Octa Journal of Biosciences
International peer-reviewed journal
Octa. J. Biosci. Vol. 1(2): 147-150

ISSN 2321 – 3663
December, 2013

Octa Journal of Biosciences

journal homepage: www.sciencebeingjournal.com

Scientific Planet

Review Article

Recent Advances in Biosensors Technology: A Review

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ARTICLE INFO

Received: 30 Aug. 2013
Revised: 19 Nov. 2013
Accepted: 27 Nov. 2013

Keywords: Biosensors, sensing element, transducer, amperometric, potentiometric, optical

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ABSTRACT

Biosensors are devices that combine biological materials and transducers for the detection of sample e.g. drugs, metabolites, pollutants, microbial load, control parameters etc. by converting biochemical signals into measurable physiochemical signals which in turn quantify the amount of sample. There are various types of biosensors depending upon the sensing elements or transducers. Since the first glucose biosensor developed by Clark in 1962 many biosensors have been commercially exploited for various applications as it offers a more specific, sensitive, rapid, real and reproducible results as compared to chemical sensors. Recently nano-biosensors, implanted biosensors and integrated biosensors are in current research and development.

INTRODUCTION

Biosensor is an analytical device that converts biological reactions into measurable signals like an electrical signal which is proportional to analyte concentration. A typical biosensor consists of two elements: biological sensing element and a transducer for the detection of analyte concentration. Biological reaction takes place in close contact with the transducer to ensure that most of the biological reaction is detected. A third element reference can be added along with the two elements which produce a small reference signal without analyte and serves as a control of the experiment. In this case the difference between the two signals is analysed which is proportional to the concentration of the material being measured. The major advantage of using biosensor as compared to the other conventional techniques used for measurement of analyte like biochemical assays, immunoassays and PCR based assays is that the sample can be used with no prior clean up, reusability and rapid response along with high specificity. The aim of this article was to give a brief overview history, types, applications and future advances in the field. Data for this review were obtained by searching research papers with key words" biosensor types", " biosensor applications", "nanobiosensors", "biochips", "current research on biosenors".

HISTORY

The first biosensor was invented by Professor Leland C Clark Jnr. and he is known as the father of the biosensor concept. In 1956, Clark published his definitive paper on the oxygen electrode. The concept was illustrated by an experiment in which glucose oxidase was entrapped at a Clark oxygen electrode using dialysis membrane (Turner, 1996). This biosensor was made from a thin layer of glucose oxidase (GOx) on an oxygen electrode. The amount of glucose was estimated by the reduction in the dissolved oxygen concentration.

Clark's ideas became commercial reality in 1975 with the successful re-launch (first launch 1973) of the Yellow Springs Instrument Company (Ohio) glucose analyser based on the amperometric detection of hydrogen peroxide (Turner 1996). In 1963 Garry A. Rechnitz together with S. Katz introduced one of the first papers in the field of biosensors with the direct potentiometric determination of urea after urease hydrolysis.

In 1969 George Guilbault introduced the potentiometric urea electrode. In 1973 Ph. Racinee and W. Mindt developed a lactate electrode. In 1976 came the first microbe-based biosensor and finally in 1977 Karl Cammmann introduced the term "biosensor". In 1979 pioneering work by J. Kulys using artificial redox mediators and in 1984 Cass *et al*. introduced first ferrocene-mediated amperometic glucose biosensor which was commercialised by MediSense Inc. in 1987. In 1997 IUPAC introduced for the first time definition for biosensors in analogy to the definition of chemosensors. In 2007 an implanted glucose biosensor (freestyle Navigator system) operated for five days (Borgmann *et al.,* 2011) and the work on biosensors continues to advance exploiting enzymes, antibodies, microbes in combination with various types of transducers.

TYPES OF BIOSENSORS

Biosensors can be broadly classified into two categories based on sensing element and transduction modes. Sensing elements include enzymes, antibodies (immunosensors), micro-organisms (whole cell biosensors), biological tissues and organelles. Transduction mode depends on the physiochemical change resulting from sensing element. Hence on the basis of different transducers biosensors can be electrochemical (amperometric, conductometric and potentiometric), optical (absorbance, fluorescence and chemiluminense), piezoelectric (acoustic and ultrasonic) and calorimetric (Corcuera and Cavalieri, 2003). Biosensors can also be classified based on their discovery order into first generation which is the simplest approach involving direct detection of either increase of an enzymatically generated product or decrease of a substrate of a redox enzymes using natural mediator for electron transfer e.g. glucose biosensor which uses enzyme glucose oxidase and oxygen detecting decrease in oxygen level or increase in hydrogen peroxide corresponding to the level of glucose. Second generation biosensors uses artificial redox mediators like ferrocene, ferricynide and quinones for electron transfer which increases the reproducibility and sensitivity e.g. self-monitoring amperometric glucose biosensors. Lastly third generation in which the redox enzymes are immobilized on the electrode surface in such a manner that direct electron transfer is possible between the enzyme and transducer. It uses organic conducting material e.g. TTF-TCQN (tetrathiafulvalne-tetracynoquinodi methane) (Borgmann *et al.,* 2011). The main types are discussed below:

Amperometric biosensor

The potential between two electrodes is set and current produced by the oxidation or reduction of electroactive species is measured and correlated to the concentration of the analyte e.g. glucose biosensors for diabetes monitoring.

Potentiometric Biosensor

Use ion selective electrodes to determine changes in the concentration of chosen ions e.g. use of H^+ ions for penicillin detection using enzyme penicillinase, triacyl glycerol using lipase.

Optical biosensor

Fibre active probes on the tip of which enzymes and dyes (often fluorescent). Light interacts with the reagents are placed near the tip of the optical fibre, after interaction light returns with an intensity which is measured and indicates the amount of analyte e.g. optic lactate sensor using lactate monooxygenase and oxygen.

Calorimetric biosensor

Many enzymes catalysed reaction are exothermic generating heat which is used as a basis for measurement of rate of reaction and hence analyte concentration. The temperature changes are determined by thermistors e.g. cholesterol biosensors using cholesterol oxidase (heat output 53 $KJmol^{-1}$).

APPLICATIONS

Biosensors have been utilized in many areas like medical and health care (for monitoring glucose, lactose levels in body, analytical measurement of folic acid, biotin, vitamin B12 and pantothenic acid as an alternative to microbiological assay, detection of molecular markers in real samples), pharmaceutical(estimation of drug residues in food, such as antibiotics and growth promoters, particularly meat and honey, drug discovery and evaluation of biological activity of new compounds), environmental (BOD biosensor, detection of pesticides and river water contaminants), defence(remote sensing of airborne bacteria e.g. in counter-bioterrorist activities),bioprocessing (monitoring reagents and control parameters, biosensor instruments to measure

product quality e.g. ethanol, mannitol, penicillin biosensor), or food technology (microbial biosensor, pathogen detection).

Several biosensors have been developed for microbial analysis of food pathogens, including *E. coli O157:H7*, *Staphylococcus aureus*, *Salmonella*, and *Listeria monocytogenes*, as well as various microbial toxins such as *staphylococcal* enterotoxins and mycotoxins. Biosensors have several potential advantages over other methods of analysis, including sensitivity in the range of ng/mL for microbial toxins and <100 colony-forming units/mL for bacteria. Miniaturization of biosensors enables biosensor integration into various food production equipment and machinery. Biosensors can also be integrated into hazard analysis and critical control point programs, enabling critical microbial analysis of the entire food manufacturing process (Rasooly and Herold, 2006).

The fastest growing area in the biosensors research involves advances in affinity-based biosensors and biosensor-related methods. Numerous biosensor techniques have been reported that allow researchers to better study the kinetics, structure, and (solid/liquid) interface phenomena associated with protein-ligand binding interactions. Affinity-based biosensor techniques show promise include clinical/diagnostics, food processing, military/antiterrorism, and environmental monitoring. The design and structural features of these devices constitute the binding of the sensing element and the analyte and detection of the strength of binding (Rogers, 2000).

Various BOD (Biochemical Oxygen Demand) biosensors have been developed including BOD-BART^{TM} biosensor; Ferricyanide mediated approach, luminous bacterial immobilized chip method. BOD-BART^{TM} Biological Activity Reaction Tests (BART) was developed and patented by Cullimore and Alford in 1999. It provides an easy and rapid (<20-hour or <72,000 seconds) measurement of the BOD based on enhanced respiration activity of the indigenous heterotrophic aerobic bacteria (HAB) inhabiting the sample. In ferricyanide mediated approach, ferricyanide has been used as electron-acceptor instead of oxygen. In Luminous bacterial cells-immobilized chip method, bacterial bioluminescence which is caused by lux genes was observed. Physiological responses is measured and correlated to BOD due to reduction or emission. Reduction in the time for the BOD test would naturally help in saving of various resources such as time, money and man power etc. However, none of these has been developed as a standard method of BOD estimation (Kale and Mehrotra, 2009).

The phenomena of surface plasma resonance(SPR) has shown good bio sensing potential and Biocore has developed BIAcore^{TM} which enables real-time detection and monitoring of biomolecular binding events so paving the way to a better understanding of biochemical mechanisms. SPR occurs during optical illumination of a metal surface and it can be harnessed for biomolecular interaction analysis (BIA) (Leonard *et al*., 2003). The Biacore sensor chip is at the heart of the technology. Quantitative measurements of the binding interaction between one or more molecules are dependent on the immobilization of a target molecule to the sensor chip surface. There are different types of chips available for various analysis e.g. Sensor Chip CM5 – for applications from basic research to quality control Sensor Chip SA – for capture of biotinylated peptides, proteins and DNA(Biocore SPR technology manual). Some commercially available biosensors from Medisense are needle-type glucose biosensor implanted in subcutaneous fatty tissue, glucose biosensor pen, glucose biosensor with big digital display.

FUTURE ADVANCES

In recent years, with the development of nanotechnology, novel nanomaterials are being fabricated, their novel properties and applications are being in biosensors. For example, nanomaterials-based biosensors, represents integration of material science, molecular engineering, chemistry and biotechnology which can improve the sensitivity and specificity of biomolecule detection, hold the capability of detecting or manipulating atoms and molecules, biomolecular recognition, pathogenic diagnosis and environment monitoring. In particular, nanomaterials such as gold nanoparticles, carbon nanotubes, magnetic nanoparticles and quantum dots have been being actively investigated for their applications in biosensors (Zhang *et al*., 2009). Some of the nanoparticle-based sensors include the acoustic wave biosensors in which quartz crystal detector changes frequency due to the deposition of mass of any material on its surface and this change in frequency is directly proportional to the concentration of the sample, optical biosensors use resonance enhancement of metal nanoclusters bound to a surface by biorecognitive interactions for use in bio-optical sensor devices. Lectin–sugar, antigen–antibody and protein–receptor interactions have been employed in these assays. Gold nanoparticles have been used as a new class of universal fluorescence quenchers to develop an optical biosensor for recognizing and detecting specific DNA sequences. Magnetic nanoparticles are a powerful and versatile diagnostic tool in biology and medicine. They usually can be prepared in the form of single domain or superparamagnetic (Fe3O4), greigite (Fe3S4), maghemite (g-Fe2O3), and various types of ferrites (Jianrong *et al*., 2004).

The development of integrated biosensors for the detection of multiple biologically relevant samples is under research. These integrated biosensor arrays use the same excitation source for all of the elements and the same measurement process have been termed as: gene chips, DNA-chips, etc. Most of the different array chips are based on the use of nucleic acids (i.e. DNA) as sensing elements. Antibodies, enzymes and cellular components can also be used (Dinh and Cullum, 2000).

Biosensors are either placed in laboratory animals for fundamental (patho-) physiological and neurochemical *in vivo* measurements or implanted in the human body for health check purposes and metabolite monitoring. The main challenges in the field of implantable sensors are the stability of the sensor, the selectivity of the sensor, and the biocompatibility of the sensor. An example of implants biosensor is miniaturized carbon fiber based biosensors for in vivo measurements of acetylcholine and choline which have been prepared by means of a co – immobilization of acetylcholine esterase and choline oxidase (Borgmann *et al.*, 2011).

Hence biosensors offer an exciting alternative to traditional methods, allowing rapid "real-time" and multiple analyses for detection, diagnosis and estimation of any sample. For medical applications nanobiosensors, integrated biosensors and biochips will reduce the cost and time thereby increasing the efficiency of the tests. Also disposable biochips offer an added advantage of in-home medical diagnostics of diseases without the need of sending samples to a laboratory for analysis. In the past 40 years various biosensors have been researched and developed encompassing a wide range of applications but the number of commercially available biosensors is limited. Nevertheless, biosensor technology presents an opportunity for the development of robust, low cost, specific detection and analyses. Future prospects of biosensor technology, with special emphasis on the development of sensing elements and transducers are under current research.

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