ADVANCED ELECTROCHEMICAL SENSORS

Materials, Interfaces and Biomedical

Editor

Prof. Dr. Sabriye PERÇİN ÖZKORUCUKLU

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CONTENTS

ELECTROCHEMICAL APTASENSORS FOR CLINICAL BİOMARKER DETECTION: PRINCIPLES AND APPLICATIONS

Gizem YILDIRIM BAŞTEMUR[1]

1. INTRODUCTION

Accurate and early detection of biomarkers has become a critical requirement for the development of personalized medicine approaches, monitoring disease progression, and evaluating treatment response. This necessitates the development of analytical systems that offer high sensitivity and selectivity while delivering performance in rapid, portable, and real sample matrices. Biorecognition elements possessing programmable molecular recognition capabilities provide significant advantages in sensor technologies, such as design flexibility and controlled surface functionalization. Accordingly, aptamer-based approaches have become a major research area in the development of biosensor platforms.

Advances in biosensor technologies have brought about multi-dimensional approaches such as miniaturization, surface engineering, nanomaterial integration, and signal amplification strategies. In these systems, which have a wide range of applications from clinical diagnosis to environmental monitoring, the structural characteristics of the biorecognition element and its target-specific binding mechanism stand out as key determinants of sensor performance. This section will discuss the basic structural characteristics of aptamers, their selection mechanisms,

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and their uses in biosensor platforms within the context of clinical applications.

2. APTAMERS

Aptamers are short, synthetic, single-stranded DNA (ssDNA) or RNA oligonucleotides capable of binding specific targets with high selectivity and affinity (Ellington et al., 1990; Liu et al., 2021). The term "aptamer" is derived from the Latin word "aptus," meaning "to fit," and has been used in the literature since the 1990s (Song et al., 2008; Zhu et al., 2023). DNA or RNA aptamers typically range between 20–80 nucleotides and can recognize a broad spectrum of targets, including small molecules, proteins, metal ions, cells, and pathogens (Stangherlin et al., 2025). Thanks to this broad target recognition capability, aptamers are increasingly considered versatile alternatives to antibodies.

Despite being single-chain, aptamers can fold internally to form various three-dimensional secondary and tertiary structures such as hairpins, stem-loops, purine-rich overhangs, quadruple loops, pseudoknots, kissing complexes, and G-quadruplexes (Khan et al., 2022; Mahmoudian et al., 2024). These conformational structures allow for structural adaptation to the target molecule, enabling the formation of a specific binding site. The unique three-dimensional conformation of each aptamer can vary depending on its sequence and binding conditions, and this dynamic folding feature allows for high-affinity binding to specific regions on the target surface (Yang et al., 2023).

2.1. Advantages of Aptamers as Biological Recognition Receptors

Aptamers are synthetic oligonucleotide sequences that can bind to target molecules with high affinity and specificity, and have been developed as alternative biorecognition elements to antibodies, which are widely used in biosensors. Dissociation constants (K_d) typically fall within the nanomolar to picomolar range and many reach femtomolar levels in optimized system. Such high affinity enables the sensitivite detection of low-abundance analytes. Their structural flexibility and target-induced conformational switching further enhance binding kinetics and signal transduction efficiency (Alnaser-Almusa et al., 2025).

A key advantage of aptamers lies in their entirely chemical synthesis-based production. Unlike antibodies, aptamers do not require live cells or animal systems, making the production process faster, more economical, and more reproducible (Koerselman et al., 2023). This minimizes variations between productions and allows for the production of high-purity products. Furthermore, while antibodies are limited to immunogenic targets, aptamers can interact with a wide range of targets, including both immunogenic and non-immunogenic small molecules, ions, and toxins (Musumeci & Montesarchio, 2023).

In terms of stability, aptamers maintain their function over a wide pH range (approximately 4–9) and under high temperature conditions. Their ability to refold after denaturation allows them to regain their biological activity, providing a reusability advantage in sensor applications (Koerselman et al., 2023; Tang et al., 2023). In contrast, antibodies are more sensitive to high temperatures and environmental changes and can undergo irreversible denaturation. However, susceptibility to nucleases degradation remains a limitation; this can be mitigated through chemical modifications such as 2′-fluoro-2′-O-methyl substitutions, or backbone modifications (Luo et al., 2025).

Another important advantage of aptamers is the ease with which different functional groups can be added to their end regions and their simple and controlled immobilization onto sensor surfaces. This modifiable structure allows for the design of specific recognition to particular regions of the target molecule, increasing the design flexibility of biosensor platforms (Crivianu-Gaita & Thompson, 2016). Considering all these features, advantages such as ease of chemical synthesis, high affinity and specificity, environmental stability, and structural modifiability make aptamers a powerful and reliable molecular recognition platform in biomedical and analytical applications, particularly in biosensor technologies (Zhang & Liu, 2023).

2.2. Aptamer Selection

The most fundamental approach in aptamer development is the SELEX (Systematic Evolution of Ligands by Exponential Enrichment) method, defined as the systematic evolution of ligands through exponential enrichment (Muhammad & Huang, 2021). This in vitro technique is based on incubating a large DNA or RNA library of random sequences with the target molecule. Sequences that do not bind to the target are removed, while specifically bound oligonucleotides are isolated, amplified by PCR, and transferred to the next enrichment step. This cyclical process is usually repeated 10–20 times, and at the end of each round, sequences with increasing specificity and binding strength to the target are enriched (Almenhali & Eissa, 2024). The SELEX cycle consists of five basic stages: library creation, incubation with the target, separation of bound and unbound sequences, amplification, and characterization of the selected sequences (Oliveira et al., 2022).

Aptamer–target interactions are mediated by conformational adaptation and stabilized through hydrogen bonding, electrostatic interactions, π-π stacking, and van der

Waals forces (Liu et al., 2024). The resulting aptamer sequences are generally 60–130 nucleotides long, but shorter and more cost-effective sequences can be obtained by applying truncation strategies to determine the functional core region (Ma et al., 2022). However, since there is a risk of losing some high-affinity sequences during repeated enrichment cycles, the separation and elution steps must be carefully optimized (Yang et al., 2023).

In addition to the classical SELEX method, hybridization-based immobilization strategies such as Capture-SELEX have been developed to facilitate the selection of small molecule targets (Stangherlin et al., 2025). The fact that this approach does not require immobilization of the target molecule provides a significant advantage, especially for low molecular weight and structurally limited targets. Furthermore, variations such as cell-SELEX, capillary electrophoresis-SELEX, microfluidic chip-based SELEX, and magnetic bead-SELEX shorten selection time and increase enrichment efficiency (Aiswarya et al., 2023). These advancements enable the more controlled, rapid, and target-specific production of aptamers with high affinity and specificity.

3. APTAMER-BASED BIOSENSORS

Aptamers are used as effective biorecognition elements in biosensor designs due to their high selectivity, chemical stability, and ease of modification with functional groups. Systems developed in line with these characteristics are called aptamer-based biosensors or aptasensors for short, and constitute a strong alternative to antibody-based platforms (Alnaser-Almusa et al., 2025). For practical analytical applications, aptamers must be integrated with appropriate signal transduction systems. Numerous analytical platforms have been successfully employed for qualitative and quantitative aptamer-based detection. (Uğurlu et al., 2023). Based on the signal transduction mechanism, aptasensors are generally into optical, mass-sensitive, and electrochemical platforms. Optical aptasensors utilize techniques such as fluorescence, luminescence, electrochemiluminescence (ECL), FRET, SERS, and SPR to generate rapid and sensitive optical responses (Kara et al., 2023; Eivazzadeh-Keihan et al., 2024), mass-based systems are used, particularly in protein interactions and toxin analysis, by monitoring mass changes due to target binding (Luo et al., 2025).

Electrochemical aptasensors represent one of the most extensively investigated platforms due to their low cost, portability, rapid response, and high sensitivity (Sheraz et al., 2024; Bao et al., 2025). In these systems, aptamers are generally immobilized on electrode surfaces modified with gold nanoparticles, carbon nanotubes, graphene, or other conductive nanomaterials; thus, electron transfer is accelerated, and detection performance is improved (Li et al., 2019). Target binding induces conformational changes in the aptamer structure, resulting in measurable alterations in current, potential, impedance, or capacitance . For this purpose, both labeled systems with redox-active molecules and unlabeled designs based on surface charge changes have been developed, and both approaches provide high sensitivity and selectivity (Luo et al., 2025).

4. CLINICAL DIAGNOSIS AND DETECTION OF DISEASE BIOMARKERS

Aptamers can be effectively used in clinical diagnosis to detect small molecules such as glucose (Nakatsuka et al., 2018), neurotransmitters (Stuber & Nakatsuka, 2024), and therapeutic drugs (Yu et al., 2021; Wang et al., 2024), as well as drugs with narrow therapeutic ranges (Lin et al., 2022). Furthermore, aptamers offer significant advantages over antibodies in detecting clinically critical protein biomarkers such as C-reactive protein, IgE, and viral proteins, thanks to their programmable structures and binding-induced conformational changes (Stangherlin et al., 2025). Recent studies have shown that advancements in aptamer-based biosensor designs are accelerating the integration of these molecules into portable, wearable, and continuous monitoring systems, and supporting their transition to clinical diagnostic applications (Yoo et al., 2020; Yang et al., 2023). The diverse electrode designs, signal generation approaches, and target biomarker diversity developed within this scope highlight the broad and multifaceted application potential of aptasensors in the field of clinical diagnosis. A summary of current studies in this area is presented in Table 1.

Table 1. Aptasensor Platforms and Analytical Performances Used in the Detection of Disease Biomarkers

Analyte/ Biomarker	**Disease/ Biomarker**	**Aptasensor Probe**	**Method**	**Linear Range**	**Limit of Detection (LOD)**	**Reference**
HER2	Breast, ovarian, lung, gastric, prostate cancers	BSA/Apt+MCH/SPAuE	EIS	5.4x10^{-15}-5.4x10^{-9} M	5.8x10^{-13} M	Ferreira et al., 2021
Lactoferrin	Urinary tract infection	MCH/Apt/SPAuE	DPV	1.3x10^{-10}-2.6x10^{-9} M	1.5x10^{-11} M	Naseri et al., 2021
Dopamine	Parkinson’s, Alzheimer’s, Tourette’s syndrome, and schizophrenia	EtOH-MCH/Apt1/AuE (iOECT)	Potentiometry	5.0x10^{-15}-1.0x10^{-9} M	5.0x10^{-16} M	Liang et al., 2020
miRNA-21	Cancers	Pd@UIO-66	DPV	20 fM-600 pM	0.713 fM	Meng, et al., 2020
BCM-7	Autism	BCM-7/Apt/NiO NPs/SPCE	DPV	0.5x10^{-9} - 1.5 µM	166.6 aM	Shahdost-fard & Roushani, 2020
living C6 glioma cells and EGFR	Cancers	$Cu_xNi_{3-x}(HHTP)_2$	EIS	1 fg mL^{-1}-1 ng mL^{-1}	0.72 fg mL^{-1}	Guo et al., 2020
Aβ oligomers	Alzheimer's disease	AbO/Apt/Th-rGO-MWCNTs/ GCE	DPV	0.0443-443.00 pM	10 fM	Tao et al., 2021
p53 gene	Breast, colon, and lung cancers	MIL-101/MB/hairpin DNA	DPV	1×10^{-14}-1×10^{-7} M	1.4×10^{-15} M	Lv et al., 2022
Thrombin	Alzheimer's disease, ischemia, and Multiple sclerosis	Thrombin/Apt/ERGO/GCE	SWV	0.1 fM-1 nM	0.03 fM	Zhang et al., 2018
Tnl	Cardiovascular	PPy-AuNPs/SPE	CV, SWV	50-500 pg/mL	25 pg/mL	Eshlaghi et al., 2023
Prostate-specific antigen	Prostate cancer	PANI/AuNPs	DPV	0.1 pg/mL-100 ng/ mL	0.085 pg/mL	Chi et al., 2020

Early diagnosis of complex pathologies such as cancer, infectious diseases, cardiovascular disorders, and neurodegenerative conditions is essential for improving patient prognosis and reducing healthcare burden. In this context, biosensor technologies have shown significant development towards point-of-care (POC) analysis systems as an alternative to traditional laboratory-based diagnostic methods (Villalonga et al., 2021). Despite increasing demand for decentralized diagnostic platforms, many current assays remain dependent on centralized laboratory infrastructure. In line with this need, research has accelerated towards the development of electrochemical biosensors, particularly aptasensors offering high selectivity and sensitivity, that can be converted into POC devices enabling early disease detection.

Villalonga et al. (2021) developed an aptasensor based on a sandwich-type architecture on a graphene oxide-coated SPCE surface modified with carboxyethylsilanetriol, and focused on the specific recognition of cardiac troponin I (cTnI). This system, in which a peroxidase-labeled second aptamer acts as the signaling element, demonstrated successful performance in real samples such as human serum with low LOD, high specificity, and reproducibility, offering a promising POC approach for the early diagnosis of heart damage. Idilli et al. (2019) developed an electrochemical aptasensor containing an immobilized aptamer labeled with methylene blue (MB) on a gold disc electrode (AuE) to determine phenylalanine in diluted and untreated blood. Based on a binding-induced folding mechanism, this system demonstrated clinically relevant accuracy and high specificity; it was also successfully adapted to screen-printed gold electrodes, enabling in-home measurements with fingertip samples. Kim et al., (2020) developed a POC aptasensor based on immobilization of NH_2-aptamer specific to α-synuclein oligomers (αSO) onto a carboxylated polypyrrole (PPy-COOH) film electropolymerized on SPCE. This impedance-measured system achieved an extremely low LOD of 1×10^{-3} fM and showed successful recovery results in artificial cerebrospinal fluid, promising portable applications for early diagnosis of Parkinson's disease.

5. CONCLUSION

Aptamers have emerged as powerful and versatile biorecognition elements in modern biosensor technologies. The advantages of chemical synthesis-based production, a wide range of targets, and conformational change-based signal generation mechanisms make it possible to effectively use aptamer-based systems in clinical biomarker detection. Advances in SELEX and various selection strategies have increased the application potential of this technology by enabling the more controlled acquisition of sequences with high affinity and specificity.

Electrochemical aptasensors, in particular, offer a significant platform for point-of-care diagnostic systems due to their advantages such as low cost, portability, and high sensitivity. Nevertheless, challenges such as matrix interference, long-term stability, and large-scale manufacturing standardization must be addressed before full clinical translation can be achieved. Aptamer-based platforms, supported by nanomaterial integration, microfluidic systems, and multi-analysis approaches, are expected to achieve more widespread clinical use in early disease diagnosis and personalized monitoring applications in the future.

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CARBON-BASED ELECTRODES FOR ELECTROCHEMICAL SENSING OF ACTIVE PHARMACEUTICAL INGREDIENTS

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1. INTRODUCTION

The literature extensively describes the diverse applications of electrochemical sensors in numerous fields. These include the detection of active pharmaceutical ingredients (APIs) and their metabolites in pharmaceutical preparations and biological samples (Wesoły, Cetó, delValle, Ciosek, & Wróblewski, 2016); the monitoring of biomarkers used in cancer diagnosis and treatment follow-up (Freitas, Nouws, & Delerue-Matos, 2018); the analysis of additives in food and agricultural products (Chugh et al., 2022; Ghaani, Azimzadeh, Büyüktaş, Carullo, & Farris, 2024); the analysis of toxic heavy metals and other inorganic ions in drinking and tap water (Lin, Li, & Burns, 2017; Yantasee et al., 2007); the determination of environmental pollutants, such as drug residues, pesticides, dyes and endocrine disruptors (Tajik et al., 2021), the determination of illicit drugs in forensic samples (Khizar, Zine, Sigaud, Elaissari, & Errachid, 2025); quality control in industrial processes (Mukherjee, Mondal, & Paine, 2025); and real-time health monitoring of biological fluids, such as sweat and saliva, on wearable platforms (Xue, Gai, Wu, liu, & Li, 2024). The determination of some ingredients is a crucial aspect of the grade of compounds used in human life being evaluated, and human health being directly

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related to (Karimi-Maleh, Karimi, Alizadeh, & Sanati, 2020). The detection of APIs are crucial for understanding biological and environmental systems, given their widespread use in our daily lives. Due to their therapeutic and remedial properties, tons of APIs are produced and consumed globally. (Theyagarajan, Sruthi, Mohanapriya, Thenmozhi, & Senthilkumar, 2024). Analytical methods help identify and quantify permitted and unpermitted compounds found in materials. Electrochemical methods illustrate several advantages over other analytical methods, such as affordability, ease of production, rapid analysis, good selectivity and high sensitivity, small size and ability to detect multiple elements simultaneously (Maddiboyina, Sunaapu, Chandrashekharappa, & Sivaraman, 2022; Pakchin, Nakhjavani, Saber, Ghanbari, & Omidi, 2017). They facilitate the consideration of the reaction mechanisms of pharmaceutical active ingredients, providing qualitative and quantitative information about their presence in the body or pharmaceutical preparations (Kumar, Salwan, Kumar, Bansal, & Kumar, 2025).

Due to their exceptional properties in many respects, carbon and its derivatives act a particular in electrochemistry of APIs analysis from pharmaceutical formulations and biological samples (Uslu & Ozkan, 2007).

2. ACTIVE PHARMACEUTICAL INGREDIENTS (APIs) IN ELECTROCHEMICAL ANALYSIS

Electrochemical sensors ensure a simple, fast, and environmentally friendly method for API detection with low system costs. Electrochemical sensors can be used to monitor API levels in real-time due to their high sensitivity, and they have the potential to be miniaturized. Additionally, electrochemical sensors have the capability to sense analytes at very low concentrations that may not be detected by other sensors. They achieve this high sensitivity through their ability to measure the smallest changes in electrical properties to determine of an analyte in a solution. The type of materials used as the working electrode and the modification material will significantly affect how well the sensor performs. Modification of the electrodes affects the linearity range, detection limits, selectivity, electrode stability during storage and repeated use, and the response repeatability of the sensor, among many other characteristics of sensor performance. (Arvas et al., 2025; Kocyigit, Dinc-Zor, Yagci, & Arvas, 2025).

The table below summarises the main pharmaceutical groups and their APIs which are frequently studied using electrochemical sensors, as referenced in the literature.

Table 1. Main pharmaceutical classes studied using electrochemical sensors

Pharmaceutical group	Some APIs detected to Electrochemical Methods	Intended use
Analgesics / Antipyretics	Acetylsalicylic acid (aspirin), ibuprofen, paracetamol (acetaminophen)	Pain relief, fever reduction
Anti-inflammatory (NSAID)	Diclofenac, naproxen	Pain, inflammation, fever
Antibiotics	Penicillin, ceftazidim, ciprofloxacin, sulfamethoxazole, tetracycline, macrolides, quinolones, amoxicillin, ceftriaxone, azithromycin,	Bacterial infections
Antivirals	Anti-hepatitis C drugs, acyclovir, oseltamivir, valacyclovir (VCV)	Viral infections
Antifungal	Fluconazole, ketoconazole, natamycin, tolnaftate	Fungal infections
Anticancer (antineoplastic)	Tamoxifen, etoposide, doxorubicin, dasatinib, flutamide, gemcitabine, cyclophosphamide, methotrexate, ımatinib, trastuzumab, nivolumab, taxol	Cancer treatment
Antidiabetic	Glibenclamide, glimepiride, insulin, metformin, sitagliptin, dapagliflozin	Diabetes mellitus (Type 1 & Type 2)
Antidepressant / Psychoactive	Benzodiazepines, fluoxetine, sertraline, venlafaxine, amitriptyline, risperidone, olanzapine	Depression, anxiety, OCD, panic disorder, schizophrenia, bipolar disorder
Opioid analgesics	Morphine, tramadol, fentanyl, heroin and its derivatives	It suppresses pain signals by binding to opioid receptors in the central nervous system and some peripheral tissues.
Antiepileptics	Carbamazepine	To prevent and control epileptic seizures

3. CARBON-BASED ELECTRODES FOR THE ELECTROCHEMICAL DETERMINATION OF ACTIVE PHARMACEUTICAL INGREDIENTS (APIs)

In recent years, carbon has become a focal point of research in materials science. Of all the different types of carbon, graphene based materials are comprehensively studied, having featured in almost 200,000 publications since 1995 (Sharma, 2018). Several advantages are offered by carbon for use in electrochemical sensors, including low cost, non-toxicity, end asy availability aa wide potential range (Gibi, Liu, Barton, Anandan, & Wu, 2024).

The majority of carbonaceous materials that have been most thoroughly researched in the context of detecting APIs via electrochemical techniques include; Pencil Graphite Electrode (PGE), Glassy Carbon Electrode (GCE), Screen-printed Carbon Electrode (SPCE), Boron-Doped Diamond Electrode (BDD), and Carbon Paste Electrode (CPE). Furthermore, modifying these electrodes to increase their analytical capabilities includes incorporating organic polymers, organic dyes, metals, metal oxides, clay, Crown Ethers, Molecularly Imprinted Polymers (MIPs), Nanocarbon Materials, and Composites. These modifications may provide significant improvements in the areas of Sensitivity, Selectivity, and Detection Limits, and assist in overcoming obstacles such as Interference and Stability. (Stoytcheva, Velkova, Gochev, Valdez, & Curiel, 2025).

The surface of the electrodes is characterised by scanning electron microscopy (SEM) and transmission electron microscopy (TEM). The electrodes are also characterised using electrochemical impedance spectroscopy (EIS), X-ray photoelectron spectroscopy (XPS), Raman spectroscopy and X-ray diffraction (XRD).

3.1. Pencil Graphite Electrode (PGE)

The electrode surface properties are primarily influenced by clay, ion exchange and structural properties of the pencil graphite electrodes. Electrochemical reactions occur due to interfacial processes; therefore, understanding the surface characteristics of electrodes is essential in electrochemistry. As such, characterizing electrode surface morphology is necessary because granularity of conductive materials will determine the degree of roughness of the electrode surface. Besides the above mentioned information, the preparation of the pencil graphite electrodes, also referred to as pencil graphite electrodes (PGEs), involves the combination of natural graphite (75-80%), an organic binder (13%), and mill oil (8%) to create a paste that can be formed into a rod shape. The rod is subsequently dried (100°C to 300°C) and then sintered (1000°C) under an inert gas atmosphere to minimize the potential for deformation. The "HB" designation of pencil leads refer to the fact that they have equal amounts of graphite as well as lead. In contrast, "B" leads contain a significant amount of graphite and are soft, whereas "H" leads contain a significant amount of lead and are hard. The degree of hardness/softness of pencil leads are indicated by the letter stamps of "H", indicating hardness, and "B", indicating blackness, and range from 9H (hardest) to 8B (softest).PGE is characterised by a surface composed of irregularly structured, nanometre-sized graphite flakes. This has been confirmed by examining the surface using SEM and TEM related to the granularity of the conductive materials. EIS, XPS, Raman spectroscopy and XRD, have also been used to characterise PGEs and confirm the presence of irregularly structured nanometre-sized graphite flakes. Overall, it can be concluded that the PGE is a cost-effective and disposable sensor for electrochemical measurements compared to more expensive commercial carbon electrodes (Annu, Sharma, Jain, & Raja, 2019).

3.2. Glassy Carbon Electrode (GCE)

Glass carbon electrodes (GCEs) are favoured due to their numerous advantages, including low cost, chemical stability, electrochemical inertness over a wide potential range, excellent electrical conductivity, high hardness, impermeability, and ease of surface modification (Abdel-Aziz, Hassan, & Badr, 2022). GCEs are useful due to their very small pore size, low oxidation rate, high chemical inertness, and low gas and liquid permeability (Dekanski, Stevanović, Stevanović, Nikolić, & Jovanović, 2001).

Glassy carbon (vitreous or glass like carbon), is a low order, non-graphitizing, isotropic carbon material that is produced when a phenol-formaldehyde resin undergoes pyrolysis at relatively slow rates and within a temperature range of approximately 300°C to 1,200°C. The resulting product has sp^2 hybridized carbon atoms that are organized in a hexagonal structure and, due to its isotropy, it will have low electrical resistance. Additionally, glassy carbon can be made into thin films, flat sheets, or powders. There are several types of glassy carbon including; reticulated glassy carbon (RGC), monolithic glassy carbon (MGC), and cellular glassy carbon (CGC). RGC is primarily used for electrodes in electrochemical sensors and is characterized by its 3D, high porosity network and very large surface area (Gibi et al., 2024). To clean a GCE, the electrode is polished using an alumina-water slurry on a polishing pad while holding it perpendicularly to ensure even movement. Afterwards, the electrode is rinsed with pure water. Modifications are generally made using carbon materials, metals, metal oxides, conductive polymers and their hybrids (Pacchioni, 2022).

3.3. Boron-Doped Diamond Electrode (BDD)

Boron-Doped Diamond Electrodes (BDDEs) are being used for electrochemical applications due to their superior physical and chemical characteristics when compared to the characteristics of most conventional electrode materials. Some of the advantages of BDD electrodes include a large electrical potential window in both aqueous and non-aqueous solutions; a chemically inert surface with low adsorptive ability; a high degree of stability and corrosion resistance; low bilayer capacity and background current; high current density electrolysis; and high overpotential for the generation of both hydrogen and oxygen. The large electrical potential window of BDD electrodes is larger than that of all other materials. BDDEs have the largest electrochemical potential window for aqueous (i.e., ~3–3.5V) and non-aqueous (i.e., ~5.0–7.5V) solutions. Decomposition reactions occur when the potential is sufficient to initiate them (e.g., in water), thus requiring adsorption process from the existence of catalytic sites present on the electrode surface. It has been demonstrated that the strong covalent bonds formed through the sp^3 hybridized carbon orbitals in the diamond structure are responsible for the stability and corrosion resistance of BDD. Stability and durability of BDD electrodes have been demonstrated under conditions of strong acidity and under long term cyclic voltammetry and hydrogen evolution reaction overpotentials. Adsorption occurs at greater rates at surfaces of electrodes containing sp^2 hybridized carbon orbitals (i.e., glassy carbon or graphite) whereas adsorption occurs at lower rates at surfaces containing sp^3 hybridized carbon orbitals (i.e., diamond). Fouling of BDD electrodes can be prevented simply by operation of the electrode above the water dissociation potential. Furthermore, BDD electrodes can clean themselves from such polymeric films by polarizing such films (Brosler, Girão, Silva, Tedim, & Oliveira, 2023; Muzyka et al., 2019).

3.4. Screen-Printed Carbon Electrode (SPCE)

Electrochemical sensors used at point-of-care or on-site locations need a rapid and easy-to-apply technique. That's why screen-printed electrodes (SPEs), which can be produced in large quantities and used once, have been gaining popularity in recent years. Research has shown that SPEs with carbon-based components are being studied by many researchers today. A Screen-Printed Carbon Electrode (SPCE) contains a working electrode composed of carbon, an additional reference electrode and a counter electrode all located on the same substrate. The process of manufacturing an SPCE includes making up and printing conductive inks for each component of the SPCE; this is based upon the characteristics of both the ink and substrate used and the ultimate application of the printed electrodes(Wahyuni et al., 2021) . SPCEs play a significant role in electrochemical sensing thanks to their low cost, disposable nature, miniaturization, wide potential range, simple electrode design, portability and ease of mass production. SPCEs integrate the working, reference and counter electrodes. They do this into PVC (polyvinyl chloride) or polyester substrates. This creates a compact sensor design. The surface of SPCEs can be modified to improve performance by enhancing sensitivity, selectivity, stability and electron transport. These modified SPCEs enable rapid, on-site analysis (Haroon & Stine, 2025; Osaki, Saito, Nagai, & Tamiya, 2024).

3.5. Carbon paste electrode (CPE)

Electrodes made from carbon paste (CPE), which can be either an electrochemical or a bioelectrochemical sensor, have a wide variety of uses as sensors for pharmaceutical and biological species, because of the inertness of the carbon, the large potential window that they provide, simple design, ease of renewal of the electrode surface and low cost. CPEs are now considered one of the most common types of working electrodes. A very important aspect of the use of CPEs is that the surfaces of these electrodes can be chemically modified by incorporating different materials into the paste to increase selectivity, response time and sensitivity. The liquid phase of CPEs has been formulated with many different insulating liquids, including paraffin oil, silicone oil, bromonaphthalene and tricresyl phosphate, and are widely used around the world. Desirable characteristics for the liquid phase of CPEs include low vapor pressure to allow the paste to remain mechanically stable over a long period of time and insolubility in the solution being analyzed and electrochemical passivation in the desired potential range when used in electrochemical sensing applications. An additional new way to modify electrodes to selectively measure pharmaceutical formulations is through the simultaneous modification of electrodes using ionic liquids, nanomaterials and other conducting mediators (Mohammadnavaz, Beitollahi, & Modiri, 2024; Vytřas, Švancara, & Metelka, 2009).

4. MODIFICATION OF ELECTRODES USED IN THE ANALYSIS OF ACTIVE PHARMACEUTICAL INGREDIENTS (APIs)

The administration of pharmaceuticals to a living organism is instrumental in maintaining health and is of crucial significance in human life. They can be used for diagnosis, prevention, treatment and cure of disease. Quantitative analysis of the active ingredient content in pharmaceutical formulations and human biological fluids is also important. Various analytical techniques have been improved, but electrochemical techniques are considered the most suitable for quick and accurate pharmaceutical analysis (Ghalkhani & Ghorbani-Bidkorbeh, 2019). Carbon-based nanomaterials have attracted significant interest in APIs due to their strong electrical conductivity, large active surface areas and other unique properties, and their development has become widespread. Sensitive and reliable electrochemical sensors, which can monitor a wide range of drugs, are widely used. The most frequently encountered carbon nanoforms given in the literature are carbon nanotubes (CNTs), carbon nanofibres (CNFs), graphene oxide (GO), reduced graphene oxide (rGO), diamond-like carbon (DLC) and nanodiamonds (Cetinkaya, Kaya, Ozcelikay, Budak, & Ozkan, 2024).

4.1. Nanomaterial-Based Electrode Modifications

Carbon nanomaterials, which include carbon nanofibers (CNFs), graphene oxide (GO), carbon nanotubes (CNTs), graphene, and rGO, are the most common modifier for electrochemical pharmaceutical sensing. Each of these carbon nanomaterials offers excellent electrical conductivity, is mechanically stable, and has a very high surface area(Kanjwal & Ghaferi, 2022). Their 2-D or tubular geometry provides many available binding sites on the surface of the material, thereby enhancing adsorption of the analyte and catalysis. Among all the carbon nanomaterials listed above, graphene has been the focus of significant research due to its electrical conductivity and its exceptionally high surface-to-volume ratio. Electrodes modified with graphene derivatives typically exhibit improved sensitivity, lower detection limits, and longer operational lifetimes compared to electrodes made using unmodified carbon materials. For example, graphene-based electrodes have been shown to be capable of electrochemically detecting several pharmaceutical compounds including paracetamol, dopamine, caffeine and antibiotics(Malode, Ali Alshehri, & Shetti, 2024). The tubular shape of CNTs and their very high aspect ratio also make them useful in modifying electrodes to facilitate faster electron transfer and increase analytical sensitivity. Electrodes modified with MWCNTs and SWCNTs have been reported to enhance the electrochemical signal of a variety of pharmaceutical analytes through promoting efficient charge transfer at the electrode-analyte interface and through increasing surface adsorption of the analyte(Karousis, Tagmatarchis, & Tasis, 2010).

4.2. Metal and Metal Oxide Nanoparticle Modifications

Nanoparticles made from both metals and metal oxides are also very commonly used in order to increase the electrocatalytic activity of the electrode surface. The most commonly used metal nanoparticle is that of the noble metals; Au (Gold), Ag (Silver), and Pt (Platinum). These are chosen for use in electrocatalysis due to their excellent catalytic properties, high conductivity, and their ability to hold analytes strongly on the electrode surface. Gold nanoparticles are of particular interest when it comes to designing an electrochemical sensor due to their biocompatibility, and their ability to enhance electron transfer at the electrode surface(Nguyen et al., 2025). Gold nanoparticles may be incorporated into the electrode surface to enhance the detection sensitivity of a pharmaceutical compound by enhancing the number of catalytically active sites available. Silver nanoparticles are another significant class of nanomaterials used in electrochemical sensing. These nanoparticles show enhanced electrocatalytic activity, and enhanced conductivity compared to other metal nanoparticles(Białas, Moschou, Marken, & Estrela, 2022). This has resulted in increased analytical performance with respect to the determination of many different classes of pharmaceutical compounds including antibiotics, analgesic agents, and anti-inflammatory drugs. Transition metal oxides, including ZnO, TiO_2, Fe_2O_3, CuO, and NiO, are another group of materials that have been used extensively to modify electrodes. These materials have been selected for use in this manner as they offer a combination of catalytic activity, chemical stability, and strong adsorption properties(Tajik et al., 2022). Additionally, these metal oxides may help to facilitate redox reactions of pharmaceutical molecules, and further assist in the enhancement of the signal-to-noise ratio during electrochemical detection.

4.3. Conducting Polymer-Based Modifications

Electrode modifier materials that are called conducting polymers offer an important other class of electrochemical sensor electrode modifiers. Conduction of electrons within each polymer is greatly enhanced by the presence of conjugated double bonds or aromatic rings within the polymer chain. These conducting polymers include polypyrrole (PPy), polyaniline (PANI), and PEDOT (poly[3,4-(2,2-diethoxy-1,2-ethanediyloxy)-1,2-thienylene]). A major advantage of these polymers is their relatively low cost and ease of synthesis compared to metal-based electrocatalysts. Additionally, all three polymers are chemically stable and highly conductive. Electropolymerization is the most common technique for creating conducting polymer films on electrodes for electrochemical sensor development. By controlling a variety of electropolymerization parameters including potential limits, scan rates, and number of cyclic voltammograms, conducting polymer films can be prepared that have controlled thicknesses, morphologies, and pore sizes(Rendón-Enríquez et al., 2023). As a result, conducting polymer films can significantly increase the sensitivity and selectivity of electrochemical sensors for detecting a wide array of analytes. Conducting polymers contain functional groups that can interact with pharmaceutical molecules via π–π stacking, hydrogen bonding, and electrostatic interactions. These interactions enhance both analyte capture onto the electrode surface and the signal intensity generated from the interaction(Karasu et al., 2024). In addition, conducting polymers are often mechanically robust and exhibit good fouling resistance, which makes them well-suited for repeated measurement studies of biological samples.

4.4. Ionic Liquid and Composite Electrode Modifications

Ionic liquids (ILs) have a variety of applications as electrode additives because of the distinct physical/chemical characteristics of ILs. The primary characteristic of an IL is that it consists of 100 % ions and thus has good ionic conductivity, a broad electrochemical window and good thermal stability(Pereira, Souza, Moita, & Moreira, 2023). When ILs are added to other electrode materials they may be able to improve the charge transfer properties and enhance the rate at which an analyte diffuses to the electrode. Additionally, ILs may act as conductive binder materials in the preparation of carbon paste electrodes and may assist in the creation of durable nanocomposites. Electrode materials consisting of composites of nanomaterials, conductive polymers, and ILs have shown significant improvement in electrochemical sensor performance(Fotouhabadi, Bahrami, & Ghatee, 2026). These hybrid composite electrodes have taken advantage of the beneficial synergies created when several types of functional materials are combined; this synergy results in improved sensitivity, selectivity, and durability over time.

4.5. Future Perspectives in Electrode Modification for Pharmaceutical Analysis

The rapid developments in nano-technology and in material-science continue to fuel advancements in the development of electrochemical-sensors. Research in the future will be focused on developing multi-functional composite nano-materials that have greater catalytic properties, better selectivity and longer term stability. Additionally, integrating electrochemical-sensors into miniaturized and portable analytical devises presents a significant opportunity for real time pharmaceutical monitoring. These systems would allow for continued measurement of drugs within biological fluids (e.g., blood) thereby allowing for better understanding of the effectiveness of treatment and the use of medication as part of a personal treatment plan. Lastly, another area of increasing importance in electrochemical-sensor research will be the development of green and sustainable electrode materials. Bio-derived nanomaterials and green synthesis approaches are likely to become increasingly important for fabricating the next generation of electrochemical-sensors.

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ENGINEERING SELECTIVITY AT CONDUCTING POLYMER INTERFACES: FROM MOLECULAR RECOGNITION TO ELECTROANALYTICAL DISCRIMINATION

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1. INTRODUCTION

The use of electrochemical sensors has become widespread within the analysis of bioanalytical, pharmaceutical, and environmental analytes due to their low costs, fast response times, high sensitivities and compatibility with both macro-and microscale systems. One of the most important factors which will influence the analytical performance of an electrochemical sensor, is its ability to selectively detect the target analyte(s) in the presence of one or more interfering electroactive species present in the same biological matrix at comparable concentration levels(Gao, Guo, He, Liu, & Chen, 2024). Conducting polymers (CPs), specifically those that include electronically conductive materials that also have chemically tunable surfaces (such as polypyrrole (PPy), polyaniline (PANi) and poly(ethylenedioxythiophene) (PEDOT)) offer significant potential as sensing interfaces due to their combined electronic conductivity and surface chemistry compatibility. These materials do not merely modify the existing sensing interface and increase the signal intensity, but also serve as active participants in interfacial electron transfer processes; this enables the recognition of molecules and subsequent signal transduction to

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occur simultaneously. Historically, electrochemical sensors were designed to incorporate biological recognition elements such as enzymes, antibodies or aptamers to achieve high selectivity for the desired analyte. However, these biological components have several limitations including stability issues, high cost, environmental sensitivity, and difficulties associated with immobilizing them onto electrode surfaces. Conducting polymer-based interfaces offer a stable, cost-effective, and non-biological alternative to biological-based interfaces, where the biomolecular recognition capabilities can be achieved using only synthetic components(Aydemir, Malmström, & Travas-Sejdic, 2016). In terms of interaction, functional groups in the polymer backbone or as side-chains provide a variety of ways that the sensor can interact with the targeted analyte (e.g., through hydrogen bonds, electrostatic attractions, π-π stacking, and coordination). The interaction of the analyte with the functional group(s) promotes preferential adsorption and local pre-concentration of the analyte at the electrode surface, which increases both sensitivity and selectivity. Dopants used in electropolymerizations are not just for balancing charges in the film, but also influence the surface charge density, porosity and the ionic transport properties of the film(Lin, Wu, & Lu, 2024). Electrostatic discrimination by the film is particularly useful in biological matrices, since many analytes and interfering substances have different ionic forms at physiological pH. Molecularly imprinted polymers (MIPs) are among the highest selective advanced selectivity methods that can provide very high structural selectivity. The method of molecular imprinting produces shape- and functionality-complementary cavities through electropolymerization of a monomer in the presence of a template molecule that will be removed after the electropolymerization step(Y. Li et al., 2024). A MIP sensor based on conducting polymers provides both structural specificity and electrochemical sensitivity. This makes MIP sensors based on conducting polymers suitable for long-term and practical use. Conductive polymers facilitate faster electron transfer rates, resulting in higher resolution redox peaks compared to traditional unmodified electrodes. Additionally, when using techniques like pulse voltammetry (such as DPV or SWV), even minor differences in redox behavior between closely related species can result in significant changes in the measured signal, which can be used to differentiate between similar species(Di Pasquale & Pollicino, 2026). The integration of nanomaterials with conducting polymers to create "smart" selective sensing devices represents another major advancement in the field of chemical sensors. By combining graphene derivatives, metal oxides or metal nanoparticles within hybrid nanocomposites, the resulting hybrid provides greater surface area, improved catalytic properties, and site specific adsorption for selective detection of analytes(Zeng et al., 2024). Specifically, graphene enables π-π interactions with analytes containing aromatic groups; metal oxides are capable of facilitating Lewis acid-base reactions with analytes that contain functional groups (e.g., carboxylates or phosphates); and metal particles can discriminate based on the kinetics of reaction catalyzed by the metal particle. The conducting polymer serves as both an electroactive matrix to bind together the recognition and transduction components of the device(Buledi, Golovynskyi, Qu, & Golovynska, 2025). Additionally, the ability to control the film thickness and morphology of the sensing film is also important to the overall selectivity of the sensor. This is due to the fact that electropolymerization parameters (i.e., voltage limits, scan rates, monomer concentrations and number of cycles) allow for the exact tailoring of the polymer's structure. However, films that are too thick may impede diffusion of analytes and decrease the sensor's sensitivity. Additionally, optimized morphology can reduce fouling, preserve active sites and maintain consistent performance of the sensor. Furthermore, due to their pH responsive properties, conducting polymers provide a dynamically variable method of regulating selectivity(Di Pasquale & Pollicino, 2026).

In summary, the above results indicate that selectivity in conducting polymer based electrochemical sensors is not a inherent property of the polymer; however it is an end result of rational interface engineering using molecular recognition, dopant controlled ionic discrimination, nanocomposite design, morphology optimization, electroanalytical technique, and pH adjustment to create a versatile and effective framework for developing highly selective and sensitive sensing systems.

2. KEY STRATEGIES FOR ACHIEVING SELECTIVITY IN CONDUCTING POLYMER–BASED ELECTROCHEMICAL SENSORS

2.1. Functional Groups and Specific Interactions

The potential for conductive polymers (such as polypyrrole (PPy)), polyaniline (PANI)) and PEDOT to be chemically selective towards biological analytes is due primarily to the incorporation of heteroatoms (N, O, S) and functional groups into their backbone or side chains. The degree of chemical selectivity exhibited in electrochemical sensors is typically derived from a combination of hydrogen bonding, electrostatic attraction, π-π interactions and coordination bonding and how these contribute to preferential adsorption and facilitated electron transfer of the target analyte at the electrode-electrolyte interface(Bhattacharyya, 2024). Hydrogen bonding is important in the recognition of many types of biological molecules (e.g., neurotransmitters, metabolites, pharmaceuticals) and is a significant interaction site on conductive polymers. Specifically, the backbone of polypyrrole contains –NH groups which can act as both hydrogen bond donor/acceptor. These sites have high affinity for hydrogen bond forming analytes that contain hydroxyl

(-OH), carbonyl (C=O), and amine (RNH_2) functional groups that are common among biological analytes. Examples of analytes that have catechol (-OH) groups that will interact with the –NH groups of PPy include dopamine, norepinephrine, and epinephrine(Merli, Cutaia, Hallulli, Bonanni, & Alberti, 2024). These interactions increase the resident time of the analyte at the electrode surface, resulting in an analyte concentration enhancement ("pre-concentration") and a greater electrochemical signal. Phenols, amino-acid derivatives, and other heterocycles present in biomolecules may also participate in hydrogen-bonded interactions with films made from conductive polymers, thus improving the ability of the film to recognize and detect analytes at low concentrations(Dube, Malode, Alodhayb, Mondal, & Shetti, 2025). Similar to PPy, the presence of –NH– and =N– groups in PANI along with their pH-dependent protonation states, modulate the hydrogen-bond based selectivity of PANI systems toward biologically-relevant acids and bases (i.e., ascorbic acid and uric acid). A positive charge will attract positively charged analytes, e.g., protonated amine groups, found in some neurotransmitters and certain drugs; while negative charges will favor the attraction of negative charged species, e.g., ascorbic acid or carboxylate containing metabolic products, that have been formed through enzymatic reactions(Zhou et al., 2024). The selective binding of certain bioanalytic compounds (such as those containing aromatic or heteroaromatic functional groups) by conducting polymers can be attributed, in part, to π-π stacking interactions; i.e., the interaction of π systems of the conducting polymer backbones with the π systems of the aromatic ring systems found in a variety of biologically important molecules (e.g. catecholamines, heterocyclic drugs, nucleobases, etc.). In addition, coordination interactions may occur through direct coordination by metal ions or association with metal centers and redox active dopants, when conducting polymers directly interact with metals. For example, the backbone –NH groups in polypyrrole based electrodes allow for simultaneous hydrogen bonding, electrostatic attraction, and dipolar interactions with phenolic, carboxylic acid, and heterocyclic biological molecules. Sites containing nitrogen in PPy and PANI, as well as oxygen-, or sulfur-containing functional groups in modified PEDOT derivatives can provide coordination sites for metal ions like Cu^{2+}, Fe^{3+}, and Hg^{2+}(Ensafi, Mousaabadi, & Fazel-Zarandi, 2022). Such properties allow for selective detection of metal ions or metal-coordinating biological molecules, e.g. thiol-containing biomolecules (e.g. cysteine or glutathione) and ligands with imidazole, or carboxylate functionalities. Dopants do not simply act as charge balancing species; they determine the surface charge density, internal porosity, and ion transport characteristics of the polymer matrix. The surface charge of a conducting polymer film is generally determined by the type of dopant used during synthesis. Anionic dopants, e.g., p-toluenesulfonate (p-TSA), dodecyl sulfate (SDS) and other sulfonate-based dopants produce a net negative character in the polymer matrix. The negative charge on the polymer matrix will attract and concentrate cationic analytes, e.g., protonated amines, neurotransmitters (e.g., dopamine), and positively charged drugs(Eun, Kim, & Kim, 2023). Conversely, cationic dopants, e.g., metal complexes or quaternary ammonium species, create positive regions within the polymer film that attract anionic analytes, e.g., ascorbate, carboxylate-containing metabolites, or negatively charged drug species(Hussain, Malik, & Iyer, 2015). An additional degree of selectivity may be obtained through the use of redox-active dopants, which provide a mechanism of potential dependent discrimination. Redox-active dopants are involved in electron transfer reactions and can modify or sharpen the redox responses of specific analytes. Analytes having overlapping oxidation or reduction potentials may be resolved more effectively using redox-active dopants, providing improved peak resolution and analytical selectivity in voltametric measurements(Manna, Sharma, & Satpati, 2022). Representative examples of some conductive polymer-based electrochemical sensors demonstrating selectivity driven by functional groups and specific intermolecular interactions are shown in Table 2.1.

Table 2.1. Representative conducting polymer–based some electrochemical sensors illustrating selectivity driven by functional groups and specific intermolecular interactions

No.	Electrode	Analyte	Linear Range	LOD	LOQ	RSD	Strategy	References
1	PP3C/PPy/AuNPs	Dopamine	5–180 µM	9.72 nM	0.032 µM	4.21%	Functional groups, AuNP-assisted ET and electroanalytical discrimination	(Janmanee & Sriwichai, 2025)
2	PEDOT–PPy hybrid	Dopamine	5 nM–200 µM	5 nM	–	<5%	Hybrid CP interface and peak resolution (DPV)	(Sanmugam et al., 2025)
3	PPy/MoO_3 bilayer on ITO	Dopamine	5–250 nM	2.2 nM	6.66 nM	–	Metal oxide–CP nanocomposite and Lewis acid–base interactions	(Alahmadi & El-Said, 2023)
4	Electrospun PANI/f-CNT nanofibers	Dopamine	50–500 nM	0.0974 µM	–	0.243%	π–π interactions and morphology-controlled diffusion	(Kaewda & Sriwichai, 2024)
5	PEDOT/SCX/MXene/GO	Glucose	0.5–8 mM	22.5 µM	–	2.1%	Ionic selectivity and enzyme immobilization	(Murugan et al., 2022)
6	MIP-PPy electropolymerized membrane	Valproate	5–75 µg mL^{-1}	17.48 µM	–	–	Molecular imprinting (gate-effect selectivity)	(Yuan et al., 2022)
7	Ag_2S/MOF–PANI& Bi_2S_3/MOF–PANI	Uric Acid	0–16 µM	0.579 µM / 0.446 µM	–	–	MOF-derived sulfide nanocomposite and CP interface	(Deffo et al., 2024)
8	T-PEDOT/SWCNHs composite	TBHQ	0.01–10 µg mL^{-1}	0.005 µg mL^{-1}	0.017 µg mL^{-1}	2.82%	π–π stacking and catalytic discrimination	(Wu, Li, Wang, Pan, & Wang, 2024)

2.2. Dopant Selection–Induced Ionic and Electrostatic Selectivity

Electropolymerization of conducting polymers such as PPy, PANI, and PEDOT relies on selecting dopant ions that significantly affect the ionic and electrostatic selectivity of the final polymer film. Dopants are not just neutralizing charges in the polymer matrix; they also control its surface charge density, porosity and ion transport properties. The charge of a conducting polymer film is primarily dependent on the type of dopant present. For example, anionic dopants like p-toluenesulfonate (p-TSA) or dodecyl sulfate (SDS) and other sulfonate-based dopants produce a net negative charge in the polymer matrix and therefore will preferably accumulate positive analytes, for instance protonated amines, neurotransmitters (like dopamine) and positive pharmaceuticals. Cationic dopants, like metal complexes or quaternary ammonium species, will create areas of positive charge in the polymer film that will tend to accumulate negative analytes, such as ascorbate, metabolites with carboxyl groups, or negatively charged pharmaceutical compounds. Thus, the choice of dopant allows for selective discrimination based on charge at the electrode interface. Depending upon whether they are large (bulky) or small (amphiphilic), dopants can produce a number of different structural changes in the film(Aubry et al., 2020). For example, bulky dopants may produce a less dense and more open polymer structure that increases both pore size and facilitates the free movement of ions through the film. Smaller dopants generally produce a more dense and compact film structure. The structural changes produced by the dopant affect two factors; first, the ease with which the target analytes can gain access to the electrochemically active sites of the film and secondly, the ability of interfering species, especially those that are larger than the target analytes or carry the same charge, to penetrate into the film(Ramachandran et al., 2019). The use of redox active dopants adds a degree of selectivity as they will respond to analyte dependent changes in the electrode potential. Redox active dopants interact with the analyte through direct electron transfer and may alter or improve the redox response characteristics of the analyte that are near each other on the oxidation/reduction scale (E°).Representative conducting polymer–based some electrochemical sensors illustrating dopant-induced ionic and electrostatic selectivity are shown in Table 2.2.

Table 2.2. Representative conducting polymer–based some electrochemical sensors illustrating dopant-induced ionic and electrostatic selectivity

No.	Conducting Polymer / Dopant System	Target Analyte	Linear Range	LOD	LOQ	RSD	Key Dopant-Induced Selectivity Mechanism	References
1	PPy/$Fe(CN)_6^{4-}$ (vs NP, SDS) on SPCE	L-Tyrosine	0.5–5.0 µM (low-range linear)	0.082 µM	0.273 µM	4.4–5.7%	Fixed anionic dopant controlling charge density, porosity, and Donnan exclusion	(Dinu & Apetrei, 2021)
2	PEDOT:PSS thin film	Dopamine	0.1–300 µM	44.4 nM	NR	NR	Polyanionic PSS dopant favoring cationic analyte accumulation	(Thirumalai et al., 2024)
3	rGO/PEDOT:PSS/Nafion composite	Dopamine	0.5–75 µM	0.17 µM (single) / 0.1 µM (mixed)	NR	NR	Sulfonated dopants (PSS, Nafion) enabling strong ionic exclusion	(Ko, Kim, Lee, & Lee, 2023)
		Serotonin	0.05–50 µM	0.16 µM (single) / 0.1 µM (mixed)	NR	NR	Same as above	(Ko et al., 2023)
4	PEDOT:PSS OECT (78 nm film)	Dopamine	1 nM–1 µM	1 nM	NR	NR	Dopant-controlled ionic–electronic coupling and electrostatic gating	(C. Li, He, Ingebrandt, & Vu, 2024)
5	PANI-doped MWCNT/SPCE	Dopamine (ex vivo brain)	1–200 µM	0.05 µM	NR	NR	Dopant-controlled surface charge enabling selectivity in complex tissue	(Rajarathinam, Jayaraman, Seol, Lee, & Chang, 2024)
6	Overoxidized PPy/Au composite	Tyramine	NR	0.01 µM	NR	NR	Fixed anionic functionalities acting as built-in Donnan exclusion layer	(Meng & Lin, 2023)

2.3. Molecular Imprinting (MIP) Approach

Molecular Imprinting (MIP) Strategy is an extremely powerful, effective method for developing highly selective Electrochemical Sensors based on Conducting Polymers, specifically for biological molecules. Unlike non-specific adsorption processes, MIP creates artificial receptor sites throughout the polymer matrix that have structural and chemical complementarity to a predetermined target molecule. As such, MIP provides enzyme-free and antibody-free detection systems and has levels of selectivity similar to those found in Biosensors. The MIP Process involves synthesizing the conducting polymer in the presence of the target analyte as a molecular template during electropolymerization. Functional monomers present in the polymer react with the template molecule via H-bonding, electrostatic interactions, π-π stacking, or coordinate chemistry based upon the type of analytical molecule. Once the template molecule has been removed, a cavity (or binding site) will remain within the polymer matrix which is highly similar to the target analyte in both size and geometry, as well as chemical functionality(Hasanah, Safitri, Zulfa, Neli, & Rahayu, 2021). As a result, these cavities provide the polymer with a high degree of specificity for recognizing the target analyte and its analogs based on the "lock-and-key" or "induced-fit" mechanisms. Therefore, when the template molecule is removed from the polymer matrix, and the resulting polymer is then placed in contact with a mixture of various molecules, the target analyte will bind specifically to the cavities left behind by the removal of the template molecule, while all other molecules present in the mixture will be excluded due to their structural differences from the target analyte(Zhang et al., 2026). Molecularly imprinted (MIP) systems represent some of the most effective means of providing biosensor-like specificity in conducting polymer electrochemical sensors through molecular recognition without using biorecognition elements. Representative molecularly imprinted conducting polymer–based some electrochemical sensors for selective detection of biological and bio-relevant analytes are shown in Table 2.3.

Table 2.3. Representative molecularly imprinted conducting polymer–based some electrochemical sensors for selective detection of biological and bio-relevant analytes

No.	MIP Conducting Polymer System	Target Analyte	Linear Range	LOD	LOQ	RSD	Key MIP-Related Selectivity Feature	References
1	MIP-PPy film on Pt electrode	SARS-CoV-2 spike protein	0–25 µg mL^{-1}	NR	NR	2.0–4.3%	Protein-templated cavities; high discrimination vs BSA	(Ratautaite et al., 2022)
2	MIP-poly(p-aminothiophenol)/AuNP	Dopamine	5 nM–20 µM	1.7 nM	5.7 nM	5.1%	Shape + functional group imprinting; serum compatibility	(Ermiş & Tinkiliç, 2021)
3	e-MIP PPy on screen-printed electrode	Dopamine	0.8–45 µM (linear)	0.8 µM	NR	NR	Portable MIP platform; direct electropolymerization	(Merli et al., 2024)
4	MIP-PPy/MWCNT/GCE	Methotrexate	0.01–125 µM	2.7 nM	9.0 nM	1.72–2.5%	Dual linear regions; high imprint fidelity	(Jara-Cornejo et al., 2023)
5	MIP-polyscopoletin (EIS)	Lysozyme	150 nM–20 µM	62 nM	NR	2.3–2.5%	Protein-size imprinting; impedance readout	(Di Giulio, Mazzotta, & Malitesta, 2020)
6	Electropolymerized MIP film	Acesulfame-K	3.57×10^{-8}–1×10^{-6} M	1.07×10^{-8} M	3.57×10^{-8} M	NR	Small-molecule imprinting with explicit LOQ	(Singh & Singh, 2023)
7	MIP on AuNP/4-ATP interface	Caffeine	1.0–6.0 µM	0.195 µM	0.592 µM	3.61–4.42%	High imprinting factor (IF = 12.43); reusable sensor	(Espinoza-Torres, Choquehuanca-Azaña, Rufino, da Silva, & Angnes, 2025)

2.4. Potential Window Optimization (Electrochemical Discrimination)

Electrochemical selectivity in conducting polymer-based biosensors may depend on both chemical recognition and electrochemical discrimination via potential window selection. Chemical recognition is based on a sensor's ability to recognize a particular molecule. Electrochemical discrimination is based on the fact that some molecules have redox states (oxidized or reduced) that are different from each other and the same for other molecules. Conductive polymers like PPy, PANI, and PEDOT have conjugated backbones and high electronic conductivities allowing for enhanced electron transfer rates relative to non-conjugated materials. These higher electron transfer rates result in sharper and better defined redox peaks that improve the resolution between the redox peaks of closely spaced analytes(Wang, Baek, Akbarinejad, Barker, & Travas-Sejdic, 2019). Additionally, the interactions between the conductive polymer and the analyte may cause small peak shifts that provide additional separation of overlapping redox peaks. The ability to increase sensitivity and improve selectivity of potential window optimizations through advanced techniques such as DPV and SWV can provide better results than simple cyclic voltammograms. Pulse based voltammetries are capable of providing higher signal-to-noise ratio's by eliminating or suppressing capacitive current from interfering with the Faradic current. Additionally, the increased separation of peaks obtained using pulse based voltammetries allows detection of small differences in redox potential that cannot be detected with cyclic voltammetry alone(Johnson, Hobbs, & Wightman, 2017).

2.5. Nanocomposite Design (Smart Selectivity)

The addition of nanomaterials (such as metal oxides, metal nanoparticles, or graphene) to a conducting polymer enhances its selectivity by providing the sensor with multiple mechanisms of discrimination. A key factor in this improvement is the synergy created by combining different types of chemically and physically distinct materials. For example, in the case of a composite material formed using both a conducting polymer and metal oxide particles, selectivity can arise not only through the molecular recognition afforded by the polymer chain but also through the modification of the surface chemistry of the polymer; catalysis provided by the metal oxide particles; and control over mass transport of the analyte. Materials like graphene, reduced graphene oxide, carbon nanotubes and nano-structured metal oxides have very large surface-to-volume ratios that allow access to more available active sites for the capture of analyte molecules. Increasing the size of the available surface area allows more of the target analyte molecules to bind to the polymer chain and increases the likelihood of an interaction occurring between the analyte and the conducting polymer matrix(Lahiff, Lynam, Gilmartin, O'Kennedy, & Diamond, 2010). Composites also greatly reduce the resistance to electron transfer within the material. Fast electron transfer occurs along highly conductive paths such as those found in the case of graphene and metallic nanoparticles. Additionally, the use of conducting polymers as part of the composite material creates a pathway for the rapid and efficient transfer of electrons from the analyte to the electrode, thus creating sharper and more well-defined voltammetric peaks and improving the resolution of the signals produced. For example, certain metal oxides can participate in Lewis acid-base type of interactions with the functional groups present in the analyte molecule. These include carboxylate, phosphate and hydroxyl groups(Limo et al., 2018).

2.6. Control of Film Thickness and Morphology

The physical properties of conducting polymer layers (thickness and morphology) affect how selectively an electrochemical sensor responds to its target analyte. Most of the characteristics of polymer layers depend on electropolymerization parameters (number of potential cycles, potential range, scan rate, and monomer concentration), which may be used to adjust the pore size distribution, diffusion rates, and access of the analyte into the polymer layer, ultimately affecting the sensor's ability to detect the analyte. Polymer film thickness is a significant factor in controlling mass transport. Morphological features (surface roughness, porosity, and uniformity) are as important as film thickness. Uniform porous films have defined diffusion paths that increase analyte access to the electrode surface(Cao, Shao, Hensley, Lavrik, & Venton, 2021). Controlling the degree of porosity allows for a certain degree of size based separation; analytes that fit into the pores of the polymer matrix will easily diffuse through the polymer, while bulkier or aggregated interfering species will be excluded to a greater extent(Nischang, 2013). The latter can be highly beneficial when detecting analytes in complex biological matrices, in which case the presence of proteins and other large molecules can dominate the electrode interface.

2.7. Surface Charge and pH-Responsive Selectivity

The use of pH as a tool for achieving selectivity in electrochemical sensors based on conducting polymers has become increasingly attractive due to the direct relationship between pH and the protonation/deprotonation of functional groups present along the polymer chain. At low pH (acidic) and neutral pH (close to the pKa), the protonation of nitrogen-based sites in polymers such as PANI and PPy produces a positively charged polymer surface. Conversely, the deprotonation of these sites at high pH (alkaline) decreases the surface charge, sometimes generating a partial neutralization of the polymer surface. A similar trend can be observed in PEDOT-based systems, especially when they contain acidic or basic functional groups. Most of the biological molecules studied in the context of electrochemistry, such as neurotransmitters, metabolites and pharmaceutical compounds, have pH-dependent acid-base equilibrium. As an example, at physiological pH or slightly acidic pH, dopamine exists mainly in the form of its protonated amine group, allowing a greater electrostatic interaction with the negatively charged or partially oxidized polymer surfaces. On the contrary, the acidic interferents can be eliminated by modifying the pH so as to suppress their ionization or electrochemical activity. The type of sulfonated polymer interface described here is relevant to your Section 2.7 as it allows for strong charge to remain on the sulfonate bearing films in aqueous solution while dopamine can be enriched at the electrode surface through electrostatic attraction due to the pH dependent speciation of dopamine, thus providing improved selectivity(Ayele, Yifiru, & Kitte, 2025).The second example utilized a graphene/PEDOT:PSS hybrid ink on a glassy carbon electrode to measure dopamine levels, and demonstrated selectivity toward common interfering substances such as ascorbic acid, caffeine and urea. Selectivity is consistent with charge based selectivity under conditions found physiologically. The authors report a linear range of 3.13 – 400 uM and an LOD of 0.19 uM. (Makaluza et al., 2025). The researchers used a GO/SiO_2@PANI nanocomposite as a dopamine biosensor to detect dopamine in urine using DPV and specifically mentioned that they used the same buffer solution with a pH of 7.4 that was "chosen to optimize bio-relevant ionization and selectivity" as described in Section 2.7. Under the optimal conditions of pH 7.4 the sensor has a linear detection range from 2 – 12 uM, a low detection limit (LOD) of 1.7 uM and a relative standard deviation (RSD) of 2.5%, and demonstrated application in synthetic urine. This is a clean example of pH anchoring because the adsorption/ electron transfer efficiency and the tolerance to interfering species are defined by both the protonation state of PANI and the speciation of the analyte (Tejwani et al., 2025).

3. RESULTS

This chapter provides a systematic evaluation of multi-level selectivity strategies for conducting polymer (CP)-based electrochemical sensing technologies that include: (i) functional group-mediated molecular recognition, (ii) dopant-mediated ionic selectivity, (iii) molecular imprinting (MIP), (iv) electroanalytical discrimination through optimized potential windows, (v) nanocomposite-based smart selectivity, (vi) film thickness and morphology control, and (vii) pH-dependent surface charge tuning. These studies demonstrate that selectivity in CP-based sensors cannot be attributed to a single predominant mechanism, but are instead based on the synergistic combination of chemical, structural, and electroanalytical characteristics.

Functional group-based sensors utilizing the inherent functional groups present within conducting polymers (PPy, PANI, PEDOT) have been shown to exhibit significant affinity-based selectivity towards aromatic and protonatable analytes (e.g., dopamine). A summary of these results is presented in Table 2.1. The results obtained for PP3C/PPy/AuNP systems illustrated a low detection limit (LOD) of 9.72 nM with a linear range of 5-180 µM, as well as satisfactory reproducibility (RSD ≈ 4.21%). Similar to the results obtained for PP3C/PPy/AuNP systems, PEDOT-PPy hybrid films also exhibited nano-molar detection capabilities (LOD=5 nM) through the use of DPV-based peak discrimination. These results clearly illustrate that hydrogen-bonding interactions (-NH...OH) between the conjugated backbone of the polymer and the catechol moiety of dopamine, π-π stacking interactions between the conjugated backbone and the catechol moiety of dopamine, as well as electrostatic interactions all make significant contributions to the concentration of the analyte at the surface of the electrode. Engineering with dopants was found to be an extremely efficient method for discriminating on the basis of charge. All of the systems containing fixed anionic dopants (PSS, Nafion, $Fe(CN)^{4-6}$) consistently favor cationic analytes as a result of Donnan exclusion effects. For example, PEDOT:PSS thin-film systems were able to achieve LOD values of 44.4 nM for dopamine detection. In addition, PEDOT:PSS-based OECT systems were able to detect dopamine at concentrations of 1 nM (Table 2.2) These results clearly show that the fixed negative charges present in the polymer matrix effectively block the presence of anionic interferents while allowing for the accumulation of protonated amine-containing analytes. However, MIP systems have several limitations. Protein-imprinted platforms (for example, SARS-CoV-2 spike protein detection) have demonstrated good discrimination, but generally lower detection limits than small molecule systems, likely due to the diffusion constraints and slower rebinding rates. Optimizing the electroanalytical operating conditions has greatly increased the practical selectivity of the sensor systems. Pulse techniques such as DPV and SWV have minimized capacitive currents and improved peak resolution, thus providing discrimination between analytes having minimal differences in their redox potentials. The interfaces of sulfonated polymers have maintained fixed negative charges over a wide pH range and promoted electrostatic enrichment of dopamine while blocking negatively charged interferents.

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