UNIVERSIDADE FEDERAL DE UBERLÂNDIA
INSTITUTO DE BIOTECNOLOGIA
CURSO DE GRADUAÇÃO EM BIOTECNOLOGIA

JÚLIA DUARTE MEGALE

NEW APPROACHES IN ANTIBIOTICS DETECTION: THE USE OF SQUARE WAVE VOLTAMMETRY

PATOS DE MINAS – MG
JANEIRO DE 2023

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Artigo Científico apresentada ao Instituto de Biotecnologia da Universidade Federal de Uberlândia como requisito final para a obtenção do título de Bacharel em Biotecnologia.

Orientadora: Profa. Dra. Djenaine de Souza

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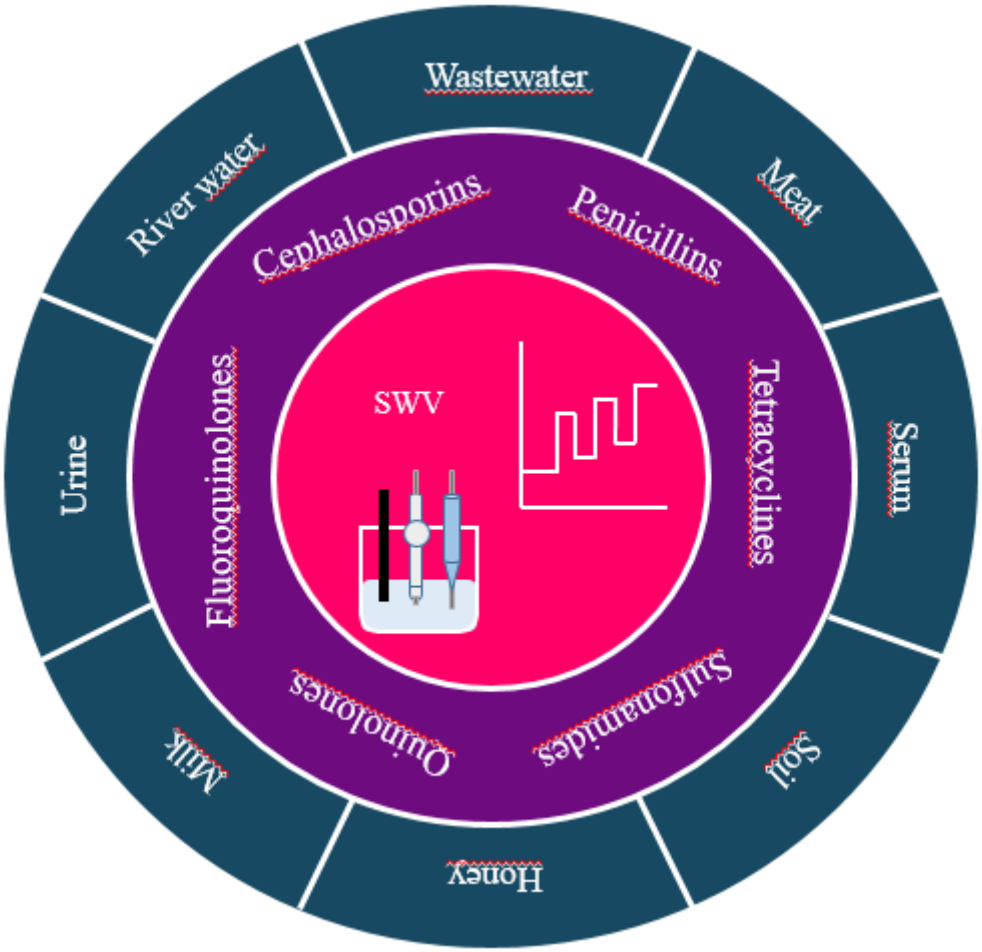
Os membros da Comissão Examinadora acima assinaram a Ata de Defesa que se encontra no Sistema Eletrônico de Informações (SEI) da Universidade Federal de Uberlândia.

Patos de Minas – MG, 27 de Janeiro de 2023

Graphical Abstract



Highlights

- Compounds, action mode and chemical structures of antibiotics allowed worldwide.
- Contamination of different samples by antibiotics residues and their detection.
- The use of square wave voltammetry in antibiotics determination.
- Influence of the working electrode materials in the antibiotics analysis.
- Challenges and trends in the antibiotic analysis by square wave voltammetry.

Abstract

Antibiotics are a class of pharmaceutical compounds widely used on account of the effectiveness against bacterial infections, which have been a major concern to humanity in the last centuries. These compounds are produced, consumed, and sometimes inappropriately disposed of in the environment resulting in environmental and public health problem. They are considered emerging contaminants because of damage their residues represent, whether in the long or short term, to different terrestrial ecosystems, in addition to bringing potential risks to agricultural sectors, such as livestock, if there is excessive use in herds or inappropriate disposal. Furthermore, there is the issue of the potential emergence of bacteria that are resistant to known treatments, due to the adaptation of these microorganisms to the cited drugs, coming from their presence, even if residual, in the environment. For this, the development of analytical methods for low concentration detection and identification of antibiotics in natural waters, wastewaters, soil, foods, and biological fluids is necessary. This review shows the applicability of square wave voltammetry for analytical determination of antibiotics, from different chemical classes and covering and large variety of samples and working electrodes.

Keywords: antibiotics, environmental waste, electroanalytical techniques, square wave voltammetry, chemically modified electrodes.

1. General considerations

In the last years, the scientific communities and governmental, environmental, and health agencies have a major concern with a specific class of contaminants called emerging contaminants, mainly because of the large number of compounds and the effects associated with their presence in natural waters, soil, atmosphere, and foods. These compounds are unregulated chemicals of synthetic origin or natural sources, which have not yet been subjected to any type of restrictive measure associated with their reduction in the environment [1,2]. The main compounds considered as emerging contaminants are disinfection by-products, hormones, illicit drugs, microplastics, nanomaterials, personal care products, perfluorinated compounds, pharmaceutical drugs, phthalates, sunscreen/UV filters, and surfactants [3].

These contaminants might occur at reduced concentrations, below $\mu g\ L^{-1}$ or $ng\ L^{-1}$, resulting in a large potential for generating adverse environmental effects and for long term human health. Unlike priority pollutants (heavy metals and specific organic chemicals), with known mutagenic, carcinogenic, and toxicity effects, all well related to exposure, little is known about the direct consequences of exposure to emerging pollutants, which raises an issue of great concern, especially considering that the effects are associated with significantly low concentrations of substances [4].

Pharmaceutical drugs are classified into various groups of active organic compounds such as antidepressants, antibiotics, antiepileptic, anti-inflammatory, cytostatic, synthetic hormones, among others. They have been abundantly found in the environment, entailing health and ecological risks due to their harmful properties, which include bioaccumulation, endocrine disruption, environmental and clinical toxicity, in addition to bacterial antibiotic resistance [5]. These problems are owing to these pharmaceutical drugs not being degraded by solar radiation or microorganisms and, therefore, not being effectively disposed of in wastewater treatment plants.

Thus, the identification and quantification of emerging contaminants, mainly antibiotics, in the environment and food needs a rigorous evaluation using instrumental methods with suitable sensitivity and selectivity, enabling the detection of these contaminants even at trace levels.

2. Scope and approach

This review aims to show an overview of the identification and quantification of

antibiotics, a harmful emerging contaminant class, using the most sensitive electroanalytical technique: square wave voltammetry (SWV). For this, a search for articles on the subject was carried out using Science Direct® and Scopus® databases, using all possible combinations of keywords "Electroanalysis", "Square Wave Voltammetry", "Antibiotics", "Pharmaceutical Compounds", and the antibiotic name with the technique. The search covered the period between January 2012 and November 2022 and subject areas evaluated were Chemistry, Engineering, Environment, and Biotechnology.

A total of 117 scientific papers were identified and considered for the development of this review, in which the SWV was used in the antibiotic detection in different samples, according to proportions shown in the Figure 1. Analysis in urine and blood, which included bovine and human, is important because it allows the evaluation of the quantities metabolized by individuals and helps to adjust the appropriate dosages, besides allowing the evaluation of metabolites and enabling the study of the mechanisms of redox reactions of antibiotics in a physiological environment. Moreover, the analysis of pharmaceutical drugs and wastewater allow quality control in the pharmaceutical industry and evaluate the environment contamination, respectively. On the other hand, the analysis in natural water, soil, and food samples (milk, honey, and meat), that represent 21.28% of all papers evaluated, have significant relevance because the population is directly exposed through daily consumption of water and food contaminated with antibiotics residues, resulting in resistance of the organism and other health problems.

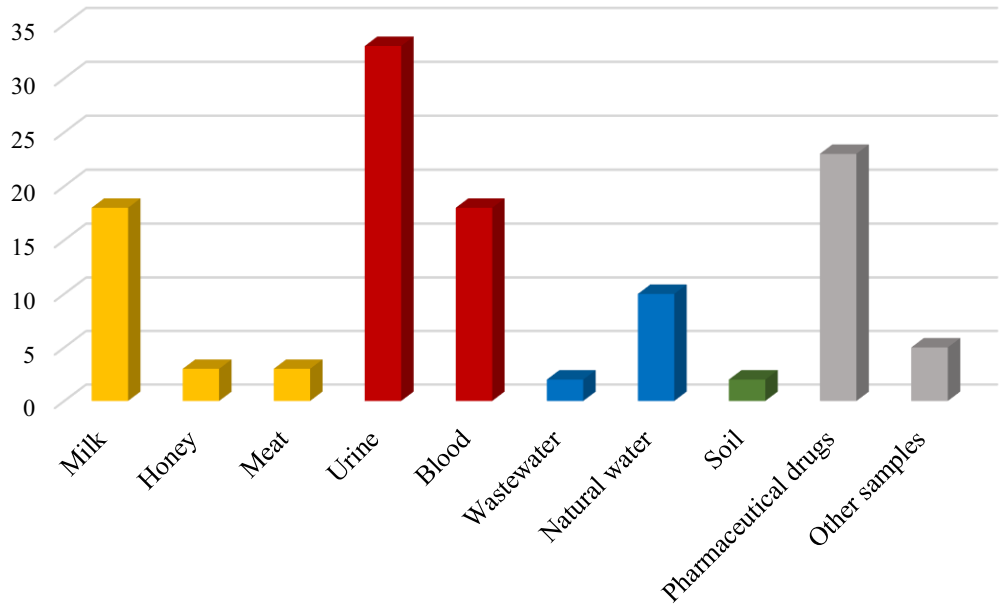


Figure 1: Scientific papers about the detection of antibiotics by square wave voltammetry

in different types of samples, considering a review in the Science Direct® and Scopus® databases, using the keywords "Electroanalysis", "Square Wave Voltammetry", "Antibiotics", "Pharmaceutical Compounds" and the antibiotic name combined with square wave voltammetry technique name, considering publication between the years 2012 to 2022.

Additionally, this review presents the main classes of antibiotics, their respective uses, some physical-chemical characteristics, and methods of detection suggested by legislation specifics. This paper also aims to present the main characteristics of SWV, important applications and analytical advantages, including the identification and quantification of antibiotics residues in complex samples. Some studies regarding the detection of antibiotics using various electrodic surfaces were also included, indicating the applicability of using different materials in the working electrode preparation used as voltammetric sensor for antibiotics.

3. Antibiotics

The use of antimicrobial agents against infectious diseases and in the control of pandemics and outbreaks is known from the use of the traditional variety of herbs to heal injuries and infections by the Chinese around 2500 B.C. to the present day. Still, it was only in 1889 that Paul Vuillemin presented the concept of antibiosis (the antagonism to growth of one species of microorganisms through substances produced by microorganisms of a different species) with the next big breakthrough being Fleming's experiments, in 1928, with the fungus Penicillium, that showed this phenomenon in *E. coli* cultures [6].

However the use of these antibiotics synthesized by microorganisms, either naturally or with artificial modifications to increase effectiveness, called semi-synthetic antibiotics, is very low, around 1% because they have drawbacks, such as toxicity and/or low selectivity [6]. So, synthetic antibiotics are largely employed as an active ingredient for chemotherapy of bacterial infections if compared to natural antibiotics since they are effective against strains that have already acquired resistance [7–10].

3.1 Physical-chemistry properties

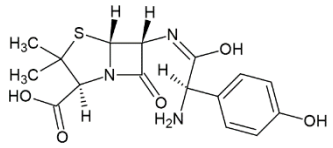
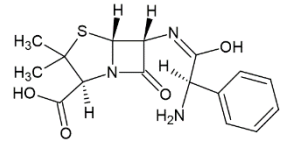
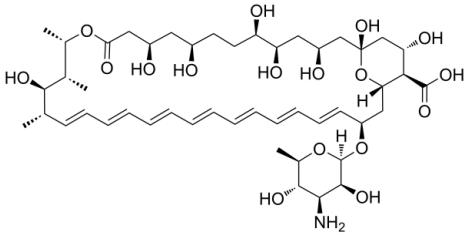
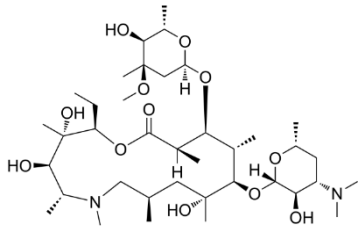
Synthetic antibiotics are divided into different chemical classes, such as aminoglycosides, carbapenem, cephalosporins, fluoroquinolones, macrolides, monobactams, penicillins, quinolines, sulfonamides, tetracyclines, among other. They are cyclic organic compounds with numerous structural variations, as shown in **Table 1**, presenting different organic radicals, which result in different mechanisms of action in controlling the growth or elimination of bacteria [11]. Carbapenems, cephalosporins, monobactams, and penicillins are the most important classes, characterized by a chemical structure called a beta-lactam ring, a heterocyclic ring formed by three carbon atoms and one nitrogen atom [12].

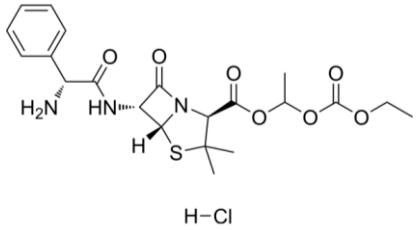
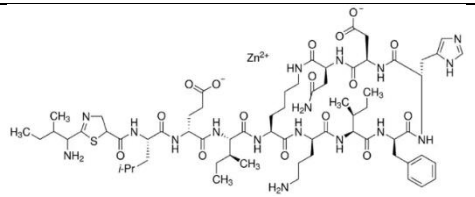
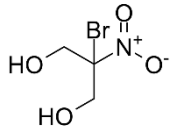
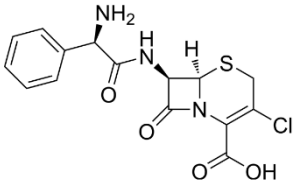
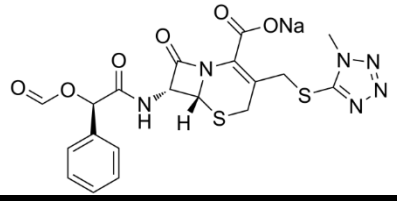
The differences in the chemical structures for each class of synthetic antibiotic also results in variation in the physical-chemistry properties. Tetracyclines, for example, are amphoteric photodegradable substances, presenting high solubility in water 0.2-55 g L^{-1}, stability in acid medium and equilibrium constants (pK_a) ranging from 3.0 to 9. 0, depending on the conditions [13], likewise sulfonamides are amphoteric substances, but due to the presence of a sulfonamide acid group (-SO_2NH-) and an amine primary group (-NH_2), they show differences in properties, such as water solubility of 0.07-1.5 g L^{-1}, and pK_a of 2.0 to 11.0. These properties are indicative that these classes of antibiotics, considering the environmental conditions, can probably be concentrated in rivers or wastewater.

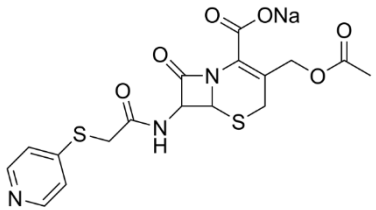
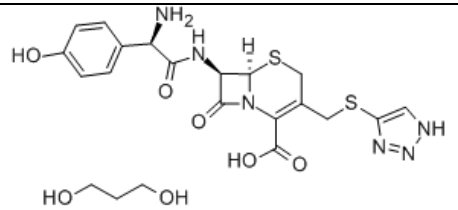
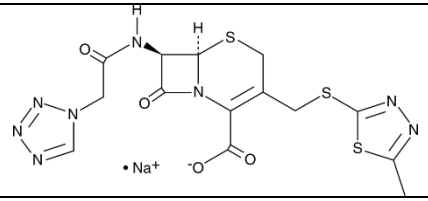
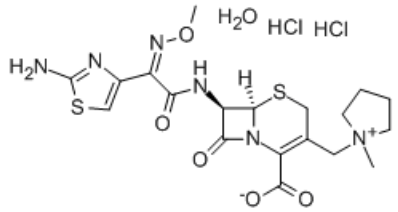
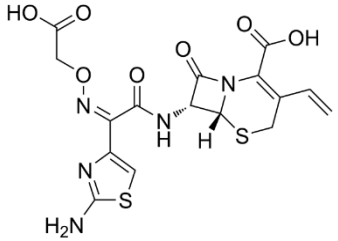
Quinolones present polarity significantly higher compared to other classes and pK_a varies from 6 to 7.5, depending on the antibiotic [14]. However, they have low water solubility, varying from 0.003-20 g L^{-1}, indicating that its environmental presence would not be mainly in water bodies, but in soil, considering that they also are adsorbed by solid substrates and have chelation potential for transition metal ions [15].

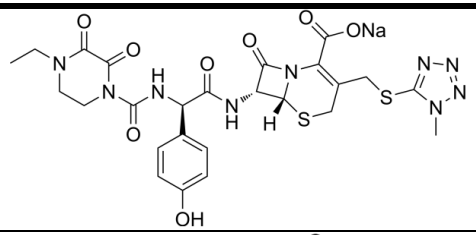
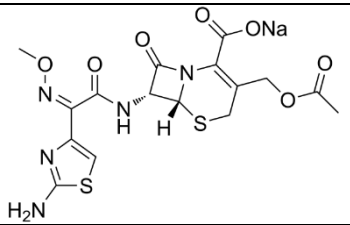
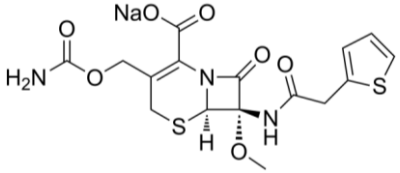
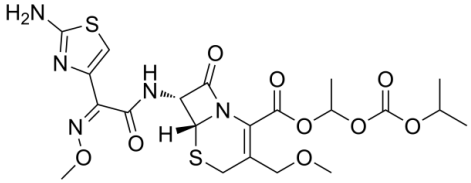
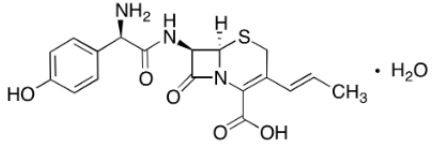
As shown in Table 1, each antibiotic class presents its characteristics, based on structure and molecule proprieties with variations within the class commonly appearing due to the influence of chemical groups that vary between them. Those characteristics are directly relevant for the analytical detection and the choice of spectroscopic, chromatographic, or electroanalytical technique, and mainly for choosing working electrodes as the sensor in the voltammetric analysis. The parenthesis of “composition” and “for related substances” both refer to alternative methods to the primary cited, in

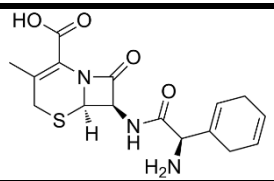
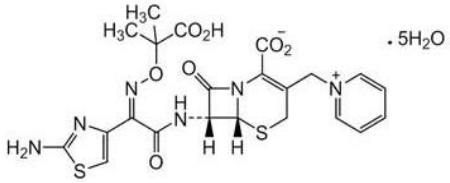
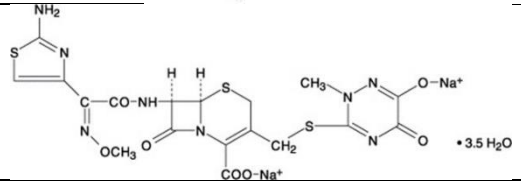
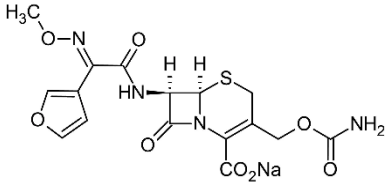
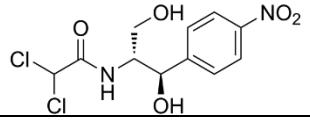
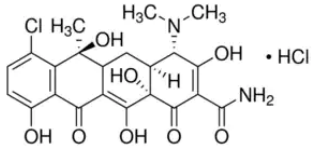
Table 1: Physicochemical properties, structure and suggested detection method for main antibiotics listed on the British Pharmacopoeia, 2022. Adapted from: [14–17].

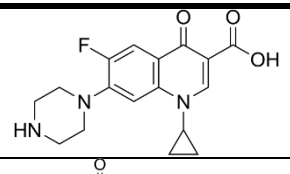
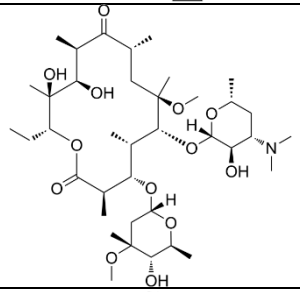
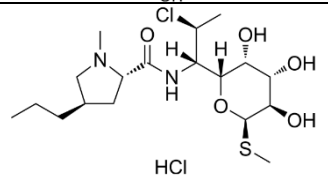
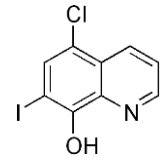
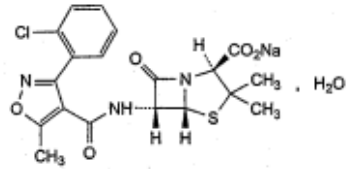
Name	Water solubillity (g L^{-1})	pK_a	Structural form	Analytical method for quality control
Amoxicillin	3.43×10^{-03}	pK_{a1} = 3.2 (acid) pK_{a2} = 11.7 (primary amine)		TLC, IRS, HPLC-UV/VIS (Composition)
Ampicillin	$1.01 \times 10^{+01}$	pK_{a1} = 2.65 pK_{a2} = 2.55 pK_{a3} = 7.14 pK_{a4} = 7.25		TLC, IRS, HPLC-UV/VIS (Composition)
Amphotericin	Insoluble	pK_{a1} = 5.5 pK_{a2} = 10.0		UV/Vis, IRS, HPLC-UV/Vis (for related substances)
Azithromycin	2.37×10^{-02}	pK_{a1} = 8.7 pK_{a2} = 9.5		IRS, HPLC/UV-Vis (for related substances)

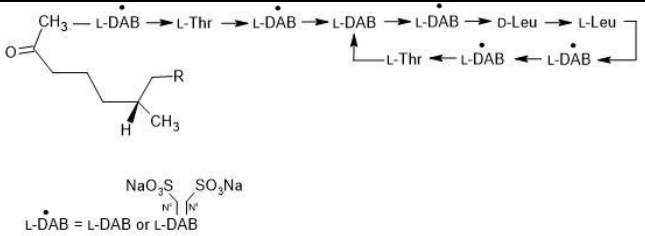
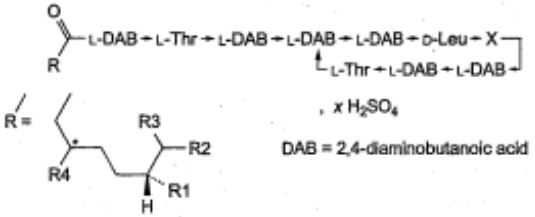
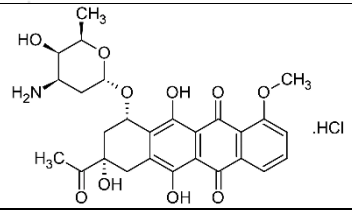
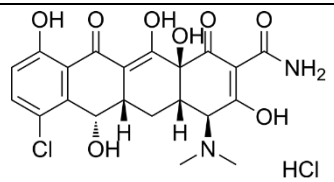
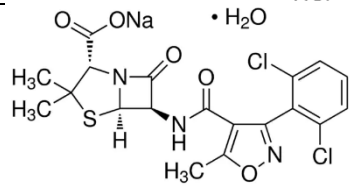
Bacampicillin Hydrochloride	1.23×10^{-01}	$pK_{a1} = 11.72$ $pK_{a2} = 7.23$		TLC, HPLC/UV-Vis
Bacitracin	2.45×10^{-02}	-		TLC, HPLC/UV-Vis (Composition)
Bronopol	$2.5 \times 10^{+03}$	12.02		IRS, HPLC/UV-Vis (Composition)
Cefaclor	2.1×10^{-01}	$pK_{a1} = 2.83$ $pK_{a2} = 7.23$		IRS, HPLC/UV-Vis (Composition)
Cefamandole Nafate	5.81×10^{-01}	3.4		IRS, HPLC/UV-Vis (Composition)

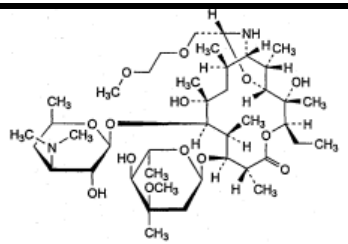
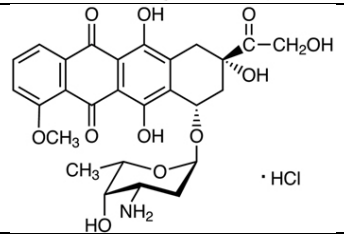
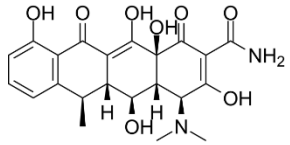
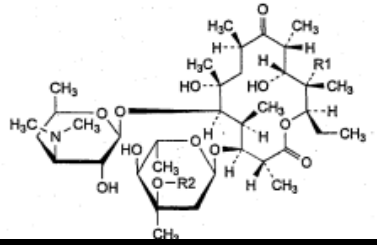
Cefapirin Sodium	5×10^{-02}	2.15		IRS, HPLC/UV-Vis (Composition)
Cefatrizine Propylene Glycol	1.49×10^{-04}	7.22		IRS, HPLC/UV-Vis (Composition)
Cafazolin Sodium	8.8×10^{-04}	$pK_{a1} = 2.84$ $pK_{a2} = 0.26$		IRS, HPLC/UV-Vis (Composition)
Cefepime Hydrochloride Monohydrate	1.7×10^{-02}	$pK_{a1} = 2.82$ $pK_{a2} = 3.62$		IRS, HPLC/UV-Vis (Composition)
Cefixime	1.04×10^{-01}	$pK_{a1} = 3.45$ $pK_{a2} = 2.92$		IRS, HPLC/UV-Vis (Composition)

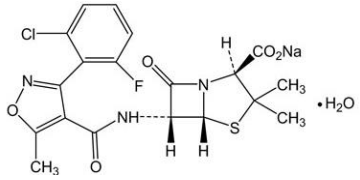
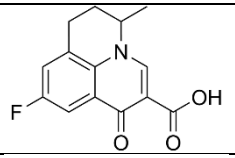
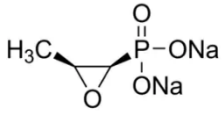
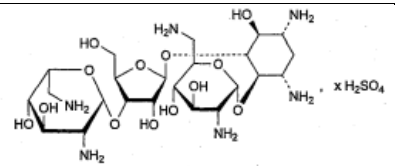
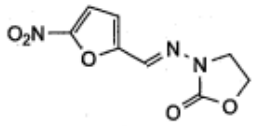
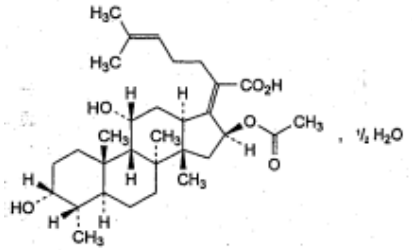
Cefoperazone Sodium	3.76×10^{-01}	2.37		IRS, HPLC/UV-Vis (Composition)
Cefotaxime Sodium	6.82×10^{-01}	$pK_{a1} = 2.74$ $pK_{a2} = 9.84$		IRS, HPLC/UV-Vis (Composition)
Cefoxitin Sodium	5.04×10^{-02}	-		UV-Vis, HPLC/UV-Vis (Composition)
Cefpodoxime Proxetil	1.03×10^{-01}	3.73		IRS, HPLC/UV-Vis (Composition)
Cefprozil Monohydrate	1.12×10^{-01}	$pK_{a1} = 2.64$ $pK_{a2} = 8.38$		IRS, HPLC/UV-Vis (Composition)

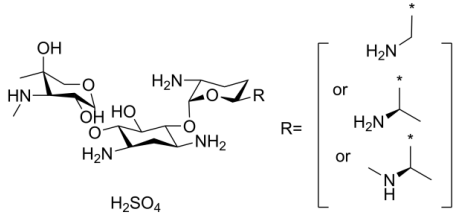
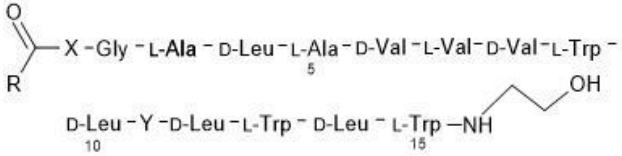
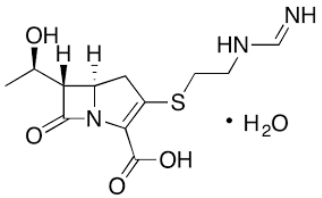
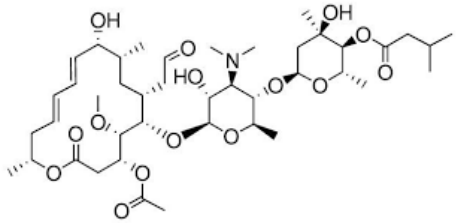
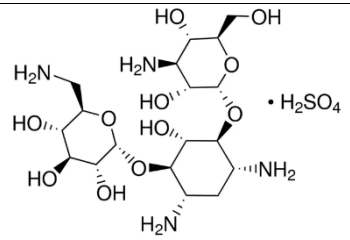
Cefradine	7.78×10^{-01}	$pK_{a1} = 2.6$ $pK_{a2} = 7.3$		IRS, HPLC/UV-Vis (Composition)
Ceftazidime Pentahydrate	5.73×10^{-03}	-		IRS, HPLC/UV-Vis (Composition)
Ceftriaxone Sodium	1.23×10^{-01}	$pK_{a1} = 3.05$ $pK_{a2} = 4.29$		IRS, HPLC/UV-Vis (Composition)
Cefuroxime Sodium	4.37×10^{-01}	3.15		IRS, HPLC/UV-Vis (Composition)
Chloramphenicol	2.5×10^{-02}	5.5		IRS, HPLC/UV-Vis (Composition)
Chlortetracycline Hydrochloride	-	$pK_{a1} = 4.5$ $pK_{a2} = 7.8$ $pK_{a3} = 9.8$		IRS, HPLC/UV-Vis (Composition)

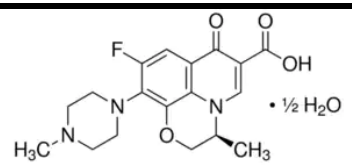
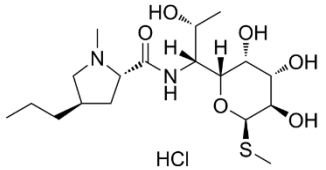
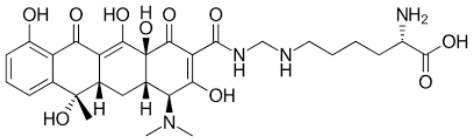
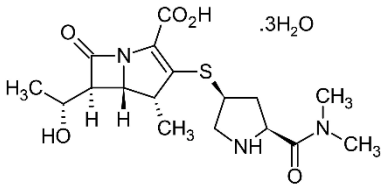
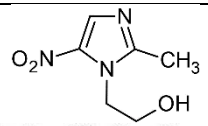
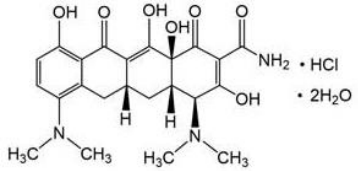
Ciprofloxacin	3.0×10^{-02}	6.09		IRS, HPLC/UV-Vis (Composition)
Clarithromycin	3.3×10^{-02}	8.99		IRS, HPLC/UV-Vis (Composition)
Clindamycin Hydrochloride	3.1	$pK_{a1} = 12.41$ $pK_{a2} = 7.55$		IRS, TLC, HPLC/UV-Vis (Composition)
Clioquinol	Insoluble	$pK_{a1} = 2.96$ $pK_{a2} = 7.6$		IRS, HPLC/UV-Vis (Composition)
Cloxacillin Sodium	5.32×10^{-02}	2.78		IRS, HPLC/UV-Vis (Composition)

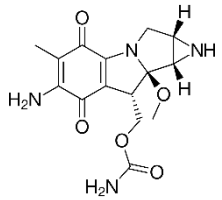
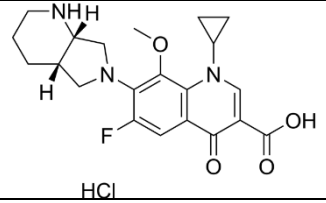
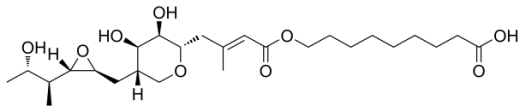
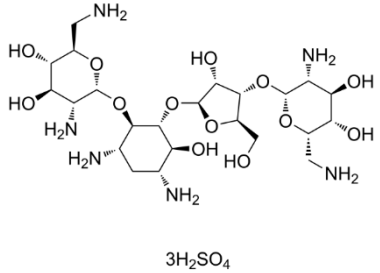
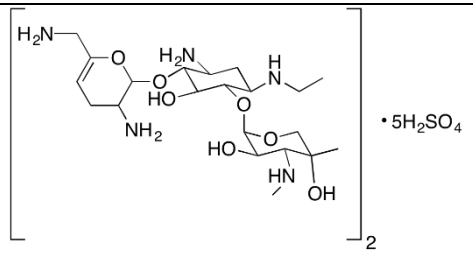
Colistimethate Sodium	4.11	-		HPLC/UV-Vis (Composition)
Colistin Sulfate	2.38×10^{-02}	$pK_{a1} = 11.57$ $pK_{a2} = 10.23$		TLC, HPLC/UV-Vis (Composition)
Daunorubicin Hydrochloride	6.27×10^{-01}	$pK_{a1} = 8.01$ $pK_{a2} = 10.03$		IRS, HPLC/UV-Vis (Composition)
Demeclocycline Hydrochloride	1.52	$pK_{a1} = 2.94$ $pK_{a2} = 9.04$		TLC, HPLC/UV-Vis (Composition)
Dicloxacillin Sodium	3.63×10^{-03}	2.8		IRS, TLC, HPLC/UV-Vis (Composition)

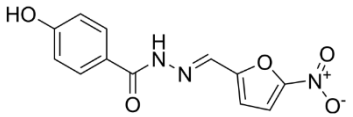
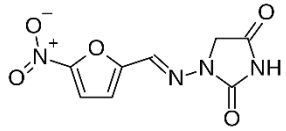
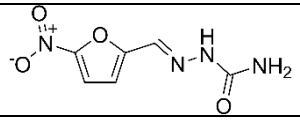
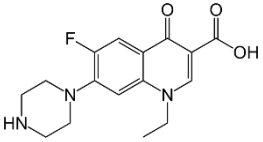
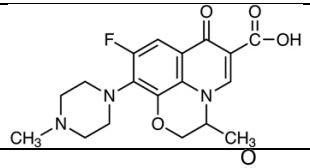
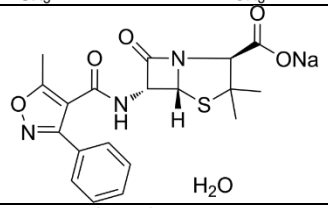
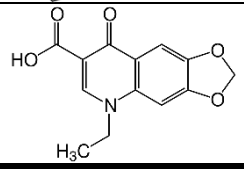
Dirithromycin	-	9.0		IRS, HPLC/UV-Vis (Composistion)
Doxorubicin Hydrochloride	1.18	pK_{a1} = 8.0 pK_{a2} = 9.93		IRS, HPLC/UV-Vis (Composistion)
Doxycycline Hyclate	6.3×10^{-01}	pK_{a1} = 3.0 pK_{a2} = 7.9 pK_{a3} = 9.2	 $0.5H_2O$ $0.5C_2H_6O$ HCl	HPLC/UV-Vis
Erythromycin	2.0	8.8		IRS, TLC, HPLC/UV-Vis (Composition)

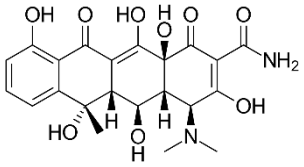
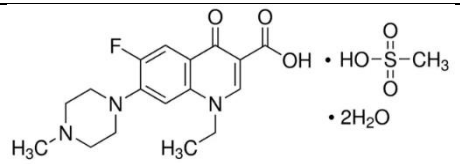
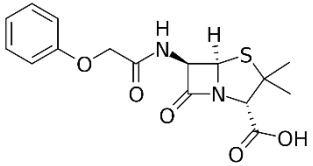
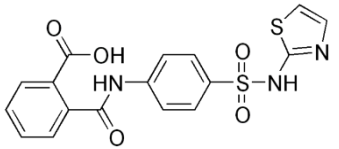
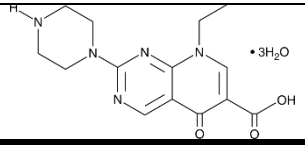
Flucloxacillin Sodium	5.45×10^{-02}	3.75		IRS, TLC, HPLC/UV-Vis (Composition)
Flumequine	Insoluble	6.5		IRS, TLC, HPLC/UV-Vis (Composition)
Fosfomycin Sodium	$5.14 \times 10^{+01}$	1.25		IRS
Framycetin Sulfate	$6.47 \times 10^{+01}$	$pK_{a1} = 12.29$ $pK_{a2} = 9.73$		HPLC/UV-Vis (Composition)
Furazolidone	4.0×10^{-03}	-		IRS
Fusidic Acid	5.21×10^{-03}	5.35		IRS, HPLC/UV-Vis (Composistion)

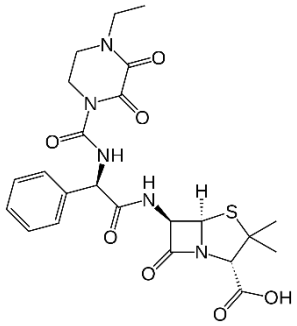
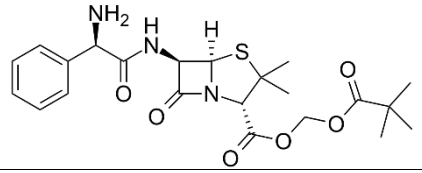
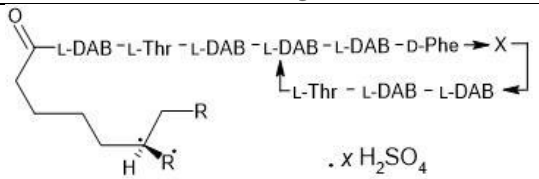
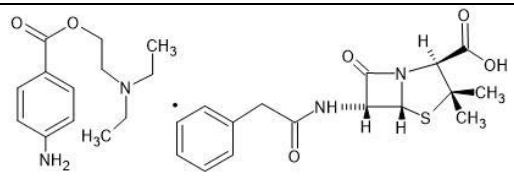
Gentamicin Sulfate	1.0×10^{-01}	-		TLC, HPLC/UV-Vis (Composition)
Gramicidin	-	-		TLC, HPLC/UV-Vis (Composition)
Imipenem Monohydrate	7.76×10^{-01}	3.2		IRS, HPLC/UV-Vis (Composistion)
Josamycin	5.35×10^{-02}	7.1		UV-Vis, TLC
Kanamycin Sulfate	Miscible	7.2		TLC

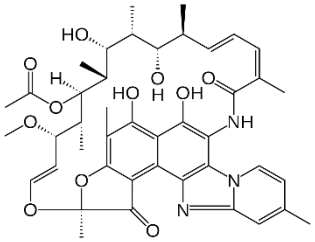
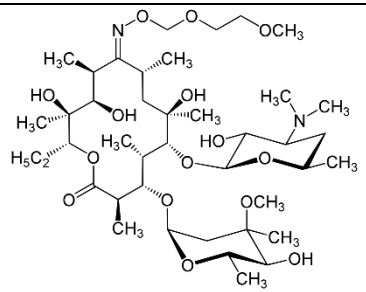
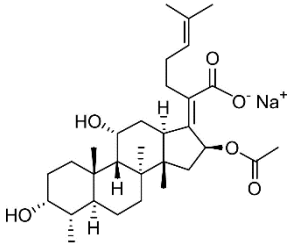
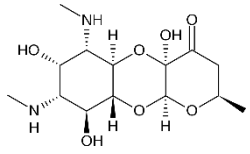
Levofloxacin Hemihydrate	1.44	$pK_{a1} = 5.45$ $pK_{a2} = 6.2$		IRS, HPLC/UV-Vis (for related substances)
Lincomycin Hydrochloride	$2.93 \times 10^{+01}$	$pK_{a1} = 12.37$ $pK_{a2} = 7.97$		IRS, HPLC/UV-Vis (for related substances)
Lymecycline	-	2.5		IRS, HPLC/UV-Vis (for related substances)
Meropenem Trihydrate	5.63	$pK_{a1} = 3.28$ $pK_{a2} = 9.39$		IRS, HPLC/UV-Vis (for related substances)
Metronidazole	$1.1 \times 10^{+01}$	2.57		IRS, HPLC/UV-Vis (for related substances)
Minocycline Hydrochloride Dihydrate	$1.23 \times 10^{+01}$	-		IRS, TLC, HPLC/UV-Vis (for related substances)

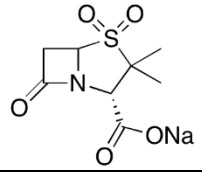
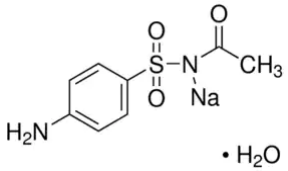
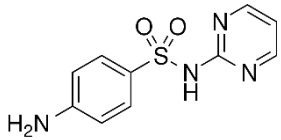
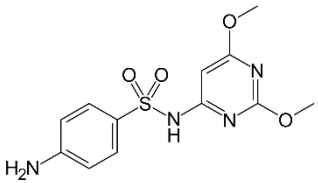
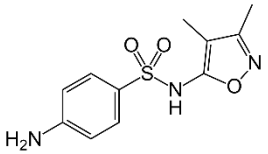
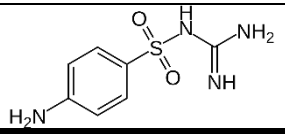
Mitomycin	8.43	10.9		IRS, HPLC/UV-Vis (for related substances)
Moxifloxacin Hydrochloride	1.68×10^{-01}	$pK_a = 5.49$ $pK_b = 9.51$		IRS, HPLC/UV-Vis (for related substances)
Mupirocin	2.65×10^{-02}	4.78		IRS, HPLC/UV-Vis (for related substances)
Neomycin Sulfate	2.5×10^{-01}	$pK_a = 12.9$ $pK_b = 9.52$		HPLC/UV-Vis (for related substances)
Netilmicin Sulfate	$1.0 \times 10^{+02}$	-		HPLC/UV-Vis (for related substances)

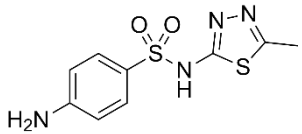
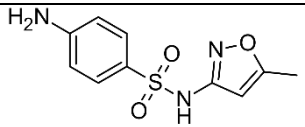
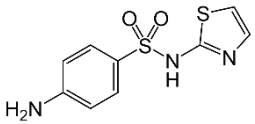
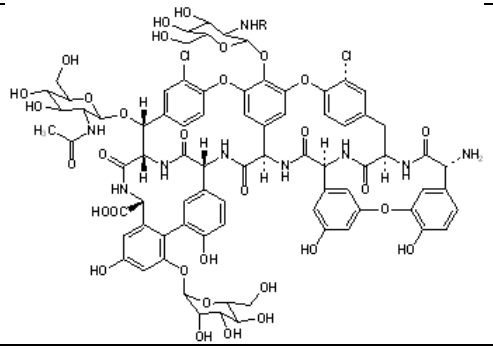
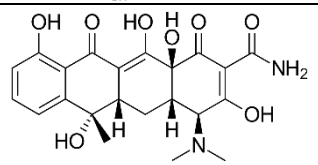
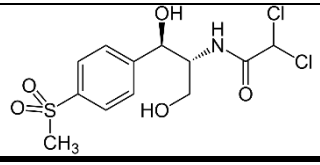
Nifuroxazide	-	-		IRS, HPLC/UV-Vis (for related substances)
Nitrofurantoin	7.95×10^{-02}	7.2		TLC (for related substances)
Nitrofurazone	2.68×10^{-01}	10.0		UV-Vis, IRS, TLC
Norfloxacin	$1.78 \times 10^{+02}$	$pK_{a1} = 6.4$ $pK_{a2} = 8.7$		IRS, HPLC/UV-Vis (for related substances)
Ofloxacin	2.83×10^{-03}	5.97		IRS, HPLC/UV-Vis (for related substances)
Oxacillin Sodium Monohydrate	8.62×10^{-02}	2.72		IRS, HPLC/UV-Vis (for related substances)
Oxolinic Acid	-	-		IRS, UV-Vis, TLC

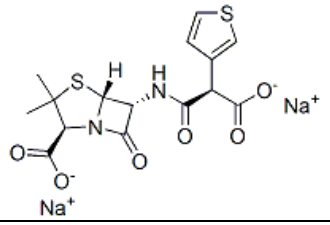
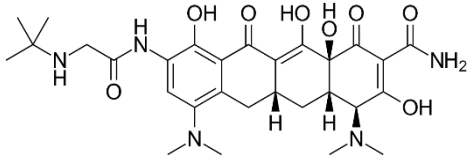
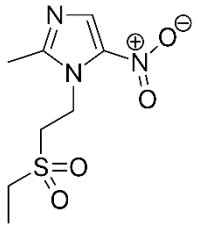
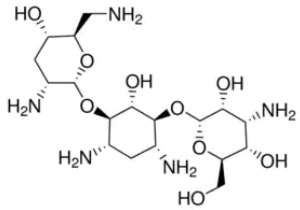
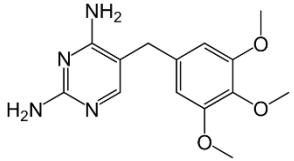
Oxytetracycline	3.13×10^{-01}	$pK_{a1} = 3.2$ $pK_{a2} = 7.5$		IRS, HPLC/UV-Vis (for related substances)
Pefloxacin Mesilate	1.23×10^{-03}	$pK_{a1} = 5.66$ $pK_{a2} = 6.47$		IRS, TLC, HPLC/UV-Vis (for related substances)
Phenoxymethylpenicillin	6.63×10^{-04}	3.39		IRS, TLC, HPLC/UV-Vis (for related substances)
Phthalylsulfathiazole	1.71×10^{-02}	2.91		IRS
Pipemidic Acid Trihydrate	7.46×10^{-01}	$pK_{a1} = 5.11$ $pK_{a2} = 8.66$		IRS, HPLC/UV-Vis (for related substances)

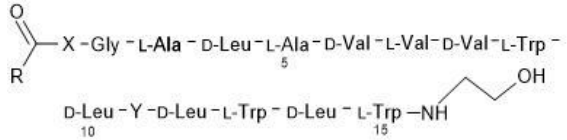
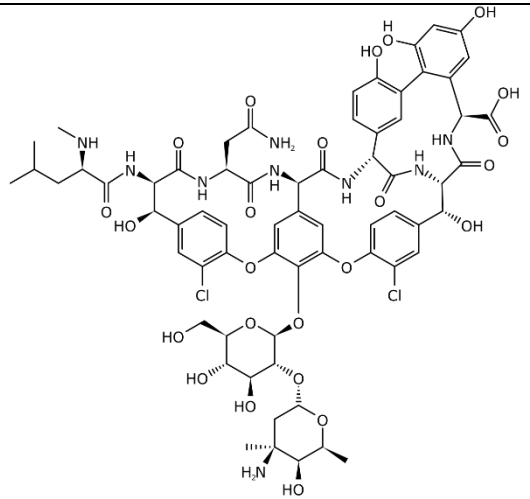
Piperacillin	1.19×10^{-01}	3.49		IRS, HPLC/UV-Vis (for related substances)
Pivampicillin	3.54×10^{-02}	11.71		IRS, HPLC/UV-Vis (for related substances)
Polymyxin B	7.44×10^{-02}	-		TLC, HPLC/UV-Vis (composition)
Benzylpenicillin (Procaine)	-	3.53		IRS, TLC, HPLC/UV-Vis (for related substances)

Rifaximin	7.38×10^{-03}	$pK_{a1} = 6.69$ $pK_{a2} = 5.88$		IRS, HPLC/UV-Vis (for related substances)
Roxithromycin	1.87×10^{-01}	$pK_{a1} = 12.45$ $pK_{a2} = 9.08$		IRS, HPLC/UV-Vis (for related substances)
Sodium Fusidate	4.37×10^{-03}	4.46		IRS, HPLC/UV-Vis (for related substances)
Spectinomycin	1.5×10^{-01}	-		IRS, HPLC/UV-Vis (for related substances)

Sulbactam Sodium	$3.38 \times 10^{+01}$	3.09		IRS, HPLC/UV-Vis (for related substances)
Sulfacetamide Sodium	8.65	4.3		UV-Vis, IRS, HPLC/UV-Vis (for related substances)
Sulfadiazine	7.7×10^{-02}	6.4		IRS, TLC, HPLC/UV-Vis (for related substances)
Sulfadimethoxin	3.43×10^{-01}	6.2		IRS, HPLC/UV-Vis (for related substances)
Sulfafurazole	3.13×10^{-01}	pK_{a1} =1.5 pK_{a2} = 5.0		IRS, TLC, HPLC/UV-Vis (for related substances);
Sulfaguanidine	8.05×10^{-01}	pK_{a1} = 10.53 pK_{a2} = 7.72		IRS, TLC (for related substances)

Sulfamethizole	-	$pK_{a1} = 2.1$ $pK_{a2} = 5.3$		IRS, TLC, HPLC/UV-Vis (for related substances)
Sulfamethoxazole	6.1×10^{-01}	5.4		IRS, TLC, HPLC/UV-Vis (for related substances)
Sulfathiazole	Insoluble	$pK_{a1} = 2.2$ $pK_{a2} = 7.24$		IRS, TLC (for related substances)
Teicoplanin	-	-		IRS, HPLC/UV-Vis (Composition)
Tetracycline	2.31×10^{-01}	$pK_{a1} = 3.3$ $pK_{a2} = 7.7$ $pK_{a3} = 9.7$		IRS, HPLC/UV-Vis (for related substances)
Thiamphenicol	2.27	8.75		IRS, HPLC/UV-Vis

Ticarcillin Sodium	1.64×10^{-01}	3.09		IRS, TLC, HPLC/UV-Vis (for related substances)
Tigecycline	1.46×10^{-02}	$pK_{a1} = 3.17$ $pK_{a2} = 8.97$		IRS, HPLC/UV-Vis (for related substances)
Tinidazole	2.00	4.7		UV-Vis, IRS, TLC, HPLC/UV-Vis (for related substances)
Tobramycin	$5.37 \times 10^{+01}$	$pK_{a1} = 12.54$ $pK_{a2} = 9.66$		TLC, HPLC/UV-Vis (for related substances)
Trimethoprim	4.0×10^{-01}	7.12		IRS, HPLC/UV-Vis (for related substances)

Tyrothricin	Insoluble	-		IRS, HPLC/UV-Vis (Composition)
Vancomycin B	-	pK_{a1} = 2.6 pK_{a2} = 7.2 pK_{a3} = 8.6 pK_{a4} = 9.6 pK_{a5} = 10.5 pK_{a6} = 11.7		IRS, HPLC/UV-Vis

GC = Gas chromatography; HPLC/UV-Vis = High-performance liquid chromatography with ultraviolet visible detector; IRS = Infrared Spectroscopy; NR = non reported; TLC = Thin-layer chromatography; UV-Vis = Ultraviolet visible absorption spectroscopy.

which the chromatograms are to be taken for the molecule composition analysis or for similar substances to the indicated pharmacological drug.

3.2 Resistance and contamination by antibiotics

Similar to the totality of evolutionarily distinct living beings, bacteria develop in complex ecosystems that involve interactions with different types of organisms and, as observed by the very effect of antibiosis, are subject to amensalism by other species [18]. Therefore, it is naturally expected that there are, among populations, genes that encode resistance transferred horizontally between individuals according to natural evolution. [19–21], resulting in selective pressure on certain portions of bacterial populations, facilitating the propagation of individuals with better mechanisms of resistance to antibiotics [18,19,22]. Consequently, the presence of antibiotic residues in the environment results in the progressive limitation of treatments for bacterial infections, mainly with the possibility of the emergence of resistant strains to multiple classes of antibiotics.

Given the uncertainty regarding the totality of the environmental impacts caused by antibiotic residues in different ecosystems, the legislation for its use is particular to different areas, with the common agreement of maintaining correct use standards because incorrect or excessive use of these drugs is the main cause of the emergence of resistant microorganisms. It is estimated that 34.8 billion doses of antibiotics are used worldwide, with a consumption growth of 65% from 2000 to 2015. In the United Kingdom, one in five antibiotic prescriptions is unnecessary, a rate that grows when referring to the United States, with one in three prescriptions [23]. According to World Health Organization (WHO), the antibiotic account for 17% of drugs that are adulterated or present quality below standards guidelines [24].

Antimicrobial resistance is among the ten greatest threats to global public health. Since only 2019, around 32 new antibiotics have been in development for priority pathogens, and only six of which had innovative mechanisms to combat them, indicating the loss of progressive efficacy of these drugs against microbial infections [25]. Data provided by the Brazilian Federal Council of Pharmacy [26], in 2019, indicated that antibiotics represent 42% of the most used drugs in each six-month period, besides showing high rates of self-medication among the population, as well as deliberate reduction of the ideal dose, or discontinuation of treatment. In addition to irregularities

regarding the use of these drugs, it was pointed out that about 76% of the sample population improperly dispose of medication waste, either by overbuy or expire the validity of the antibiotics.

The contamination of natural waters, wastewaters and soil by antibiotics residues occurs mainly by inadequate discharge of residues and disposal in domestic sanitary sewers, resulting in environmental contamination and health problems. Agricultural production that uses water or soil contaminated by antibiotics residues results in consumer contamination and probable increase of bacterial resistance to these drugs.

Another important source of antibiotic contamination is the livestock practice, because meat production requires the use of antibiotics, whether it's for the treatment of cattle, pigs and poultry in general, against infections by microorganisms, or as a prophylaxis measure, ensuring the increase and quality of the herds. These pharmaceuticals are also used as growth promoters and improvement of reproductive capabilities, if added to the animal's rations [27]. According to data provided by the Food and Agriculture Organization of the United Nations (FAO), the use of antibiotics in animals and plants world production is growing exponentially, expected to double until 2030 [28], resulting in a major environmental and public health concern.

Aquaculture is another important production sector on regards to the use of antibiotics on a large scale. In this case, antibiotics are present mainly in the food, incorporated into rations [29] and brings risks associated with the accumulation of residues, toxicity when in high concentration [30], and, mainly, selection of resistant bacteria [31–34].

The volume of antibiotic residues that reach the environment due to livestock and aquaculture practices, is directly related to the amount of drug that is effectively administered, absorbed, and metabolized by the animal. And the degree of metabolism, in turn, is dependent on several factors, both related to the drug itself, including its class, route of administration, dosage, and half-life; and to the treated animal, with factors such as age, health status, or the treated species interfering. In this way, there is the contamination of the manure produced (biological fluids), whose destination can be the pasture of the creation or application as fertilizer, with distribution through soil, giving room for the arrival of non-metabolized substances to the population from consumption of contaminated foods and water [35].

3.3. Detection of antibiotics

According to the British Pharmacopoeia [16] the detection of antibiotics in pharmaceutical formulations can be performed using infrared absorption spectroscopy (IRS), as indicated in Table 1. In this technique a source of infrared radiation is focused on the sample that absorbs radiation and produces rotational and vibrational transitions in the chemical structures of organic molecules. Measurements of absorbance of infrared radiation result in a spectrum for identification (wavelength) and quantification (absorbed radiation intensity) [36]. Normally, the atoms of complex molecules, such as antibiotics, are grouped into functional groups, which provides the basis for infrared spectroscopy, as the vibrational and rotational frequencies of specific functional groups are similar and independent of the rest of the molecules [37]. In Near Infrared Spectroscopy (NIR), the absorbance of electromagnetic radiation with wavelengths from 780 nm to 2500 nm is measured, altering factors associated with analytical instrumentation and, consequently, sensitivity [37].

Furthermore, the Fourier-transform infrared spectroscopy (FTIR) simultaneously measures high-resolution spectral data over a wide spectral range, from the mid infrared region radiation of 2 μm to 25 μm (5,000 - 400 cm-1) to near infrared region radiation from 1 μm to 2.5 μm (10,000 - 4,000 cm-1), because the instrumentation contains a configuration of mirrors, one of which is moved by a motor (Michelson interferometer). The use of a Fourier transform (a mathematical process) results in the conversion of raw data in a spectrum for quantitative and qualitative analysis [38].

Molecular spectroscopy in the ultraviolet and visible (UV/Vis) region is based on measures of electromagnetic radiation absorbance in the range 190 nm to 700 nm that promote electronic, rotational, and vibrational transitions, according to the presence of specific chemical groups (chromophores) and the concentration of the absorbing species [39]. These transitions allow absorbance spectrum used in the identification and quantification of antibiotics.

The sensitivity and selectivity of analysis using spectroscopic techniques is only suitable for quality control in the pharmaceutical industry, where the chemical composition and the quantities of antibiotics present are exactly known. Detection in complex samples such as natural waters, soils and foods requires the use of more specific

and selective techniques that allow the identification of antibiotics in lower concentrations and samples of poorly known chemical composition.

To improve the analytical parameters in spectroscopic analysis of antibiotics, a previous separation can be performed by thin layer chromatography (TLC), an affinity-based method of separation of complex samples. In TLC, each pharmaceutical formulation will have different affinities for the mobile and stationary phases, and this affects the speed at which it migrates. The stationary phase is a thin adsorbent material layer, usually silica gel or aluminum oxide, coated onto an inert plate surface, typically glass, plastic, or aluminum. The pharmaceutical formulation is spotted onto one end of the TLC plate and placed vertically into a closed chamber with an organic solvent (mobile phase). The mobile phase travels up the plate by capillary forces and sample components migrate varying distances based on their differential affinities for the stationary and mobile phases. When the solvent reaches the top, the plate is removed from the developing chamber and dried. The separated components appear as spots on the plate and the retention factor (R_f) of each component of pharmaceutical formulation is assessed by spectroscopy [40].

High-performance liquid chromatography with ultraviolet and visible detection (HPLC-UV/Vis) can also be used in the separation and detection of antibiotics in pharmaceutical formulations, as indicated in Table 1, according to the antibiotic solubility in a liquid phase. The suitable separation depends on the interaction of antibiotic between the mobile phase, that can be modified according to the polarity of the pharmaceutical compound, and the stationary phase. The antibiotics separation is based on differences in species mobility through a stationary phase that follow specific mechanisms (adsorption, partition, ion exchange, size exclusion, or affinity), that are entrained by a mobile phase flow (liquid, gaseous or supercritical fluid). At the end of the stationary phase, the separated antibiotics can be identified by a detector, which define the detection chromatographic technique [41].

However, considering the environmental impact generated by the presence of antibiotics residues in the different types of samples, it was necessary the development of more suitable analytical methodologies for their identification and quantification, resulting in the establishment of information for taking measures against the damages arising from this contamination. In this way, the most sensitive, selective, and accurate forms of detection gain focus, considering factors associated with cost and analytical

practicality, resulting in the development of high-efficiency analytical methods for practices application.

Among these, the microbiological inhibition methods, based on the ability of antibiotics to inhibit the growth of test bacteria, have been used with success in the detection antibiotic residues in natural water, soil, and foods samples. They are still commonly used for preliminary screening of antibiotic residues in complex samples such as edible tissues of animals and sewage sludge due to their low cost, portability, easy operation, broad spectrum, and high throughput [42–44].

Advances spectroscopic methodologies using mathematical modeling [45], carbon quantum dots as fluorescent sensor [46], magnetic substrate based on metal-organic frameworks as sensitive surface-enhanced Raman spectroscopy platform [47], or microfluidic paper-based analytical device in colorimetric analysis [48] also have been proposed in antibiotic detection. These methodologies are fast, specific, low cost, environmental friendly, operationally easy, however present low sensitivity for ultra-trace detection of antibiotics.

Besides, modern chromatographic methods have been carried out by using high performance liquid chromatography (HPLC), ultra-high performance liquid chromatography (UPLC) and liquid chromatography tandem mass spectroscopy (LC-MS/MS) in antibiotic analysis in biological samples, food samples, manure, soil, solid wastes, water, and wastewater samples [49–51]. The employ of these techniques present excellent sensitivity and selectivity, and some procedure present high specificity for antibiotic. However, the instrumentation is very expensive and requires highly trained personnel, sophisticated sample pre-treatment and they can only be applied under special laboratory conditions.

In the last two decades, the electroanalytical techniques have been largely used in the detection of antibiotics in complex samples [52]. These techniques involve measurements of electrical properties, which can be related to identity and quantity of compounds of interest [4,50]. Among them, the voltammetric techniques, which are related to application of an electrical potential difference that present sufficient energy to promote electrons transfers, are suitable in the quantification of low concentrations of antibiotics even in complex systems, and allow information about redox properties providing important information about the formation of intermediaries compounds, and general reactions mechanisms in an aqueous and biological medium, since in these medium the main reaction that occurs are redox.

The analytical signals obtained from voltammetric techniques present profile and intensity strongly of mode of potential application in function of time, which define the type of voltammetric technique. The potential can be applied in linear, triangular or pulse form, which pulse form result in chronoamperometry-based techniques and include normal pulse voltammetry (NPV), differential pulse voltammetry (DPV), staircase voltammetry (SV), and square wave voltammetry (SWV) [53]. However, SWV presents the best sensitivity and applicability in electroanalysis, including antibiotics detection.

4. Square wave voltammetry

In SWV, a series of equal amplitude pulses are applied under a staircase potential, in each forward pulse the chemical specie diffuses to the electrode surface, and it is immediately reduced or oxidized. During the backward pulse the chemical specie that was just oxidized or reduced returns to the initial condition in a reversible reaction, or no reaction occurs if the system is irreversible. So, the current values are measured just before and at the end of each pulse, and the net or resulting currents are plotted as a function of the corresponding potential of the staircase waveform, resulting in a well-defined gaussian signal. The resultant signals are greater than the forward and reverse signals, due to significant reduction in the capacitive currents [54,55], allowing in a high sensitivity and better selectivity than other electroanalytical techniques. So, the SWV results in a technique comparable to chromatography and spectroscopy in terms of detection limits, exceeding, sometimes in sensitivity and, mainly, in speed of analysis [56].

The voltammetric parameters of SWV are the range potential, scan rate potential, pulse height (pulse amplitude, *a*), pulse duration (frequency inverse, *f*) and step height (scan potential increment, ΔE_s), that need previous optimization for each redox compound evaluated, since their values have a significant effect on the analytical signals [55,56]. Furthermore, the results depend on working electrode materials and the experimental parameters (solvent, supporting electrolyte, and pH of the medium) and electroanalytical parameters (range potential, scan rate potential, technique parameters). The peak current (Ip) and the peak potential (Ep) in the maximum signal, respectively, are used to identify and quantify, respectively, the compound of interest. Besides, the half-height width (W1/2) of the voltammetric peak defines the selectivity of the voltammetric analysis [57].

The speed analysis, sensitivity, selectivity, good analytical frequency, low cost of instrumentation and consumables, and ease of operation have broadened the applicability of SWV in detection of pharmaceutical compounds [58], such as neurotransmitter [59], antidepressants [4], antimalarial drugs [60], antiretroviral drugs [61], anticytomegalovirus drugs [62], antiviral drugs [63], anticancer drugs [64], among others.

Furthermore, like other voltammetric techniques, SWV present good robustness and the voltammetric analysis require simple and fast sample extraction steps, even in the case of very complex samples, such as biological fluids, foods, natural waters, pharmaceutical compounds, soil and wastewater, as will be explained below. So, SWV can be use with success in the quality control in pharmaceutical industries since the suspended solids present in solution from pharmaceutical drugs practically does not interfere with sensitivity and selectivity in the analysis.

4.1. Antibiotics detection by SWV

Detection of antibiotics and other pharmaceutical compounds by SWV is possible due to presence of some functional groups such as amide, amine, aromatic rings, carbonyl, double-bonds, triple-bonds, and sulphur-bonds groups, that can be oxidized and or reduced allowing a measurable electrical signal (quantitative) in a specific potential (qualitative). Furthermore, I_p, E_p and $W_{1/2}$ can be previously optimized resulting in excellent analytical sensitivity and selectivity for antibiotics detection even in complex samples [53].

In this context, the quinolones and fluoroquinolones present in their chemical structure, shown in Table 1, a central amine group containing a non-bonding electron as donor, which can be electrochemically oxidized resulting in current values directly related to antibiotic concentration. In antibiotics of this class, the oxidation reaction take place in the secondary amine (-NH) group might get electrochemically oxidized to hydroxylamine (-N-OH) in a redox reaction involving two protons ($2H^+$) and two electrons ($2e^-$), a typical redox mechanism in organic electrochemistry.

Similarly, the cephalosporins, β-lactam antibiotics whose action is related to blocking cell wall synthesis in the infection process, are chemically and electrochemically active molecules because of its β-lactam ring structure, which can be easily hydrolyzed in the environment allowing one of the major controlled pollutants all over the world, or

hydrolyzed in the electrochemical cell resulting in peak currents directly related to cephalosporins concentration [65]. Furthermore, the penicillins also contain a β-lactam ring which can be electrochemically oxidized, in an irreversible electrons transfer, resulting current and potential peaks used in the quantification and identification, respectively, of penicillins antibiotics in complex samples, such as urine [66], food samples [52,67], commercial formulations [67].

So, a detailed evaluation in the scientific databases Scopus® and ScienceDirect® over the last 10 years from 2012 - 2022 using the keywords "Electroanalysis", "Square Wave Voltammetry", "Antibiotics", "Pharmaceutical Compounds", and the antibiotic name combined with square wave voltammetry technique name was performed. All relevant information obtained are presented in Figure 2, where can be observed that, in this period, almost all classes of antibiotics have been analyzed using SWV. The perceptual values correspond to around 90 papers published in this period.

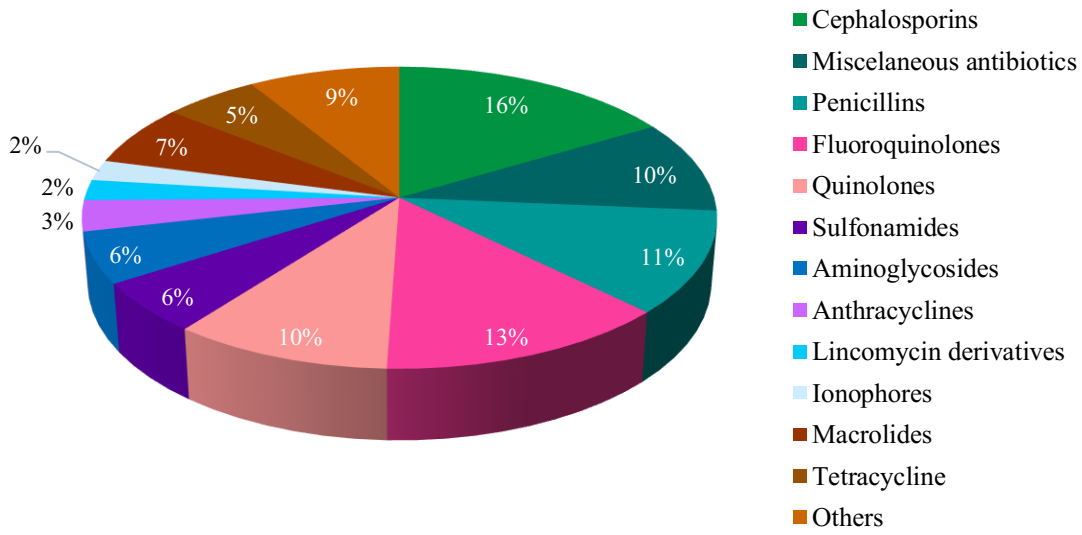


Figure 2: Analytical determination of different classes of antibiotics using SWV with information obtained from the Science Direct® and Scopus® databases, using the keywords "Electroanalysis"; "Square Wave Voltammetry"; "Antibiotics"; Pharmaceutical Compounds, in the period of 2012 to 2022.

Furthermore, the analysis of Figure 2 indicated the predominance in the detection of cephalosporins, β-lactam antibiotics whose action is related to blocking cell wall synthesis in the infection process [68], which has as its official method of detection,

mainly, HPLC/UV-Vis [16]. Karadurmus et. al [69] point to the fact that most drugs belonging to this class are electroactive, with defined redox processes that make them suitable for the use of various voltammetric methods. Recent studies evaluate some of these methods, such as cyclic voltammetry for characterization of cefotaxime in aquatic samples [70], and differential pulse voltammetry for quantification of cefixime and cefadroxil in biological samples [71,72], with high detection limits and satisfactory results, considering the limitations of the respective methods.

However, antibiotic detections require more sensitive and selective methods, due to their present in biological fluids, natural waters, soil, and food samples in very low concentrations, and for this, the SWV is more convenient electroanalytical technique for ultratrace detection of antibiotics and other pharmaceutical compounds.

Table 2 shows an overview of the application of SWV in the antibiotics detection, showing the working electrode employed, experimental and voltammetric parameters, the experimental conditions, the LOD obtained, and the type of the sample where the SWV method was used, considering to the main classes of antibiotics.

In this context, many different samples are observed throughout the evaluated articles and it is important to highlight their purpose. For example, Guerra and Cestarolli [73] present the detection of azithromycin with vanadium dioxide films in aquatic environments, focused in wastewater. They mention the relevance of the detection in such samples, mainly considering the increasing consumption of water, allied with the crescent necessity for pharmaceuticals to treat human and animal diseases, resulting in direct increase of wastewater volume. 90% of those pharmaceuticals reach urban wastewater treatment plants unchanged or as metabolites and only 14% is removed via wastewater treatment. Pan et al. [74] reinforce this with their work, also on the detection of azithromycin, with the analysis of the fact that macrolide antibiotics have excellent clinical performance and, therefore, growing application and excretion into nature. They presented a table with the concentration of 27 personal care products in the secondary effluents and the effluents after ultrafiltration treatment of 5 sewage treatment plants and showed that azithromycin roxithromycin carried the most worrying health risks.

There are also many food samples, generally, with varying concerns and objectives. Milk is one of the most common and Wei et al [75] mention the expressive concern about pharmacological residues in food events, especially related to the use in the form of veterinary medicines. Bezzat, Z. Pourghobadi and R. Pourghobadi [67] talk

Table 2: Detection of various classes of antibiotics by SWV, indicating the working electrode used, experimental and voltammetric conditions, LOD values obtained, and the type of the samples analyzed.

	Antibiotic	Electrode	Conditions	Limit of detection (nmol L^{-1})	Sample	Reference
Cephalosporins	Cetiofur	Mercury	Britton-Robinson buffer; pH 10; f = 90 s^{-1}; ΔEs = 4 mV; a = 25 mV	3.73×10^{-01}	Milk	[76]
	Cefixime	Modified carbon paste with gold nanoparticles	Britton-Robinson buffer; pH 3.0; f = 40 s^{-1}; a = 0,1	3.00	Urine and pharmaceutical samples	[77]
		Modified gold with monolayer of cysteine and gold nanoparticles	Phosphate buffer; pH 2,6; f = 150 s^{-1}; a = 0.05 V; ΔEs = 0.01 V	$3.80 \times 10^{+02}$	Human serum	[77]
		Modified gold with monolayer of cysteine and gold nanoparticles	Phosphate buffer; pH 2.6; f = 150 s^{-1}; a = 0,05 V; ΔEs = 0.01 V	$3.20 \times 10^{+02}$	Urine	[77]
		Modified gold with monolayer of cysteine and gold nanoparticles	Phosphate buffer; pH 2,6; f = 150 s^{-1}; a = 0,05 V; ΔEs = 0,01 V	$3.50 \times 10^{+02}$	Milk	[77]
	Cefquinome	Modified graphite with carbon nanotubes	Phosphate buffer; pH 2; a = 25 mV; f = 10 s^{-1}	$5.00 \times 10^{+01}$	Milk	[68]
	Cefuroxime Axetil	Hanging mercury drop	Buffer Borate Phosphate; pH 7.0; f = 40 s^{-1}; ΔEs = 5 mV; a = 35 mV	NR	Pharmaceutical samples	[69]
		Glassy carbon modified with graphene oxide	Britton-Robinson buffer; pH 2.0; f = 40 s^{-1}; ΔEs = 5 mV; a = 35 mV.	NR	Pharmaceutical samples	[69]

	Cefdinir	Hanging mercury drop	Britton-Robinson buffer; pH 4.2; a = 65 mV;	$2.00 \times 10^{+02}$	Human serum and pharmaceutical samples	[70]
		Glassy carbon	Britton-Robinson buffer ; pH 5.0; a = 65 mV	$2.60 \times 10^{+02}$	Human serum and pharmaceutical samples	[70]
	Cefepime	Solid mercury amalgam with silver nanoparticles	Britton-Robinson buffer; pH 2.5; f = 60 s^{-1}, ΔEs = 5,0 mV; a = 30 mV	8.51	Breast milk	[71]
	Cefditoren pivoxil	Hanging mercury drop	Britton-Robinson buffer; pH 6.0; f = 25 s^{-1}; a = 65 mV	$3.00 \times 10^{+01}$	Human serum e Pharmaceutical samples	[72]
		Glassy carbon	Britton-Robinson buffer; pH 4.0; f = 25 s^{-1}; a = 65 mV	$2.40 \times 10^{+02}$	Human serum e Pharmaceutical samples	[72]
	Demeclocycline	Boron-doped diamond	Britton-Robonson buffer with sodium dodecylsulfate (SDS); pH 2.0; f = 50 s^{-1}, ΔEs = 8 mV; a = 30 mV	$2.3 \times 10^{+10}$	Urine	[78]
		Boron-doped diamond	Britton-Robonson buffer with cetyltrimethylammonium bromide (CTAB); pH 9.0; f = 50 s^{-1}, ΔEs = 8 mV; a = 30 mV	$4.8 \times 10^{+09}$	Urine	[78]
	Cefitizoxime	Hanging mercury drop	KCl (1.0 mol L^{-1}) in purified water; f = 100 s^{-1}; a = 50 mV	$7.60 \times 10^{+02}$	Wastewater	[79]
Miscellaneous antibiotics	Chloramphenicol	Glassy carbon	Phosphate buffer, pH 4.0; a 25 mV; ΔEs = 4 mV.	3.00×10^{-01}	Fish	[80]
		Modified glassy carbon with exfoliated porous carbon	Phosphate buffer; pH 7.5; ΔEs = 4 mV; a = 25 mV; f = 15 s^{-1}.	2.90	Honey	[81]
		Modified thin film of platinum by electropolymerization with o-phenylenediamine	Phosphate buffer; ΔEs = 10 mV; f = 10 s^{-1}; a = 25 mV.	3.90×10^{-01}	Honey and milk	[82]
		Modified glassy carbon with aptamer	Phosphate buffer; pH 7.4; f = 35 s^{-1}; a = 25 mV; ΔEs = 4 mV.	2.10×10^{-05}	Milk and fish	[83]

		Modified screen printed electrode with iron oxide nanoparticles embed N-doped graphene	Phosphate Buffered Saline; pH 7.0	10	Milk	[84]
		Modified screen-printed carbon with eriochrome black polymer T	[Fe(CN)6]/ACN; a = 10 mV.	2.90×10^{-02}	Water from fish tank	[85]
		Modified glassy carbon with aptamer	Buffer HAc-NaAc; pH 4.5; f = 25 s^{-1}; a = 25 mV; ΔEs = 4 mV.	1.90×10^{-04}	Milk	[86]
		Modified glassy carbon with aptamer	Buffer HAc-NaAc; pH 4.5; f = 25 s^{-1}; a = 25 mV; ΔEs = 4 mV.	3.30×10^{-05}	Milk	[87]
	Pyrazinamide	Screen-printed carbon	Phosphate buffer; pH = 1.0; f = 75 s^{-1}, a = 50 mV; ΔEs = 5 mV.	$5.70 \times 10^{+02}$	Urine	[88]
		Modified glassy carbon with diamond nanoparticles	Phosphate buffer; pH 3,0; f = 50 s^{-1}; a = 50 mV; ΔEs = 5 mV.	$2.20 \times 10^{+02}$	Urine and human serum	[89]
Penicillins	Amoxicillin	Modified glassy carbon with carbon black immobilized on diexadcyl Phosphate film	Phosphate buffer; pH 7.0; f = 20 s^{-1}; a = 50 mV; ΔEs = 5 mV.	$1.20 \times 10^{+02}$	Urine and water	[90]
		Modified glassy carbon with reduced graphene oxide and Nafion	Britton-Robinson buffer; pH 2.0; f = 100 s^{-1}; a = 50 mV; ΔEs = 2 mV	$3.60 \times 10^{+02}$	River water	[91]
		Modified glassy carbon with quantum dots on poly(3,4-ethylenedioxythiophene) sulfonate polystyrene film	Phosphate buffer; pH 6.0; f = 20 s^{-1}; a = 75 mV; ΔEs = 5 mV	$5.00 \times 10^{+01}$	Urine, Milk, Pharmaceutical products	[92]
		Modified carbon paste with carbon nanotubes and ZnO	Phosphate buffer; pH 7.0; a = 50 mV; f = 12 s^{-1}	$5.00 \times 10^{+02}$	Blood, urine, and pharmaceutical samples	[93]
		Modified glassy carbon electrode with poly(A_2P_2CuC) film	Phosphate-buffered saline; pH 7.0; *a* = 0.01 V; ΔEs = 0.23 V	$1.15 \times 10^{+05}$	Pharmaceutical and biological samples	[94]
		Modified carbon paste with polyaniline film	Acetate buffer; pH 2.0–6.5; f = 40 s^{-1}; a = 25 mV	3.50×10^{-01}	Pharmaceutical and biological samples	[95]
		Modified glassy carbon with graphene nanoparticles and polyglutamic acid	Phosphate buffer; pH 7.0; a= 0.025 V; ΔEs = 4 mV	$1.18 \times 10^{+05}$	Urine	[96]
		Modified glassy carbon with graphene, gold, and palladium oxide nanoparticles	Phosphate buffer; pH 2,4 – 10.0; μ = 1.0 mol L^{-1}	$9.00 \times 10^{+02}$	Urine	[97]

		Graphite	Phosphate buffer; pH 7.0	$2.24 \times 10^{+02}$	Water	[98]
	PenicillinsV	Boron-doped diamond	Acetate buffer; pH 5.0; a = 60 mV; f = 80 s^{-1}; ΔEs = 7 mV.	$3.20 \times 10^{+08}$	Urine	[66]
	PenicillinsG	Modified carbon paste with liquid ionic carbon and TiO2 nanoparticles	Phosphate buffer; pH 7.0; ΔEs = 6 mV; a = 40 mV; f = 50 s^{-1}	2.09	Milk, plasm, and human serum	[67]
Fluoroquinolones	Balofloxacin	Modified glassy carbon with Bi2O3/ZnO nano-compound	Britton-Robinson buffer; pH 4.5	$4.05 \times 10^{+01}$	Blood serum	[99]
	Enrofloxacin	Glassy carbon	Phosphate buffer; pH 7.0; f = 20 s^{-1}; a = 25mV	$1.64 \times 10^{+03}$	Soil	[100]
		Modified graphite with polymer p(Py-co-OPD)	Buffer acetic acid; pH 3.5; f = 20 s^{-1}	6.57×10^{-04}	Pharmaceutical samples	[101]
		Modified gold aptamer	Tris-HCL; pH 7.4	3.40	Water and milk	[102]
		Boron-doped diamond	Britton-Robinson buffer; pH 2.0-10; f = 50 s^{-1}, a = 50 mV;	$5.70 \times 10^{+03}$	Pharmaceutical samples and urine	[103]
	Norfloxacin	Graphite pyrolytic	Phosphate buffer; pH 7.2; a = 25 mV; f = 15 s^{-1}	$2.83 \times 10^{+02}$	Pharmaceutical samples and urine	[104]
		Glassy carbon	Britton-Robinson buffer; pH 7.0; a = 10 mV; f = 10 s^{-1}; ΔEs = 2 mV.	$7.90 \times 10^{+02}$	Urine	[105]
		Modified glassy carbon with carbon nanotubes	0.1 mol L^{-1} H_2SO_4; f = 25 s^{-1}	$4.60 \times 10^{+01}$	Urine	[106]
		Modified glassy carbon with carbon nanotubes	Phosphate buffer; pH 2.1; f = 20 s^{-1}; a = 20 mV	$4.07 \times 10^{+04}$	Urine	[107]
		Graphite pyrolytic	Phosphate buffer; pH 7.2; a = 25 mV; f = 15 s^{-1}; ΔEs = 4 mV	$2.83 \times 10^{+01}$	Urine	[104]
	Ofloxacin	Carbon paste modified with graphene oxide	Phosphate buffer; pH 6.0; f = 15 s^{-1}, a = 75 mV, ΔEs = 5 mV.	2.80×10^{-01}	Urine	[108]
		Modified carbon paste with graphite fragments and carbon nanotubes	Britton-Robinson buffer; pH 7.0; f = 70 s^{-1}; a = 25 mV; ΔEs = 8 mV.	2.40×10^{-01}	Urine	[109]
	Lomefloxacin	Modified glassy carbon with graphene, gold, and palladium oxide nanoparticles	Phosphate buffer; pH 2.4 – 10; μ = 1.0 mol L^{-1}	$8.10 \times 10^{+01}$	Urine	[97]

Nitroimidazoles	Metronidazole	Boron-doped diamond	pH 11; f = 5-100 s^{-1}; ΔEs = 4 mV.	$6.50 \times 10^{+01}$	Urine	[110]
		Screen printed covered with fullerene, graphene oxide, and Nafion	Phosphate Buffer; pH = 7.0; f = 15 s^{-1}; a = 75 mV; ΔEs = 5 mV	$2.10 \times 10^{+02}$	Urine and synthetic serum	[111]
	Ornidazole	Silver and glassy carbon	Na_2SO_4; pH 5,0; *a* = 12 mV	$4.38 \times 10^{+02}$	Human blood	[112]
Quinolones	Levofloxacin	Modified pencil graphite	Phosphate buffer; pH 7.0; f = 0,1 a 10^{-3} k s^{-1}	$1.20 \times 10^{+03}$	Serum and urine	[113]
		Boron-doped diamond	Na2SO4; pH 5.5; f = 100 s^{-1}; a = 50 mV; ΔEs = 5 mV	$2.88 \times 10^{+03}$	Urine e human serum	[114]
		Modified glassy carbon with carbon black and silver nanoparticles and poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonacte) film	Phosphate buffer; pH 6.0; f = 15 s^{-1}, a = 75 mV; ΔEs = 7 mV.	$1.40 \times 10^{+01}$	Synthetic urine and river water	[115]
		Glassy carbon	Phosphate buffer; pH 7.0; a = 10 mV; f = 10 s^{-1}; ΔEs = 2 mV	$2.97 \times 10^{+02}$	Urine	[105]
	Moxifloxacin	Modified graphite-epoxy composite with bismuth film	Acetic acid/acetate buffer; pH 3.81; f = 25,0 s^{-1}; a = 25 mV; ΔEs = 5 mV	5.00×10^{-01}	Biological models	[116]
	Gemifloxacin	Modified glassy carbon with carbon nanotubes	Electrolyte KCl; pH 2.0	$9.00 \times 10^{+02}$	Pharmaceutical samples	[117]
	Ciprofloxacin	Modified glassy carbon with graphene oxide and nickel oxide nanoparticles	Phosphate buffer; pH 6.0; a = 30 mV, f = 80 s^{-1}, and ΔEs = 4 mV	6.00	Human serum and urine	[118]
		Modified screen-printed carbon with gold nanoparticles polymerized with chitosan	Phosphate buffer; pH 5.5; ΔEs = 5 mV;	1.00	Human serum, plasm, and urine	[119]
		Graphite electropolymerized with pyrrole and o-phenylenediamine	$K_3[Fe(CN)_6]$/ KCl; ΔEs = 5 mV; a = 50 mV; f = 20 s^{-1}	7.58×10^{-02}	Pharmaceutical samples	[120]
		Modified screen printed electrode with nanocellulose-polypyrrole matrix and single-walled carbon nanotube	Phosphate Buffered Saline; pH 7.0; *f* = 23 s^{-1}; *a* = 45 mV; ΔEs = 2 mV	0.196	water, biological fluids and pharmaceutical samples	[121]

		Modified glassy carbon with graphene oxide and gold nanoparticles	$K_3Fe(CN)_6$/KCl	1.00	Milk	[122]
		Glassy carbon	Britton-Robinson buffer; pH 2.0; a = 50 mV; ΔEs = 4 mV; f = 70 s^{-1}	$9.20 \times 10^{+02}$	Urine and human serum	[123]
Sulfonamides	Sulfanilamide	Boron-doped diamond	Phosphate buffer; pH 7,0; a = 25 mV; f = 10 s^{-1}; ΔEs = 4 mV	$2.41 \times 10^{+01}$	Water	[124]
	Sulfamethoxazole	Modified glassy carbon with copper and phthalocyanine films	Phosphate buffer; pH 7,0; a = 40 mV; f = 10 s^{-1}; ΔEs = 5 mV	$6.00 \times 10^{+02}$	Water	[125]
	Trimethoprim	Graphite impregnated with poly 1,5-diaminonaphthalene	Phosphate buffer; pH 7.2; f = 15 s^{-1}; a = 25 mV;	$1.10 \times 10^{+02}$	Pharmaceutical samples	[126]
	Sulfacetamide	Modified glassy carbon with molecularly printed polymer and graphene oxide	HAc-NaAc b; pH = 5.2;	NR	Milk	[75]
	Sulfonamide	Screen printed carbon	Phosphate buffer; pH 3.0; a = 25 mV; f = 15 s^{-1}	$1.60 \times 10^{+02}$	Food samples	[127]
	Sulfadimidine	Glassy carbon	Phosphate buffer; pH 7.0	$1,40 \times 10^{-01}$	Egg and milk	[128]
Aminoglycosides	Tobramycin	Modified graphene with iron and silver nanoparticles	Phosphate saline buffer; pH 7.4	$1.50 \times 10^{+01}$	Pork	[129]
	Kanamycin	Modified glassy carbon with aptamer	Buffer HAc-NaAc; pH 4.5; f = 25 s^{-1}; a = 25 mV; ΔEs = 4 mV.	1.60×10^{-04}	Milk	[86]
		Modified glassy carbon with aptamer	Phosphate buffer; pH 7.4; f = 35 s^{-1}; a = 25 mV; ΔEs = 4 mV.	3.50×10^{-05}	Milk and fish	[83]
		Tin and indium oxide	Phosphate buffer; pH 7,0 ; a = 25 mV; f = 15 s^{-1}; ΔEs = 4 mV.	$1.00 \times 10^{+01}$	Milk and honey	[130]
	Streptomycin	Modified screen printed with gold nanoparticles and carbon nanotubes	Buffer HAc–NaAc; pH 4.5; a = 25 mV; f = 25 s^{-1}	2.50	Blood	[131]
Anthracyclines	Epirubicin	Renewable silver amalgam film	Britton-Robinson buffer; pH 2.0-8.0; a = 20 mV; f = 50 s^{-1}; ΔEs = 20 mV	$8.00 \times 10^{+10}$	Urine	[132]
	Doxorubicin	Boron-doped diamond	H_2SO_4 with sodium dodecyl sulfate; a = 25 mV; f = 50 s^{-1}; ΔEs = 10 mV.	$3.10 \times 10^{+01}$	Pharmaceutical samples and wine	[133]

	Natamycin	Modified glassy carbon with graphene oxide and gold nanoparticles in chitosan film	Phosphate buffer; pH 7.0; f = 10 s^{-1}; a = 50 mV; ΔEs = 4 mV	$2.90 \times 10^{+02}$	Urine and water	[134]
Lincomycin derivatives	Clindamycin	Modified carbon paste with carbon nanotubes and ZnO nanoparticles	Britton-Robinson buffer; pH 2.0; f = 50 s^{-1}; a = 50 mV.	$8.5 \times 10^{+01}$ and $7.8 \times 10^{+01}$	Plasm	[135]
Carbapenems	Ertapenem	Hg(Ag)FE combined with renewable silver amalgam film	Britton-Robinson Buffer; pH 7.0; a = 100 mV; f = 150 s^{-1}; ΔEs = 4 mV	$7.80 \times 10^{+01}$	Soil	[136]
Ionophores	Salinomycin	Silver amalgam film	Britton-Robinson Buffer; pH 7.0; f = 150 s^{-1}, a = 80 mV, ΔEs = 1 mV	$1.27 \times 10^{+01}$	Horse feed	[137]
	Monensin	Silver amalgam film	Britton-Robinson Buffer; pH 7.0; a= 20 mV; f = 50 s^{-1}; ΔEs = 5 mV;	$1.36 \times 10^{+06}$	Urine	[138]
Macrolides	Erythromycin	Modified carbon paste with gold nanoparticles	Britton-Robinson Buffer; pH 8.0; a= 20 mV; f = 50 s^{-1}; ΔEs = 5 mV;	$1.80 \times 10^{+07}$	Pharmaceutical samples	[139]
	Erythromycin ethylsuccinate	Modified carbon paste with gold nanoparticles	Britton-Robinson Buffer; pH 11.98; a= 20 mV; f = 50 s^{-1}; ΔEs = 5 mV	$4.50 \times 10^{+04}$	Pharmaceutical samples	[139]
	Azithromycin	Vanadium dioxide	Phosphate buffer; pH 6.0;	$8.40 \times 10^{+01}$	Water	[73]
		Modified glassy carbon electrode with molecularly imprinted polymer	Phosphate buffer saline; pH 7.2; f = ; *a* = 25 mV; ΔEs = 2 mV	$1.2 \times 10^{+05}$	Wastewater	[74]
		Modified carbon paste with gold nanoparticles	Britton-Robinson buffer; pH 11.98; a= 20 mV; f = 50 s^{-1}; ΔEs = 5 mV	$1.43 \times 10^{+06}$	Pharmaceutical samples	[139]
	Clarithromycin	Modified carbon paste with gold nanoparticles	Britton-Robinson buffer; pH 11,98; a = 20 mV; f = 50 s^{-1}; ΔEs = 5 mV	$3.00 \times 10^{+05}$	Pharmaceutical samples	[139]
	Roxithromycin	Boron-doped diamond	Britton-Robinson buffer; pH 4.0; f = 50 s^{-1}; a = 30 mV; ΔEs = 8 mV.	$5.00 \times 10^{+04}$ and $1.2 \times 10^{+05}$	Pharmaceutical samples	[140]
Oxazolidinone derivatives	Linezolid	Boron-doped diamond	Britton-Robinson buffer with sodium dodecyl sulfate ; pH	$2.30 \times 10^{+03}$	Urine	[78]

			2.0; f = 50 s^{-1}; ΔEs = 8 mV; a = 30 mV.			
Tetracyclines	Demeclocycline	Modified gold with cysteine monolayer and gold nanoparticles	Phosphate Buffer; pH 2.6; f = 150 s^{-1}; a = 50 mV; ΔEs = 10 mV	$5.40 \times 10^{+02}$	Human serum	[141]
	Tetracycline	Modified gold with cysteine monolayer and gold nanoparticles	Phosphate Buffer; pH 2.6; f = 150 s^{-1}; a = 50 mV; ΔEs = 10 mV	$4.20 \times 10^{+02}$	Urine	[141]
		Modified gold with cysteine monolayer and gold nanoparticles	Phosphate Buffer; pH 2.6; f = 150 s^{-1}; a = 0,05 V; ΔEs = 0,01 V	$5.20 \times 10^{+02}$	Milk	[141]
		Modified glassy carbon with aptamer	Buffer HAc-NaAc; pH 4.5;f = 25 s^{-1}; a = 25 mV; ΔEs = 4 mV.	4.80×10^{-05}	Milk	[87]
	Oxytetracycline	Modified glassy carbon with metal-organic nanoparticles	Buffer Britton–Robinson; pH 6.0; f = 80 s^{-1}; a = 10 mV	$4.90 \times 10^{+02}$	Wastewater	[142]
Dihydroxyphenols	Resorcinol	Glassy carbon	Britton-Robinson Buffer; pH 4,5; a = 5mV; ΔEs = 0,5 V	4.77×10^{-02}	Sodium lauryl sulfate sample	[143]
Nicotinic acid derivatives	Ethionamide	Boron-doped diamond	HNO_3, f = 50 s^{-1}; ΔEs = 10 mV; a = 40 mV.	$1.71 \times 10^{+02}$	Serum, plasma and pharmaceutical samples	[144]
Rifamicin	Rifaximin	Boron-doped diamond	Buffer Britton–Robinson; pH 4.0; ΔEs = 4 mV; a = 50 mV; f = 80 s^{-1}	$2.69 \times 10^{+01}$	Pharmaceutical samples	[145]
Nitrofuran derivatives	Nitrofurantoin	Boron-doped diamond	Buffer Britton–Robinson; pH 4.0; ΔEs = 4mV; a = 50mV; f = 80 s^{-1}	$2.69 \times 10^{+01}$	Pharmaceutical samples	[145]

specifically about the use of Penicillin G in veterinary practice not only for treatment of infections, but also for prevention and promotion of animal growth, what shows the magnitude of residues generation, considering that not all administered drugs are fully metabolized. Besides, as mentioned in the review by Ribeiro, Ferreira and Franco [146], the market for milk production is billionaire and the use of antibiotics for the mentioned porpoises have a projection to increase to more than double in the next decade.

Milk production, however, is not the only concerning industry, as there are many other food samples between the analysed works, including other animal products, like eggs [128] and honey [127,130], or the meat itself from pork [129] and fish [83] which all essentially have the same problem of over administration of antibiotic drugs to rations or directly to the animal, resulting in the observed accumulation or excretion. Mielech-Łukasiewicz and Leoniuk [133] bring an interesting addition, having accomplished detection of natamycin in wine samples, emplying cathodic-conditioned boron-doped diamond electrode (BDD) for a detection limit of 3.1×10^{-8} mol L^{-1}. This antibiotic is naturally occurring compound produced from *Streptomyces natalensis* bacteria in the process of fermentation, meaning some wines may have it excessively. Besides, it has also common usage as protection product for food in general, meaning its detection for quality control also has importance.

Directly associated with food samples are urine samples, due to the excretion of the unmetabolized antibiotics. Is the case of Elfiky et. al [109] that determined the fluoroquinolone ofloxacin in human urine using carbon paste modified with flake graphite and carbon nanotubes, in Britton-Robinson buffer pH 7.0 as supporting electrolyte, $f = 70$ s^{-1}, $a = 25$ mV, and $\Delta E_s = 8$ mV, allowing a LOD of 2.40×10^{-01} nmol L^{-1}. Another fluoquinolone, the enrofloxacin, was studied by Dönmez, Yardım, and Şentürk [103], also in human urine samples, this time using boron-doped diamond electrode, with Britton-Robinson buffer and surfactant sodium dodecyl sulfate, $f = 50$ s^{-1}, $a = 50$ mV, and $\Delta E_s = 2$ mV, resulting in a LOD of $5.70 \times 10^{+03}$ nmol L^{-1}.

Ultimately, Kergaravat, Gagneten, and Hernandez [116] applied the technique for determination of quinolone family, using a graphite-epoxy composite as working electrode, modified with bismuth film. The detection of moxifloxacin, specifically, was carried out in biological models for posterior ecotoxicity studies, which is different from the proposed by other studies. The limit of detection was 5.0×10^{-1} nmol L^{-1}, in acetic acid/acetate buffer; pH 3,81. Frequence and amplitude were 25,0 Hz and 25,0 mV respectively, and potential step was 5 mV. Some of the same authors [147] developed a

SWV method for simultaneous electrochemical detection of ciprofloxacin and silver ions also for ecotoxicity studies. The analytical signals were improved by use of previous pre-concentration of antibiotic in the electrode surface, followed by anodic stripping performed using experimental and voltammetric parameters and screen-printed electrode of carbon. So, the potential was scanned from − 0.6 to 0.2 V using $f = 25\ s^{-1}$, $a = 50$ mV and $\Delta E_s = 5$, allowing in a linear range from 8 to 200 ng L^{-1} and LOD of 34 ng L^{-1}.

Aside from direct detection SWV also can be used in the electrochemical mechanism studies of antibiotics, due to well-developed theoretical models that relate I_p, E_p and $W_{1/2}$ values and their relationship with a, f and ΔE_s providing information about the kinetics and mechanism of electron transfer in an electrochemical cell. This information can be used to better understanding of general reactions mechanisms in an aqueous and biological medium, since antibiotics having redox active groups in their molecular structure to design new strategies for their therapeutic and toxic effects. INCLUIR REFERÊNCIA

4.2. Working electrodes used in antibiotics detection

As the redox reaction occurs in the interface electrode/solution, alterations in this interface will significantly change the position, intensity, and width of the analytical signals due to these parameters are strongly dependent of the redox behavior of antibiotic over working electrode surface. The material used in the preparation of these electrodes consider the physical, chemical, and electronic properties of resultant electrode, due to allows in sensor with different electrochemical properties, such as ability of carrier electrons and adsorption of reactants and or products in the interface. So, these properties alternate the kinetics of the electron transfer and in the mechanisms of the redox system, and consequently modify the sensitivity and selectivity of the SWV method [55].

So, various electrodes have been reported for antibiotics detection by SWV, among them gold and platinum are recurrent for aqueous solutions in which the potential of the reactions is scanned in the positive direction, or oxidation reaction. Already, for negative scan potentials or reduction reaction, the use of mercury is notorious due to the expressive voltage in the hydrolysis reaction of water [148], however, the toxicity of waste its routine use made unfeasible.

The papers considered in this review, following sources parameters previously

described, indicated the predominance in the use of carbon-based electrodes, with numerous microstructures that affect the surface interaction with the sample, changing its properties according to the type of carbon material and the type of modification in the surface [149]. Figure 3 show the main classes of antibiotics evaluated using SWV methodology and different working electrodes used.

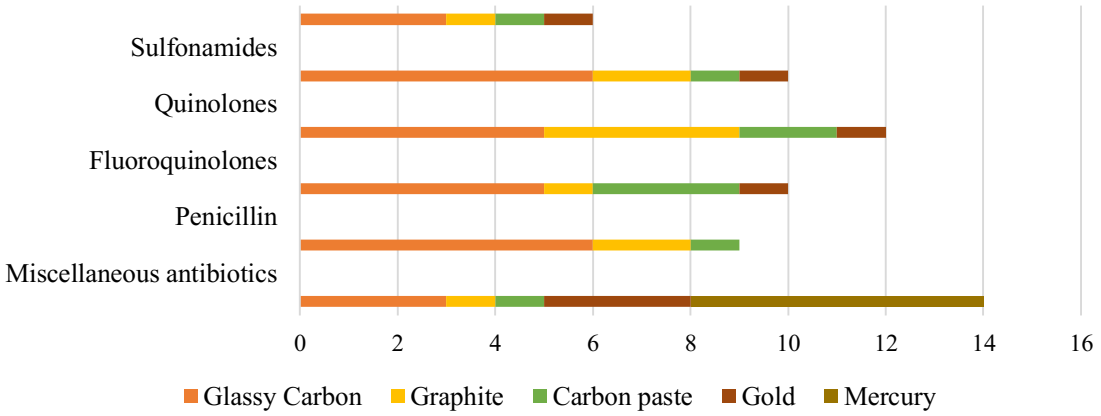


Figure 3: Materials used as working electrodes in antibiotics determination by SWV, with information from the Science Direct® and Scopus® databases, using the key terms: "Electroanalysis"; "Square Wave Voltammetry"; "Antibiotics"; Pharmaceutical Compounds in the period from 2012 to 2022.

Recently Azriouil et. al [150] reviewed the working electrodes used in the electrochemical determination of ciprofloxacin, a quinolone antibiotic, in biological fluids, environmental resources, foodstuffs and pharmaceutical formulations. The predominance of carbon-based electrodes was observed, as it is in the present work, due to their material present commercial availability, reduced cost, high chemical stability, non-toxicity and mainly allow modifications with different recognition elements (nanoparticles, enzymes, polymers films, graphene, among others), resulting in electrochemical sensors with excellent electroanalytical performance. In another work, the same group, this time with Ettadili as leading author [112] optimized a SWV method for detection in human blood, with three different electrodes, metallic silver electrode (MSE), metallic gold electrode (MGE), and GCE, in order to compare their suitability for the detection of ornidazole. Their voltammograms showed a cathodic peak well presented in MSE that indicated its superior electroactivity towards the reduction of the drug. This reinforces the importance of knowing the proprieties of the utilized materials and of the desired molecule, far beyond base conceptions.

Another work, by Rudnicki et. al [137], also utilizes a silver electrode, this time in the form of a renewable silver amalgam film electrode Hg(Ag)FE in electrolyte Britton-Robinson buffer pH 7,0, frequency of 150 Hz, amplitude of 80 mV, and step potential 1 mV. Their work is based on the reduction of the ionophore antibiotic monensin. The applicability was determined with samples of horse feed and limits of detection and quantification were 1.27×10^{-8} mol L^{-1} and 4.23×10^{-8} mol L^{-1} respectively, plus the results of antibiotic determination were precise with findings of 0.39 ± 0.09 μmol L^{-1} when addition was 0.40 μmol L^{-1} (p = 95%, n = 5), recovery 97.6%. Their results are consistent with the expected behavior of the material for reduction, and show the possibility of application of amalgams as working electrodes. The cited use, however, is rather common, because it increases the applicability and may be the solution for downsides of other materials.

It is, basically, the case of mercury electrodes, witch also present excellent suitability for reduction reactions and in negative scan potentials, as mentioned before, being, therefore greatly appropriate for detection of cephalosporins, for example, as indicated by Karadurmus et al., Yue et al., and Kassa and Amare [69,70,72]. It is well known, however, that mercury has significant toxicity essues, and have fallen out of its utilization trend. The alternative with amalgamation, especially combining different materials that can enhance eachother features, reduces mercury waste expressively, and Barbosa et al. demonstrated this working with solid silver mercury amalgam electrodes manufactured with silver nanoparticles for the detection of cefepime and their limits of detection and quantification of 8.51×10^{-09} and 2.84×10^{-08} mol L^{-1}, comparable to the previously cited amalgam work, even though it is almost a decade older.

In addition to these electrodes, it is possible to observe certain constancy in the use of boron-doped diamond without modifications. These are also old electrodes, with well-established use, which have interesting properties for electroanalytical detection, such as a potential window close to 3V, low secondary current, good reactivity, and low sensitivity to dissolved oxygen [148].

Furthermore, the notable use of carbon-based electrodes is related to the easiness in promoting modifications on their surface, improving detection capability. Valenga and collaborators [91] modified a GCE with reduced graphene oxide and Nafion for the detection of amoxicillin in river water samples with limits of detection and quantification of $3,6 \times 10^{+02}$ nmol L^{-1} and $1,2 \times 10^{+04}$ nmol L^{-1}, under the following parameters: Britton-Robinson Buffer as the electrolyte, pH 2,0, frequency of 100 s^{-1}, pulse amplitude of 50

mV, and step potential of 2 mV. The recovery was analyzed in presence of growing ratios of interferents with amoxicillin and it was adequately near 100% until the proportion of interferent was 2:1. In a similar work, Chen et. al [96] employed the same electrode, for the detection of the same pharmaceutical, but with different modifications (three-dimensional graphene and polyglutamic acid) and, this time, in human urine. Their limit of detection was higher than the previous work ($1{,}18 \times 10^{+05}$ nmol L^{-1}), but recovery was equally satisfactory. Main optimization conditions could contribute to the higher results, in this case they were pH 7,0 for a phosphate buffer electrolyte, amplitude of 0,025 V and step potential of 0,004 V. Also in modified GCE, Mahmoudpour and colleagues [122] detected quinolone antibiotic, ciprofloxacin in raw milk samples. The achieved limit of detection was 1.00 nmol L^{-1}, which is notably much lower than both of the anterior papers. This time, however, the modifications include the utilization of reduced graphene oxide and nanogold-functionalized poly(amidoamine) dendrimer, that may be described otherwise as a aptasensor created with nanoparticles.

The employ of nanoparticles, not exclusive to carbon electrodes, is frequent, with metallic gold and silver nanoparticles, which take advantage of the electrical properties of these materials and the unique properties provided by dimensional confinement, or carbon nanoparticles, including nanotubes and nanofilms which, due to the allotropy of the material, present unique characteristics of interaction [151]. In addition, nanoparticles, as a whole, have as one of their main attributes the increase in surface area and consequent improvement in sensitivity when applied to electrodes [152].

Besides, with the crescent development of biotechnology, the use of aptamer based detections is more and more common. Aptamers are acid nucleic molecules that bind to specific molecules, similarly to antibodies, but with some superior aspects, such as wider-range of targets, higher specificity and binding affinity, easier modification, lower-cost, and non-immunogenicity [153]. Their use is demonstrated by Chen and fellow researchers [49] that utilizing a carbon glass electrode, immobilized an aptamer encoded with metal ions which are responsible for the electrochemical signal. They achieved a multiplex detection of chloramphenicol and oxytetracycline, with measurement carried in $f = 25\ s^{-1}$, $a = 25$ mV, and $\Delta E_s = 4$ mV. The obtained LOD were of 3.3×10^{-5} nmol L^{-1} and 4.8×10^{-5} nmol L^{-1}, respectively. Recovery efficiencies were determined by addition of antibiotics to real milk samples, and all obtained values were between 84.0 and 102.8%. Huang and collaborators [83] also applied an aptasensor for multi-antibiotics detection (chloramphenicol and kanamycin) medium of in phosphate buffer pH 7.4, $f =$

35 s^{-1}, a = 25 mV, and ΔE_s = 4 mV. This method was also carried in milk samples and obtained LOD were $2.10x10^{-05}$ nmol L^{-1} and $3.50x10^{-05}$ nmol L^{-1}, being very close or lowest to the previous published works.

5. Concluding remarks

The presence of antibiotics in natural waters, wastewaters, soil, and foods is an environmental and public health concern since some these compounds have been considered endocrine disrupting and promoters of bacterial resistance. The detection of these pharmaceuticals in biological fluids allow information about metabolic formation, adequation in dosages and kinetic of absorption. However, all samples contaminated by antibiotics residues present complex composition, resulting in a tedious, time-consuming, high-cost, inaccurate procedure with few selective steps for extraction and clean up, aiming to remove the interference from these samples before chemical analysis. For this, electroanalytical techniques have been considered in antibiotics detection, enabling faster, more precise, and sensitive analysis with minimal sample preparation steps.

The sensitivity obtained using SWV as detection method is similar, and sometimes, lower than calculated from chromatographic and spectroscopic procedures, besides needing simplified procedures for extraction and clean in complex samples. The analytical signals are results of redox reactions that occurs in the interface electrode/solution, and the profile and position can be adequately optimized using different materials as working electrodes preparations and previously optimization of experimental and voltammetric parameters. Additionally, based on the information reviewed in this work, there is a wide range of materials used as working electrode, predominantly carbon-based materials.

Carbon-based electrodes are more used for antibiotics detection due to the presence of functional groups that can be oxidized in this electrode, in addition to this material being easily modified to improve the selectivity and sensitivity. However, the procedures for obtainment of an electrode more reproducible, less adsorptive of reaction products that block its surface, as well as with lower cost materials, still needs to be improved to make SWV a standard technique, accepted by environmental and health agencies, for antibiotic detection.

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