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A REVIEW ON BIO SENSORS & APPLICATIONS IN MEDICAL DEVICES

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ABSTRACT
Biosensor-integrated drug delivery systems are innovative devices in the health area, enabling continuous monitoring and drug administration. The use of smart polymer, bioMEMS, and electrochemical sensors have been extensively studied for these systems, especially for chronic diseases such as diabetes mellitus, cancer and cardiovascular diseases as well as advances in regenerative medicine. Basically, the technology involves sensors designed for the continuous analysis of biological molecules followed by drug release in response to specific signals. The advantages include high sensitivity and fast drug release. Electrochemical biosensors include a recognition component and an electronic transducer, which detect the body fluids with a high degree of accuracy. More importantly, they generate timely readings of the related physiological parameters, and they are suitable for integration into portable, wearable and implantable devices that are significant relative to point-of-care diagnostics scenarios. As an example, the personal glucose meter fundamentally improves the management of diabetes in the comfort of the patients' homes. This review paper analyzes the principles of electrochemical biosensing and the structural features of electrochemical biosensors relative to the implementation of health monitoring and disease diagnostics strategies.

KEYWORDS: Biosensors; drug delivery systems; smart polymers; biomedical applications; chronic treatments.

INTRODUCTION

Biosensor-integrated drug delivery systems have been extensively studied, especially for the treatment of chronic diseases such as cardiovascular diseases (CVD), diabetes mellitus, and cancer, where regular drug administration and continuous monitoring are relevant. The conventional modes of treatment have been associated with serious side effects; thus, over the years, controlled drug delivery systems have been explored as a promising alternative to improve the efficacy and safety by optimizing the duration and kinetics of release. Moreover, the use of systems that can initially sense markers associated with regenerative medicine and diseases, and subsequently release their payloads, has shown a great impact on the treatment of chronic diseases. Biosensors are analytical devices composed of two maincomponents: abio-recognition element and a transducer. The bio-recognition element of the sensor identifies the target analyte, while a transducer converts the result of the molecular recognition into an electrical signal. Different biomolecules such as enzymes, nucleic acids, antibodies, proteins, and peptides can be used as a bio-recognition element and biosensors can thus be used to detect specific physiochemical changes in the body (associated with the diseases) with high sensitivity and specificity.[8] Biosensors have been widely utilized for diagnostic and imaging, however, they are not originally equipped with therapeutics to treat the diseases. Several studies that merge biosensing and drug delivery concepts have been described in the last few decades. These systems are a special class of biosensor designed for the continuous analysis of biological molecules followed by drug release in response to specific signals.

Relevant Types of Biosensors

Electrochemical Detection of Biomarkers Considering the electrochemical biosensing devices, the detected signal is usually generated by the transfer of electrons or ions over a conductive transducer. This essentially generates a biorecognition process. The physical components or properties of the signals are current, potential, impedance, capacitance, conductivity, and light, which are generally determined by intensity, propagation direction, frequency or wavelength spectrum, and polarization. Thus, the impedimetric biosensors usually generate superior outcomes relative to POC diagnosis, and also concerning the integration to devices, considering that they are proper to detect biorecognition events through measurements of the non-Faradaic.

1. Voltammetric and Amperometric Biosensors

Voltammetric and amperometric biosensing devices function using a system with three electrodes. This includes a biosensing device in the form of a working electrode (WE), which detects the target entity, a counter electrode that generates the current, and a reference electrode that induces a stable potential. The signals of the current are produced byelectrochemical reactions on the WE, which aregenerated by a properly applied potential. The voltammetric detection is different from amperometric measurements considering the applied potential, which is constant for amperometric biosensors, and variable for voltammetric biosensing devices. More precisely, the measurements that relate to three electrodes are based on the usage of a potentiostat.

2. Potentiometric Biosensors

Potentiometric biosensing devices generally consider a two-electrode system, which relates to a sensing electrode, and a reference electrode. These allow direct detection of targets using the value of the potential signal concerning the change in surface charge on the target recognition of the sensing electrode. Usually, these consider ion-selective electrodes made of ion-selective membranes and a liquid contact structure that determines the potentiometric sensing electrodes. More details are provided in Figure 1c, which represents ion-selective electrodes featured by three different structures. The process includes the recording of potential (E) for the determination of quantitative values. Thus, this functional model is able to detect enzymes, nucleic acids, and proteins through the integration of the respective biological compound over the ion-selective electrode. This acts as a catalyst of the reaction that generates the ions through the combination of the target event with an ion-based reaction.

3. Photoelectrochemical Biosensors

The scientific field of photoelectrochemistry assesses the effects of light on photoelectrodes and photosensitive materials, as well as the processes of sun light conversion to electricity. Photoelectrochemical biosensors blend photoelectrochemistry with sensor-based bioanalysis. Thus, light serves as the source of excitation, and the generated electrical current constitutes the produced data readout. Photoelectrochemical biosensors generally relate to three electrodes and a source of light, as it is also suggested in Figure 1e, which relates to a photoelectrochemistry biosensing process based on a three-electrode system anda light source. This includes the storage of the photoelectrode photocurrent's values. The detection is possible considering the modification of the photocurrent on the determination of the target at the surface of the biosensing component. This essentially creates a charge or energy transfer that is determined by the photoelectrochemical reaction between a donor electron, an acceptor, and a photoactive material placed on the surface of the electrode.

Biosensing and Bioimaging Based on Electrochemiluminescence Electrochemiluminescence (ECL) is an energy relaxation process that is triggered electrochemically, in which a luminophore goes through a transfer of electrons. The process generates excited states that produce light. Thus, ECL biosensors are proper for the quantitative detection of specific molecules using ECL emission signals. Comparable to amperometric and voltammetric biosensors, ECL components consider three electrodes. The working electrode is customized so that the detection component acts as the biosensing electrode, as it is suggested in Figure 1f, which displays the ECL biosensing of cells using an aptamer-modified electrode. The approach is connected to a sandwich-sensing format. Considering the hybrid detection model that relates to electrochemistry and spectroscopy, these biosensors work in the absence of light. They generate very low levels of background noise, and they are highly sensitive. These features recommend electrochemiluminescent biosensors as efficient analysis instruments for the determination of various disease molecules, such as DNA, miRNA, proteins, and tumour cells.

Integration Into Wearable Devices

Electrochemical biosensing components may be built into portable, wearable, or implantable devices, as suggested by Figure 1g, which presents the integration strategies of electrochemical biosensors into portable, wearable, and implantable devices. Relative to this figure, the following components may be observed: CE (counter electrode), D (drain electrode), Medox (oxidized form of mediator), Medred (reduced form of mediator), RE (reference electrode), S (source electrode), and WE (working electrode). Thus, amperometric biosensors are mostly used for the analysis of metabolites. Considering the particular enzymatic reactions, they generally produce a sufficient level of selectivity. Additionally, the enzymatic catalytic signal may be improved through the usage of nanomaterials, which generates a superior sensitivity. These enzymatic biosensors are configured in batches, and the process is easily reproducible. Nevertheless, the enzymatic dynamics may be affected by certain features of the environment. Therefore, it is necessary to design reliable sensing electrodes that are proper for various environmental conditions. Potentiometric biosensors may be considered as components of wearable sweat monitoring systems, which specifically analyze the electrolytes. Relative to the ion-selective membranes, the potentiometric biosensors exhibit the necessary selectivity, reproducibility, and stability. Their main disadvantage is represented by the low sensitivity. By contrast, a flexible all-solid-state wearable ion-selective electrode may sustain a continuous sweat monitoring process. It is also relevant to note that voltammetric, photoelectrochemical, OECT, and electrochemiluminescent biosensing components are proper for the determination of proteins and nucleic acids, considering their physical capacity to select, and also their high sensitivity. Nevertheless, they are more

difficult to manufacture than the enzyme electrodes.

Portable Electrochemical Biosensing Devices

These have been initially proposed to measure the levels of glucose relative to patients with diabetes. The personal glucose meter represents a portable electrochemical biosensor that offers a quick quantitative analysis of the glucose levels in blood. Technically, this is generally an amperometric biosensor that relates to a redox enzyme. It features a disposable test strip and a handheld electrochemical reader. The disposable test elements may be manufactured using economically effective materials like plastics and conductive pastes. The glucose meter is the typical example of a biosensors that has been continuously improved in order to improve its reliability, accuracy, and user friendliness. It is also relevant to note that the personal glucose meter may also be considered for the detection of metal ions, drugs, enzymes, proteins, organic metabolites, DNA, and influenza viruses. The detection mechanism analyzes the reference detection events relative to the usage of glucose, considering both its generation and consumption. Relevant real-world use cases imply that the glucose meter can detect cocaine, uranium, and even adenosine in related blood samples. Additional relevant contributions were reported in articles. Thus, the functional logic of the personal glucose meter is presented, which suggests that the portable blood glucose meter is composed of a handheld electrochemical detection sensor and disposable test strips. These contain a bottom electrode layer, an adhesive spacer layer, and a hydrophilic cover layer. The blood sample enters the reaction cell through capillary force.

Implantable Devices

Implantable devices designate a category of wearable devices that include various biosensors in real-world scenarios. Thus, implantable electrochemical biosensing components blend the high accuracy of invasive finger-prick assessments with the long-term monitoring model of non-invasive evaluations based on wearable devices.Implantable biosensing devices are usually considered for monitoring the levels of glucose and also for the detection of certain biomarkers, such as neurochemicals that are found in the brain. Relative to electrochemical biosensors, the detection takes place on the surfaze of the electrodes. Therefore, these sensors may be integrated into an implantable capsule along with the necessary electronic circuitry.Implantable biosensing devices, such as intravascular or subcutaneous, may offer real-time or near-real-time updates regarding the levels of glucose. This may further support the proper adjustments of clinical treatment regimens.Additionally, spatiotemporal electrochemical detection of neurochemicals, such as dopamine andacetylcholine, may effectively indicate the pattern of brain activity and help to discover any potential abnormalities. The mechanical and general physical in compatibilities between implantable biosensors and the target tissuesmare also studied in the surveyed literature. These may lead to the failure of the implanted devices or even to problematic or life-threatening inflammatory reactions. Consequently, the implanted components (electrodes) should be sufficiently soft and flexible in order to ensure the maximum possible physical compatibility with the target tissues. Implantable biosensing devices usually stay in the body over a long time period. This requires proper reliable power supply which is featured in a high-density energy storage model. Batteries fulfill the energy storage density constraints, but need to be replaced periodically. This poses easily discernible medical risks, such as the possible infection of target tissues. Therefore, as it has already been mentioned, it is possible to manufacture self-sufficient implantable biosensors which generate the necessary power using piezoelectric materials, triboelectric materials, or fuel cells. It is also interesting to note that electrical power may be generated wirelessly through the consideration of technical solutions that pertain to the scope of near-field communication. In such a scenario, the power transmission channel may also act as the data transmission link.

CONCLUSION

Biosensor-integrated drug delivery systems have been a multidisciplinary technological advancement that allows for both the monitoring and delivery of the drug with precision. Several technologies were described in this review for chronic diseases (e.g., diabetes, cancer, cardiovascular diseases) and regenerative medicine, which promise personalized treatment favoring clinical success. The gold standard for the treatment of diabetes would be wearable biosensors with improved specificity and sensitivity, and of a low detection limit for the precision delivery, aside from overcoming the challenge of the oral delivery of insulin. Regarding cancer treatment, the use of smart nanomotors with a biosensing and delivery capacity at the cellular level would revolutionize chemotherapy in the shortterm. Wearable devices for pre-programmed intravenous drug delivery would reduce adverse side effects as the systemic drug exposure would be lower. Electrochemical biosensors have been continuously and intensely enhanced during the past forty years, although the first functional biosensors for oxygen detection was proposed in 1956 by Leland C. Clark. The sustained research and practical efforts generated increasingly complex technical solutions, which also tend to fail more often than the past biosensing devices. The sensitivity of the detection process and the selectivity essentially relate to the recognition reaction that occurs on the delicate electrolyte–electrode interface. The operation of this component is influenced by several factors, like the friction between electrodes and biological tissues and the variation of pH values. The flow rate of the biological fluids and the related temperatures are especially important relative to wearable devices. Consequently, the robustness and reliability of the electrochemical biosensors should be improved, which would allow the design and implementation of long-term health

monitoring systems. Thus, the reviewed literature suggests that the principle of enzymatic chemistry may be replaced by solutions related to nanomaterial-based catalytic sensing chemistry, which is less prone to be affected by environmental conditions like temperature, pH, and ionic strength.

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