However, with the expanding demands for more complex measurements, the rapid development of materials science and the emergence of micro- and nanoprocess technology, indirect electrochemical methods in simple biosensors to monitor enzyme activity have gradually been replaced by more direct, but more complex processes. Methods for the preparation of electrochemical electrodes are well established. Some of these techniques are used to prepare the conductive supporting substrate, while others are employed to achieve an efficient electrical communication between the chemical reaction site and the electrode surface, high levels of integration, sensor miniaturization, measurement stability, selectivity, accuracy and precision. In addition, the technique used to immobilize the biological recognition components of the sensor can affect biosensor performance significantly.

3.1. Transducer/Electrode Fabrication

The electrode supporting substrate can be a noble metal (gold or platinum), carbon rod or paste, or an organic conducting salt or polymer. Techniques used for the production of conductive supporting substrates can be roughly classified as: (1) printing, (2) deposition, (3) polymerization, (4) plasma induced polymerization, (5) photolithography and (6) nano-technology.

(1) *Screen-printing* is one of the thick-film techniques that have been widely used in industry for mass production. Paste material is printed onto a matrix directly through a mask-net with a designed pattern. The technique of carbon, or graphite, screen printing is now frequently used to prepare electrodes for biosensors. Turner's group recently improved this technique by using solvent resistant materials; heat stabilized polyester sheet, carbon base tracks and an epoxy-based polymer [60]. These electrodes have no problems with solvent induced baseline shift and are therefore suitable for work in water-miscible organic solvents. Sensor arrays for the detection of more than one parameter by different sensing techniques, or to assemble a package of sensors to measure the same parameter, have potential practical applications. For this purpose, the screen printing technique has been used to prepare a seven-channel electrode for simultaneous amperometric and potentiometric measurements. The array contains 14 gold working and counter electrodes and one Ag: AgCl reference electrode [61]. This sensor can be used to analyse blood and serum electrolytes and metabolites. A printable paste is prepared by mixing glucose oxidase adsorbed organic charge transfer complex crystals with a binder and a solvent [62]. This paste is printed onto a matrix cavity and dried under vacuum. A thin layer of gelatin is then cast on the electrode. The developed sensor provides a huge response current with minimum interference from oxygen and an extended linear range up to 100 mM glucose. Techniques (2), (3), (4) and (5) are thick-thin-film techniques that are used in biosensors to form mono or multi-layers of conducting film onto a supporting substrate in order to obtain a direct electrical communication between the chemical: biochemical reaction site and the supporting surface. Factors affecting electron transfer from biological molecules to electrode surface have also been reviewed [63].

(2) *Traditional chemical*, or electrochemical, deposition methods can be used to deposit an electroconductive film on a supporting substrate. The deposited film can be metal such as platinum, catalytic material such as TiO, or a metal complex. Biological elements can also be simultaneously coupled during the film deposition process. Lorenzo et al. (1998) discussed the analytical strategies for various electrodeposited films [64].

(3) *Polymerisation* takes place due to the condensation of small molecules in monomers, or by free radical creation and reaction by rearranging the bonds with in each monomer. Free radicals are produced when the double bond is broken by initiation activated by heat, light, or electro-chemicals. Electrical conductivity can be achieved by the introduction of metal powder into the monomer before polymerization, or through electrons that are not conjugated in the monomer. A new technique has been developed to generate polymethylene blue-modified thick-film on gold electrodes by electropolymerisation to form an electrocatalytically active conducting layer that is in intimate and stable contact with the electrode surface. This process allows for a reduced applied potential of only 200 mV, the avoidance of inference from co-oxidisable species and the minimization of electrode fouling [65]. By depositing a thin electropolymerised film of poly(1,3-diaminobenzene), electrochemical interference from ascorbate, urate, acetaminophen and other oxidisable species can be greatly diminished. It was reported that a photo-initiated free-radical polymerised redox hydrogelpolymer entrapped enzymes efficiently [66] and increased the transfer of electrons from enzyme oxidation:reduction reactions through the gel to the electrode surface [23].

(4) *Plasma-induced polymerization* is performed under high vacuum. The principle is to introduce functional groups onto the substrate surface and then 'polymerisable' gas plasma is coated onto this

surface to form a layer of film. Plasma-polymerised film, generated in a glow discharge, or plasma in a vapor phase, may offer a new alternative for biosensor interface design. The advantage of this technique is that it can produce an extremely thin (B1 mm) film that adheres firmly to substrates. Furthermore, the film is pin-hole free and both mechanically and chemically stable, and it allows a large amount of biological material to be loaded onto the surface [67].

(5) *Photolithography techniques* have long been used in the semiconductor industry to produce integrated chips. Light passes through a photo-mask and is cast upon a photo degraded material surface to form a pattern. This technique was used to fabricate micro-lens arrays for sensors [68]. The manufacture of integrate transducer arrays for measurements of a single parameter, or for several different parameters, is now possible by means of photolithography and plasma technology. These techniques have been used to increase the dynamic range and sensitivity of urea sensors [69].

(6) *Nano-techniques* have recently appeared with the maturation of modern technologies such as surface probe microscopy and lithography, atomic force microscopy (AFM), AFM lithography and lateral force microscopy (LFM). A brief historical overview, in which recent developments in miniaturisation, microfabrication, nanotechnology, immuno-sensors and gene-sensors are, discussed [70]. Patterns were produced with resolutions in the nanometer range based upon photo- and AFM-lithography with an orgaosilane monolayer resists [71].

The combination of techniques mentioned above leads to multilayer structures that may well prove to be useful in the development of new types of biosensor. Bilayer polymer coatings consisting of polypyrrole acid poly (*o*-phenylenediamine) on a supporting substrate may improve selectivity and reduced inference from electroactive species like uric and ascorbic acids that are often present in biological samples [72] proposed a multilayer architecture to predefine electron-transfer pathways, integrate redox mediators, immobilise enzymes and restrict diffusional access by interfering compounds [73]. A multilayer wafer can also be formed by depositing a thin functionalized polypyrrole film on the supporting surface and then covalently bonding a redox dye of polymerized quinoidic species to prevent electrode fouling. The top of this layer is coated with polypyrrole with entrapped tyroinase. Electrons transfer from the quinone to the electrode surface via the immobilized redox dye. Other new techniques have been suggested that could be useful in the design and construction of new biosensors. The most promising of these may be the formation of a direct electrochemical communication between the active enzyme site and the electrode surface using a biocatalyst with a very low molecular weight, such as microperoxidase MP-11, immobilised on a thio-monolayer. In this case, the distance between enzyme and electrode surface is greatly reduced in comparison with earlier constructions and this modification significantly increases the strength of the output signal [74]. Khan (1996b) reported a stable organic charge-transfer-complex (CTC) electrode for the direct oxidation of flavoproteins [75]. To construct the CTC electrode, tetrathiafulvalene-tetracyanoquinodimethane is grown at the surface of an electro conductive polyanion-oped polypyrrole film in such a way that it makes a tree shaped crystal structure, standing vertically on the surface. By immobilizing a glucose enzyme on the CTC electrode, direct electron transfer is achieved between the active enzyme and the crystal electrode and this leads to remarkably improved sensor performance. An electrically conductive and mechanically flexible composite polymer was prepared to construct a glucose sensor [76]. Using this technique, fine palladium particles are dispersed in polypyrrole:sulfated poly(beta-hydroxyethers) by thermally decomposing the bis(dibenzylideneacetone)-palladium complex. With Ag:AgCl as a reference electrode, a conventional platinum electrode responded to glucose at a working potential of 650 mV, whereas the new electrode responded at 400 mV. Fibrinogen film were used to provide a porous, non-reactive layer over a carbon paste electrode to control the mass transfer rate of diffusing species [77] and the technique of pulsed LASER deposition (PLD) was introduced with optimized LASER parameters and reaction atmosphere to obtain more efficient enzyme activities than the conventional platinum film electrode produced by argon sputtering [78].

3.2. Immobilization Methods

Considerable progress has been made in the development of new methods of immobilizing biological recognition elements onto sensor surfaces. The use of self-assembled mono- and multi-layers (SAMs) is increasing rapidly in various fields of research, and this applies especially to the construction of biosensors. SAMs can be used as interface layers upon which almost all types of biological components, including proteins, enzymes, antibodies and their receptors, and even nucleotides for DNA recognition, can be loaded [79]. The use of biomembranes as recognition elements was introduced by the pioneering work [80]. Lipid membranes provide a relatively biocompatible surface and mass diffusion based sensors constructed with lipid membranes having fast response rates and high sensitivities. However, there was no practical use of lipid films until the development of physically stable bilayer lipid membranes (BLMs). BLMs can be formed on metal surfaces, conductive polymer supports, or agar plates. The technique usually proceeds by two steps. First, the support substrate is coated with the lipid layer by immersing it in a lipid solution and then placed in an electrolyte solution to create the self-assembled lipid bilayer. The incorporation of biological recognition molecules into lipid layers and their immobilisation on BLMs depend upon the degree of access to reactive sites on the molecules. The various techniques used for this purpose have been described [81]. The technique used to construct an immuno-sensor based on a self-assembled BLM supported on a metal surface was described [82]. Avidin modified monoclonal antibodies, originating from the E2:G2 clone (AMab), and matched antigens were incorporated in the membrane. Amperometric biosensors for glucose and urea measurement have also been produced by the immobilization of glucose oxidase and urease into BLMs through the avidin–biotin interaction [83]. A layer-by-layer deposition technique may be used to optimize enzyme loading in bienzyme systems [84]. With up to ten monomolecular layers containing avidin, biotin residues and choline oxidase (ChOx), and two superficial layers containing cholinesterase, the sensor exhibits an increased response to acetylcholine. A technique to prepare gold electrodes with nanometersized openings for the immobilization of biological recognition elements, such as antibodies, has been described [85]. Latex spheres are used as a masking material to create 60 nm diameter holes in gold film evaporated onto a supporting substrate. The nanometer-scale proximity of the recognition components to the conducting surface may facilitate the development of biosensors without mediators. A multi-enzyme sandwich comprised of layers of separately immobilised enzymes was prepared [86]. Factors controlling the concentration of enzyme, enzyme kinetics, and the permeability and thickness of the coating components had been evaluated previously. Enzyme multilayer composed of avidin, biotin-labelled glucose oxidase and ascorbate oxidase are considered to be resistant to ascorbate interference [87]. By the use of avidin to crosslink and immobilize the glucose oxidase, an electro reduction current may be measured at the extremely low potential of 100 mV [88].

4. Conclusion and Future Prospects

Technology advances are enabling new procedures in hospitals while increasing the possibilities for self-care. For the biosensor to be of optimal use, it must be at least as precise and standardized as other available technology. Reducing blood specimen volumes to micro (μ) level may permit continuous on-line monitoring of critical blood chemistries and has the advantage of creating less blood to clean up hence reducing the potential for infectious contamination from patient blood. In addition, a single chip insert may measure multiple parameters. Mass production of disposable biosensors will make medical diagnosis cheaper. Despite huge market potential & except for few commercial successes, many of the prototypes of biosensors in our laboratories are not commercially viable. The gap between research and the market place still remains wide and commercialization of biosensor technology has continued to lag behind the research by several years. Some of the many reasons includes: cost considerations, stability and sensitivity issues, quality assurance and competitive technologies. Until all these issues

are addressed it would be difficult to move these devices from the research lab to market place. In addition, partial industrial participation must be encouraged so as to reduce the complexity in transferring of prototype or modern technological innovation into market place.

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Guide for Contributors

Aims and Scope

Sensors & Transducers Journal (ISSN 1726- 5479) provides an advanced forum for the science and technology of physical, chemical sensors and biosensors. It publishes state-of-the-art reviews, regular research and application specific papers, short notes, letters to Editor and sensors related books reviews as well as academic, practical and commercial information of interest to its readership. Because it is an open access, peer review international journal, papers rapidly published in *Sensors & Transducers Journal* will receive a very high publicity. The journal is published monthly as twelve issues per annual by International Frequency Association (IFSA). In addition, some special sponsored and conference issues published annually.

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