STIMULI-RESPONSIVE POLYMERS BASED COMPOSITES AS BIOSENSORS

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CANDIDATES' DECLARTION

We, Princi Singh (2K21/MSCCHE/33) and Vipul Kumar (2K21/MSCCHE/49), students of M.Sc. Chemistry hereby declare that the project titled "Stimuli-responsive Polymers based composites as Biosensors" which is submitted by us to the Department of Applied Chemistry, Delhi Technological University, Delhi in the partial fulfillment of the requirement for the award of the degree of Master of Science, is original and not copied from any source without proper citation. This work has not previously formed the basis for the award of any Degree, Diploma Associateship. Fellowship or other similar title or recognition

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CERTIFICATE

I hereby certify that the Project titled "Stimuli-responsive Polymers based composites as Biosensors" which is submitted by Princi Singh (2K21/MSCCHE/33) and Vipul Kumar (2K21/MSCCHE/49), Department of Applied Chemistry, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the Master of Science, is a record of the project work carried out by the student under my supervision. To the best of my/our knowledge this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

Place: Delhi

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ABSTRACT

Polymeric materials that respond quickly chemically and/or physically to changes in their surroundings are known as stimuli-responsive polymeric materials. The action should ideally be reversible, meaning that if the stimulus is removed, the sensitive polymeric material goes back to its original state. These smart materials are able to self-control the communication with their environment or stimuli; thus, they might be key devices for various biomedical applications in the upcoming century with new modification for biosensing, Smart Polymeric materials offer new possibilities to incorporate biological sensing elements. The creation of nanocomposite material and polymer-based composites to enhance their qualities, including improved mechanical strength, toughness, electrical conductivity, and others. A broad variety of uses for these materials are possible, including biomimetic materials and technologies, intelligent materials, renewable energy sources, packaging, etc. This article examines how polymer-based composites are used in biosensing. We outlined the status, benefits of particular polymer-based sensors, and future prospects in this article.

Keywords:

Stimuli-responsive material, conducting polymers, Biosensors, Polymer-based composites, molecularly imprinted polymers (MIPs)

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PRINCI SINGH

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CHAPTER 1

INTRODUCTION

1.1 Biosensors

The field of sensing exemplifies a new technology with great capacities and adaptability to identify distinct analytes in varied matrices and plays a vital role in performance detection in numerous fundamental processes in many systems (1-3). The role of nature for inspiration when thinking about new sensory technologies has always helped this field. The living things have created the most sophisticated chemical sensors. Many insects have extraordinary sensitivity and excellent specificity for chemical signals. Mammalian olfaction uses a variety of less discriminating sensors and a learned response pattern to recognize a particular smell. It is crucial to understand that biological systems do not rely on a single component to produce their exceptional sensory abilities. Actually, the analyte transport and removal processes serve the receptor, receptors provide selectivity, and analyte-triggered biochemical cascades provide sensitivity, resulting from a completely interacting system (4). Natural identifying components have a strong attraction for their targets, but given their low endurance under high pressure, temperature, and in organic solvents, as well as their low viability in buffers with high and/or low pH, they cannot be used in real applications. So, devices have been fabricated of materials which can be used in a physiological environment and which responds to the change in stimuli. Fig. 1.1 shows a schematic of a sensor system, illustrating the three main elements, the sample (or analyte), transduction/platform, and signal-processing step.

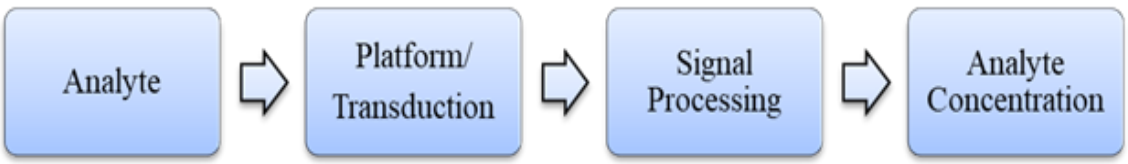

Figure 1.1: Principal steps in a sensor's functioning.

In order to mimic natural sense systems, polymers have received astounding acclaim over the past ten years in the area of synthetic sensors. By substituting conventional sensing materials with polymers utilizing nanotechnology and utilizing either the intrinsic or extrinsic functions, improved selectivity and quick readings (5). The two crucial parts of analytical devices, known as sensors, are a transducer and recognition elements. Transducers are used to detect analytes for the purpose of evaluating their structural properties, and recognition elements perform this task by converting responses into signals. Optical sensors (6-8), electrochemical sensors (9-11), piezoelectric sensors (12,13), magnetic sensors (14), micromechanical sensors (15), and temperature sensors are among the many types of sensors that use detecting polymers (16,17). Polymeric materials have expanded in academic curiosity and actual application in sensor technology with the passage of time (18). Molecularly imprinted polymer-based sensors, poly(3,4-ethylenedioxythiophene) (PEDOT), polyaniline (PANI) and polypyrrole (PPy) as transducer materials for biosensor applications, as well as the improved characteristics and parameters for analysis of a biosensor created using these polymer-based nanocomposites, are all thoroughly reviewed in this article.

1.2 Classification of Biosensors

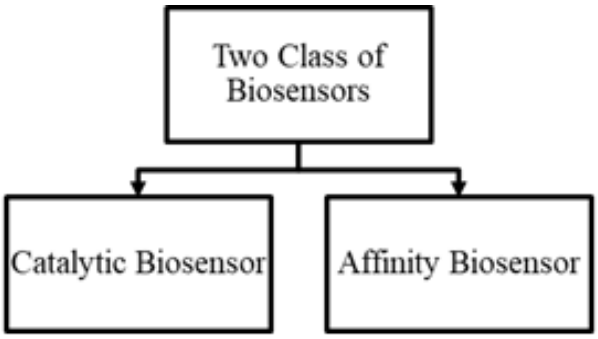

Figure 1.2: Classification of biosensors

1.2.1 Affinity Biosensor

A receptor is loosely attached to an indicative analog fixed on a transducer surface in bio-affinity sensors (19). By using biomolecules like antibodies (Ab), membrane receptors, or oligonucleotides, specifically and strongly attached to a target analyte, affinity sensors can generate a quantifiable electrical signal (20). The main factors of molecular recognition in affinity biosensors are the corresponding size and

structure of the binding region with respect to target analyte (20). Since the biomolecule's strong affinity and selectivity for its ligand, these sensors are both extremely sensitive and discriminating. Antibody-based affinity biosensors known as immunosensors can recognize analytes like antigens or haptens by attaching to particular Ab regions (21). Complementary portions of the Ab bind with great specificity and affinity to an antigen (Ag) that was utilized to fabricate the antibodies in a host organism.

1.2.2 Catalytic Biosensor

The catalytic biosensors make use of biocomponents that can recognize biochemical species and use a chemical reaction to transform them into a finished product (22). Enzymes are commonly utilized in electrochemical biosensors because of their both high biocatalytic sensitivity and activity (23), even though a variety of biological recognition components have been used in biosensing devices. However, other factors, such as activators and inhibitors, typically control enzyme activity (24). Biocatalytic sensors through detection of target analyte, produce functionalized species or additional observable outputs by using biological components as enzymes, entire cells, or tissues (20). Enzymes, which are globular proteins consisting mostly of the 20 naturally occurring amino acids that catalyze biological activities, are the earliest and still most extensively employed biorecognition component in biosensors (20,24). Many biochemical analytes of interest cannot be detected by enzyme electrodes because there are insufficient enzymes that are suitably selective for the analyte or the analyte is infrequently present in biological systems (1,25). Then, affinity biosensors are taken into account as a different approach.

CHAPTER 2

POLYMER BASED BIOSENSORS

There are many different types of biosensors, but they lack separation capabilities unless they are connected to the appropriate extra devices, which complicates the system and increases the amount of energy it uses (26) This prevents sensing from being integrated with imaging. Hence, the sole basis for specificity might be selective biomolecular identification. Use of more or less specialized biorecognition components, like antibodies, enzymes, oligonucleotides, and even cells and tissues, is made to accomplish this purpose (22). To find biomolecules for the diagnosing various illnesses, sensors are now widely employed in clinical chemistry, agriculture, pharmaceutical research, and biomedical research. To actualize the notion of entire polymer based biosensors that are independent of standard nanocatalysts such as metal, metal oxides, dyes, or carbon materials, conduction polymers must have strong nanostructured morphology, electrochemical attributes, and capabilities for bioconjugation (26).

The usage of polymers offers special opportunities for the expansion and improvement of global health. Targeted therapies, bioimaging, drugs delivery, and cancer therapies are just a few of the medical applications where polymers are excelling (27). Conducting polymers (CPs) offer a variety of opportunities for coupling targeted and nonspecific interactions with analyte receptors into perceptible (transducible) reactions (28). The creation of polythiazyl signaled the beginning of the CP period, then came the polyheterocyclic substances with an S or N group and polyaniline (PANI). A major advantage of CP-based sensors over those that employ small molecule (chemosensor) components is the ability for the CP to express collective properties that are susceptible to incredibly minute disturbances. The electrical conductivity, rate of energy movement, or transport properties of the CP are especially important in providing increased sensitivity (29). In many biological and medical uses, including tissue engineering and biosensors, CPs have surfaced as among the most proclaiming materials (30). The

biocompatibility and distinctive electrical features of the CPs, which may translate the biological detailed information into electrical signals, are what account for their broad range of applications. A well-organized scaffold biosensor might also be made since CPs include a range of diverse functional groups that come into contact with the functional groups of polymers for enhancement in enzyme loading (31). As the enzyme and electrode effectively "interacted," the greatest sensing efficacy was given by biosensors built on nanocomposites of π–π conjugated polymers. Additionally, such forms of biosensors are more resilient with several interfering elements (32-35). Fig. 2.1 illustrates the phases and parts of a typical sensor schematically. Transducers in this case are biosensors based on conducting polymers. A transducer is a device that changes the form of energy. Here, PEDOT, polyaniline, and conducting polypyrrole may all function as biosensors. Electrochemical, optical, and piezoelectric transducers are the three main types of transducing processes.

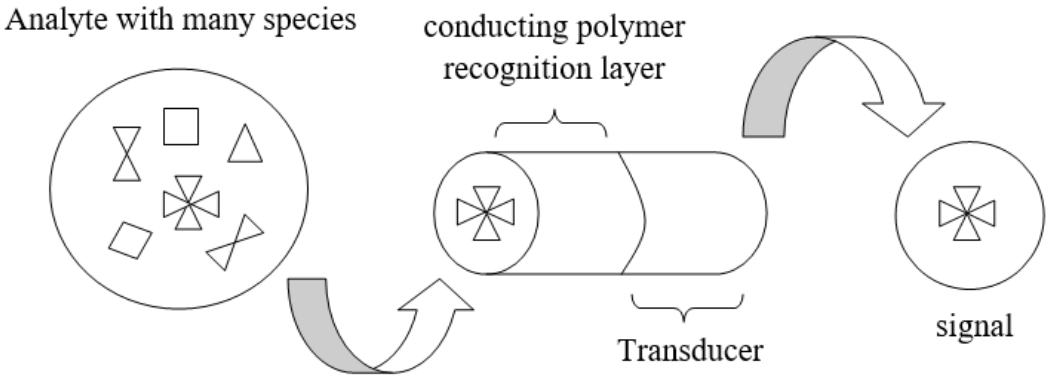

Figure 2.1: Basic components and steps involved in a sensor.

2.1 Polyaniline (PANI)

PANI, a CP belonging to the family of semi-flexible polymers, was identified more than 150 years ago. The scientific community has taken notice of PANI because of its excellent conductivity and inexpensive cost. PANI is a good candidate to be employed in a variety of applications since it is also renowned to have a wide range of controllable characteristics due to its flexibility, which has led to numerous uses across a variety of fields (26). PANI has been shown to be an exciting substance for sensor and biosensor junctions because it works as an effective facilitator for electron transfer in redox or enzymatic reactions and may be employed as an ideal ground substance for biomolecule incapacitation (36). It is made up of alternate repeated structural units of benzenoid amine

(reduced form) and quinoid imine (oxidized form), which demonstrate distinct redox forms of PANI (Fig. 2.2). While pernigraniline (PG) is totally oxidized and has an imine group rather than amine group, leucoemeraldine (LE) is fully reduced. PANI is either neutral or imine nitrogen-doped when it is in its emeraldine base (EB). Owing to its high thermal stability, EB is thought to be the most beneficial form of PANI. It is thought of as an appealing polymer because it has both redox pairs in the right potential range to aid in charge transfer between enzymes and polymers and works as an independent electron transfer intermediary. PANI provides a wide range of possibilities for coupling specific and non-specific analyte receptor affinity towards perceptible responses. Particularly enhanced sensitivity is provided by PANI's electrical conductivity, transport characteristics, or pace of energy flow. It has both structural and chemical flexibility around its amine nitrogen connections enabling effective immobilization and binding of biomolecules. Being immobilized on a ground substance, which restricts the biomolecule's overall movement and retains it in a reasonably restricted area of space, can make a biological component more stable and recyclable (37).

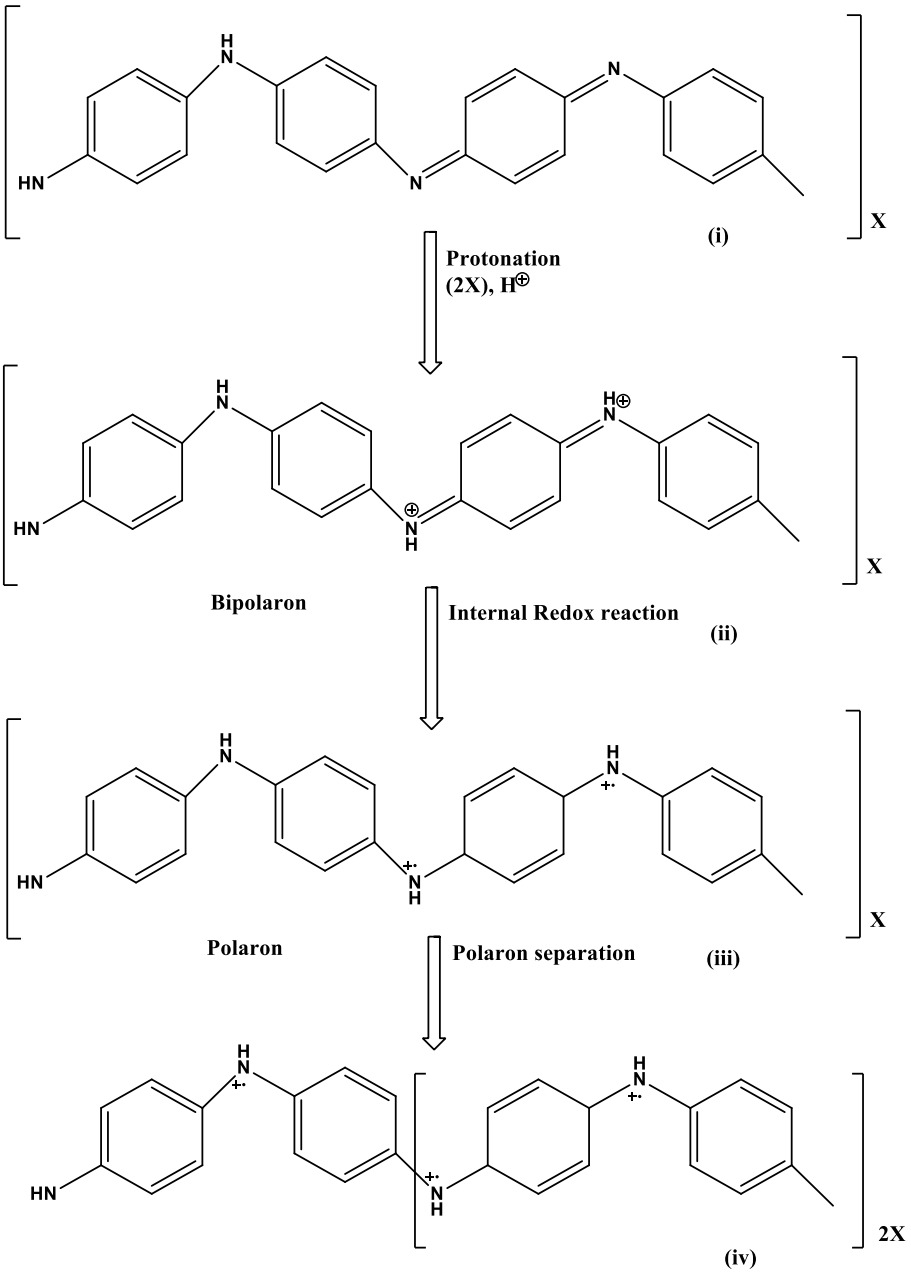

Figure 2.2: Chemical structures of emeraldine (i) before protonation (emeraldine base), (ii)–(iv) after 50% protonation, (ii) formation of bipolaron, (iii) formation of polaron and (iv) separation of two polarons.

(37)

Devices based on graphene and PANI nanocomposites with sensitivity 16.5% toward 1% of H_2 gas were developed by Al-Mashat et al., in contrast to the responsivity demonstrated by graphene and PANI alone (38). Due to its carboxyl groups' negative charges, graphene oxide (GO) serves like a potential dopant. GO is initially an insulator, but when it is exposed to powerful reducing reagents like hydrazine (NH_2NH_2) or sodium tetrahydroborate ($NaBH_4$), it reduces itself into graphene and acquires electrical

conductivity (39). For the purpose of achieving applications that are likely to be successful in the realm of sensing, conducting polymers are combined with metal nanoparticles (MNPs) to improve the resultant nanocomposites' unique physical and chemical characteristics. Platinum nanoparticle matrix is thought to be very effective at identifying macro- and biomolecules, such as antibodies, DNA, and enzymes (40). Conducting polymers like PANI in Pt nanocomposites, are typically produced in both nanofibers and nanotubes. It has been found that Pt nanoparticles can more easily disperse into polymeric matrices due to the numerous heterogeneous nucleating sites that nanofibers offer. Pt/PANI hydrogel heterostructures were created by Zhai et al. and utilized to detect glucose enzymatically. There has been evidence of a detection limit of 0.7 μM and broad linear calibration range of 0.01–8 mM (41). Chowdhury et al. explored the creation of biosensing AuNPs/PANI nanowires for the detection of Lamin A protein, complementary DNA, and glucose using three distinct biomolecules, including Lamin A antibody, single-stranded DNA, and glucose oxidase. It was shown that the glucose sensor is more sensitive having a sensitivity of 14.63 μA $mM^{-1}cm^{-2}$, outstanding stability and specificity, and a detection limit of 1 μM (42). Another three component system of nanocomposites, namely NiOCuO/PANI, has been created using an electrochemical approach to create inexpensive, enzyme-free glucose sensors. The non-enzymatic recognition of glucose in a basic electrolyte using the NiO-CuO/PANI-based amperometric sensor demonstrated excellent sensitivity, decent selectivity, and quick reaction with a detection limit of 2.0 μM. Human blood samples have also shown impressive outcomes in addition to the existence of undesired interferences compared to what was exhibited by two component systems of CuO/PANI and NiO/PANI separately (43). There have been reports of taking advantage of the benefits of CPNs by the modification of glassy carbon electrodes using TiO_2/PANI nanocomposites. In this sensor, hydrothermal transformation of TiO_2 nanoparticles into TiO_2 nanotubes (TNTs) was followed by ozone-induced polymerization of aniline forming uniform TNT/PANI composites. Then, to create an electrochemical biosensor, glucose oxidase (GOD) was adsorbed on the altered surface, resulting in a measurement of glucose with a sensitivity of 11.4 μA and a detection limit of 0.5 μM (44).

2.2 Polypyrrole (PPy):

It is simple to form polypyrrole, a conjugated heterocyclic ring containing conductive polymer possessing outstanding processability, chemical stability, and

electroconductivity by the Pyrrole monomer polymerization in different organic analytes. Contrary to classical PPy, which exhibits high stiffness, low mechanical durability, poor solubility in typical organic solvents, and shortcomings in its biological, electrical, and optical capabilities, nanostructured PPy has optimized bioactivity, electrochemical activity and higher electrical conductivity, superior mechanical properties, improved optical qualities and is easy to process due to the increased surface area and nanostructure. Since polypyrrole is compatible with biological systems (Fig. 2.3), it has been extensively researched for the immobilization of enzymes, antibodies, and nucleic acids (45,46). The polypyrrole is an excellent conducting polymer in the presence of protons, which restricts its use as a biosensor in a neutral environment (47). As a result, this is frequently used in medical applications (48,49). Electropolymerization was used to create ZnO/PPy nanocomposites films on the Pt electrode. Additionally, physisorption has immobilized Xanthine Oxidase (XOD) on its surface. A biosensor which is amperometric was created at pH 7.0 and 35°C using the produced electrode XOD/ZnO/PPy, with a 5s ideal response time. The detection limit of xanthine has been observed to be linear from 0.8 μM to 40 μM (50).

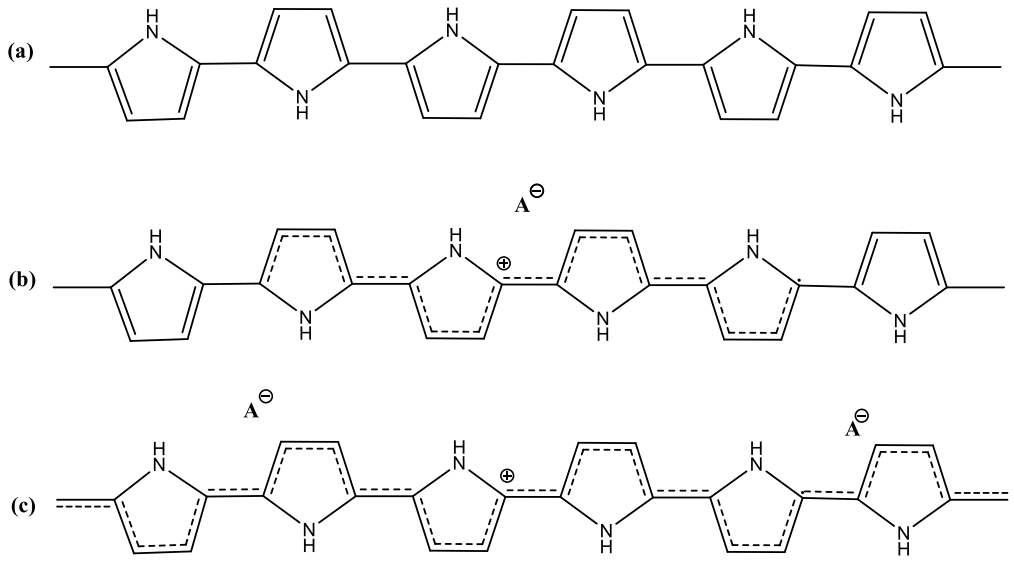

Figure 2.3: Structures of polypyrrole in (a) neutral, (b) partially oxidized (low doping) (c) highly oxidized (highly doped) states.

Through the use of the Plasmon resonance technique and chemical polymerisation, MWCNTs (Multi-walled carbon nanotubes) combined with PPy have been used to detect lead (Pb), mercury (Hg) and, iron (Fe) in trace amounts (51). Teh et

al. studied an MWCNTs/PPy-based biosensing device for the measurement of glucose with a 20 nM detection limit range, an anatomical significant value for the assessment of diabetics (52). It has also been discussed how encapsulating enzymes in the synthesized nanocomposite could create new sensing platforms to diagnose hormones, metabolites, biotoxins and others. Dopamine, serotonin, glucose, uric acid, and ascorbic acid are among the many substances that can be detected using nanocomposites made of gold nanoparticles and conducting PPy. Pt NPs and polypyrrole film have been combined to produce a novel biosensor for human C-reactive protein (CRP) detection. The space between the transducer and the biomolecules is provided by the long PPy chain. Pt nanoparticles lessen steric resistance and maintain inhabitant conformation, which aid in improved probe direction and biomolecule approachability to the analyte. These created nanocomposites have demonstrated large surface area and excellent functionality (53).

2.3 Poly(3,4-ethylene dioxythiophene) (PEDOT)

Poly(3,4-ethylene dioxythiophene), often known as PEDOT, is a highly resilient conductive polymer with several uses in lighting, photovoltaics, thermoelectricity, sensing analytes, coatings, bioelectronics transparent electrodes, and other domains, has attracted a lot of attention (54). PEDOT is a suitable active material for sensor development and selective drug delivery systems because of its polymeric structure, which enables electrostatic interaction with ions in the environment (55,56). In vitro and in vivo electronic device-biomaterial interfaces are possible with PEDOT-based nanofilms, nanoparticles, and nanocomposites (57,58). Only a few tens of monomer units can make up a PEDOT chain (59,60). Doping causes the aromatic state of neutral PEDOT to transition to a quinoid state. Here’s Fig. 2.4 showing the structure of PEDOT in different state:

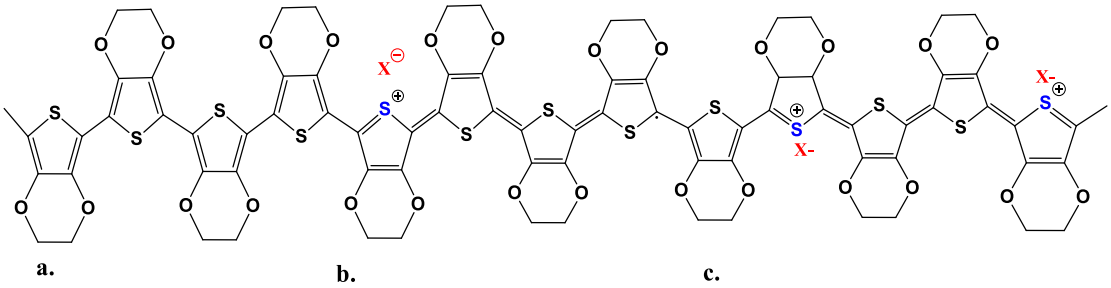

Figure 2.4: PEDOT in different states: a) Neutral, b) polaron, c)bipolaron

Because of their attractive catalytic, optical, and electronic properties, palladium nanoparticles are essential in many organic and inorganic reactions (61,62). A glucose sensor built on Pd/PEDOT nanofibers and using the chronoamperometric method has been developed which has a 1.6 µM detection limit for glucose (63). The electrochemical reduction method used to create GO/PEDOT nanocomposites, which were later accumulated on glassy carbon electrodes (GCE), can be used to detect dopamine when uric acid and ascorbic acid are present (64). The porous surface that graphene offers allows for better adsorption and detection.

CHAPTER 3

CURRENT DEVELOPMENT IN MOLECULAR IMPRINTED POLYMER BASED SENSORS (MIPs)

The development of molecularly imprinted polymer (MIP) based sensors, a significant subset of affinity sensors, is a marvel of technique that allows molecular affinity sites into homogeneous polymeric matrices (65). It has been used to successfully prepare selective polymeric matrices for a range of samples, from viruses to biomolecules, irrespective of size (66). MIPs are multifunctional porous substances that provide high-affinity sites for binding to facilitate analyte-based attack that can be tailored to their dimensions, functionality, and function. Natural antibody-antigen (Ab-Ag) and enzyme-substrate (E-S) systems have analogues in MIPs. So, to selectively recognize the target molecule, during the synthesis stage, a "key-lock" mechanism is imitated (67). The MIP-based biosensors have been discussed in the following sections:

3.1 Optical biosensors

Throughout the past three decades, research into optical biosensors has expanded. Experts in the subject have released a variety of books and review papers that highlight the benefits of optical sensing over other transduction techniques (68-70).

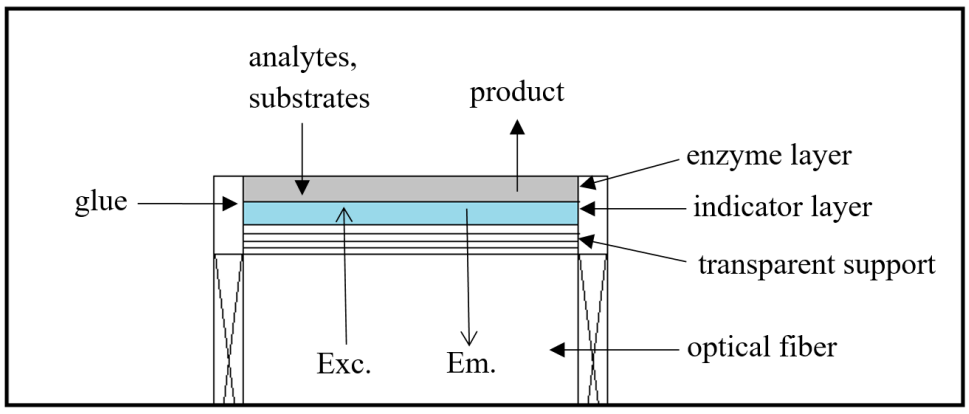

Figure 3.1: Cross section of a fiber-optic enzymatic biosensor

Cross section of the typical Fiber-optic enzymatic biosensor is depicted in Fig. 3.1 above. A polyester film-based transparent inert support is covered with an indicator layer. An indicator dye is either physically adsorbed or covalently immobilised on the surface of microbeads, which are subsequently distributed in the matrix polymer, or it is directly dissolved in the polymer matrix. The cosubstrates consumed or the products created during the enzymatic reaction are sensed by the indicator layer. On the surface of a polymer membrane, enzymes can be chemically immobilised. This sensor's "sandwich" is installed on the end of an optical fiber, which transmits light from a light source to the sensor foil for excitation and light from the sensor foil for emission (reflection) back to a photodetector for detection. The analyte (substrate) moves into the enzyme layer, where it undergoes product synthesis. The indicator (sensor) layer is made up of an indicator dye encapsulated in a polymer layer and it tracks the production of reaction products as well as the consumption of reactants like oxygen. The transparent support serves merely as a manufacturing aid and is inert. It could as well not exist. Exc and Em represent, respectively, the excited and emitted light pathways (22). When a complex is produced by the interaction of the target and recognition constituent, optical sensors concentrate on sensing the optical properties alteration of the transducer surface (71). There are two groups of these sensors. The complex formation on the transducer's surface serves as the foundation for signal generation in direct optical sensors. The unintended optical sensors are frequently constructed with a number of labels in order to detect binding events and amplify the signal (72). Time-resolved fluorescence, optode-based fiber, evanescent wave fiber, interferometric, surface plasmon and resonant mirror resonance are a few examples of optical sensors that are available in the literature and on the market (73-76). They can recognize many different biomolecules in biological and physiological samples due to their broad detection window (77). Research on a surface plasmon resonance (SPR) sensor system based on an imprinted nanoparticles for uric acid recognition was published by Göçenolu et al. Uric acid is a byproduct of purine biosynthesis in humans and is associated with a variety of diseases, including hypouricemia and hyperuricemia (78). Emulsion polymerization is used to create nanoparticles with uric acid imprints that were later described using various techniques. The SPR sensor was made by modifying the nanoparticles that had been imprinted with uric acid. They tested various uric acid solutions with varying concentrations to ascertain the sensing capacity of the uric acid imprinted SPR sensor. Finally, they arrived at 0.825 mg/L and 0.247 mg/L as the measurement values and limit of detection (78). Dopamine

is a neurotransmitter that is important in the central nervous system and is involved in cellular metabolism and hormonal systems. Zhou et al. promoted a fluorescence sensor to detect dopamine that uses graphene quantum dots and a composite material. They discovered that adding dopamine to the sensing device induces fluorescence quenching owing to covalent binding. They computed the limit of detection to be 2.5×10^{-9} M with a dopamine concentration range of 5×10^{-9}-1.2×10^{-6} M. Lysozyme levels in serum and bodily fluids are aberrant in many disorders, including leukemia, renal diseases, conjunctivitis, and meningitis. Zhang et al. developed a fluorescent membrane employing manganese-doped quantum dots to detect lysozyme (79). Dibekkaya et al. developed a cyclic citrullinated peptide antibody-imprinted SPR sensor for antibody detection. Cyclic citrullinated peptide antibodies aid in the diagnosis of rheumatoid arthritis, which is an autoimmune disease with common chronic joint inflammation. To do this, they first created a pre-complex by combining acrylamide monomer and cyclic citrullinated peptide antibody, and then created an antibody-imprinted SPR sensor by reacting with this precomplex, crosslinker, and initiator/activator pair (80). Microfluidic sensors based on polymers imprinted with ions for the detection of mercury and copper ions were suggested by Qi et al. Mercury is an extremely harmful heavy metal pollutant that can result in coronary heart disease and mobility issues. Copper, a crucial trace element that is also closely related to human health, puts a strain on the liver and other organs, which can result in liver cirrhosis, metabolic disorders and other diseases.

3.2 Electrochemical biosensors

Inherently bioselective biological elements are combined with the sensitivity of electroanalytical techniques in electrochemical biosensors. The biological element of the sensing device recognizes its analyte, causing a catalytic or binding event that finally results in an electrical signal that is regulated by a transducer and is analogous to analyte concentration. Few of these sensing device technologies have passed the prototype step and are currently being used in industrial, commercial, and farming settings (81). Due to their accessibility, portability, affordability, and convenience of use, electrochemical detection is the transducer of choice for the majority of biosensors (20). These characteristics make the electrochemical sensors ideal for sensing applications and allow patients to use them as point-of-care devices at house or in a clinic (82). An electrochemical monitor for myoglobin detection was constructed on an imprinted polymer by Wang et al. A biomarker called myoglobin, an oxygen-binding heme protein,

is utilized to detect acute myocardial ischemia. According to their findings, the electrochemical monitor exhibited a high level of selectivity and sensitivity. They were able to acquire an oxidation peak current with a 9.7 nM detection limit that varied in relation to myoglobin concentration (60.0 nM-6.0 M) at a potential of 0.3 V. They used this electrochemical sensor to measure the quantity of myoglobin in plasma that had been spiked, and it showed average recoveries of 96.5%. Medical medication treatment, which seeks to ensure the efficacy of drugs while avoiding their side effects, requires therapeutic drug monitoring. Naloxone, a particular opioid antagonist and a morphine derivative, has a strong interaction towards opiate receptors without triggering them. For increased sensitivity, they added multi-walled carbon nanotubes to the carbon anode. With limits of detection and measurement of 0.20 M and 0.67 M, respectively, they showed that the relationship between peak intensity and naloxone concentration (0.25-10.0 M) for the electrochemical sensor was continuous. Additionally, they confirmed the electrochemical sensor's usefulness in human serum and urine (83). A research about the sensing of sarcosine was released by Nguy et al. Urine sediments from males with metastatic prostate cancer have higher levels of Sarcosine, a modified glycine amino acid compound. They achieved the limit of detection below 1 nM by electropolymerization the poly-aminothiophenol layers atop screen-printed gold electrodes that are imprinted with sarcosine. High repeatability, impressive stability, and minimal cross-selectivity were all characteristics of their sensor system (84). For cocaine detection A potentiometric sensing device based on imprinted nanoparticles was presented by Smolinska-Kempisty et al. With millions of users across all age groups, we know cocaine is the most often used drug globally. They used two protocols and four compositions. Dissociation constants between 0.6 nM and 5.3 nM were observed, demonstrating a high affinity for cocaine. They looked at the various forms of cocaine in the human body and revealed that blood samples with cocaine concentrations between 1 nM and 1 mM could be detected by the sensor (85).

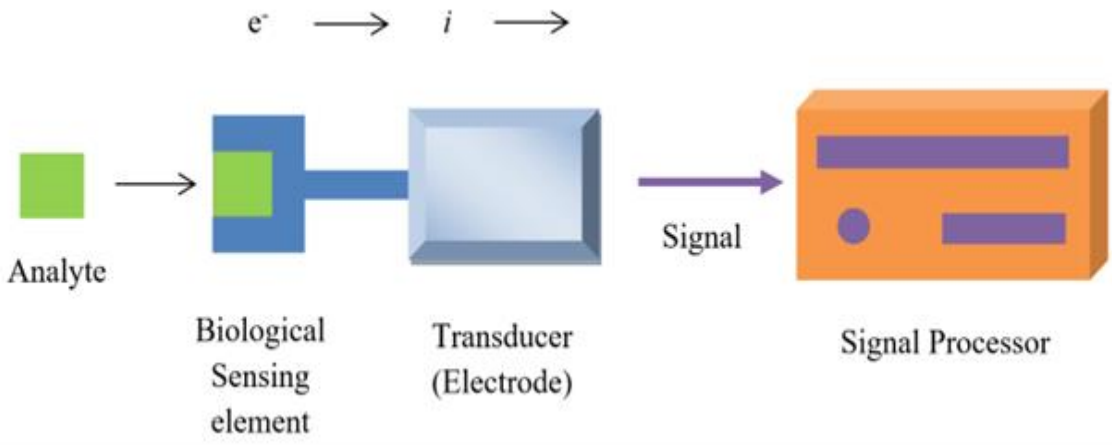

Figure 3.2: Schematic of a biosensor with an electrochemical transducer

3.3 Piezoelectric biosensors

These transducers are thought to be very sensitive to use in biosensing. The fundamental concept behind the functioning of these biosensors is the linkage of a molecular species to the surface of the crystal, which causes a variation in mass and, ultimately, a change in crystal frequency (19,86). One of the varieties of piezoelectric sensors is the QCM sensor, which stands for quartz crystal microbalance, attracting researchers' attention due to its portability, high specificity, stability, and simplicity. The interactions are observed by the QCM sensors using an oscillating crystal with incapacitated biomolecules on its surface. As a result of the binding reaction, the mass increases, and the oscillating frequency decreases. Affinity for the sample, the utmost selective binding sites, and extremely sensitive sensing systems based on uniformity in a large number of recognition sites are brought about by the coupling of quartz crystal microbalance sensors with sample molecule memory comprising molecularly imprinted polymers (87-90).

A QCM monitor for cytochrome c identification was recently developed by Ma et al. The mitochondrial respiratory chain's heme-containing electron carrier is called cytochrome c. The LOD value for real-time cytochrome c was established to be 3.6 ng/mL with a zone of 5 mg/mL to 50 mg/mL. The sensor with cytochrome c imprinting, according to their findings, exhibited high selectivity and sensitivity towards cytochrome c and could be used for real sample studies with high accuracy and reproducibility. They claimed that the novel sensor construction procedure based on polymers with epitope imprints enables new ways for selective biomolecule detection (91). Kartal et al. proposed

a QCM monitor for insulin detection in both aqueous and synthesized plasma fluids. A crucial polypeptide hormone and a key controllable factor in the metabolism of blood sugar, insulin is secreted by pancreatic cells. They obtained the kinetic parameters using affinity studies after adding an amino-acid monomer to the sensor's gold surface. Additionally, they tested the repeatability of sensors imprinted with insulin over four binding cycles. The LOD value was determined to be 1.58×10^{-9} mg/mL. A QCM sensor imprinted with amantadine was created by Yun et al. using reduced gold nanoparticles and graphene oxide. In the clinical treatment of both animals and people, amantadine, a tricyclic amine having a stable structure, is typically utilized to cure both Parkinson's disease and influenza. They improved various remodeling steps in the sensor manufacturing process before characterizing the sensor using different techniques. With a small LOD of 5.4×10^{-6} mmol/L, they were able to obtain a continuous relationship with the amantadine concentration (1.0×10^{-5}-1.0×10^{-3} mmol/L). They also determined that amantadine's imprinting factor was 7.1 (92). Qiu et al. created an imprinted QCM sensor to detect sialic acid in urine samples. Sialic acid, a negatively charged monosaccharide, is widely known as a blood serum marker that is expressed less frequently in diabetes patients than in the general population. Total sialic acid levels can represent human body malfunction and even an early stage of various malignancies or cardiovascular disease. Following the characterisation investigations, they used recognition studies to evaluate the sensor's selectivity performance. They got a linear response in the range of 0.025-0.50 µmol/L and determined the detection limit for sialic acid as 1.0 nmol/L for urine samples with high recovery values (87.6-108.5%) (93).

Table 3.1: Summarized list of Conducting Polymer (CP) based nanocomposite accompanied by their analyte and detection limit.

Sr. No.	CP based nanocomposites	Target analyte	Detection limit	Ref.
1.	TNT/PANI	Glucose	0.5 µM	(44)
2.	ZnO/PPy	Xanthine	0.8 µM	(50)
3.	Pt NPs/PPy	human C-reactive protein (αCRP)	NA	(53)
4.	Pd/PEDOT	Glucose	1.6 µM	(63)
5.	G/PANI	Dopamine	0.00198 nM	(94)
6.	GO/PANI	DNA	20.8 fM	(95)
7.	MWCNTs/PPy	6-mercaptopurine Magnolol	0.08 µM 3 nM	(96) (97)

Table 3.1 (continued)

8.	CNTs/PEDOT	Dopamine *Mycobacterium tuberculosis*	20 nM 0.5 fg/ml	(98) (99)
9.	GO/PEDOT	Dopamine	90 nM	(100)
10.	RGO/PEDOT	Dopamine	78 fM 39 nM	(101) (102)
11.	Au/PANI	Dopamine Melamine	0.1 μM 1.39×10^{-6} μM	(103) (104)
12.	Pt/PANI	Uric acid Cholesterol Triglyceride	10^{-5} M 0.3×10^{-3} M 0.2×10^{-3} M	(105)
13.	Au/PPy	Dopamine Serotonin DNA	0.15×10^{-9} M 10^{-9} M 0.84×10^{-13} M	(106) (107)
14.	Au/PEDOT	Triglyceride	89 μM	(108)
15.	NiO/PPy	Glucose	0.33 μM	(109)
16.	$NiCo_2O_4$/PANI	Glucose	0.38 μM	(110)
17.	TiO_2/PPy	Ascorbic acid Diclofenac	20 nM 30 nM	(111)
18.	ZrO_2/PEDOT	Vitamin B_2 Vitamin B_6 Vitamin C	0.012 μM 0.2 μM 0.45 μM	(112)

CHAPTER 4

CONCLUSION

Although much effort has been done to produce effective sensors, the need to build effective composites for sensing combined with high selectivity, sensitivity, and superior detection limit is still required selectively for various pharmaceutical medications. Three major conducting polymers such as PANI, PPy, PEDOT based nanocomposites and medical use of sensors manufactured by molecularly imprinted polymers were discussed in the current review paper. Besides, nanocomposites based on metal oxide nanoparticles or CP have not been studied much. Due to their visible-color alteration effects, nanocomposites, particularly those made of transition metals, can contribute more to biosensors than other composites. Sensor systems based on molecularly imprinted polymers are expected to quickly and endlessly proliferate in biomedical applications. The capabilities described in this analysis, gained by CP-based sensors, will similarly alter the healthcare sector by reducing treatment costs and improving clinical outcomes when these sensors are developed in the future as portable devices that people may use to check and analyze the data without medical help.

CHAPTER 5

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