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## Chapter

# Electrochemical Impedance Spectroscopy (EIS) in Food, Water, and Drug Analyses: Recent Advances and Applications

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# Abstract

Electrochemical impedance spectroscopy (EIS) is a *potent* electrochemical technique with a variety of applications. EIS measurements involve the application of an alternating current (AC) voltage (or current) to the system under investigation, followed by measurement of the response in the form of AC current (or voltage) as a function of frequency. By and large, EIS is an exceptionally attractive in terms of applications. Being nondestructive with a feasibility of implementation to the system to be measured and the usefulness of data obtained in characterizing the studied systems, electrochemical impedance spectroscopy has realms of applications. As food and water safety and security is becoming a universal concern, the need for a technique that can detect water and food contaminants with relatively high sensitivity and selectivity is evolving. EIS has started to realize its potential with a wide-term use in water and food analyses.

**Keywords:** electrochemical impedance spectroscopy, electrochemical techniques, food analysis, drug analysis, water analysis

## 1. Introduction

Electrochemical impedance spectroscopy (EIS) is a usually described as a *potent* (if not the most powerful) electrochemical analytical technique. The history of EIS goes back to the late nineteenth century, thanks to the foundations established by Heaviside on his work on the linear systems theory (LST). By the end of the same century, the success achieved by Warburg to broaden the conception of *impedance* to the electrochemical systems (ES) came to the scene. It was close to the middle of the twentieth century, when the EIS started to realize its potential! That came with the invention of the potentiostat in the 1940s, followed by the frequency response analyzers in the 1970s. This progress has led to the application of EIS chiefly in investigation of corrosion mechanisms [1–3].

Later on, this has opened the doors for realms of applications of EIS. Applications encompassed electrocatalysis and energy [3–5]; characterization of materials, e.g. corrosion phenomenon surveillance [6, 7]; and depiction of quality of coatings [8], exploring mechanisms of processes such as electrodeposition and electro-dissolution [9, 10], food and drug analysis [11–13], detection of biomarkers [14, 15], and water analysis [16, 17].

It is noteworthy to mention that impedance spectroscopy (IS), depending on the material used, the device, and the system or process to be studied, has two main categories: EIS (the topic of this chapter) and dielectric IS. A major difference is that EIS applies to systems/materials involving chiefly ionic conduction, in contrast to electronic conduction in the case of dielectric IS. Therefore, it can be observed from the fields of EIS applications that EIS usually applies to systems like electrolytes (solid/liquid), polymers, and glasses [18–21].

In general, EIS measurements involve the application of an alternating current (AC) voltage or current to the system under investigation, followed by measurement of the response in the form of AC current (or voltage) as a function of frequency. Measurements are usually performed using the potentiostat, and the measured response is analyzed using a frequency response analyzer (FRA) [18]. By and large, three factors make EIS exceptionally attractive in terms of applications:

- 1. Capability to explore the ES at relatively low frequencies using the minimal perturbation that in turn serves to keep the kinetic information of the system under investigation at near zero conditions (steady state). Therefore, EIS is said to be a steady-state and nondestructive technique. The majority of the electrochemical techniques, however, involve an application of large perturbation for sensing the membrane/electrolyte interface, with the purpose of obtaining mechanistic data following the driving of the reaction to a state that is far from equilibrium [3].
- 2. Feasibility of implementation of EIS into the system to be measured.
- 3. The usefulness of data obtained in characterizing the studied ES, where EIS provides on-site data on the relaxation data over a range of frequencies, from as low as  $10^{-4}$  Hz and up to  $10^{6}$  Hz.

A combination of the three advantages led to the wide use of EIS as previously mentioned.

The current chapter throughout the following sections is investigating the applications of EIS in a variety of matrices, mainly in food, drug, and water analysis, and the recent advances in these fields as well as comparisons between EIS and other electroanalytical approaches applied for the same purposes.

## 2. Chapter taxonomy

Throughout the current chapter, readers will be exposed to the different analytical techniques, especially the electrochemical-based approaches, which are generally used for detection of pollutants in food, drug, and water.

Readers will be more focused on the applications of EIS in specific. A comparison between EIS and the other techniques commonly used in water and food analysis will be exhibited.

#### 3. Food and water security: the global concern

The safety, quantity, and the quality of food and water are becoming worldwide concerns. Water is the most crucial source for human development. With the advancement of human life, uncountable contaminants are intimidating the aquatic system. These intimidations include but not limited to automation/

industrialization, widespread use of chemicals, increased population, and suburbanization. Subsequently, water pollution is becoming a significant health and environmental concern.

By and large, the safety of food and water is influenced by contaminants. Among these pollutants, heavy metals, elevated anions (sulfates, phosphates, fluoride, etc.), dyes, agricultural waste, pesticides, drugs, and pharmaceuticals are the most common. Heavy metals, in specific, are widely used in many industrial, domestic, and agricultural applications, and they are nondegradable, an issue that raises the concern about their potential influence on public health, water systems, and the ecosystem in general. As, Cd, Cr, Pb, and Hg have been reported to be the highest systemic toxicant elements.

According to the US EPA and the International Agency for Research on Cancer (IARC), these toxic elements are probable to be carcinogenic. Moreover, accumulation of Pb, Cd, and Hg in the human body over time can cause serious health problems [22–26].

Similarly, food, leather, and textile industries discharge huge amounts of polluted wastes. With the various structures of the chemicals used in these industries, numerous problems develop. Dyes, a key water pollutant and even if discharged as traces (as low as 1 ppm), would color large volumes of water. Reports show that amount of dyes as huge as  $7 \times 10^5$  tons per annum are being produced annually, demonstrating the magnitude of the problem. Released dyes do not only affect the aquatic beings but also the human health. Their impact includes carcinogenicity, mutagenicity, poisoning, disturbance of the metabolism in aquatic bodies, etc. [27, 28].

On the other hand, and representing a significant category of aquatic pollutants, pharmaceutically active materials (PhAMs) are usually released into the aquatic systems from different sources, including but not limited to the effluents of the manufacturing sites and hospitals, illegal disposal, veterinary applications, and landfill leachate. Daily use by humans and the subsequent conversion of PhAMs into various metabolites with variable chemical structures is also a major source. The fate of these metabolites, and probably their parent drug compound, is usually the wastewater [29–33].

The increasing understanding of the assembly of the food chain and the probability of infection of human with these resilient microorganisms, either directly or via the food chain, has explained largely the spread of these species. Therefore, the process of food production and commercialization is posing rigorous regulations nowadays. Different societies, such as the Food and Drug Administration (US FDA), European Union (EU), and World Health Organization (WHO) in collaboration with the Food and Agriculture Organization of the United Nations (FAO) creating the FAO/WHO Codex Alimentarius Commission (CAC), are setting up standards for the maximum residue levels (MRLs) permissible in raw and processed food products of animal or poultry origin. Yet, any food product that would conform to these criteria and the preceding risk assessments cannot be banned by countries of the World Trade Organization (WTO) [34–38].

The elevating concerns on food and water safety and the existence of these materials at relatively low concentrations have created the need to find sturdy as well as sensitive detection and removal/remediation technologies. Detection technologies included traditional techniques such as spectrophotometry, spectro-fluorimetry, atomic absorption spectrometry (AAS), as well as electrochemical and the more sophisticated chromatographic approaches [27, 28, 39–49]. Each of these techniques has its pros and cons.

Electrochemical techniques are among the widely used techniques for detection of pollutants in food and water analyses. The following subsections will be focused

on the electrochemical approaches and EIS in specific in detection of contaminants in water and food samples.

# 3.1 Electrochemical techniques: principles, advantages, and sensing mechanisms

As an analytical approach, electroanalysis offers many advantages including but not limited to simplicity, sensitivity, specificity, and applicability in various matrices and cost-effectiveness. These advantages are of specific importance when it comes to detection of drugs and pharmaceuticals, especially in food and water samples as well as in quality control (QC) and quality assurance (QA) laboratories. According to the signal being measured (voltage/potential, current, conductance, impedance), electroanalytical techniques can be categorized into potentiometric, amperometric, conductometric, and impedimetric techniques. Subcategories for each technique also exist, and coupling with other technologies has been investigated.

Sensors, and in particular those based on the classical potentiometric technique, or the new polyion, galvanostatic, or voltammetric sensing mechanisms, now possess the foothold in analytical chemistry. Offering irresistible advantages, on the in vitro scale, such as operation simplicity, sturdiness, and remarkable sensitivity hitting nine orders of magnitude, selectivity, and functionality over wide range of matrices, suitability for on-line or real-time analyses, and most prominently their liability for miniaturization, make the use of sensors indispensable [50–53].

**Figure 1** shows an illustration of ISE (ion-selective electrode) potentiometric sensor and generation of potential across the different phase boundaries.

The sensing mechanism especially if the target analyte is a biomolecule depends on tailoring the surface of the sensor with a bio-receptor that can selectively bind to the target bio-analyte. Following the adsorption of the bio-analyte from the solution on the surface of the probe, a change in the electrochemical signal can be observed and measured. Such a change is correspondingly dependent on the bioanalyte concentration.

**Figure 2** shows a schematic illustration of the sensing mechanism in plastic microfluidic channels. The left panel shows the generation of streaming potential,



Figure 1.

Schematic illustration of ISE cell assembly and the generation of EMF across different phase boundaries.



#### Figure 2.

Schematic illustration of the generation of streaming potential as a result of pressure-driven flow and surface charge at the electric double layer (EDL)—left upper panel. The right panel shows a sensogram with signal inversion upon adsorption of the analyte. The bottom graph shows the pulsed streaming potentials as a function of heparin with immobilized protamine on a surface of a cyclo-olefin copolymer (COC) microchannel. Data points were fitted using Langmuir isotherm. Graphs are replicated from the authors' own work with permission from Copyrights@ American Chemical Society (ACS) [45].

 $\Delta E$ , as a result of pressure-driven flow and surface charge at the electric double layer (EDL). The right panel shows a sensogram with signal inversion upon adsorption of the analyte. The bottom graph shows the pulsed streaming potentials as a function of heparin with immobilized protamine.

EIS as an electrochemical technique entails measurement of the change in the charge transfer resistance ( $R_{ct}$ ) following the interactions between the analyte and the receptor and the consequent change in the interfacial electron transfer kinetics. The following sections will be dealing with the application for EIS for sensing different target analytes in different matrices [53, 54].

### 4. EIS in drug analysis

The effects of presence of the PhAMs either in waste and drinking water or even in wastewater treatment plants (WWTPs) are still inarticulate. However, what is well understood is that the impact extends to humans and animal's health, the aquatic environment, and in the long run the ecosystem. This effect is greatly dependent on the released dose of the PhAMs as well as their pharmacological effects. The issue becomes of concern when we know that the metabolites might be of a higher risk than the parent drug compound. At the microbial level, microorganisms upon prolonged exposure to anti-infectives, for example, become more tolerant, and new strains, which cannot be cured using the conventional antimicrobials, are now in the scene [55–57].

EIS, being capable of detecting as low as 10<sup>-12</sup> M of the target analyte, is widely used in drug analysis. Several drug categories were analyzed using EIS. **Table 1** shows some examples of drugs analyzed using EIS, as well as the matrices and type of electrode used together with the sensing interface, sensing strategy (label-free or labelled), and limit of detection (LoD).

The electrochemical properties of raloxifene, an important chemotherapeutic agent, were assessed using different techniques including EIS. Three electrodes were tested for this investigation: (1) bare screen-printed carbon electrode (SPCE), (2) graphene oxide (GO)/glassy carbon electrode (GCE), and (3) neodymium sesquioxide nanoparticles  $Nd_2O_5$  NPs@GO/GCE. The target was to assess the interface properties of these electrodes. Results showed that the  $R_{ct}$  of the third electrode was much smaller than the other electrodes. Other electrochemical techniques such as cyclic voltammetry (CV) were used in the same work [58].

Other examples included the determination of an important class of PhAMs, which is antibiotics, a subclass of antimicrobials. Label-free detection of oxytet-racycline (OTC) in milk samples was performed using a mixture of iron oxide and mesoporous carbon (Fe<sub>3</sub>O<sub>4</sub>@mC) together with nanocomposites made of Fe(II)-based metal-organic frameworks (525-MOF) by calcination at different temperatures. The sensor showed a very high sensitivity with a LoD = 0.027 pg mL<sup>-1</sup> and a linear range of 0.005–1.0 ng mL<sup>-1</sup>. Moreover, the fabricated aptasensor showed a high selectivity for oxytetracycline in the presence of similar drugs like tetracycline, doxycycline, and chlortetracycline [59].

Similarly, label-free detection of tetracycline (TET) was performed using two aptasensors made of carbon paste electrode (CPE) with oleic acid (OA) and a magnetic bar carbon paste electrode (MBCPE) with Fe<sub>3</sub>O<sub>4</sub> magnetic nanoparticles and oleic acid (OA) following the modification of electrode surfaces using anti-TET. The LoD were  $1.0 \times 10^{-12}$  to  $1.0 \times 10^{-7}$  M and  $3.0 \times 10^{-13}$  M for the two aptasensors, respectively, and the sensors were applied to pharmaceutical formulations, serum samples, as well as food products (milk and honey) [60].

A sensor based on nanocomposites of mC with  $SnO_x$  and  $TiO_2$  nanocrystals was used to determine tobramycin (TOB) in urine and serum samples selectively and in the presence of kanamycin, oxytetracycline, and doxycycline. The aptasensor showed an excellent sensitivity with a LoD of 0.01 nM [61].

Chloramphenicol was also determined in eye drop formulations using N-doped graphene nano-sheet-Au NP composite (Au/N-G). The LoD was 0.59  $\mu$ M, and the sensor showed a selectivity in the presence of interferences like oxytetracycline, chlortetracycline, ascorbic acid, and metronidazole [62]. Other applications included sulphamethoxazole using molecularly imprinted polymers (MIPs) decorated with Fe<sub>3</sub>O<sub>4</sub> magnetic nanoparticles (MNPs) on SPCE [63].

Immunosensors for  $17\beta$ -estradiol composed of Au electrode nanoparticlethiolated protein G-scaffold. This structure has facilitated the anchoring of a mouse monoclonal anti-estradiol antibody. The LoD was 26 pg mL<sup>-1</sup>. As per the authors, square wave voltammetry (SWV) was more sensitive (18 pg mL<sup>-1</sup>) and required less time and effort compared to EIS [64].

Target drug	Sensing interface	Electrode	Matrix	Sensing measurement method and strategy	LoD	Re
Raloxifene	Nd <sub>2</sub> O <sub>5</sub> NPs@GO/GCE	GCE	ND Serum and urine	EIS CV Amperometry (Label-free)	ND ND 18.43 nM	[58]
ОТС	Aptasensor (Fe <sub>3</sub> O <sub>4</sub> @mC <sub>900</sub> )	GCE	Milk samples	EIS (Label-free)	$\begin{array}{c} 0.027\mathrm{pg}\\\mathrm{mL}^{-1}\end{array}$	[59]
TET	Aptasensor 1: CPE/OA/anti-TET Aptasensor 2: MBCPE/Fe <sub>3</sub> O <sub>4</sub> NPs/OA/ anti-TET	CPE MBCPE	Tablets, milk, honey, and serum	EIS (Label-free)	$10^{-1}$ - $10^{-7}$ M $3.0 \times 10^{-13}$ M	[60]
ГОВ	Aptasensor/ SnO <sub>x</sub> @TiO <sub>2</sub> @mC	GCE	Urine and serum	EIS (Label-free)	0.01 nM	[61]
Chloramphenicol	Au/N-G	GCE	Eye drops	EIS (Label-free)	0.59 μΜ	[62]
Sulphamethoxazole	MIP-decorated Fe <sub>3</sub> O <sub>4</sub> MNPs	SPCE	Seawater	EIS (Label-free)	0.001 nM	[63]
17β-estradiol	Au nanoparticle-thiolated protein G-scaffold	Au	Serum	EIS (Label-free)	26 pg mL- <sup>1</sup>	[64]
BPA	AuNPs/PB/CNTs-COOH/GCE	GCE	Water	EIS (Labelled detection)	0.045 pM	[65]
P4	ssDNA/Au	Au	Tap water	EIS (Labelled detection)	$0.90 \text{ ng}$ mL $-^1$	[66]

Bisphenol A (BPA), a xenoestrogen with an estrogen-mimicking effect and that is widely used as a precursor in plastics industry, has been determined using a labelled aptasensor made of gold nanoparticles (AuNPs), Prussian blue (PB), and functionalized carbon nanotubes (AuNPs/PB/CNTs-COOH).

Determination of progesterone (P4) in water and other clinical samples was performed using single-stranded ssDNA aptamers with high binding affinity to P4 [66].

# 5. EIS in food analysis

In addition to food contamination with antimicrobials and other drugs, bacteria and other pathogens like mycotoxins (secondary metabolites of microfungi) or chemicals such as pesticides are also other sources of food contamination. Food contamination can occur at any stage of food production, storage, or dissemination. Sicknesses caused by foodborne pathogens include symptoms such as diarrhea, nausea, vomiting, septicemia, meningitis, and even death [50, 53, 67, 68]. Pathogens include famous strains of bacteria such as different species of Salmonella (e.g., *S. enteritidis* and *S. typhimurium*), *Escherichia coli* (*E. coli*), and *Staphylococcus aureus* (*S. aureus*).

**Table 2** shows examples of different bacterial strains that have been determined in food products using EIS-based aptamers.

A highly specific DNA—aptamer to *S. enteritidis* in pork products—was developed using gold NPs, i.e., modified SPCE (GNPs-SPCE). The developed aptasensor

Target	Sensing interface	Electrode	Matrix	Sensing method	LoD	Ref
	Bacter	ia (LoD is meas	ured as/CFU mL	<i>.</i> –1)*		
S. enteritidis	GNPs@SPCE	SPCE	Poultry products	EIS	600	[69]
S. typhimurium	GNPs@SPCE	SPCE	Animal- based products	EIS	600	[70]
Salmonella	GO+AuNPs@ GCE	GCE	Pork meat	EIS	3.0	[71]
$rac{1}{2}$		Mycotoxins				
ОТА	Diazonium modified-SPCE	SPCEs	Cocoa beans	EIS	0.15 ng mL <sup>-1</sup>	[72]
ОТА	Thiolated DNA aptamer	Au	Food products	EIS	0.12– 0.40 nM	[73]
AFB <sub>1</sub>	Cys-PAMAM- modified electrode	Au	Peanuts and corn snacks	EIS	0.40 ± 0.03 nM	[74]
		Pestic	ides			
Acetamiprid	Ag-NG/GCE	GCE	Cucumber and tomatoes	EIS	0.033 pM	[75]

#### Table 2.

Applications of EIS in analysis of food and food products.

was selective towards *S. enteritidis* and showed a negative response towards mixture of other pathogens [69]. Similarly, the same electrode was used as a sensor for *S. typhimurium* [70]. The developed sensors were capable of differentiating between the targeted *Salmonella* species (S. *enteritidis* and S. *typhimurium*) and the other *Salmonella*.

Another *Salmonella* sensor was fabricated using a GO/Au NP-modified GCE. The sensor was applied for pork samples and achieved a LoD of 3.0 colony-forming unit (CFU mL<sup>-1</sup>) in this case [71] compared to 600 CFU mL<sup>-1</sup> using the GNPs@SPCE aptasensors [69, 70].

The mycotoxin ochratoxin (OTA) has been determined in a variety of samples, e.g., in cocoa beans, using EIS aptasensor developed using a diazonium-coupling reaction mechanism for the immobilization of anti-OTA-aptamer on screen-printed carbon electrode (SPCE) [72]. EIS was also applied for the determination of OTA using a thiolated DNA aptamer immobilized by chemisorption to the surface of Au electrode [73]. Other mycotoxins, e.g., Aflatoxin B<sub>1</sub> (AFB<sub>1</sub>) were detected using layer coating of cystamine (Cys), poly (amido-amine) dendrimers of generation 4.0 (PAMAM G4) and DNA aptamers (on Au electrode) specific to AFB<sub>1</sub> [74].

Pesticides, e.g., acetamiprid, were determined in samples of vegetables (tomatoes and cucumber) using AgNP-modified nitrogen-doped graphene (AgNPs/ NG). The designed aptasensor was sensitive, selective, and economical and did not require intricate labelling procedures [75].

#### 6. EIS in water and wastewater analysis

Discharge of heavy metals (HMs) into the water bodies via industrial activities and other sources, e.g., mining, acid rain, agricultural waste, etc., denotes a worldwide challenge. As previously mentioned in this chapter, HMs and other emergent contaminants possess a significant influence on the environment and human health. The intensifying flux of HMs into aquatic environments and the properties of HMs (toxicity, degradation rates, accumulation, uptake, bioavailability, etc.) necessitate the presence of firm rules and action plans for monitoring, detoxification methodologies, and treatment technologies to keep their concentrations within the permitted levels [23–26, 76].

**Table 3** shows examples for the applications of EIS in determination of water contaminants such as HMs, pesticides, drugs, and pharmaceuticals.

EIS has been applied for quantitative determination of HMs in water samples. In one of the investigations, a bi-enzymatic biosensor was constructed by immobilizing *Arthrospira platensis* cells (Spirulina) on gold interdigitated transducers. Consequently, phosphatase and esterase activities were inhibited by HMs and pesticides, respectively. This approach was used to determine Hg<sup>2+</sup> and Cd<sup>2+</sup> as well as parathion, paraoxon, and triazine pesticides, alone or in mixture with the HMs [77].

In another approach, a three-electrode sensor was printed on a polyethylene terephthalate film (PET) and was applied for impedimetric determination of Pb<sup>2+</sup> and Cd<sup>2+</sup> in water samples at nanomolar level [78]. An electrochemical DNA biosensor based on microspheres of cuprous oxide (Cu<sub>2</sub>O) and nano-chitosan (NC) was used for Hg<sup>2+</sup> detection in river water samples with a LoD of 0.15 nM [79].

Other contaminants like pesticides and herbicides as well as drugs and pharmaceuticals were also determined using EIS [63, 65, 66, 75, 77] (**Table 3**).

Target	Sensing interface	Matrix	LoD	Ref				
Heavy metals								
Hg <sup>2+</sup> , Cd <sup>2+</sup>	Arthrospira platensis cells (Spirulina)	Municipal wastewater	10 <sup>-20</sup> M and 10 <sup>-20</sup> M	[77]				
Pb <sup>2+</sup> , Cd <sup>2+</sup>	PET-SPE	Water	1 nM for both metals	[78]				
Hg <sup>2+</sup>	Cu <sub>2</sub> O@NCs	River water samples	0.15 nM	[79]				
Pesticides and herbicides								
Parathion-methyl	Arthrospira platensis cells (Spirulina)	Municipal wastewater	10 <sup>-20</sup> M	[77]				
Paraoxon-methyl	Arthrospira platensis cells (Spirulina)	Municipal wastewater	$10^{-18} \mathrm{M}$	[77]				
Triazine	Arthrospira platensis cells (Spirulina)	Municipal wastewater	$10^{-20} \mathrm{M}$	[77]				
Acetamiprid	Ag-NG/GCE	Wastewater	0.033 pM	[75]				
	Drugs and pharn	naceuticals						
Sulphamethoxazole	MIP-decorated Fe <sub>3</sub> O <sub>4</sub> MNPs@SPCE	Seawater	0.001 nM	[63]				
BPA	BPA AuNPs/PB/CNTs-COOH/ GCE		0.045 pM	[65]				
P4	ssDNA/Au	Tap water	$0.90 \text{ ng mL}^{-1}$	[66]				

#### Table 3.

Applications of EIS in analysis of water.

# 7. Conclusions

The literature is rich in articles and reviews that investigate the applications of electrochemical impedance spectroscopy in detections of various contaminants such as heavy metals, drugs, and pharmaceuticals, as well as pesticides. The advantages that impedance spectroscopy introduces as an electrochemical technique are innumerable. High sensitivity, specificity, selectivity, no time or effort consumption, and being label-free are the major advantages reported in the majority of the surveyed literature. As the mentioned contaminants usually exist as traces in complicated matrices, impedance spectroscopy with the mentioned advantages was usually the electrochemical technique of choice for the detection of these contaminants in water, food, and drug matrices.

## **Conflict of interest**

The authors declare no conflict of interest.

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