

Sensor Applications in Analysis of Drugs and Formulations

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ABSTRACT

Biosensors are currently widely used in biomedical diagnostics, as well as point-of-care assessment of therapy and disease advancement, environmental sensing, food safety, drug development, forensics, and biomedical research. Biosensors may be developed using several different approaches. Due to the growing requirement for efficient and low-cost analytical methods, biosensors have gained increasing attention for application in the quality analysis of pharmaceuticals and other pharmaceutically relevant analytes. Biosensors enable the analysis of active ingredients in pharmaceutical formulations as well as the determination of degraded products and intermediates in biological matrices. The current study discusses several types of biosensors and their applications in drug analysis and formulations.

Keywords: Analyte, Biosensors, Drug analysis, Sensors, Signal, Transduction.

1. INTRODUCTION

A sensor is a device that senses physical, chemical, and biological signals and allows them to be analyzed and reported. Heat, weight or gravity, noise intensity, pressure, illuminance, vibration, rate of flow of liquids and gases, magnitude of electronic and magnetic fields, and amounts of different compounds in different forms (solid, liquid or gaseous) are all physical characteristics that may be detected. Even though sensors currently are where computers were in 1970, therapeutic uses of sensors are growing off because of improvements in microprocessor technology and chemical science.¹

Several sensing techniques employed in industry could be used in pharmaceuticals, and when novel sensors and micro-electro-mechanical devices which depend on sensors are developed and verified, in future other sectors will utilize these technologies for industrial purposes. There seems to be a growing convergence between digital technologies and biotechnology in the medical field, and the function of sensing devices, actuators, micromachines, and signal transducers will grow as well.¹

The development of micro sensor systems for biological applications is gaining popularity. The medical uses of this kind of sensors are immense, notably in point-of-care and intensive care diagnostics. Significant developments

are anticipated to deliver the desired enhancements in convenience, patient safety, affordability, and response time, or even have a significant influence on healthcare in the early twenty-first century. During the last 2 years, the latest findings have emerged, such as sensor convergence with micromachined analysis tools, massive development of genosensors, the genetic configuration of biorecognition element, extremely fast supervision of dynamic events in microscopic settings, electrodes, and the adoption of innovative sensing materials. Such new domains, coupled with ongoing research into innovative biocatalysts and selective biosensors based on acoustic, electrochemical, optical, or piezoelectric transducers, will undoubtedly increase the therapeutic use of biosensors and electroanalysis.²

The latest advancements of sensors and biosensors is mostly owing to two factors, one of technological nature and another of sociological nature. For several years, the necessary monitoring to assure people's safety and protection was dependent on separation methods, primarily chromatographic strategies paired with high-sensitivity detection techniques, beginning with mass spectroscopy. This method is highly capital intensive, lengthy, and laborious, thus fast and inexpensive methods are explored. However, civil society is paying more attention and focus to the safety of foods and nutritional supplements, owing to a widespread desire to live a safer life.³

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2. BIOSENSORS

A biosensor is a device that detects biological and chemical responses by producing signals corresponding to the concentration of the analyte in the reaction. Biosensors should be incredibly precise and consistent, irrespective of external factors such as pH and temperature. Biosensors are used in the medicinal field for disease management, drug development, as well as for detecting contaminants, infective microorganisms, and disease markers in biological fluids (blood, urine, saliva, sweat).⁴ The components of a typical biosensor include a bioreceptor, a transducer and a signal amplifier (Figure 1). DNA probes, antibodies, enzymes, and cell receptors that bind with the analyte can all be used as biosensing substances. The transducers, which can be made of acoustic, optical, physicochemical, or piezoelectric material, convert biological input to optical and electrical output.

2.1. Placement of Biosensors

In clinical applications, biosensors are divided into two types: *in vitro* and *in vivo* devices. In an *in vitro* biosensor, measurement is performed outside living organisms in a petri dish, test tube, microplate plate, or another container. An enzyme-conductimetric biosensor for blood glucose monitoring is an example of an *in vitro* biosensor. The development of a biosensor that works on the concept of point-of-care testing, i.e. at the site where the testing is required, is challenging.

In vivo biosensors are devices that are implanted and work within the body. Of course, biosensor implants must adhere to strict sterilization to minimize an inflammatory response following implantation. One more concern is long-term biocompatibility, or the relatively harmless interplay between product and the bodily milieu. Malfunction is yet another problem that comes up. If the device failure is detected, it should be removed and replaced immediately. Insulin management inside the body is an example of an *in vivo* biosensor which is currently unavailable.

2.2. Types of Biosensors

Biosensors can be classified into several types based on how they transmit signals. Leland C. Clark first demon-

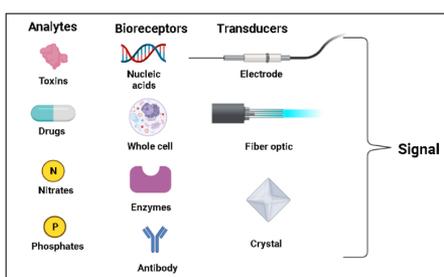


Fig. 1: Different components of biosensors

strated electrochemical sensors in 1962. In this biosensor, interactions can occur between molecules and reactants to produce an electrical signal corresponding to the analyte concentration. It utilizes amperometric, conductometric, and potentiometric devices to transform sensory input into a quantifiable output, based on this concept.⁵

2.2.1. Electrochemical

Electrochemical sensors have been extensively used in forensic science fields, notably in the detection and analysis of drugs, employing a wide range of devices to attain the necessary specificity and sensitivity. Despite their apparent benefits, electrochemical sensors must be expanded to analyze numerous drugs or illegal narcotics, and common additives and chemicals, in terms of providing the forensic community with a comprehensive and efficient analyzing tool.⁶

2.2.2. Optical

One of the most widely used types of biosensors is an optical biosensor. Optical biosensors are anticipated to acquire the most popularity in the pharmaceutical, biomedical, and biopharmaceutical industries. These sensors can give novel analytical techniques that are smaller in size, along with allowing large-scale high-throughput sensitivity analysis of a large number of analytes for a variety of parameters. Numerous techniques for improving the sensitivity of optical biosensors were designed to enhance the signal-to-noise ratio and lower the detection limit. Optical biosensors have been experimentally validated in a variety of disciplines including medicine, pharmaceuticals, food standards, the environment, bioengineering, and civil defense. Optical biosensors, however, are still in the early stages of research and are primarily used in the educational and pharmaceutical sectors.⁷

2.2.3. Thermometric

Thermometric biosensors make use of a significant component of biological processes, namely heat absorption or release. The temperature of the reaction system alters as a result of this. Thermometric measurement is essential to determine the amount of energy produced or absorbed during a biological reaction. Several compounds, including ethanol, glucose, lactate, triglycerides/peroxides, oxalate, urea, ascorbate, cellobiose, and sucrose, as well as penicillin, were analyzed employing different versions of the thermometric devices.⁸

2.2.4. Piezoelectric Biosensor

Piezoelectric biosensor is a type of analytical biosensor that works on the concept of monitoring affinity interactions. A piezoelectric platform, also known as a piezoelectric crystal, is a sensing component that works based on oscillatory alterations as a result of a mass binding to

the piezoelectric crystal surface. The variety of piezoelectric platforms is fairly large, and numerous articles have indeed been published on the subject. The number of biorecognition components and biosensor designs increases with the increase in the number of adaptations.⁹

2.2.5. Immunosensors

Immunosensors are a type of specificity biosensors that are based on associations between an antigen and a specified antigen immobilized on the surface of a transducer. Because of the precise affinity between the antibody and associated antigen, immunosensors have great sensitivity and selectivity, allowing them to be an ideal tool for a wide range of applications, particularly in the medical and bioanalysis areas.¹⁰

2.2.6. Magnetic Biosensors

By enabling analyte identification, modification, and sorting, magnetic biosensors can replace or enhance current fluorescence-based in vitro biosensor methods. Nevertheless, despite the presence of early initiatives including magnetic actuation for cellular functioning control as well as detecting endogenously generated magnetic nanoparticles by a tunnel magneto-resistance (TMR) sensor, applications of in vivo magnetic biosensor remain a challenge for the future.¹¹

2.2.7. Acoustic Biosensors

Acoustic biosensors are built on specialized surface acoustic wave (SAW) technology that would allow for the very sensitive identification of biorelevant chemicals in liquid media. The majority of the current investigation focuses on the following acoustic systems for their applications: Bulk acoustic wave (BAW)-based biosensors employing quartz crystal microbalance (QCMs) and surface acoustic wave (SAW)-based biosensors. Nevertheless, only SAW-based biosensors use high frequencies in the range of 100 MHz to GHz, suggesting larger mass sensitivities as relative to QCMs.¹²

2.2.8. Enzyme Biosensor

Enzyme biosensors are chemical biosensors based on biological detection. To function, the enzymes should be accessible to catalyze a particular biochemical process and be persistent under the biosensor's typical working circumstances. Biosensor design is influenced by an understanding of the analyte of interest along with the intricacy of the matrices in which the sample must be measured. Even though these biosensors can be thoroughly described in a monitored laboratory setting, their application in biological matrices like body fluids seems to be more difficult. This final phase distinguishes between biosensor development and its application in research, diagnostics, and follow-up analytical equipment.¹³

2.2.9. DNA Biosensor

DNA biosensors (genosensors) are made up of an immobilized strand of DNA that detects complementary sequences by DNA–DNA pairing, which occurs directly on the surface of a physical transducer. In a broader sense, these biosensors can still be used to accurately detect analytes, with the probing molecule often taking the form of an aptamer. Genosensor has been used because of their intrinsic physicochemical resilience and ability to distinguish between various strains of organisms. Clinical applications specially need large-scale, distributed DNA testing. DNA chips and microfluidic devices, which integrate DNA sensing with preconcentration in an in vivo-like hybridization setting, are two new methods for DNA diagnostics. Nanotechnology materials, such as carbon nanotubes (CNTs) and DNA/protein conjugates, may result in increased sensitivity and specificity.¹⁴

2.2.10. Nanobiosensors

Nanobiosensors use the distinct biological and physical characteristics of nanomaterials to detect a target molecule and perform electrical signal transduction. When compared to current large electrodes used in biosensors, the benefits of nanobiosensors include quick response, small size, sensitivity and selectivity, and mobility. The main technology that permits small medication is systems integration. The convergence of nanoparticles, microfluidic devices, automated samplers, and transduction devices on a microchip offers several benefits for point-of-care technologies like biosensors.¹⁵

3. APPLICATIONS OF BIOSENSORS¹⁶

Biosensors have been used in a variety of areas, including the food industry, pharmaceuticals, and the marine sector. They give more stability and sensitivity than traditional techniques.

- In the case of a biological attack, biosensors have been utilized for strategic operations. The primary goal of these biosensors is to detect and identify organisms that pose a danger on time, known as biowarfare agents (BWAs), like bacteria, toxic chemicals, and viruses. Numerous efforts have been made to design such biosensors utilizing molecular methods capable of recognizing the biomarkers of BWAs.
- Biosensors can be used to evaluate processing conditions passively by analyzing the presence of products, biomass, enzymes, antibodies, or by-products of the process. Because of their simple apparatus, impressive selectivity, low costs, and ease of automated processes, biosensors accurately manage the fermentation process and give consistent results.
- Biosensors are widely utilized in the medical community to detect infectious conditions. A potential

biosensor technique for diagnosing urinary tract infections (UTIs), detection of pathogens, and anti-microbial vulnerability is being researched.

- The advent of biosensors as a result of the requirement for simplified, authentic, precise, and low-cost approaches, appears to be advantageous in food processing, control, food validity, safety, and quality. Biosensors have been employed to detect pathogens in food.
- Biosensors have also been used to discover lacking components related to analyte metabolism, modulation, or transportation. A transportation process in phloem loading-sucrose outflow is performed by a fluorescence resonance energy transfer (FRET) sensor for sucrose, which is important for protein detection.
- Fluorescent biosensors have been employed in drug discovery and development to identify drugs using high throughput, high content testing techniques, as well as for the postscreening interpretation of the findings and lead optimization. These are thought to be effective methods for the clinical and preclinical analysis of prospective drugs' therapeutic properties, bioavailability, and pharmacokinetics.
- Because of their capacity to interact only with the toxic components of metal ions, biosensors have been used to detect particular toxic metals and overall toxicity.

3.1. Biosensors in Drug Analysis

Biosensors can be used to analyze drug molecules quantitatively, but their main application is in the mechanical and kinetic features of drug-biocomponent interplay.

Considering that the pharmacopeia techniques are sometimes time-consuming and costly, biosensors have emerged as an intriguing substitute. Substantial studies have been conducted to optimize immobilization procedures and get the analytical signal. There has been researched towards new biological and biomimetic recognizing systems. The use of the enzyme aryl-acylamidase to recognize aminophenol rendered from

acetaminophen for the implicit analysis of paracetamol; the use of teophyllin oxidase paired with the ferrocyanate (electron mediator) for analysis of theophylline; salicylate hydroxylase for detection of salicylates; and tyrosinase for analysis of catecholamines and peroxides are some of the examples of biological recognizing substances linked with electro-chemical biosensors.¹⁷

Amino acid oxidase is utilized to create enantio-selective biosensors for the detection of chiral pharmaceuticals with an amino acid-related component in their molecular structure. Amperometric biosensors containing immobilized dismutase or cytochrome c may easily analyze antioxidant compounds of both synthetic as well as natural origin.¹⁸

A transducer monitors the physicochemical relationship of the analyte with the bio-recognizing agent. The detection of signals in electrochemical biosensors happens at the electrode/solution junction, which could either be dynamic or static. The dynamic techniques, such as voltammetry, must entail a redox reaction succeeded by the transfer of electrons. Nevertheless, in static techniques such as potentiometry, a potentiometric biosensor analyzes the amount of charge carrier as a result of the electrochemical process. The usage of any biosensor is determined by the analyte's properties. Therefore, inorganic or organic species should experience a redox reaction at active potentials, i.e. electro-active species, for amperometric biosensors, whereas static techniques are suitable for charged species. The right selection of the recognizing agent and biosensor, both of which are appropriate for the intended analyte, is critical to producing an optimal biosensor.¹⁷

3.1.1. Salicylates

Various biosensors based on Salicylate Hydroxylase (SH) have been developed, either alone or in combination with other enzymes such as glucose oxidase or tyrosinase. The analytical signal is generated in such biosensors, by transfer of electrons during the redox reaction of catecholic product, that arises from the salicylate hydroxylation

Table 1: Applications of biosensors

Transduction	Biosensor type	Applications
Electrochemical	Acetylcholinesterase (AChE) inhibition biosensors	Pesticidal study
	Hba1c biosensor	Determining glycosylated hemoglobin
	Uric acid biosensors	Diagnosis of various clinical abnormalities or illness (e.g., diagnosis of cardiovascular disease)
Optical	Polyacrylamide based hydrogel biosensors	Immobilization of biomolecules
	Silicon biosensor	For biosensing, bio-imaging, and cancer therapy
	Micro fabricated biosensor	In novel drug delivery (e.g., in optical corrections)
Electrochemical or optical	Nanomaterials biosensors	For diagnosis and in drug delivery

and decarboxylation. The SH biosensor allowed for salicylate analysis in the range of 7.25×10^{-6} mol/L to 4.35×10^{-3} mol/L.¹⁷

3.1.2. Acetaminophen

Horseradish peroxidase (HRP) catalyzes the oxidation of acetaminophen to form N-acetyl-p-benzoquinoneimine in the presence of hydrogen peroxide. Therefore, the primary analytical methods for the analysis of paracetamol are amperometric biosensors based on direct immobilization of enzymes on the surface of transducer.¹⁷

3.1.3. Citalopram

Citalopram is an antidepressant agent used in the treatment of depression and mood disorders. For citalopram analysis, a citalopram-tetraphenyl borate ion-pair oriented polyvinyl chloride (PVC) membrane sensors have been developed. The electrodes with a membrane composed of 30% PVC, 66% DBP, and 4% ion-pair, demonstrated a rapid (~5 s) consistent and Nernstian response across a reasonably large citalopram concentration range of 1×10^{-5} to 1×10^{-2} M and a pH range of 3.0–5.5. The approach was validated, and the sensors were shown to be suitable for the QC analysis of citalopram hydrobromide in pharmaceutical formulations and in urine as well.¹⁹

3.1.4. Catecholamine

Palm fruit biosensors were utilized to analyze epinephrine in pharmaceutical preparations at concentrations ranging from 0.05 to 0.35 mM. When compared to official procedures (USP XXX), the findings demonstrated high precision (3.1 percent) and consistency. These biosensors and the guariroba (*Syagrus oleracea*) biosensors are two more palm tissue-based biosensors used in the analysis of catecholamines.¹⁷

3.1.5. Methylxanthines

Several scientific research utilizing biosensors for methylxanthine detection is focused on theophyllin analysis. The use of DNA biosensors, as well as other nucleic acid derivatives in research, has been emphasized. On gold electrodes, RNA aptamers have been co-immobilized with ferrocene (electron mediator). Using voltammetry, this RNA-based sensor was tested for theophyllin detection, yielding a constant value from 0.2 to 1.0 mmol/L.¹⁷

3.1.6. Neuroleptics

Several sensors for analysis of neuroleptic drugs have been developed, which, although having modest redox activity, could be measured using amperometric or potentiometric methods. As a result, haloperidol exhibits a permanent anodic peak (Epa ~0.86V) when measured

with glassy carbon electrodes enhanced with CNT. Chlorpromazine ion-selective electrodes were developed by integrating chlorpromazine-tetraphenylborate combinations into PVC matrices.¹⁷

One of the most popular biosensors for the analysis of MAO inhibitors have been developed based on monoamine oxidases coupled with amperometric transducers. These biosensors were used to analyze pirlindole, fluoxetine, and desipramine with the enzyme immobilized on screen-printed platinum electrodes. The device was very sensitive, with detection limits of 8.0×10^{-7} , 8.0×10^{-10} , and 8.0×10^{-9} mol/L for pirlindole, fluoxetine, and desipramine, respectively.¹⁷

3.1.7. Antineoplastic Drugs

Owing to their relatively greater sensitivity, minimal cost, and high speed of operation, electrochemical sensors and biosensors are appealing options for antineoplastic drug analysis. An electrochemical sensor for the analysis of methotrexate (an antineoplastic agent) and folic acid have been developed by modifying a glass carbon electrode (GCE) with multi-walled carbon nanotubes (MWNTs) functionalized with quaternary amine (q-MWNTs).²⁰

3.1.8. Illicit Drugs

Nanomaterial-based optical sensors have been utilized for analyzing the presence of illicit drugs in medical and government institutions. Nanomaterials can be used as signaling reporters, allowing for quick and sensitive detection. Colorimetric and fluorescent optical sensor systems are two types of nanomaterial-based optical sensor systems currently available.²¹

3.1.9. Other Drugs

Penicillamine, methimazole, and pipemidic acid have also been analyzed using a tyrosinase-based amperometric biosensor with signal inhibition. The pharmaceutical compounds were identified by inhibiting the substrate recycling mechanism between tyrosinase and the electrode. The interaction between the substrate and the drug was found to have a significant impact on the analytical performance of biosensor. As substrates, 4-tert-Butylcatechol, catechol, and 4-Methylcatechol were investigated. Catechol was considered for its sensitivity to pipemidic acid, whilst 4-tert-Butylcatechol was chosen for penicillamine. Amperometric biosensors containing immobilized superoxide dismutase or cytochrome c may easily detect antioxidant compounds, both naturally derived and those of synthetic origin. The enzyme selectively interacted with the superoxide anion present in solution at the cytochrome c mounted gold electrode, and the output decreased when the antioxidant was present.²²

4. CONCLUSION

In biosensing devices, a variety of transduction methods, such as electrochemical sensors, optical sensors, and acoustic-sensitive sensors, can be employed. Besides traditional pregnancy tests, lateral flow systems hold great potential for the advent of low-cost, easy-to-use point-of-care sensors, whilst lab-on-chip tools combine multiple microfabrication strategies, allowing biosensors to be used in a broad array of applications with small volumes of the analyte. The analysis of compounds in real-time basis is a concept in analytical chemistry that may be accomplished through the use of sensors. Biosensors are a potential technology that satisfies the needs of relatively cheap, the convenience of analysis, selectivity, and high sensitivity. This study summarised some of the most important uses of these technologies for pharmacological analysis. Despite issues with the consistency of electrochemical techniques and the enzyme's stability as well as other biological recognizing agents, the biosensor continues to be a research priority. As a result, several investigations on the invention of novel transducers, as well as strategies for immobilizing the recognizing agents, can be reported in the literature. Nevertheless, additional research is needed to standardize these sensors for usage in pharmaceutical analysis and to introduce approved procedures.

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