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BIOSENSORS IN PHARMACEUTICAL INDUSTRY: A REVIEW

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ABSTRACT

Biosensors are analytical devices containing a biological or biologically derived sensing component which is either closely related to or integrated within a physicochemical transducer. These sensors overcome the difficulty in conversion of biological data to electrical signals which can be easily read and monitored. The use of biosensors has increased tremendously over the years due to new techniques and developments. They find their applications in many fields including medicine, diagnostics, military, veterinary, agriculture, and quality control. Research in the field of biosensors is likely to have a significant impact on the development of modern electronics. This review article focuses on the elements of a biosensor and the applications of biosensors in the pharmaceutical industry. Beginning with blood glucose monitors, improvements on the technological front have led to the manufacture of bio nano sensors, electronic noses, wireless endoscopy capsules to name a few. Current research in biosensors is based on miniaturization of the sensors and increasing their biological sensitivity.

Keywords *–Biosensors, wireless capsules, drug delivery, bioelectronics, transducers*

1. INTRODUCTION

A biosensor is an analytical device containing a biological or biologically derived sensing component which is either closely related to or integrated within a physicochemical transducer. Biosensors generally yield a digital electronic signal. This signal is proportional to the concentration of a specific analyte or group of analytes. Although most cases the signal is continuous, devices can be configured so that their outputs are single measurements that meet specific requirements[1].

A recently proposed IUPAC definition states that, "A biosensor is a self-contained integrated device which is capable of providing specific quantitative or semi-quantitative analytical information using a biological recognition element (biochemical receptor) which is in direct spatial contact with a transducer element. A biosensor should be clearly distinguished from a bioanalytical system, which requires additional processing steps, such as reagent addition. Furthermore, a biosensor should be distinguished from a bio-probe which is either disposable after one measurement, i.e. single use, or unable to continuously monitor the analyte concentration"[2].

Owing to recent scientific and technological progress, biosensors are likely to play an increasingly important role in the generation of analytical information in various fields, right from medicine to the military. In particular, biosensors will become the basis of economical, simple devices for acquiring chemical information and the ability to manage sophisticated analytical data to the non-specialist and

general public. The existing opportunities for the rapid exploitation of new developments in this area are substantial. Research in the field of biosensors is likely to have a significant impact on the development of modern electronics[3].

The first biosensor was an enzyme-based glucose sensor developed by Clark and Lyons. Hundreds of biosensors have been developed since then in many research laboratories around the world. More than 200 research papers a year have been published on biosensors for the few years[4]. The aim of this article is to review the principles of different biosensors, their production and working, their existing and potential applications in the pharmaceutical industry.

Classification of biosensors is based on their biological component or transducer component. Biological components include enzymes, antibodies, micro-organisms, biological tissue, and organelles. Immunosensors are antibody-based biosensors. An affinity sensor is one in which the binding of the sensing element and the analyte is the event that is detected. In a metabolism sensor, the interaction between the biological element and the analyte is either accompanied or followed by a chemical change in which the concentration of any one of the substrates or products is measured. Lastly, a catalytic sensor converts a secondary substance to produce a signal rather than chemically changing the bound analyte. The method of transduction depends on the type of physicochemical change resulting from the sensing event[5].

2. BASIC ELEMENTS OF A BIOSENSOR

A biosensor is a device composed of two elements:

(i) A bioreceptor – it is an immobilized sensitive biological element such as an enzyme, microbe, antibody, etc. which recognizes the analyte. Enzymes are by far the most commonly used biosensing elements in biosensors. Antibodies and oligonucleotides are also frequently employed.

(ii) A transducer – it is used to convert a biochemical signal which results from the interaction of the analyte with the bioreceptor into an electronic one. The intensity of generated signal is related to the analyte concentration either directly or indirectly[6].

2.1 Sensing elements

2.1.1 Enzymes

Enzymes are proteins having high catalytic activity and selectivity towards substrates[7]. Their commercial availability at high purity levels make them attractive for the large scale production of enzyme sensors. Their main limitation is that their activity is affected by pH, ionic strength, chemical inhibitors, and temperature. Enzymes have been immobilized on the surface of transducers by adsorption, covalent attachment, trapping them in a gel or an electrochemically generated polymer, in bi-lipid membranes or in solution behind a selective membrane[8]. Enzymes are commonly coupled to electrochemical and fiber optic transducers.

2.1.2 Antibodies

Antibodies are proteins showing extremely high selectivity. Many antibodies are commercially available and commonly used in immunoassays. They are usually immobilized on the surface of transducers by covalent attachment by conjugation of amino, carboxyl, aldehyde, or sulfhydryl groups. The surface of the transducer must be previously activated with an amino, carboxyl, hydroxyl, or other group[9]. Antibodies have similar limitations as those of enzymes. Efforts are being made to manufacture economical, disposable sensors. They have the potential advantage that they could allow faster in-field measurements.

2.1.3 Microbes

Measurement of microbial metabolism is the basis of the use of microbes as biological components in biosensors. In many cases this measurement is accompanied by the measurement of consumption of oxygen or carbon dioxide. IT is measured electrochemically in most cases[10]. The advantage of using microbial cells is that they are cheaper than enzymes or antibodies and are comparatively more stable and are able to carry out more complex reactions. The limitations of using microbes are that they are less selective than enzymes and have

longer response and recovery times[11]. Micro-organisms can be immobilized on nylon nets, cellulose nitrate membranes or acetyl cellulose[12].

2.2 Transducer Elements

2.2.1Electrochemical transducers

The most commonly used electrochemical transducers include amperometric, potentiometric and conductometric transducers. When a fixed potential between the two electrodes is set and the current produced by the oxidation or reduction of electroactive species is measured and correlated to the concentration of the analyte under consideration, the type of transducer in known as amperometric transducer. A selective membrane or an electron mediator that reacts at lower potential is integrated into the immobilization matrix or to the sample containing the analyte is used. Potentiometric transducers measure the potential of very low current electrochemical cells. Potentiometric devices based on the measurement of potential at an insulator– electrolyte interface are called Field effect Transistors (FET). A pH transducer (pH ISFET) is made by substituting the metal gate of a FET with an ion selective membrane. Enzymes can be immobilized on the surface of pH transducers[13]. Conductometric transducers measure the change in electrical conductivity produced by change in concentration of ionic species in the cell solution. They can detect any reactive change occurring in a solution[14].

2.2.2 Optical transducers

Fibre optic biosensors measure both catalytic and affinity reactions. They consist of a light source, an optical fibre, a sensing material and a detector[15]. Fibre optic probes on the tip of which enzymes and dyes (often fluorescent) have been co-immobilized are used. These probes consist of at least two fibres. A light source of a given wave length range produces an excitation wave. This source is connected to one of the fibres. The other fibre is connected to a photodiode which detects changes in optical density at appropriate wavelengths. Surface Plasmon Resonance (SPR) transducers have been proposed. SPR measurement is based on the detection of the attenuated total reflection of light in a prism coated with metal on one side[16,17]. A few SPR biosensors have been commercialized but no compact inexpensive portable device is available yet. The most common fibre optic biosensors in use are – absorbance, fluorescence, reflectance and luminescence biosensors[18,19].

2.2.3. Acoustic transducers

Acoustic transducers are also known as piezoelectric transducers. Electroacoustic devices used in biosensors are based on the detection of changes in mass density or elastic, viscoelastic, electric and dielectric properties of a membrane made of chemically interactive materials in contact with a piezoelectric material. Bulk acoustic wave (BAW) and surface acoustic wave (SAW) propagation transducers are commonly used. One major limitation of acoustic transducers is that they are difficult to use to analyze analytes in a solution[20].

2.2.4 Calorimetric transducers

Thermometric or Thermal transducers are other names for calorimetric transducers. They measure the heat of a biochemical reaction at the sensing element. Thermal transducers can be classified based on the way heat is transferred. Devices that maintain the reaction cell at constant temperature using Joule heating or Peltier cooling are known as Isothermal calorimeters. They also measure the amount of energy required. Heat conduction calorimeters measure the temperature difference between the reaction vessel and an isothermal heat sink surrounding it. The most commonly used is the Isoperibol calorimeter. It is a type of heat conduction calorimeter[21].

3. BIOSENSORS IN THE PHARMACEUTICAL INDUSTRY

3.1 Blood Glucose Monitors

The very first biosensor was based on amperometric enzyme method for measurement of blood glucose. It was made by Clarke and Lyons in 1962[22].

The first blood glucose biosensor system, the ExacTech, was launched in 1987 by MediSense. It used an enzyme electrode strip developed in the UK at Cranford and Oxford universities. The strip contained an enzyme, glucose oxidase, and an electron transfer

mediator, ferrocene, which replaced oxygen in the original glucose oxidase reaction; the reduced mediator was re-oxidised at the electrode to generate a current detected by an amperometric sensor[23]. The meter was available in two unique forms, a slim pen or a thin card the size of a credit card.

3.2 Electronic Tongues

Electronic tongues are sensor array systems that are capable of detecting single substances as well as complex mixtures with the help of particular sensor membranes and electrochemical techniques. The Insent taste sensing system and the αAstree electronic tongue are the two systems which are commercially available. Various laboratory prototypes exist. Increased interest of developing palatable formulations, especially for children has led to the growing employment of electronic tongues in the pharmaceutical industry. Challenges faced during taste assessment of drugs are - possible toxicity and subjectivity of the people assessing the taste of the formulations. Electronic tongues could offer a safe and objective alternative to drug tasting. Other applications of the electronic tongue include system qualification, quality control and formulation development. Absolute statements regarding taste were difficult to obtain. To overcome this difficulty the need for more validated data is required in future research[24].

3.3 Bio Nano Sensor (BNS)

A Bio Nano Sensor (BNS) is a new diagnostic approach in the direct detection of HIV in blood or other body fluids. This approach is rapid, sensitive and potentially applicable in a point-of-care setting. The BNS makes use of a piezoelectric transducer to detect the presence of the HIV surface glycoprotein gp120 on a nanoscale[25]. The detection range of the BNS device for the biomarker gp120 displayed lower-end sensitivity of 6.5×10^4 HIV viral particles/ml. The fluid sample used was (5µl) and the sensor had a reaction time of less than 30 seconds. Its performance indicated that the BNS has utility for direct detection of HIV particles before antibody formation as well as independent of antibody formation. This device holds utility to monitor the status of HIV infection both early after exposure to virus as well as during chronic HIV infection. The advantages of BNS include requirement of a small sample volume, compact device size, and detection sensitivity. These advantages indicate that the BNS is potentially useful in the point-of- care and/or home setting for monitoring decisions regarding HIV treatment on a real-time basis[26].

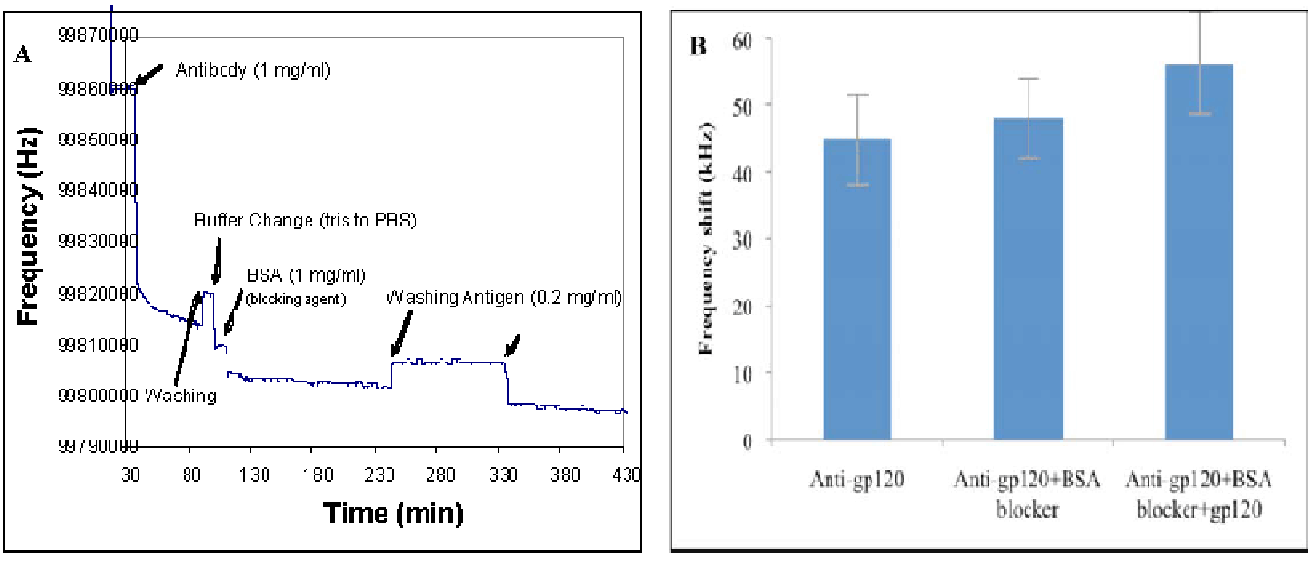

Figure 1: Response of the BNS sensor to gp120 binding: (A) The sensor resonant frequency change following sequential steps of the immobilization process and sensor exposure to gp120. (B) The difference in frequency response after each successive step of the BNS reaction.

An assessment of the capacity and sensitivity for the BNS device to detect HIV was first conducted by measuring the sensor wave deflection in response to binding of the major HIV surface glycoprotein gp120. The reaction was conducted using a TSM surface first

coated with polyclonal sheep anti-HIV-1 and then probed with a commercial preparation of gp120. As shown in above Figure 1 (A), the sensor assembly binding inflection was monitored continuously at a frequency of 100/200 MHz as a series of 5 µl blocking and sample solutions were placed in contact with the sensor. Reference measurements showed initial negative resonance deflection. An increase in BNS frequency response of 5-8,000 Hz was consistently observed following the sequential addition of antibody, antibody/blocker, and then antibody/blocker in the presence of gp120 as shown in Figure 1 (B)[27].

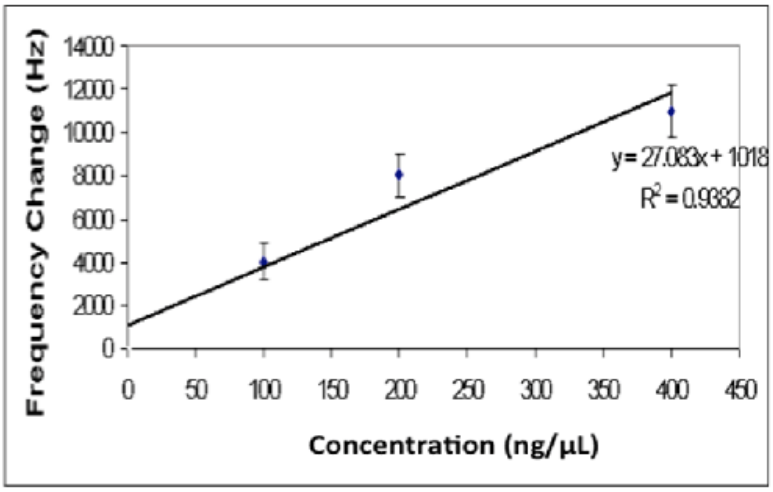

Figure 2: Frequency response change to gp120 binding: The magnitude of sensor frequency change was measured following the addition of gp120, over the range of 0.1-0.4 mg/ml, to the BNS device.

The sensitivity of the BNS for gp120 detection was next measured by mapping responses to a serial dilution of gp120 concentrations (0.1- 0.4 µg/µl). The resulting sensitivity curve, shown in Figure (2), predicts a current lower limit of BNS detection at 25 ng/µl gp120.

Significant progress towards HIV diagnosis, tracking of virus levels in infected individuals and the management of the AIDS disease progression in patients has been made by validating detection of the HIV biomarker gp120 using the BNS device. The limitation is the sensitivity of the biosensor. A 1.5 order of magnitude improvement over current measurements is required. Approaches to increasing the detection sensitivity include advancement of the sensor micro-fabrication technology and sensor electrode geometry, modification of the measurement technique used to detect small changes in the operational frequency of the sensor, and altering properties of the biological sensing surface interface to increase binding probe density and/or signal amplification[28].

The results hold promise for development of a new form of diagnostic assay – the multicomponent BNS. In a final configuration, a hand-held BNS device would launch a sharp needle marginally through the epidermis of the finger in order to allow a small amount of blood (~10-100 µl) to enter onto a disposable testing strip that is coupled to a biochip housing the BNS sensor, piezoelectric transducer and fluidic nanosystem. The sensor would be coupled to an electronic interface complete with a digital LCD monitor. Much like a portable blood glucose measuring apparatus, the BNS device would then enable periodic assessment of HIV status administered by the infected person her/himself and shared through remote monitoring to a healthcare professional[29].

3.4 Wireless Endoscopy Capsules

Wireless capsules are one of the most recent developments in the field of biosensors. They are used for the purpose of endoscopy. A Wireless Endoscopy Capsule can image the parts of the human gastrointestinal tract that were previously inaccessible for conventional endoscopy examinations. Wireless Capsules provide an alternative investigative technique for the examination of the gastro intestinal (GI) tract. It is in the shape of a pill that the patients ingest. The capsules contain miniature on-board cameras to capture images as it passes through the GI tract[30].

A promising solution to power a freely moving capsule robot for a long duration is wireless power transmission based on near field inductive coupling. Existing receiving coils are normally multi-dimensional solid cylinders, which increase the total length of the capsule robot. A design has been proposed using a three-dimensional hollow cylinder-like receiving scoil to avoid increasing the length and to reduce space consumption. This receiving coil has a hollow cylinder-like ferrite core and it consists of a circular coil and two pairs of planar coils. Optimization of the number of turns and the wire diameter of the receiving coil, as well as the transmission frequency has been done after taking into consideration human safety and space limitation of the capsule. This receiving coil could output electric power ranging from 206 mW to 1130 mW. When integrated to an inchworm-like capsule robot, it could successfully power the robot to travel through the ex-vivo intestinal tract and capture satisfactory intestinal videos for diagnosis[31].

A future potential for wireless capsules is to harvest energy directly from the digestive system for powering them. A micro-fabricated electrochemical cell on flexible parylene film is proposed as a gastric battery. Gastric juice is used as a source of unlimited electrolyte. Planar made zinc [Zn] and palladium [Pd] electrodes serve as anode and cathode respectively. Due to planar geometry, no partition is needed. The internal resistance of the cell is reduced due to annular structure which provides lower distance between cathode and anode. Both electrodes are biocompatible and parylene provides flexibility to the system. For a surface area of 15 mm^2, 1.25 mW is generated which is sufficient for most implantable endoscopy applications. This battery has an open circuit output voltage of 0.75 V. Since this gastric battery does not require any external electrolyte, it has low intrinsic weight, and since it is flexible and is made of biocompatible materials, it offers a promising solution for power in implantable applications[32].

3.5 Arrhythmia Monitoring Sensor

An implantable Electrocardiograph (ECG) sensor to monitor atrial fibrillation was developed. The implantable sensor consists of a micro controller unit, a signal converter (from analog to digital), a signal transmitter, an antenna, and two electrodes. The ECG signals from the two electrodes are detected by the sensor which transmits these to an external receiver carried by the patient. The battery consumption of the sensor is very high due to continuous signal transmission. Thus, the sensor includes a wireless power transmission module that makes it possible to charge wirelessly from an external power source. The dimensions of the integrated sensor are about 0.12 in x 1.18 in x 0.19 in. This is small enough to be inserted into a patient's body without the need for major surgery. The unit's signal and power transmission data sampling rate and frequency are 300 samples/s and 430 Hz, respectively[33].

An ECG tracks the electrical potential difference between electrodes placed on the body's surface. A 1mV action potential gives rise to the contraction and relaxation of the cardiac muscle. This potential difference is tough to measure. To overcome this difficulty, operational amplifiers (op-amp) are used to amplify the electrocardiographic data. An op-amp amplifies an input electrical potential to the level needed and desired by the user and produces an output potential augmented to this intended level. Micro-fine ECG signals were amplified by a factor of 100 using a Band Pass Filter (BPF) in an instrumentation amplifier with op-amps. The proposed ECG sensor consumes a current of about 11 mA and a noise generation inversely proportional to length of the wireless communication antenna within the sensor.

3.6 Wireless capsules for autofluorescence detection

Variations and changes in tissue autofluorescence (AF) can be used to detect early signs of intestinal cancer. But currently endoscopic AF systems are only able to inspect the oesophegus and large intestine[34]. The principle of Autofluorescence Imaging (AFI) is that cancerous intestinal tissue shows a considerably lower autofluorescent response than healthy tissue when excited by blue or UV light. This improved prospects for cancer detection as compared to white-light inspection[35,36].

The prototype consists of an Application Specific Integrated Circuit (ASIC), illumination LED, optical filters to reduce and minimise sensor response to crosstalk from the illumination wavelength, a pulse counter/control unit and a radio transmitter. A Single Photon Avalanche Diode detector (SPAD) and an integrated high voltage (up to 37.9 V) charge pump power supply are implemented in an

ASIC. The SPAD operates in its Geiger mode and is biased above its breakdown voltage. It shows a detection efficiency peak at 465 nm which is sufficiently close to human tissue's autofluorescence peak of 520 ± 10 nm. The ASIC was made using a commercial high-voltage Complementary Metal Oxide Semiconductor (CMOS) process. The whole device uses an average power of only 21.4 mW. The implemented system has been characterised against controlled solutions of fluorophores and tested in vitro with biological samples. Studies have proved that it is capable of inducing and detecting fluorescence in fluorophore solutions with concentrations as low as 1 nM[37].

3.7 Electronic nose

A fast procedure for the early diagnosis of microbial contamination of commercial food products was presented by Electronic Nose. Mixed vegetable soup samples were artificially contaminated by *Enterobacter hormaechei* and *Escherichia coli*. A huge dataset of 584 samples, across two experimental campaigns, was examined and studied by the electronic nose EOS507C. This operation of this electronic nose was based on a four metal oxide sensors array. Diagnosis of the contamination was obtained after 21 h and 18 h from the inoculation of *E. hormaechei* and *E. coli* respectively. EOS detection thresholds at 24 h were as few as 8 cells/100 ml for *E. hormaechei* and 3 cells/100 ml for *E. coli*. The LDA classification performance of contaminated samples obtained was 98%. Also a consequential correlation between the sensors responses and the inocula concentrations was obtained[38]. Good long-term repeatability and reliability was shown by comparing the two experimental campaigns' results that were carried out over a period of 14 months. The EOS resulted in fulfilling all the major requirements of an ideal industrial screening system: specificity, sensitivity, early diagnosis, operational simplicity, reproducibility and economical.

3.8 Sensor for Paracetamol

An electrochemical sensor for paracetamol was described on the basis of a glassy carbon electrode. This carbon electrode was modified with multi-walled carbon nanotubes and dopamine nanospheres which were functionalized with gold nanoparticles. The functionalized nanospheres were made by a chemical route and characterized by scanning electron microscopy. The well-dispersed gold nanoparticles were anchored on the dopamine nanosphere through a chemical reduction of the gold precursor. Cyclic voltammetry and electrochemical impedance spectroscopy were used in the evacuation of step wise production of the modified electrode and to obtain electrochemical response from paracetamol. The modified electrode displayed improved electro-catalytic activity towards paracetamol. It had a lower oxidation potential (371 mV) and a greater peak current as compared to a bare electrode or other modified electrodes. The kinetic parameters governing the electro-oxidation of paracetamol were observed, and the analytical conditions were amplified. The peak current was directly proportional to the concentration of paracetamol in 0.8–400 μM range, and the detection limit was 50 nM. This method was then successfully used in the determination and deduction of paracetamol in spiked human urine samples and gave recoveries between 95.3 and 105.2 %[39].

3.9 Wireless sensors for analysis of bio-fluids

Many materials and architectures for ultrathin, stretchable wireless sensors that mount on functional elastomeric substrates for epidermal analysis and study of bio-fluids have been initiated and launched. Measurement of the volume and chemical properties of sweat via dielectric detection and colorimetry showed some aptitude. Inductively coupled sensors consisting of LC resonators with capacitive electrodes showed systematic responses to sweat collected in microporous substrates. Interrogation occurs via external coils placed close to the devices. The substrates enable spontaneous sweat collection through capillary forces, without the requirement of complex microfluidic handling systems. Also, colorimetric measurement modes are possible in the same system by introducing indicator compounds into the depths of the substrates, for sensing specific components (OH^-, H^+, Cu^+, and Fe^{2+}) in the sweat. The whole devices offer Young's moduli which are similar to skin, which allow highly effective and reliable skin integration without external fixtures. Experimental results indicate the volumetric measurement of sweat with an accuracy of 0.06 μL/mm^2 with good stability and low drift.

Colorimetric responses to pH and concentrations of various ions yield the capabilities relevant to analysis of sweat. Similar materials and device designs can be used in observing and examining other body fluids[40].

4. CURRENT RESEARCH AND TRENDS

As in many cases the transduction technology is well established, most of the researchers focus on improving immobilization techniques of the biological elements of biosensors to increase their sensitivity, selectivity, and stability. While critical, the latter has received relatively lesser recognition maybe in part because there is a tendency to design disposable devices that are most useful in quality assurance labs but do not allow on-line implementation for process control. Another vital area of research is miniaturization of sensors. Development of these technologies is mainly driven by the requirement for in vivo uses for pharmaceutical purposes and medical diagnosis. After many years of research, a wide gap still exists between research done and application. The lack of validation, standardization, and certification of biosensors has resulted in a very slow shift in technology. Faster computers and automated systems should speed up this process in the future.

5. RECENT DEVELOPMENTS

5.1 BioCapacitor

Research regarding biofuel cells using biocatalysts like enzymes and microorganisms as electro-catalysts has been conducted on a large extent over the last twenty years. Due to their environmental safety and sustainability, biofuel cells are expected to be used as clean power generators.But, the innate issue of biofuel cell principle is the low power of a single biofuel cell. The experimental voltage of biofuel cells is limited by the redox potential of cofactors and/or mediators used in the anode and cathode, which are insufficient for operating any devices used for biomedical application. These limitations prompted the researchers to develop a novel biodevice based on an enzyme fuel cell that generates enough stable power to operate electric devices, designated as "BioCapacitor." To obtain a rise in voltage, the enzyme fuel cell is connected to a charge pump. To get a power and voltage that is enough to operate an electric device, a capacitor is used to store the potential produced by the charge pump. Using charge pump and capacitor together with an enzyme fuel cell, high voltages with sufficient temporary currents to operate an electric device were generated without altering the design and construction of the enzyme fuel cell[41].

A BioCapacitor consists of three main elements. The first element is an enzyme fuel cell, wherein the enzymes oxidize or reduce the substrate to generate electric power. Next is the element that optimizes the voltage supply from the enzyme fuel cells and the element is charge pump circuit. The third and final element is a capacitor that stores the optimized electric power. (Refer to Figure (3)).

The BioCapacitor completes repeat charge or discharge cycles to supply enough electric power to electric devices as follow. (i) The charge pump circuit is driven by the supply of electric power from the enzyme fuel cells. (ii) The power is converted into stepped-up electric power in the charge pump circuit. (iii) The stepped-up electric power output from the charge pump circuit is slowly charged to the capacitor until the voltage reaches the discharge start voltage. (iv) The comparator in the charge pump circuit compares the capacitor voltage with the discharge start voltage and outputs the digital signal indicating which is larger among the two. When the capacitor voltage exceeds the discharge start voltage, discharge control switch turns on by the output signal of the comparator. Hence, the charge pump circuit switches from the charge step to the discharge step. (v) Electric power is supplied from the capacitor to the electric device. (vi) The capacitor voltage is compared with the discharge stop voltage by the comparator in the charge pump circuit . When the capacitor voltage decreases in the discharge stop voltage, discharge control switch turns off due to which the charge pump circuit switches to the charge step.

Greater electricity-generating power leads to short charge or discharge intervals in the BioCapacitor. On the other hand lower electricity-generating power results in long charge or discharge intervals. The charge or discharge frequency of the BioCapacitor depends on the

fuel concentration. Also, the charge or discharge frequency depends on the capacitance of the capacitor too. A greater capacitance results in longer charge or discharge intervals and the discharge of greater quantities of electricity at a time.

The BioCapacitor can produce enough power to operate electric devices intermittently without any external power supply. The interval of output signal from the BioCapacitor-connected enzyme fuel cell depends on the power supply from the enzyme fuel cell, which is dependent on the concentration of fuel (substrate) in the cell. This means that stand-alone, self-powered sensing systems can be built using a BioCapacitor and enzyme fuel cells. Biosensing devices making use of a BioCapacitor include – Infrared Phototransistor and BioRadioTransmitter system[42,43].

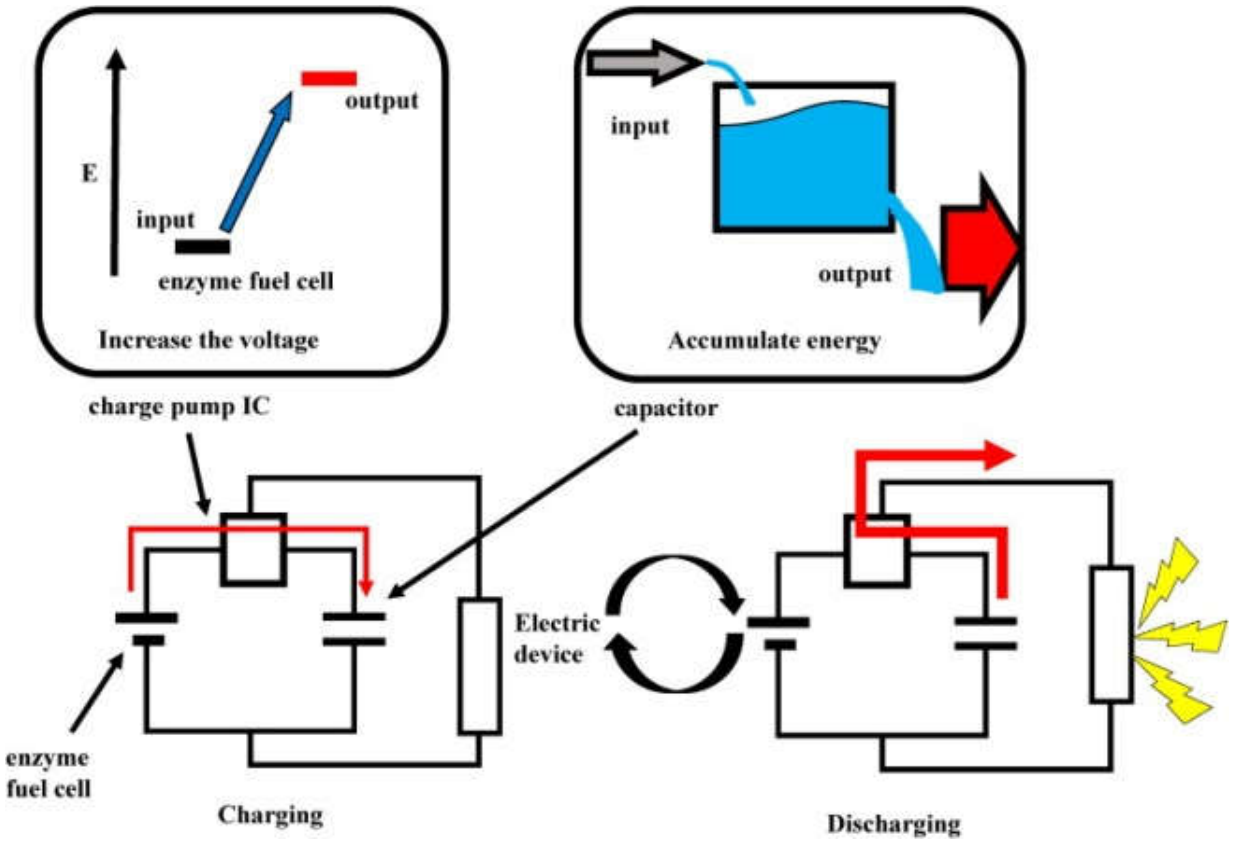

***Figure (3) The principle of BioCapacitor. A charge pump boosts the voltage and a capacitor stores the electrical energy. When the capacitor voltage reaches the discharge start voltage, it is stored the boosted electric energy discharge from capacitor to electric power. The BioCapacitor repeats charge or discharge cycles to supply sufficient electric power to electric devices.**

**Source: Koji Sode, Tomohiko Yamazaki, Inyoung Lee, Takuya Hanashi, WakakoTsugawa. BioCapacitor: A novel principle for biosensors. Biosensors and Bioelectronics.*

5.2 Biomedical Microelectromechanical systems (BioMEMS)

Microelectromechanical system is the technology of small compact devices and its use in the biomedical field is known as Biomedical Microelectromechanical systems (BioMEMS). MEMS techniques were originally developed in the microelectronics industry. Microelectronic process engineering is a branch that developed due to the rapid growth of the integrated circuit (IC) industry[44]. These systems have allowed development of miniscule compact diagnostic tools and large data screening assays for drug discovery and tissue engineering[45]. Progress in this field has helped in the microfabrication of polymeric substrates and the development of a new class of controlled drug delivery devices[46].

Products constructed in combination with MEMS technology offer ground-breaking opportunities to address pharmaceutical requirements related to dosing. These products have the potential to have thorough control over drug release, thus meeting requirements for on-demand adaptable continuous administration for extended periods, programmable dosing, progressive dose delivery and diagnostic feedback dispensing[47]. If small-scale biosensor and drug reservoir units are integrated and implanted, a wireless integrated system can regulate drug release, receive sensor feedback and transmit updates. For example, an implementation of integrated therapeutic system as ''artificial pancreas'' would improve management of diabetes. The tools of microfabrication technology, information science, and systems biology are being considered together to design increasingly sophisticated drug delivery systems that promise to significantly improve medical care[48]. MEMS are used in oral drug delivery, transdermal drug delivery, localized drug delivery and bio capsules.

BioMEMS devices should be made of biocompatible materials that are chemically inert, reliable and useable. The rush to find effective diagnostic and the therapeutic tools is under way, as BioMEMS are getting closer to the clinical application of intelligent drug delivery devices and substantially enhanced the analytical devices as never before.

5.3 Cantilever array biosensors

Microcantilever-based systems are proficient at real-time, complex detection of unlabelled disease markers in extremely small volumes of samples. Currently available production technology allows the combination of electronic readout and sample introduction into a single unit, thereby reducing the device size, time of detection and cost[49]. Biosensing technologies based on microfabricated cantilever arrays involve multiple cantilevers and electronic processing. Even local telemetry on a single chip has the potential of satisfying the need for highly sensitive and specific multi-target detection in very small samples. Implantable biosensors are being fabricated using cantilever platform[50,51]. Since regeneration of a biosensor is very challenging, the implanted sensors were then used for detection of blood gases, for example blood alcohol. For this purpose, the cantilevers were coated with a hydrophobic coating on the back and a polymer ThiolatedSiloxanefluoro alcohol (TSXFA) coating on the gold side of the cantilevers. The TSXFA coating is capable of absorbing alcohol differentially causing a cantilever bending.

6. CONCLUSION

Biosensors have attained considerable success in both commercial and academic areas and the need for new, easy-to-use, at home diagnostics is greater than ever. Biosensors employing amperometric transducers presently lead the market. Electrochemical biosensors are available for a range of distributed analyses, including medical, food and environmental uses. Array-based fluorescence sensors are now accepted for biomedical assays. Label-free assays based on Surface Plasmon Resonance (SPR) lead the affinity biosensor market, especially in the development of drugs. The search continues for better and ground – breaking technologies.

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