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Review

Recent Trends in the Development of Carbon-Based Electrodes Modified with Molecularly Imprinted Polymers for Antibiotic Electroanalysis

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Abstract: Antibiotics are antibacterial agents applied in human and veterinary medicine. They are also employed to stimulate the growth of food-producing animals. Despite their benefits, the uncontrolled use of antibiotics results in serious problems, and therefore their concentration levels in different foods as well as in environmental samples were regulated. As a consequence, there is an increasing demand for the development of sensitive and selective analytical tools for antibiotic reliable and rapid detection. These requirements are accomplished by the combination of simple, cost-effective and affordable electroanalytical methods with molecularly imprinted polymers (MIPs) with high recognition specificity, based on their "lock and key" working principle, used to modify the electrode surface, which is the "heart" of any electrochemical device. This review presents a comprehensive overview of MIP-modified carbon-based electrodes developed in recent years for antibiotic detection. The MIP preparation and electrode modification procedures, along with the performance characteristics of sensors and analytical methods, as well as the applications for the antibiotics' quantification from different matrices (pharmaceutical, biological, food and environmental samples), are discussed. The information provided by this review can inspire researchers to go deeper into the field of MIP-modified sensors and to develop efficient means for reliable antibiotic determination.

Keywords: antibiotics; molecularly imprinted polymer; carbon electrodes; modified electrodes; electroanalysis

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1. Introduction

Antibiotics are common drugs that have revolutionized medicine in the last decades. The word "antibiotic" derives from "antibiosis", which means "without life". Despite the fact that the first antibiotic, penicillin, was accidentally discovered in 1928 by Sir Alexander Flemming [1], the term "antibiotic" was introduced only in 1941 to describe small molecules produced by a microbe, which have the capacity to inhibit the development of other microbes or even to be lethal to these [2]. Antibiotics are either secondary metabolites of certain bacterial and fungal species [3–5] or semi-synthetic [6–8] or synthetic compounds [2]. Thus, antibiotics are used in modern healthcare to treat bacterial infections. In a very simplistic approach, they "kill" bacteria or stop bacterial growth by preventing their multiplication, being thus considered bactericidal (aminoglycosides, β-lactams, fluoroquinolones, etc.) or bacteriostatic (tetracyclines, macrolides, sulphonamides, etc.) antibiotics, respectively [9]. However, this delimitation is not very strict because there are also bacteriostatic antibiotics with bactericidal activity (e.g., linezolid) or vice versa, and some bactericidal antibiotics

can act as bacteriostatic antimicrobials in certain conditions [10]. Regardless of this classification, these drugs help the living organisms to fight against various bacterial infections (gastrointestinal, urinary [6], genital tract [11], skin [2], abdominal [12], central nervous system [13] and ear infections, strep throat, pneumonia, typhoid, bronchitis, sinusitis [8], arthritis, mastitis [3], tuberculosis, leprosy, malaria [14], etc.), contributing thus to the improvement of human and animal health and reducing their mortality rate. Unfortunately, like many other drugs, the different antibiotics also have some side effects such as poor cell membrane permeability, fever, myalgia, hepato- and/or nephrotoxicity, rashes, tendon rupture [15,16], hyperactivity, inflammation at the injection site [12], yellow teeth, digestive and cardiovascular disorders [17], carcinogenicity [18], etc.

Based on their chemical structure (Figure 1) most antibiotics belong to one of the following commonly known main classes [1,15]: (i) AGs (classified based on the substitutions of the 2-DOS ring in monosubstituted 2-DOS AGs (neamine), 4,5-disubstituted 2-DOS AGs (neomycin), 4,6-disubstituted 2-DOS AGs (KANA, gentamycin) and streptomycin) [19]; (ii) amphenicols (with a phenilpropanoid core -CAP, thiamphenicol, florfenicol); (iii) β-lactams (penicillins, cephalosporins, carbapenems and monobactams); (iv) macrolides (e.g., AZY, ERY); (v) oxazolidinones (e.g., linezolid, sutelizolid); (vi) quionolones (e.g., nalidixic acid, NFX, CIP); (vii) sulphonamides (e.g., SMX, SDZ, SM_2); (viii) tetracyclines (e.g., TC, oxytetracycline, doxicycline); (ix) glycopeptides (e.g., VAN [13]) and (x) polypeptides (e.g., bacitracin [20]).

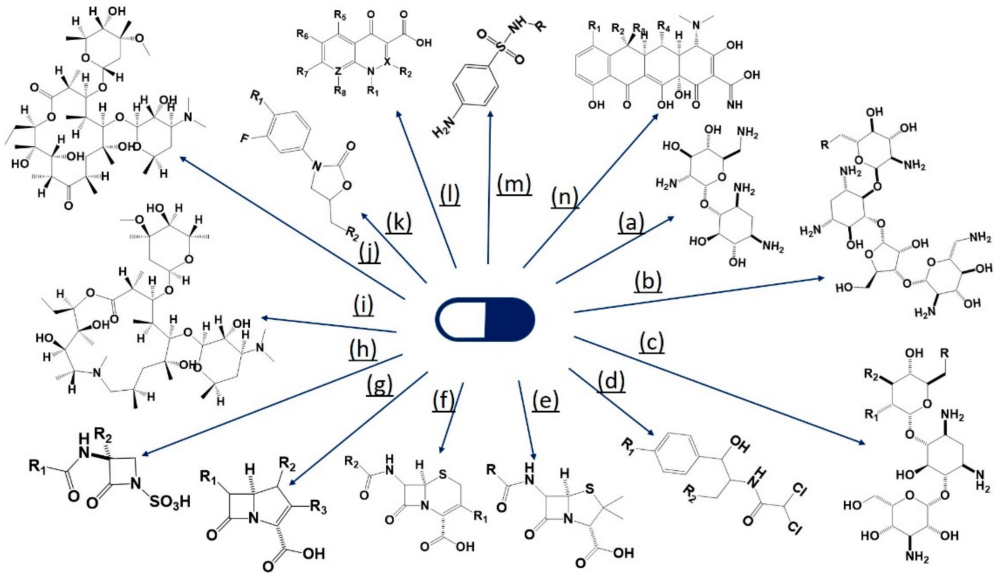

Figure 1. Chemical structures of the main classes of antibiotics: (**a**) monosubstituted 2-DOS AGs; (**b**) 4,5- and (**c**) 4,6-disubstituted 2-DOS AGs; (**d**) amphenicols; (**e**) penicillins; (**f**) cephalosporins; (**g**) carbapenems; (**h**) monobactams; (**i**) AZY (**j**) ERY; (**k**) oxazolidones; (**l**) quinolones [21]; (**m**) sulfonamides; (**n**) TC.

Besides the large use of antimicrobial drugs in human medicine, these compounds are also extensively employed for the prophylaxis or treatment of infections in plants and domestic (dogs, cats) and food-producing animals (livestock, horses, pigs, goats, sheep, etc.) [6,22,23]. On the other hand, many antibiotics present growth-promoting effects at sub-therapeutic dose levels [15], thus being used as growth promoters in the livestock and aquaculture industries [18,24]. Antibiotics were seldom applied in crop production (e.g., in China) [25] and sometimes (e.g., CAP) as a disinfectant agent in aquaculture to prevent diseases [26]. The extensive use of antibiotics is argued by the fact that only the macrolide antibiotics market reached worldwide sales of billions of dollars [27], while around 63,150 tons of antibiotics are consumed alone in the veterinary sector, the global use of antimicrobials in animals being double compared to humans [28]. However, the misuse and the overuse of antibiotics due to self-medication, over-the-counter (OTC) availability

and household storage for later use are relatively common and a recent paper discussed these aspects with regard to aminoglycosides [29].

The widespread and continuously growing use of antibiotics has led to the contamination of various matrices such as human body fluids, food products (e.g., meat and derivatives, eggs, dairy products), beverages (e.g., milk, drinking water) and environmental resources (e.g., surface and ground waters, soil, sediments) with these parent drugs as well as with their metabolites. Antibiotic residues can exist in the food chain and can accumulate in foodstuffs [30], mainly as a result of their administration to food-producing animals [31], but also due to their addition to dairy products as chemical preservatives (e.g., tetracycline) [32]. Antibiotics can enter the environment directly from the pharmaceutical producers (including research laboratories and industrial production) as contaminated wastewaters or after their use in human or veterinary medicine (excreted through urine and feces or discarded as domestic or hospital waste) [6] or from agricultural activities (e.g., runoff from agricultural land and from animal farms, soils enriched with manure) [5,15,25], including aquaculture [26]. Antibiotics' concentration decreases from the point sources (e.g., the wastewater treatment plants' effluents) to the receiving waters (e.g., river or lake) due to an environmental attenuation mechanism, which includes dilution, hydrolysis, photolysis by the natural solar radiation, and sorption on suspended particles and sediments [25]. Nevertheless, the improvements brought to the antibiotic stability resulted in both their persistence for a long time and accumulation in the environment [15]. Therefore, due to their potential negative effects on humans, animals and ecosystems, even at low concentrations (ranging from mg/L to ng/L [24]), they are considered emerging pollutants [11,25]. The concentrations of β-lactam antibiotics in aquatic systems, which are at ng/L levels, are lower when compared to other classes of antibiotics. This fact was attributed to the reactive and unstable β-lactam ring, which is degraded in abiotic (hydrolyzed under ambient pH and temperature) and biotic conditions [25].

Regular consumption of water or food containing residues of antibiotics or their metabolites poses various health problems (tiredness, headache, diarrhea, muscles pain, blurred vision, hypertension, [30], allergic reactions, cancer [15]) and AMR, which means that the microorganisms (viruses, bacteria, parasites and fungi) underwent transformations so that they no longer react to antibiotics [2]. Besides affecting human and animal health and also increasing the mortality rate [33,34], AMR also has destructive effects on the ecosystems and generates severe economic problems due to annually supplementary health care costs and productivity loss [35].

Considering the impact of different antibiotics or antibiotic classes on the AMR, the WHO Expert Committee on Selection and Use of Essential Medicines developed the AWaRe Classification of antibiotics in 2017 in order to emphasize their appropriate use and to support antibiotic stewardship and monitoring [36]. In order to protect consumers' health, the international authorities [37] (such as the European Union and the United States Food and Drug Administration [31]) set up regulations that specify the MRL of the antibiotics in foods of animal origin [16,38–40], while in some countries the use of certain antibiotics (e.g., CAP [26], FZD [18], etc.) are even prohibited in food-producing animals.

Therefore, in order to reduce human, animal and ecological health risks due to antibiotic contamination, there is an increasing need for the development of simple, rapid and reliable methods for the straightforward sensitive in situ or ex situ monitoring of these contaminants in various biological, food and environmental samples. Most approaches for the detection of antibiotics are based on different chromatographic techniques either as such [41–44] or coupled with extraction methods [45–47]. Microbiological assays and chromatographic methods applied for antibiotic identification and determination were reviewed in 2020 by Pauter et al. [48]. Recently, synthesized metal-organic frameworks were applied for the sensitive luminescence detection of different antibiotics [49–53]. Various biosensors (with aptamer, antibody, molecularly imprinted polymers and dual recognition systems) [54] and sensors modified with metal-based and carbon-based quantum dots, which were developed and applied for colorimetric, photoelectrochemical, photo-, chemi-

and electrochemiluminescence detection of residual antibiotics in food products, were reviewed [55]. All these methods are very sensitive and selective but tedious, time and reagent-consuming. On the contrary, electrochemical techniques offer simpler, more rapid alternatives and have the major advantages that the instrumentation is cheaper and can be miniaturized, thus enabling in situ analysis. Works regarding antibiotic electroanalysis using both bare [56–58] or modified electrodes [59], including aptasensors [60,61], can be found in the literature of the last few years. There are also some general reviews regarding the various types of electrochemical sensors (mainly modified with graphene [62–64] or nanomaterials [65,66]) and methods developed for antibiotic analysis [37,40,67]. Besides nanomaterials, MIPs are often chosen as electrode surface modifiers due to their ease of preparation and high stability, but mainly due to their inherent nature-inspired molecular recognition properties based on their tailored structure, which enhance both the selectivity and the sensitivity of the detection method owing to the preferred interaction with specific or closely related target molecules [68]. Our paper systematizes all types of carbon-based sensors modified both with MIPs alone and in combination with manifold other materials recently reported for antibiotic electroanalysis.

2. Molecularly Imprinted Polymers

MIPs are a class of polymers synthesized from at least a template molecule (target molecule) and a functional monomer, but, depending on the polymerization method, a cross-linking reagent, a porogenic solvent, and an initiator may also be required. Functional monomers can be linked to the templates through non-covalent (hydrogen bond, ionic or hydrophobic) or covalent interactions to form complexes before the cross-linking reaction in the solvent [3]. A general procedure for MIP synthesis involves three simple steps (Figure 2): (1) pre-polymerization complex (pre-complex) formation in solution by a combination of the template molecules with the functional monomer via covalent or non-covalent bonds; (2) initiation and propagation of polymerization in the polymerization mix (pre-complex, initiator and cross-linkers) under photo/thermal conditions in an adequate solvent, obtaining a 3D polymer that includes target molecules; (3) removal of the target molecules from the polymer through extraction, elution or by applying an electrical potential. The final MIP contains microcavities with a 3D structure complementary in shape and chemical functionality to templates generated after template removal. MIPs containing microcavities have excellent capabilities for specifically and sensitively rebinding targets with a similar shape and microstructure of the templates, generating an analytical signal which thus enables sensitive and selective determinations using an adequate sensing device [69].

Due to the variety of monomers (4-vinylpyridine, MAA, acrylamide, etc. [70]), templates (ions, small or even large molecules [71] such as proteins, viruses and bacteria [72]) and polymerization methods, as well as the possibility of different combinations of them including with other (nano)materials, the literature contain a huge number of publications regarding MIPs. MIPs have attracted much attention due to their unique properties, such as simplicity, low cost, facile preparation, high stability, selectivity and sensitivity. They are used as biomimetic synthetic receptors based on their specific cavities for targets, being superior to natural antibody recognition. MIPs are mechanically and chemically stable even at extreme pH and temperature values and, therefore, suitable for MIP-based sensors preparation even if they are single-use or multi-use [73,74]. Owing to these advantages, MIPs found applications in catalysis [75], immunoassays [30], separation [76] and sensing [77–79] procedures, in the pharmaceutical and medical fields [68,70,74,80], as well as in food [81,82] and environmental monitoring and control [68,70,80,83,84].

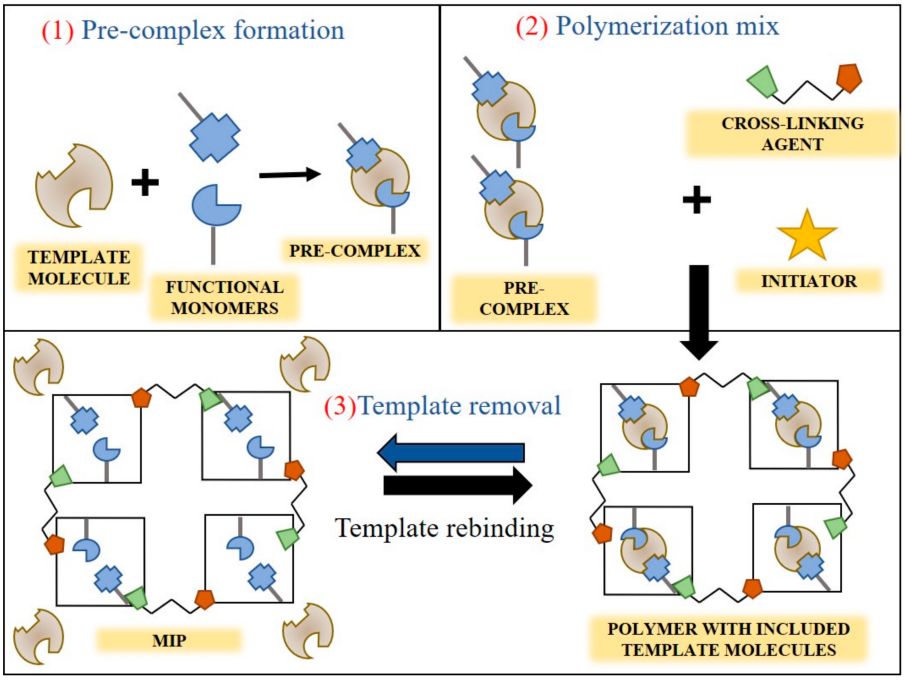

Figure 2. Schematic representation of the main steps involved in MIP synthesis.

3. MIP-Based Electrochemical Sensors

The instrumentation used for sensing applications consists of the following interconnected parts: (1) a sensor, which is the sensing device composed of (i) a receptor (recognition element, e.g., the MIP) for the sensitive and selective detection of the target analyte in the presence of possible interfering species and (ii) a physical transducer (e.g., the electrode, like the GCE, on which the MIP was immobilized) that converts the chemical information into a measurable signal (in the case of electrochemical transducers this is a voltage or a current) [78], and (2) a suitable device (e.g., a computer running dedicated software) to process and offer the analytical information (Figure 3) [85]. MIP-based sensors were used in various detection methods (electrochemical, optical, fluorescence, ECL, surface plasmon resonance, ELISA) [81].

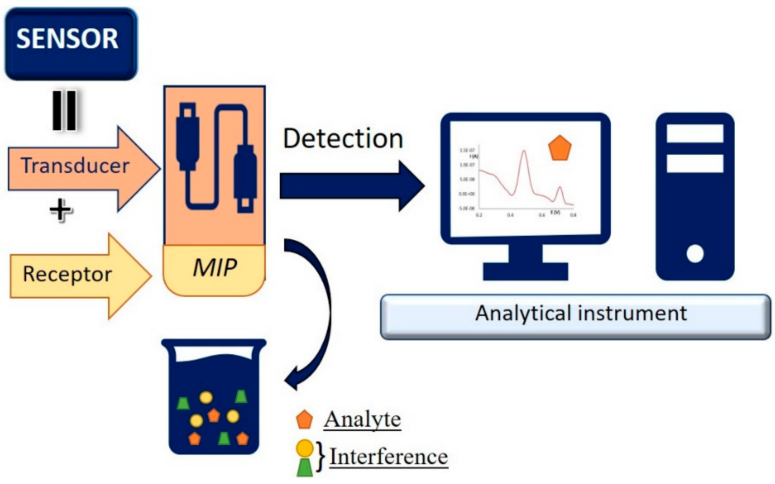

Figure 3. The main constituents of a sensing device: receptor, transducer and analytical device.

In recent years, electrochemical sensors are employed even more in the chemical analysis due to their high sensitivity, low cost, fast response and facile modification and miniaturization along with the less expensive instrumentation. MIP-based electrochemical sensors combine the MIP's advantages with those of the electrochemical sensors, resulting

in tools with high selectivity and sensitivity, chemical/mechanical stability, reusability, low LOD, facile preparation, low cost, ease of preparation and possibility of miniaturization [70,78]. It is obvious that all these characteristics are influenced by both the electrode (transducer) type, in this review being considered only carbon-based electrodes, and the modifier(s), which act(s) as a receptor, being the sensing core of the sensor.

Due to these advantages, the huge variety of monomers, templates and substrates and hence the resulting large applicability of the MIP-based electrochemical sensors, the number of research articles and therefore also of reviews discussing them is continuously and rapidly increasing. Most reviews present information regarding the preparation, structures and the use of MIP-based electrochemical sensors for the detection of various species such as agrochemicals, phenolic compounds, heavy metals, biomolecules (amino acids, fatty acids, vitamins, etc.) and emerging pollutants including hormones, drugs and drug metabolites [86]. A very recent paper detailed the application of electrochemical sensors obtained by molecularly imprinting technology in food and drug safety control by detecting low levels of antibiotics, pesticides, heavy metals, toxins and pathogens in contaminated food [87]. Some aspects regarding the preparation of electrochemical sensors modified with conducting polymers imprinted by proteins and other large biomolecules and their applications in pharmaceutical and biomedical fields were summarized by Ramanavicius et al., 2022 [88], special attention being paid to the biocompatibility of conducting polymers with the basic biological molecules, absolutely necessary in the development of wearable sensors. Despite the fact that most reviews on MIP-based sensors are oriented toward their application in specific areas, some of them are focused on special types of electrochemical sensors such as molecularly imprinted polymer-carbon paste electrodes reported for the sensitive detection of pollutants in environmental samples [89] or MIP-based potentiometric sensors for monitoring of inorganic (e.g., Pb^{2+}, Cu^{2+}, etc.), organic (e.g., melamine, chlorpyrifos) and biological (e.g., proteins, trypsin, east cells, etc.) species in environmental and biological samples [90].

3.1. Types of Carbon-Based Electrodes Used as Transducers

In molecular imprinting techniques for antibiotic electrochemical sensing, diverse carbon-based electrodes such as GCE, BCE, BPPGE, SPCE, CPE, PGE are employed as a substrate. The most used electrode in MIP construction is the GCE, this choice is based on its accessibility, good conductivity, high resistance to chemical attack, wide usable potential range, and easy maintenance. Another quality of this type of electrode is its ability to be modified, presenting a large contact area. Before use, these electrodes are sometimes subjected to different treatment procedures to improve their performances. In the case of GCE, it must be at least cleaned carefully, usually being just rinsed with water or other solvents [91] or most often polished with alumina-water slurry and rinsed with ultrapure water [92] and/or other solvents (e.g., methanol [17]), while some authors also recommend further ultrasonication [25,93,94]. Some researchers perform an electrochemical activation before proceeding to the electrode surface modification steps. This procedure was reported by Tan et al. [95], who activated the GCE by cycling the potential from −0.2 V to −1.2 V, in H_2SO_4, until stable CVs were recorded. Long et al. [4] used a homemade BCE because they could control the surface of the electrode (size of 5 × 4 mm^2). To obtain a smooth mirror-like surface, the electrode surface was polished with alumina slurry, this step was followed by sonication in distilled water, as is usually performed in the GCE case, such as was previously mentioned [87]. A similar cleaning procedure, but employing metallographic sandpaper instead of alumina slurry, was applied also to the BPPGE prior to covering its surface with a MIP layer. The MIP-modified BPPGE was then used as a substrate for a hybrid sensor, coupling the action of MIP with an enzymatic reaction (the H_2O_2 electroreduction catalyzed by horseradish peroxidase), in order to obtain the bioelectrocatalytic amplification of the signal used for KANA determination [96].

SPCEs are disposable and have small dimensions, therefore, they allow the analysis of very small sample volumes. Usually, they are used without any pre-treatment [31,38,97].

Only one report indicated that before modifying the SPCE with MIP, the electrode surface was cleaned by applying a potential of 1.7 V for 180 s in 0.10 M KCl to increase the electrode response reproducibility. Afterward, the following steps were performed: the EDOT electropolymerization at constant potential in order to obtain higher and more stable currents, and the incubation with 4-aminophenol, which allowed the formation of a covalent link between the PEDOT and the subsequently formed MIP [26].

Despite the fact that the use of PGEs in electrochemistry brings certain benefits (cost-effective, easily accessible, stable, etc.), a fact emphasized by the huge number of papers related to its use [58,62,98], there is only one report regarding the application of this transducer for the development of a MIP-based sensor for antibiotics, namely MMZ [99]. In that study, before modification with MIP, the PGE was electrochemically pre-treated by CV in an H_2SO_4 medium in order to enhance the sensitivity and obtain stable signals.

Some research groups used CPE due to the facile electrode surface renewing by removing and repacking the MIP-containing carbon paste, thus avoiding any cleaning or pre-treatment steps [6,18,27].

3.2. Modification of the Original Carbon-Based Electrode

Besides polymers, with the special category of MIPs, there are four other main classes of modifiers: (i) various carbon materials (SWCNTs and MWCNTs, graphene and GO either as such or in the reduced form), (ii) ILs, (iii) nanomaterials such as NPs, NWs, QDs, etc., and (iv) COF. The use of CNTs is correlated with a series of properties regarding light weight, corrosion resistance, reduced processing temperature, lead-free, electrically conductive and high mechanical strength. Some researchers observed that MIP-decorated MWCNTs significantly enhanced the electrochemical response of antibiotics, giving rise to remarkably low detection limits (Table 1) [100,101]. Therefore, carbon-based nanomaterials, such as the MWCNTs, are often used as a platform for the MIP deposition with the aim to increase the electrode surface area (e.g., up to 350% [22]) and thus the amount of imprinting sites [100] and also to enhance the conductivity and the electron transfer rate [18] of the modified electrode. The MWCNTs were immobilized on the GCE surface either by drop-casting [100] or electrochemically [22]. MWCNTs [102] and GO [38,93] can also be used as functional monomers in MIP synthesis.

ILs are widely used in synthetic organic chemistry and polymer chemistry due to many unique advantages. They can be used as functional monomers, the resulting MIP having the characteristics of both polymers and ILs, with considerable electrocatalytic activity and adsorption capacity towards the analyte. Yang and Zhao [102] immobilized the IL 3-propyl-1-vinylimidazolium bromide on the MWCNT's surface by an ion-exchange process. The obtained MWCNTs@IL were used to prepare the MWCNTs@MIP using AMOX as a template. ILs were also implied in the fabrication of the IL1-SMIP/MWCNT-IL/GCE sensor for CTC detection which involved two drop-casting steps. The GCE was covered with IL-MWCNTs (where the IL was 1-hydroxyethyl-3-methylimidazolium tetrafluoroborate) followed by the IL1-SMIP deposition. IL1-SMIP was obtained using CTC as a template, CAVImBr as a functional monomer and EGDMA as a cross-linker [23].

Metallic NPs are often used to improve sensor stability, sensitivity and reproducibility. For example, a chitosan-gold nanocomposite was employed as supporting material for the preparation of a MIP which was further drop-cast on a GCE to obtain a sensor for CIP determination [16]. There are also interesting approaches that use magnetic materials such as Fe_3O_4 with and without other NPs in order to amplify the sensor electrochemical response [32,103]. Due to their cost-effectiveness, high chemical stability and good sensitivity, magnetic nanoparticles covered with MIPs were incorporated into CPEs developed for the detection of AMOX [6] and TC [32] at μM levels in water and milk samples, respectively.

COFs are in great demand due to their high specific surface area, high thermal stability and low density, being attractive materials for gas storage, catalysis, pseudocapacitors and photoconductive devices [93,104]. These chemical structures have also gained increasing interest in the sensor's development. For example, the GCE/Cu-MOF/MC electrochemi-

cally modified with a doubly imprinted PPy film enabled the simultaneous detection of RIF and INZ at nM levels [7].

Table 1. Materials and steps involved in the preparation of MIP-based sensors reported for antibiotic electroanalysis.

Antibiotic	MIP-Based Modifier	Polymerization Type	Polymerization Reagents	Template Removal	Ref.
AMOX	MWCNTs/MIP/SWCNTs; MWCNTs/MIP/dendritic Pt-Pd bimetallicNPs-SWCNTs	Bulk	AMOX, MWCNTs suspension, EGDMA, AIBN, methanol:H_2O (4:1, *v*/*v*)	Immersion in methanol:acetic acid (9:1, *v*/*v*)	[102]
AMOX	Mag/MIP	Bulk	AMOX, AAM, Fe_3O_4@SiO_2-MPS, MBAA, KPS, ultra pure water	Soxhlet extraction with methanol:water (9:1, *v*/*v*) and methanol/water (7:3, *v*/*v*)	[6]
AZY	MIP	Precipitation	AZY, MAA, EGDMA, AIBN, methanol:acetonitrile (1:4, *v*/*v*)	Immersion in methanol:acetic acid (9:1, *v*/*v*)	[27]
AZY	MIP/GNU/GO	CV (−0.5 to 1.0 V); 0.075 M HNO_3, 0.025 M H_2SO_4	AZY, aniline	Immersion in ethanol:water	[8]
AZY	MIP	CV (−0.85 V to +1.35 V); 0.10 M 4BA6FPh in methanol	AZY, 3-TBA, 2,2′-Bth	Immersion in methanol:acid acetic (9:1, *v*/*v*)	[17]
AZY	MIP	CV (−0.2 to 1.4 V); PBS pH 7.0	AZY, 4-ABA	Extraction in PBS pH 10.0	[24]
AZY	MIP	CA: 1.65 V; 30 s; 0.10 M TBAP in acetonitrile	AZY, Ph-3-TBA, 4,4′ -Br-3,3′ -Bth, 3-Me-Th in acetonitrile containing 5% DMF	Immersion in glacial acetic acid:acetonitrile (1:9 *v*/*v*) and ultrasonation	[105]
CAP	MWCNTs/MIP/CKM-3/P-r-GO	Bulk	CAP, MWCNT suspension, EGDMA, AIBN	Immersion in methanol:acetic acid (9:1, *v*/*v*)	[101]
CAP	3D CNTs@Cu NPs@MIP	Bulk	CAP, MAA, EGDMA, AIBN, THF	-	[106]
CAP	MIP/PEDOT	CA: 0.95 V; 250 s; 0.20 M $LiClO_4$ in acetonitrile	CAP, Eriochrome Black T	CV in 0.20 M $LiClO_4$ in acetonitrile	[26]
CFE	AgDs/MIP/cMWCNTs	Surface molecular imprinting	CFE, AAM, MBAA, APS	Immersion in 0.50 M HCl	[94]
CFE	AuNW/GO/MIP	CV (−0.35 to 0.64 V); HNO_3/H_2SO_4 solution (3:1)	CFE, aniline	Immersion in ethanol:water solution	[91]
CFLX	MIP	CV (−1.0 to 1.2 V); PBS pH 7.2	CFLX, indole-3-acetic acid	Immersion in methanol, 0.10 M NaOH, PBS pH = 7.20	[92]
CFX	MIP/Ag@AuNPs/ILs	CV (0 to 1.0 V); BRB pH 3.00	CFX, phenol	Immersion in 1.00 M NaCl	[107]
CFZ	AgDs/MIP/cMWCNTs	Surface molecular imprinting	CFZ, AAM, MBAA, APS, PBS pH 3.00	Immersion in 0.50 M HCl	[12]
CIP	Ch-AuNPs/MIP	Bulk	CIP, MAA, EGDMA, AIBN, dimethylamide:methanol (2:3)	Immersion in methanol:acetic acid (9:1, *v*/*v*)	[16]
CLO	GO/AuNPs/MIP	Bulk	CLO, MAA, EGDMA, AIBN	Soxhlet extraction with methanol	[97]
CTC	MWCNT-IL/MIP	Bulk	CTC, MWCNT-IL, CAVImBr, EGDMA, AIBN, methanol:H_2O (5:1, *v*/*v*)	Soxhlet extraction with methanol:acid acetic (9:1, *v*/*v*)	[23]
DAP	MIP/AuPtNPs	CV (0 and 0.8 V)	DAP, o-phenylenediamine	Immersion in 0.10 M NaOH	[108]

Table 1. *Cont.*

Antibiotic	MIP-Based Modifier	Polymerization Type	Polymerization Reagents	Template Removal	Ref.
DMZ	P-Arg@MIP	CV (−2.0 to 2.2 V); PBS pH 7.4	DMZ, L-arginine	Incubation in 0.25 M NaOH	[109]
FZD	MWCNTs/MIP	Precipitation	FZD, AMPS, EGDMA, AIBN	Washing with acetic acid:methanol (1:9, *v*/*v*)	[18]
KANA	MWCNTs/Fe_3O_4/PMMA	Bulk	KANA, MAA, EGDMA, AIBN in acetonitrile	Washing with methanol:acetic acid (8:2, *v*/*v*)	[4]
KANA	MIP	CV (−0.4 to 0.15 V); PBS pH 6.8	KANA, pyrrole	Immersion in 0.01 M HCl	[96]
KANA	target/ APT/Fc/β-CD-SH/ Au@Fe_3O_4/MIP	CV (0 to 0.8 V)	KANA, 3-aminophenylboronic acid	Washing with 5%HCl	[110]
MMZ	MIP	CV (−1.0 to 2.0 V); 0.10 M $NaClO_4$	MMZ, pyrrole	DPV in BR pH 3.00	[99]
MNZ	MIP/MWCNTs	CV (−0.8 to 0.8 V)	MNZ, dopamine	CV in diluted H_2SO_4	[100]
MNZ	MIP	CV (0 to 0.8 V)	MNZ, o-phenylenediamine	Immersion in diluted H_2SO_4	[111]
MNZ	$CuCo_2O_4$/N-CNTs/MIP	CV (−0.2 to 1.2 V); 0.10 M PBS	MNZ, aniline	Immersion in methanol:acetic acid (9:1, *v*/*v*) solution	[112]
MTX	MIP	CV (0 to 0.8 V); 0.01 M HCl	MTX, β-cyclodextrins	Immersion in PBS pH 9.00	[113]
NFX	fMWCNTs-MIP	Precipitation	NFX, MAA, EGDMA, AIBN, fMWCNTs	Soxhlet extraction with methanol:acetic acid (9:1, *v*/*v*)	[114]
OXC	MIP/GNU/GO	CV (−0.2 to 1.0 V); 0.025 M H_2SO_4, 0.075 M HNO_3	OXC, aniline	Immersion in ethanol:water (1:1, *v*/*v*) solution	[38]
SDZ, AP	MIP/GO@COF	CV (−0.6 to 1.2 V); 0.10 M TBAP in acetonitril	SDZ, AP, pyrrole	PPy overoxidation CV (−0.6 to 1.2 V) in 0.05 M NaOH	[93]
SM_2	MIP/GQDs-PtNPs	CV (−0.5 to −0.8 V); PBS (pH 6.5)	SM_2, EDOT, MAA	Immersion in methanol:acetic acid (90:10, *v*/*v*)	[39]
SMX	oxMWCNTs/$UPPy_{MIP}$	CA: 0.75 V; 600 s; 0.20 M K_2HPO_4	SMX, pyrrole	CV in BRB pH 2.36	[22]
TC	MIOPPy-AuNP	CV (0.0 to 0.8 V); 0.10 M KCl	TC, pyrrole	PPy overoxidation CV (0 to 1.2 V) in 0.05 M NaOH	[31]
TC	Mag/MIP	Bulk	TC, acrylic acid, Fe_3O_4-C=C, EGDMA, AIBN, ethanol:methanol (30%, *v*/*v*)	Soxhlet extraction with methanol:acid acetic (9:1, *v*/*v*)	[32]
TS	MIP/CoN NWs	Ultrasound assisted bulk	TS, MAA, EGDMA, AIBN, acetonitrile	Immersion in acetic acid:methanol (1:9, *v*/*v*)	[115]
VAN	MIPDA/peptide/AuNPs	CV (−0.5 V to 0.5 V); PBS pH 7.4	VAN, dopamine	Immersion in ethanol:acetic acid (18:1, *v*/*v*)	[95]
RIF, INZ	Cu-MOF/MC/MIP	CV (−0.5 V to 0.8 V); 0.1 M $LiClO_4$	RIF, INZ, pyrrole	Immersion and stirring in a methanol:water (1:1, *v*/*v*) solution	[7]

There are also new trends in obtaining MIP-based hybrid sensors used in complex matrices. For this purpose, Tan et al. developed a hybrid biosensor that, in addition to MIP, had as a recognition element a peptide with high affinity and specificity towards VAN [95].

3.3. Polymerization Procedures

For MIP preparation there are various polymerization techniques used, their application depending on factors such as simplicity, time of preparation, the desired size of resultant MIP and shape [116].

From all the polymerization techniques used in general for MIP synthesis (bulk [6], suspension [117], precipitation [18], emulsion [118], electrochemical [8], swelling [119], sol-gel [120], ultrasound [121], microwave [122], surface imprinting [94]) the most used for electrochemical sensing of antibiotics are bulk, precipitation, surface imprinting and electropolymerization (Figure 4).

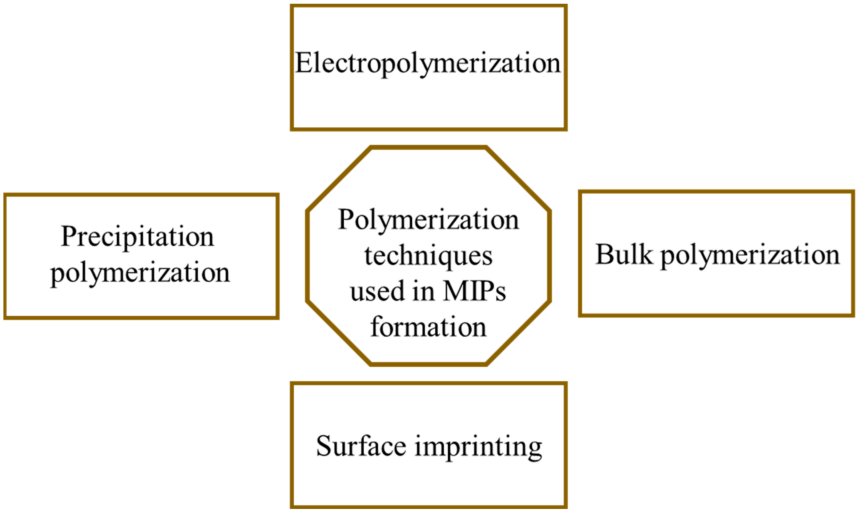

Figure 4. Polymerization techniques used for MIP synthesis for electrochemical sensing of antibiotics.

The bulk method is the most commonly used because it is a simple, easy and effective way to obtain the desired polymer. It involves firstly the formation of a pre-polymerization complex between the template and the functional monomer, followed by the addition of a cross-linker and the initiator (Figure 2), the thermo- or photo-initiation of the polymerization process being triggered. The ratio of the above-mentioned components was optimized in order to assure the best structural stability and binding efficiency of the desired MIP [84,102,106,115]. The adequate amounts of monomer (AAM) and cross-linker (MBAA) were also assessed using the response surface methodology [12]. Usually, the process takes place in an inert atmosphere of N_2 and lasts a long time (e.g., 3 h [6], 12 h [23] or even 24 h [32,97,101]). For example, the pre-polymer mixture for the synthesis of a CAP-imprinted polymer was obtained by dissolving the template in MAA, the addition of EGDMA, THF and finally AIBN. This mixture was purged with N_2 and subsequently heated for 45 min at 75 °C in a water bath to perform the polymerization [106]. Zhang et al. [115] applied a modified bulk polymerization method which consisted of the replacement of the higher temperature step by ultrasound-assisted dissolution and mixing of the polymerization components. The template (TS) and the monomer (MAA) dissolved in acetonitrile were ultrasound until a transparent solution was obtained (10–15 min). To prepare the MIP, EGDMA and AIBN were added to the solution and the ultrasonication was continued for 10–15 min, under an N_2 atmosphere. The formed polymer must be crashed, grounded and sieved to obtain particles with an optimum average size for the intended application. However, the drawbacks of this technique consist of the irregular shape of the particles with a possible reduction in the recognition capacity during the grinding step and extensive time consumption [84]. Several magnetic molecularly imprinted polymers were obtained by this procedure [4,6].

Precipitation polymerization is a one-step technique similar to bulk technology, but it has the drawback of requiring about ten times more porogenic solvent and the benefit that the obtained particles have regular shapes. As the polymerization reaction progresses, the polymer precipitates out of the solution as its density becomes higher than that of the solvent [116]. For example, using this procedure FZD- and AZY-based MIPs were synthetized as follows: the reaction mixture containing the corresponding template, monomer (FZD, AMPS [18], AZY, MAA [27]), EGDMA and AIBN in acetonitrile [18] or

methanol/acetonitrile (1/4, *v*/*v*) solution [27] was purged with nitrogen (10–15 min) to eliminate the oxygen and then magnetically stirred at about 60 °C for 24 h to perform the polymerization. The 3D framework of functionalized MWCNTs decorated with MIP used in the preparation of the electrochemical sensor for norfloxacin detection was obtained in a similar way, the only difference was that the reaction mixture also included fMWCNTs [114].

The surface imprinting method implies the formation of a pre-polymerization complex from the template molecule and the functional monomer on the surface of a solid substrate. After the initiator and a cross-linking agent are added, an imprinted polymer layer is formed at the substrate surface [85,123]. For example, CFZ or CFE (templates) were linked to the carboxylated-MWCNTs-modified GCE by covalent bonds between the -COOH groups of the MWCNTs and the -NH_2 group of CFZ/CFE after immersion of the electrode in the template solution for 4 h at room temperature. Then, the electrode was incubated with a solution containing the functional monomer, a cross-linker and the initiator, and the polymer was formed around by CFZ/CFE, generating the corresponding MIP [12,94]. Another interesting procedure was applied by Tan et al. [95] to prepare a hybrid recognition interface combining a peptide and a MIP for VAN detection. Thus, a VAN-binding tripeptide was immobilized through Au-S bonds on the surface of a GCE modified with gold nanoparticles. The resulting electrode was immersed into a VAN solution to form a VAN-peptide complex (through five hydrogen bonds) and afterward, this electrode dopamine was electropolymerized to obtain the VAN-imprinted polymer. After the template extraction, the 3D cavities remained in polymeric film attached to the electrode surface [85,95]. Electropolymerization is easy to carry out and generates reproducible size- and shape-controlled particles [84].

In the electropolymerization technique, a specific potential is applied to the CPE, and the monomer is oxidized and generates free radicals, which lead to the formation of a polymer layer at the electrode surface. Electropolymerization can be achieved mainly either potentiodynamically (by CV) or potentiostatically [72] (by applying to the electrode a given potential for a well-established time). The thickness and the porosity of the MIP film at the transducer surface can be controlled by the proper selection of the applied voltage, the scan rate, the number of scans [8,24,95] and potential range (in the CV procedure), the deposition time as well as the monomer and template concentration [124], as it was carried out for the preparation of MMZ-imprinted polypyrrole [99]. This rapid and sensitive method is used when expensive or very small amounts of template molecules are available.

Despite the fact that usually the electropolymerization is performed in the solution containing the monomer, the template and the supporting electrolyte are dissolved in an appropriate solvent, Pan et al. [105] reported a GCE modification method involving in the first step the drop-casting onto the electrode surface of acetonitrile with 5% DMF solution containing AZY (template), benzothiophene-3-boronic acid (monomer), 4,4′-dibromo-3,3′-bithiophene (cross-linker) and 3-methyl-thiophene (linker). After incubation at 60 °C, the electrode was subjected to CV electropolymerization. DMF was added to the solution to generate the "coffee ring" effect, while 3-methyl-thiophene had the role of avoiding steric hindrance between the monomer and the template [105].

3.4. Polymerization Reagents

The template molecule is present in the initial polymerization mix. Despite the fact that there are situations (the so-called pseudo- or dummy template method) where the template is different from the target [125,126], in the MIP-based electrochemical sensors developed in recent years for antibiotic detection, the template was the analyte (Table 1). The importance of the template species in the MIP generation results from the MIPs function mechanism, which is based on the "lock-and-key" principle. It is actually the "key" that tailored the "lock". This means that it provides the MIP with that specific pocket that is exploited within the analysis. The template molecule needs to have a physical and chemical affinity with the functional monomer because that generates the main property of the MIP-selectivity. A

GCE modified with a PPy imprinted with SDZ and AP was developed for the simultaneous detection of the two drugs in pork and chicken samples [93].

The functional monomer represents the basis for the future 3D structure of the MIP. When selecting the monomer and the monomer: template ratio it is important to elucidate the interaction mechanism between the functional groups of the monomer and of the analyte and this can be performed by UV-Vis spectrometric investigations [114] or by computer simulation [18,23,32,39,99]. A monomer frequently employed in the generation of MIPs for antibiotic sensing was pyrrole [7,22,31,93,99], due to the fact that PPy can be easily obtained, it is stable, biocompatible and possesses good conductivity and redox properties [72]. However, according to the recent literature data (Table 1), the most used monomer in the fabrication of MIP-modified carbon electrodes for antibiotic detection was MAA [16,27,97,106,114,115], owing to its capacity to interact well with both weak acids and bases, presenting high interaction energies with the template molecules [127]. Other functional monomers used in the synthesis of polymers imprinted with different antibiotic molecules were dopamine [95,100,103,111], aniline [8,38,112], acrylic acid [32], AMPS [18] and other less usual ones based on ILs or MWCNTs [23,101,102]. There was also reported a MIP for SM_2 detection obtained by copolymerization of MAA and EDOT [39].

The cross-linking agent is basically a bifunctional monomer with the role of enlarging the structure of the polymer and creating a macroporous surface. The cross-linker affects the MIP durability and the use of more cross-linkers resulted in stable porous polymers. Some studies revealed that the concentration of the cross-linker influences the morphology and thus the binding capacity of the MIP, lower cross-linker concentrations being more favorable to attain a higher binding capacity [70,128]. Despite the fact that various compounds (e.g., p-divinyl- or 1,3 diisopropenyl benzene, 1,4-diacryloyl piperazine, allyl methacrylate, polyethylene glycol dimethacrylate, trimethylolpropane dimethacrylate, etc.) [129] were reported as cross-linkers, only EGDMA [16,27,32,97,106,114,115], MBAA [6,12,94], bithiophene derivatives [17,99] were used in bulk or precipitation polymerization procedures to prepare MIPs for antibiotic sensing (Table 1).

The solvent is used to bring all the polymerization components (template, monomer, cross-linker, initiator) into the same phase (solution), but it must not interfere with the polymerization process. Depending on the solubility of the involved polymerization components, acids [8,38,91,107,113], salts [22,31,99] and buffer [12,24,39,92,95,96,109,112] aqueous solutions or organic solvents [4,7,16,17,26,27,32,105,106,115] were used in obtaining MIPs for antibiotic detection (Table 1). The solvent has an important role in the template-functional monomer interaction and therefore in the formation of the pre-polymerization complex. Due to its influence on the pore (size and shape) generation and thus the morphology of MIPs, it is called a "porogenic" solvent [116]. Less polar solvents promote the formation of the template-monomer functional complex, whereas more polar solvents interfere with the interactions in the template-monomer functional complex that forms [70].

The initiator is an important component in MIPs preparation, being responsible for free radical polymerization. They can be activated by heat or photochemical (when the monomer is unstable at high temperature) [116]. The initiator most often used in MIP preparation for antibiotic sensing is AIBN [16,23,27,32,106,114], which can be thermally activated (50–75 °C). Other studies reported the use of KPS [6] or APS [12,94] as initiators.

The main benefits of the electropolymerization process for creating MIPs are its simplicity and rapidity, along with the fact that there is no need for using a cross-linking agent or an initiator, only the monomer(s) and the template are required. As already mentioned, the important parameters of electropolymerization are related to the functional monomer (type and concentration) and the procedure of the potential application (scan rate, number of cycles, potential range or potential values, time). However, in this procedure a supporting electrolyte is necessary. For water-soluble monomers and templates, the most used supporting electrolytes were acids (HCl [113]) or mixtures of acids (e.g., H_2SO_4 and H_3PO_4 when aniline was the monomer [8,38,91]), salts (KCl [31], K_2HPO_4 [22,99], $NaClO_4$ [99], PBS [24,39,92,95,96,109,112] and BRB [3,107]) with different pH values. If the polymeriza-

tion was performed in organic solvents, then the preferred supporting electrolytes were $LiClO_4$ [7,26], TBAP [93,105] and 4BA6FPh [17].

3.5. Template Removal

Template removal is a critical step in the preparation of most MIPs and the applied method is important because incomplete removal of the target molecules determines a low sensitivity and may lead to false-positive errors [85]. Sometimes, the polymer chain makes removal difficult, with the preservation of the formed polymeric structure, due to the links existing between the template and the MIP functional groups or due to sterically hindrance. There are several methods used for template removal, which can be grouped into two categories: extraction and electrochemical procedures.

Template extraction from the polymer covering the electrode can be carried out by the electrode washing [4,18,110] or immersion in the proper solvent or solvent mixtures [38], usually with stirring of the solution [16,17,95,107,108,112], Soxhlet extraction (sometimes can last very long, e.g., 8 h [6], 48 h [23] or even 5 days [32]), and ultrasound-assisted extraction [105]. In order to achieve the complete template removal, extraction parameters such as the removal reagent (e.g., NaOH, acids, methanol, acetic acid and mixtures of them, etc.) [16,24], washing/extraction time [16,24,115], stirring rate, pH of the extraction solution [24,27,97], were optimized. The significance of the proper solvent selection is demonstrated by the following situations: due to AZY solubility in an aqueous medium, it was simply extracted by immersion in a water:ethanol mixture [8], in other situations, extraction was performed in an acidic solution to break the bonds between the template and the polymer functional groups [12]. In the case of TS, the eluent both dissolves the template and destroys the bonds formed with MAA [110]. For example, the washing time for the VAN removal from the MIPDA/peptide/AuNPs/GCE [95] was optimized by monitoring the DPV and EIS signals with washing time. The DPV current increased and the impedance decreased with washing time until remaining constant and that time period was selected as optimum for the template elimination from the polymeric structure.

Electrochemical template removal was carried out by DPV [99], but most often by CV [22,26,100]. For example, CV scanning led to SMX oxidation and the decrease in its affinity to the polymeric matrix, being thus released and generating the cavities of the MIP. The SMX's complete removal was confirmed by the absence of its anodic signal. This procedure allows the real-time monitoring of the template release from the polymeric matrix [22]. The eluent type and concentration must be also optimized when voltammetric techniques are applied for the template removal. In some situations, the potential applied to the electrode modified with the polymer containing the target molecule (CAP [26], MNZ [100,111]) was cycled until the peak current of the redox probe ($Fe(CN)_6^{3-/4-}$) remained constant. In other studies, the potential was scanned continuously for several cycles, in a properly selected electrolyte solution, until the analyte current response was no longer observed [18,113]. It must be mentioned that in the case of SPCE, the adequate extraction solvent was dropped at the sensing surface [22,24] and the selected template removal procedure was applied. Electrochemical overoxidation of PPy was also a useful method to eliminate the entrapped TC [31] and SDZ and AP [93] from the polymeric matrix.

4. Voltammetric Techniques and Sensor Performances

The analytical performances of the MIP-based sensors depend on the conditions of the MIPs preparation, which were discussed in the previous sections, but also on the analyte rebinding to the MIP. Therefore, the proper parameters such as the MIP amount [16], solution pH [8], incubation time [8,16,32,95,115] and temperature [8] used for the analyte rebinding must be selected. The optimization can be performed either by monitoring the analyte signal on the MIP-modified electrode by varying one parameter while all the others are kept constant [95] or by applying computational methods [8].

Antibiotic detection using MIP-modified carbon-based electrodes was carried out either directly by measuring the analyte reduction (e.g., FZD [18], CAP [106], MNZ [112]) or

oxidation (AMOX [6,102], AZY [8,24], CFZ [12], SMX [22], CTC [23], MMZ [99], CFX [107]) response or indirectly by measuring the difference between the peaks (either reduction or oxidation) of a redox probe (e.g., $Fe(CN)_6^{3-/4-}$) recorded at the MIP films after the target removal and after target re-binding (e.g., CIP [16], AZY [17,105], CAP [26], KANA [96], MNZ [100,111], DAP [108], TS [115]). The $K_3[Fe(CN)_6]$ CV signal could be amplified by the addition of H_2O_2 and horseradish peroxidase [96]. In the same paper, Liu et al. [111] reported both the indirect CV and the direct DPV detection of MNZ based on the reduction of its-NO_2 group, emphasizing that the direct method was more sensitive, while the indirect one presented a larger linear range (Table 2).

Table 2. Sensor's performances and sample analysis.

Antibiotic	Electrode	Technique	Sample	Sensor Performances	Ref.
AMOX	MWCNTs/MIP/SWCNTs/GCE; MWCNTs/MIP/dendritic Pt-Pd bimetallic NPs-SWCNT/GCE	DPV	Milk, honey	LOD = 8.9×10^{-10} M Linearity: $1.0 \times 10^{-9} - 1.0 \times 10^{-6}$ M; $1.0 \times 10^{-6} - 6.0 \times 10^{-6}$ M	[102]
AMOX	Mag/MIP/CPE	SWV	River water, milk	LOD = 7.5×10^{-7} M Linearity: $2.5 \times 10^{-6} - 5.7 \times 10^{-5}$ M	[6]
AZY	MIP/CPE	ECL	Blood, urine	LOD = 2.3×10^{-11} M Linearity: $1.0 \times 10^{-10} - 4.0 \times 10^{-7}$ M	[27]
AZY	MIP/GNU/GO/ GCE	DPV	Human blood	LOD = 1.0×10^{-10} M Linearity: $3.0 \times 10^{-10} - 9.2 \times 10^{-7}$ M	[8]
AZY	MIP/GCE	CV (indirect)	Human plasma, tears, urine	LOD = 8.5×10^{-10} M Linearity: $1.33 \times 10^{-8} - 6.66 \times 10^{-5}$ M	[17]
AZY	MIP/SPCE	DPV	Water	LOD = 8.0×10^{-8} M Linearity: $5.0 \times 10^{-7} - 10.0 \times 10^{-5}$ M	[24]
AZY	MIP/GCE	SWV	Tap and sewage water	LOD = 1.20×10^{-7} M Linearity: $4.0 \times 10^{-7} - 1.0 \times 10^{-4}$ M	[105]
CAP	MWCNTs/MIP/CKM-3/P-r-GO /GCE	DPV	Milk, honey	LOD = 1.0×10^{-10} M Linearity: $5.0 \times 10^{-9} - 5 \times 10^{-7}$ M; $5.0 \times 10^{-7} - 4.0 \times 10^{-6}$ M	[101]
CAP	3D CNTs@Cu NPs@MIP /GCE	CV	PBS, milk	LOD = 1.0×10^{-5} M Linearity: $1.0 \times 10^{-5} - 5.0 \times 10^{-4}$ M	[106]
CAP	MIP/PEDOT/SPCE	EIS/SWV	Aquarium fish water	LOD = 2.6×10^{-10} M/6.5×10^{-10} Linearity: $1.0 \times 10^{-9} - 1.0 \times 10^{-7}$ M	[26]
CFE	AgDs/MIP/cMWCNTs/GCE	ASDPV	Tablets, serum	LOD = 1.0×10^{-9} M Linearity: $1.0 \times 10^{-8} - 6.0 \times 10^{-4}$ M	[94]
CFE	AuNW/GO/MIP/GCE	CV/ DPV	Human serum, urine	LOD = 7.1×10^{-9} M Linearity: $2.0 \times 10^{-8} - 9.5 \times 10^{-7}$ M	[91]
CFLX	MIP/GCE	DPV	Untreated river water, pharmaceuticals	LOD = 4.9×10^{-9} M Linearity: $1.0 \times 10^{-8} - 1.0 \times 10^{-6}$ M	[92]
CFX	MIP/Ag@AuNPs/ILs/GCE	DPV	BRB	LOD = 2.0×10^{-12} M Linearity: $1.0 \times 10^{-11} - 1.0 \times 10^{-9}$ M	[107]
CFZ	AgDs/MIP/cMWCNTs /GCE	ASDPV	Serum	LOD = 5.5×10^{-10} M Linearity: $2.0 \times 10^{-9} - 5.0 \times 10^{-7}$; $5.0 \times 10^{-7} - 7.0 \times 10^{-6}$ M	[12]

Table 2. *Cont.*

Antibiotic	Electrode	Technique	Sample	Sensor Performances	Ref.
CIP	Ch-AuNp/MIP/GCE	DPV	Tablets, water	LOD = 2.1×10^{-7} M Linearity: $1.0 \times 10^{-6} - 1.0 \times 10^{-4}$ M	[16]
CLO	GO/AuNp/MIP/SPCE	DPV	Milk	LOD = 3.6×10^{-8} M Linearity: $1.1 \times 10^{-7} - 7.5 \times 10^{-7}$ M	[97]
CTC	MWCNT-IL/MIP/GCE	LSV/ DPV	Eye ointments, milk, tap water	LOD = 8.0×10^{-8} μM Linearity: $4.0 \times 10^{-7} - 5.5 \times 10^{-5}$ M	[23]
DAP	MIP/AuPtNPs/GCE	DPV	Serum, human plasma	LOD = 1.61×10^{-13} M Linearity:$1.0 \times 10^{-12} - 2.0 \times 10^{-11}$ M	[108]
FZD	MWCNTs/MIP/CPE	DPV	Tap water, river water	LOD = 3.0×10^{-8} M Linearity:$1.0 \times 10^{-8} - 1.0 \times 10^{-6}$ M	[18]
KANA	MWCNTs/Fe_3O_4/PMMA/CE	DPV	Chicken/ pig liver, milk	LOD = 2.3×10^{-11} M Linearity: $1.0 \times 10^{-10} - 1.0 \times 10^{-6}$ M	[4]
KANA	MIP/ BPPGE	CV (indirect)	Milk, honey	LOD = 3.9×10^{-6} M Linearity: $5.0 \times 10^{-6} - 5.0 \times 10^{-5}$ M	[96]
KANA	target/ APT/Fc/β-CD-SH/Au@Fe_3O_4/MIP/GCE	DPV	Milk, tap, artesian and groundwater	LOD = 1.87×10^{-9} M Linearity: $1.0 \times 10^{-8} - 5.0 \times 10^{-7}$ M	[110]
MMZ	MIP/PGE	DPV	Tablets, human blood serum	LOD = 3×10^{-6} M Linearity: $7.0 \times 10^{-6} - 6 \times 10^{-3}$ M	[99]
MNZ	MIP/MWCNTs/GCE	CV (indirect)	Tablets, fish meat	LOD = 2.87×10^{-10} M Linearity:$1.0 \times 10^{-9} - 1.2 \times 10^{-6}$ M	[100]
MNZ	MIP/GCE	DPV/CV (indirect)	Mouse serum	$LOD_{DPV} = 3.33 \times 10^{-10}$ M $LOD_{CV} = 6.67 \times 10^{-10}$ M $Linearity_{DPV}$: $1.0 \times 10^{-9} - 1.0 \times 10^{-8}$ M $Linearity_{CV}$: $2.0 \times 10^{-9} - 1.0 \times 10^{-7}$ M	[111]
MNZ	$CuCo_2O_4$/N-CNTs/MIP /GCE	DPV	Tablets, human serum; urine	LOD = 4.8×10^{-10} M Linearity: $5.0 \times 10^{-9} - 1.0 \times 10^{-7}$ M; $1.0 \times 10^{-7} - 1.0 \times 10^{-4}$ M	[112]
MTX	MIP/GCE	DPV	Urine	LOD = 3×10^{-8} M Linearity: $6.0 \times 10^{-8} - 1.0 \times 10^{-5}$ M	[113]
NFX	fMWCNTs-MIP/GCE	DPV	Tablets, rat serum	LOD = 1.58×10^{-9} M Linearity: $3.0 \times 10^{-9} - 3.9 \times 10^{-7}$ M; $3.91 \times 10^{-8} - 3.125 \times 10^{-6}$ M	[114]
OXC	MIP/GNU/GO/SPCE	DPV	Milk	LOD = 2.0×10^{-10} M Linearity: $7.0 \times 10^{-10} - 5.75 \times 10^{-7}$ M	[38]
SDZ	MIP/GO@COF/GCE	DPV	Beef, fodder	LOD = 1.6×10^{-7} M Linearity: $5.0 \times 10^{-7} - 2.0 \times 10^{-4}$ M	[93]
SMD	MIP/GQDs-PtNPs/GCE	DPV	Milk, pork	LOD = 2.30×10^{-11} M Linearity: $1.00 \times 10^{-10} - 1.00 \times 10^{-4}$ M	[39]
SMX	oxMWCNTs/$UPPy_{MIP}$ /GCE	DPV	Milk	LOD = 4.13×10^{-11} M Linearity: $1.99 \times 10^{-6} - 1.08 \times 10^{-5}$ M	[22]
TC	MIOPPy-AuNP/SPCE	DPV	Shrimp	LOD = 6.5×10^{-7} M Linearity: $1.0 \times 10^{-6} - 2.0 \times 10^{-5}$ M	[31]

Table 2. *Cont.*

Antibiotic	Electrode	Technique	Sample	Sensor Performances	Ref.
TC	Mag/MIP/CPE	SWV	Milk	LOD = 1.5×10^{-7} M Linearity: $5.0 \times 10^{-7} - 4.0 \times 10^{-5}$ M	[32]
TS	MIP/CoN NWs/CC	DPV	Tear, plasma, spiked urine	LOD = 5.5×10^{-12} M Linearity: $8.6 \times 10^{-11} - 6.7 \times 10^{-5}$ M	[115]
VAN	MIPDA/peptide/AuNPs/GCE	EIS	Fetal calf serum, probiotic drink, honey	LOQ = 1.0×10^{-12} M Linearity: $1.0 \times 10^{-5} - 1.0 \times 10^{-4}$ M	[95]
RIF, INZ	Cu-MOF/MC/MIP/GCE	CV/ DPV	Pharmaceutical formulations, blood serum, urine	$LOD_{RIF} = 2.8 \times 10^{-10}$ M $LOD_{INZ} = 3.7 \times 10^{-10}$ M Linearity: $8.0 \times 10^{-8} - 8.5 \times 10^{-5}$ M	[7]

When EIS was used as a detection technique the impedance of a redox probe (usually $[Fe(CN)_6]^{3-/4-}$) was monitored as a function of the analyte concentration. The charge transfer resistance (R_{ct}) increased with the concentration of the target molecule (e.g., CAP [26], VAN [95]), indicating that this was a rebound to the MIP cavities, hindering thus the transfer of the probe species to the electrode surface. According to the literature data summarized in Table 2, EIS allowed a somewhat more sensitive CAP detection than SWV [26].

It can be seen from Table 2 that most MIP-based electrochemical sensors have very low LODs, even at pM levels [95,107,108,115], enabling thus the sensitive determination of antibiotics from various matrices. Taking into consideration the risk posed by the presence of the antibiotics in the environment and the attempt to limit such emerging pollutants in the environmental samples, the EU introduced four antibiotics (amoxicillin, ciprofloxacin, sulfamethoxazole, and trimethoprim) in a 2020 updated watch list of potential water pollutants that require monitoring [130,131]. However, it must be mentioned that there is no regulation providing maximum acceptable limits for any antibiotics in environmental samples.

On the other hand, due to the fact that many antibiotics are administered to food-producing animals in order to stimulate their growth and increase productivity, the concentration levels for these pharmacologically active substances were restricted in foodstuffs of animal origin. For example, Commission Regulation No 37/2010 establishes the MRLs for food-producing species [132]. In order to develop sensors fitted for the purpose, which possess analytical characteristics allowing the reliable determination of the antibiotics exemplified in Table 2, it is useful to know the mentioned MRLs. Thus, for all food-producing species, the MRLs are given for: AMOX (4–50 μg/kg), CLO (30–300 μg/kg), CTC (100–600 μg/kg), KANA (100–2500 μg/kg), OXC (30–300 μg/kg), TC (100–600 μg/kg), TS (50–200 μg/kg). There are exceptions, for example, CFLX, for which the MRLs (100–1000 μg/kg) are set for bovine tissues. More than that, on the prohibited substances list are found CAP, MNZ and nitrofurans (including FZD), for which MRLs cannot be established.

5. Conclusions

Without a doubt antibiotics are of great importance in our daily life but, unfortunately, they also have negative effects on the health of living organisms and consequently at an economical level too. In order to reduce the risks generated by uncontrolled or excessive antibiotic consumption, one main way is to monitor their concentration in different matrices. These aspects lead to the increasing need to develop analytical devices and methods for the reliable detection of these compounds. Electrochemical methods offer the possibility to easily and rapidly obtain selective and sensitive results. Moreover, the instrumentation is not as expensive and voluminous as that employed in other analytical techniques and allows on-site measurements due to the possibility of miniaturization.

The "heart" of every electroanalytical device is the sensor, whose performances depend on the electrode (transducer) substrate (e.g., glassy carbon, pencil graphite, screen printed, carbon paste, etc.) and on the material used to modify its surface, in order to improve the sensitivity and selectivity of the sensor. There exist an enormous and even increasing number of compounds developed with the aim to act as modifiers, among them special attention is being paid to MIPs. Besides the MIPs' unique recognition properties, there are many other reasons for choosing MIPs to prepare electrochemical sensors and it can be started with the ease of preparation, moreover, if the electropolymerization procedure is employed. From the examples presented in this paper, it is obvious that the combination of more modifiers of various types (e.g., MIPs, carbon-based and metallic nanomaterials [91,94,97,106]) resulted in synergistic effects that significantly improve the performance characteristics of the sensors (e.g., LODs lower then nM levels [4,12,38,39,112]) and wide linear ranges of three [8,17,27,99,100,102,105], four [4,94] or even six orders of magnitude [11,39]). The possibility to combine a huge variety of monomers with different chemical species acting as a template and with the various types of substrates to be modified opens the door for the development of even more sensitive (e.g., the MIP/CoN NWs/CC having the LOD of 5.5×10^{-12} M TS [115]) and selective electrochemical sensors for the detection of antibiotic traces in samples such as pharmaceuticals, body fluids, food and environmental samples. On the other hand, nowadays there are several computational methods [18,23,32,123] allowing for the more accurate and less time-consuming selection of the proper combination between monomer, template and cross-linker, giving rise to more stable and selective MIPs.

By systematizing recent literature data, this review aims to make researchers aware of the importance and usefulness of employing MIPs in the development of sensitive and selective electrochemical sensors for monitoring antibiotics in complex samples, both at low concentrations (as should be found in food and environmental samples) and in the quality control of pharmaceuticals. However, there are some aspects that may be improved in the development of MIP-based electrochemical sensors, among them being (i) minimization or even elimination of electrode surface fouling during the measurements (this can be realized by fabrication of disposable electrodes), (ii) miniaturization in order to perform analyzes of small sample volumes and to enable the sensors incorporation into portable instruments to achieve on-site, in real-time determinations, and (iii) making them biocompatible with the aim of being used in vivo measurements. On the other hand, it is worth searching for less toxic, greener reagents and substrates. We believe that the current knowledge related to the development of MIP-based electrochemical sensors for antibiotic detection, most of which are summarized in this review, constitutes a good basis for achieving these goals with the final target to offer these types of sensing devices a commercial potential.

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Abbreviations

2-DOS	2-deoxystreptamine
2,2′-Bth	2,2′-bithiophene
3D CNTs	3D carbon nanotubes

3-Me-Th	3-methyl-thiophene
3-TBA	3-thienyl boronic acid
4,4′-Br-3,3′-Bth	4,4′-dibromo-3,3′-bithiophene
4-ABA	4-aminobenzoic acid
4BA6FPh	tetrabutylammonium hexafluoro-phosphate
AAM	acrylamide
AgDs	silver dendrites
AGs	aminoglycosides
AIBN	2,2-azo-bis-isobutyronitrile
AMOX	amoxicillin
AMPS	2-acrylamido-2-methyl-1propanesulfonic acid
AMR	antimicrobial resistance
AP	acetaminophen
APS	ammonium persulfate
APT/Fc/β-CD-SH	aptamer/ferrocene/β-cyclodextrin
ASDPV	anodic stripping differential pulse voltammetry
AWaRe	Access, Watch and Reserve
AZY	azithromycin
BCE	bare carbon electrode
BPPGE	basal plane pyrolytic graphite electrode
BRB	Britton Robinson buffer
CA	chronoamperometry
CAP	chloramphenicol
CAVImBr	1-carboxymethyl-3-vinylimidazolium bromide
CE	carbon electrode
CFE	cefixime
CFLX	cefalexin
CFX	ceftizoxime
CFZ	ceftazidime
Ch	chitosan
CIP	ciproflaxin
CKM-3/P-r-GO	mesoporous carbon/three-dimensional porous graphene
CLO	cloxacillin
cMWCNTs	carboxyl functionalized MWCNTs
CNTs	carbon nanotubes
COF	covalent organic framework
CPE	carbon paste electrode
CTC	chlortetracycline
CV	cyclic voltammetry
DAP	daptomycin
DMF	Dimethylformamide
DMZ	dimetridazole
DPV	differential pulse voltammetry
ECL	electrochemiluminescence
EDOT	3,4-ethylenedioxythiophene
EIS	electrochemical impedance spectroscopy
EGDMA	ethyleneglycol dimethacrylate
ELISA	enzyme-linked immunosorbent assay
Fe_3O_4@SiO_2-MPS	3-methylpropyltrimethoxysilane functionalized Fe_3O_4@SiO_2 nanoparticles
fMWCNTs	functionalized MWCNTs
FZD	furazolidone
GCE	glassy carbon electrode
GNU	gold nanourchins
GO	graphene oxide
GQDs	graphene quantum dots
ILs	ionic liquids
INZ	ioniazid
KANA	kanamycin
KPS	potassium persulfate
LOD	limit of detection

LOQ	limit of quantification
LSV	linear sweep voltammetry
MAA	methacrylic acid
Mag/MIP	magnetic nanoparticles coated with MIP
MBAA	N,N′-methylenebisacrylamide
MIOPPy	molecularly imprinted overoxidized polypyrrole
MIPDA	molecularly imprinted polydopamine
MIPs	molecularly imprinted polymers
MMZ	methimazole
MNZ	metronidazole
MOF/MC	metal-organic framework/mesoporous carbon
MRLs	maximum residue limits
MTX	mitoxantrone
MWCNTs	multiwalled carbon nanotubes
N-CNTs	nitrogen-doped CNTs
NFX	norfloxacin
NPs	nanoparticles
NWs	nanowires
OPPy	overoxidized polpyrrole
OTC	over the counter
OXC	oxacillin
oxMWCNTs/UPPy$_{MIP}$	oxidized MWCNTs/ultrathin molecularly imprinted PPy
P-Arg	poly-arginine
PBS	phosphate buffer solution
PEDOT	poly(3,4-ethylenedioxythiophene)
PGE	pencil graphite electrode
Ph-3-TBA	benzothiophene-3-boronic acid
PMMA	poly(methacrylic acid)
PPy	polypyrrole
QDs	quantum dots
RIF	rifampicin
SDZ	sulfadiazine
SM_2	sulfadimidine
SMIP	surface molecularly imprinted polymer
SMX	sulfamethoxazole
SPCE	screen-printed carbon electrode
SWCNTs	single-walled carbon nanotubes
SWV	square wave voltammetry
TBAP	tetra-n-butylammonium perchlorate
TC	tetracycline
THF	tetrahydrofuran
TS	tylosin
UV-Vis	ultraviolet-visible
VAN	vancomycin

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