A BDDP-MODIFIED CPE FOR ELECTROCHEMICAL DETERMINATION OF AZITHROMYCIN IN REAL WATER SAMPLES

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Abstract

The presence of antibiotic residues in aquatic environments has become a growing environmental and public health concern due to their persistence, potential ecological impacts, and contribution to the development of antimicrobial resistance. Continuous monitoring of these emerging contaminants requires analytical methods that are sensitive, selective, and cost-effective. Although conventional techniques such as liquid chromatography–mass spectrometry (LC–MS) and gas chromatography (GC) offer high sensitivity and accuracy, their application is often limited by high operational costs, complex sample preparation, and lengthy analysis times. In contrast, electrochemical methods have attracted considerable interest because of their simplicity, rapid response, low cost, and potential for portable and in situ applications. In this study, an electrochemical sensor based on a boron-doped diamond powder (BDDP)-modified carbon paste electrode was developed for the determination of azithromycin (AZI), a widely used macrolide antibiotic. Experimental parameters, including modifier concentration, electrochemical technique, and operating conditions, were systematically optimized to improve analytical performance. Using square-wave voltammetry in acetate buffer solution (pH ~ 5), the proposed sensor exhibited a linear response over the concentration range of 75 ppb -449 ppm and achieved a detection limit of 74.8 ppb. The method was successfully applied to spiked river/lake water samples, providing recoveries between 86% and 107% and relative standard deviation values below 20%. These results demonstrate the sensor's accuracy, precision, and suitability for azithromycin determination in complex environmental water matrices.

***Key words**: antibiotics, carbon paste electrode, boron-doped diamond powder, nanomaterials.*

Përmbledhje

Prania e mbetjeve të antibiotikëve në mjediset ujore përbën një shqetësim në rritje për mjedisin dhe shëndetin publik për shkak të qëndrueshmërisë së tyre, ndikimeve të mundshme ekologjike dhe rolit në zhvillimin e rezistencës antimikrobike. Monitorimi i vazhdueshëm i këtyre ndotësve emergjentë kërkon metoda analitike të ndjeshme, selektive dhe me kosto të ulët. Megjithëse teknikat konvencionale, si kromatografia e lëngshme e shoqëruar me spektrometri mase (LC-MS) dhe kromatografia e gaztë (GC), ofrojnë ndjeshmëri dhe saktësi të lartë, zbatimi i tyre shpesh kufizohet nga kostot e larta, përgatitje komplekse e mostrave dhe koha e gjatë e analizës. Për këtë qëllim, metodat elektrokimike kanë tërhequr vëmendje të vazhdueshme për shkak të thjeshtësisë, përgjigjes së shpejtë, kostos së ulët dhe potencialit për aplikime portative dhe analiza in situ. Në këtë studim u zhvillua një sensor elektrokimik i bazuar në një elektrodë paste karboni të modifikuar me pluhur diamanti të dopuar me bor (BDDP) për përcaktimin e azitromicinës (AZI), një antibiotik makrolid i përdorur gjerësisht. Parametrat eksperimentalë, duke përfshirë përqendrimin e modifikuesit, teknikën elektrokimike dhe kushtet operative, u optimizuan për të përmirësuar performancën analitike. Duke përdorur voltametrinë me valë katrore (SWV) në pufer acetat (pH ~ 5), sensori i propozuar tregoi një përgjigje lineare në intervalin e përqendrimeve 75 ppb -449 ppm dhe arriti një kufi diktimi prej 74.8 ppb. Metoda u aplikua me sukses në mostra të ujërave të lumenjve dhe liqeneve me metodën e shtesave standarde, duke dhënë rikuperime nga 86% deri në 107% dhe vlera të devijimit standard relativ nën 20%. Këto rezultate dëshmojnë saktësinë, precizionin dhe përshtatshmërinë e sensorit për përcaktimin e azitromicinës në matrica komplekse ujore mjedisore.

***Fjalë kyçe:** antibiotikë, elektrodë pastë karboni, pudër diamanti e dopuar me bor, nanomateriale.*

Introduction

The discovery and widespread use of antibiotics represent one of the most transformative achievements in the history of modern medicine. Since their introduction, antibiotics have dramatically reduced morbidity and mortality associated with bacterial infections, contributing to increased life expectancy and enabling complex medical interventions such as organ transplantation,

major surgical procedures, chemotherapy, and intensive care treatments (Muteed et al., 2023; Kaplan et al., 2004; Iskandar et al., 2022). Their impact extends beyond human healthcare, playing a crucial role in veterinary medicine and agricultural production. However, the remarkable success of antibiotics has also led to their excessive and often inappropriate use, creating significant environmental and public health concerns worldwide. Over the past several decades, large quantities of antibiotics have been continuously released into the environment through various pathways, including domestic wastewater, hospital effluents, pharmaceutical manufacturing discharges, livestock farming activities, and agricultural runoff (Canecchi et al., 2023; Varela et al., 2021). Conventional wastewater treatment plants are frequently unable to completely remove these pharmaceutical compounds, resulting in their persistence and accumulation in aquatic ecosystems. Consequently, antibiotic residues have been detected in surface waters, groundwater, sediments, soils, and even drinking water supplies at concentrations ranging from nanograms to micrograms per liter (Phonisiri et al., 2019).

Although these concentrations are often considered trace levels, prolonged environmental exposure may exert selective pressure on microbial communities, alter ecosystem functioning, and contribute to the dissemination of antibiotic resistance genes (Bengtsson et al., 2016). The emergence and rapid spread of antimicrobial resistance (AMR) has become one of the most urgent global challenges of the twenty-first century. According to the World Health Organization (WHO), AMR threatens the effectiveness of essential medicines and has the potential to undermine decades of progress in healthcare.

Resistant microorganisms can spread across environmental, animal, and human compartments, highlighting the interconnected nature of health systems under the One Health framework. Consequently, the development of reliable analytical methods for the detection and monitoring of antibiotic contaminants has become a critical priority for researchers, regulatory agencies, and policymakers. Effective monitoring strategies are essential not only for environmental protection but also for safeguarding public health and supporting evidence-based decision-making (Salam et al., 2023; Wiliams et al. 2016; Centers for Disease Control and Prevention, 2023; Samreen et al., 2021; WHO 2022).

Currently, chromatographic techniques, particularly liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), are regarded as the

gold standard for the determination of pharmaceutical residues due to their excellent sensitivity, selectivity, and accuracy. Nevertheless, these methods are associated with several limitations, including high operational costs, extensive sample preparation requirements, sophisticated instrumentation, and the need for highly trained personnel (Tuzimski et al., 2020; Adaway et al., 2012; Patel et al., 2017). Such constraints may hinder their routine application for large-scale environmental monitoring, especially in resource-limited settings. For these reasons, there is growing interest in alternative analytical approaches that can provide rapid, cost-effective, and reliable detection of emerging contaminants. Among these alternatives, electrochemical sensing technologies have attracted considerable attention due to their inherent advantages, including simplicity, low cost, short analysis times, high sensitivity, and compatibility with portable and miniaturized devices. Electroanalytical methods offer the possibility of real-time and on-site monitoring, making them particularly attractive for environmental applications (Mello et al., 2025; Baranwal et al., 2022; Qian et al., 2020; Motoc et al., 2021). The performance of electrochemical sensors, however, strongly depends on the properties of the working electrode, and significant research efforts have focused on developing advanced electrode materials capable of improving sensitivity, selectivity, and operational stability (Salimi et al. 2019; Majer et al., 2023).

Boron-doped diamond (BDD) has emerged as one of the most promising electrode materials for electrochemical applications (Kondo et al., 2021; Baluchova et al., 2023; Cobb et al., 2018). Owing to its unique physicochemical properties, including exceptional chemical inertness, wide electrochemical potential window, low background current, resistance to surface fouling, and excellent mechanical durability, BDD has demonstrated outstanding performance in the detection of a wide variety of organic and inorganic analytes. Despite these advantages, conventional solid BDD electrodes often require expensive fabrication procedures, specialized instrumentation, and complex processing techniques, which may limit their widespread adoption and practical implementation. To overcome these limitations, recent research has explored the use of boron-doped diamond powder (BDDP) as a more versatile and economically viable alternative (Muzyka et al., 2019; Moraes et al., 2017; Shi et al., 2020; Weeks WB 2023). BDDP can be readily incorporated into conventional carbon paste electrodes (CPEs), enabling the fabrication of composite electrodes with enhanced electrochemical properties while maintaining simplicity and low production

costs. This strategy combines the beneficial characteristics of BDD with the ease of preparation and adaptability of carbon paste electrodes, creating a promising platform for the development of sensitive and robust analytical sensors.

In the present study, we investigated the electrochemical determination of azithromycin (AZI), a widely used macrolide antibiotic frequently detected in pharmaceutical effluents, municipal wastewater, and aquatic environments. Due to its extensive consumption and environmental persistence, AZI has emerged as an important target analyte in environmental monitoring. The main objective of this work was to optimize the composition of boron-doped diamond particle (BDDP)-modified carbon paste electrodes for the sensitive detection of AZI using square wave voltammetry (SWV). Three BDDP materials with different particle size distributions were evaluated at various proportions within the carbon paste matrix to assess their influence on the analytical performance of the sensor. The effects of electrode composition and SWV operating conditions were systematically investigated to identify the optimal configuration capable of providing enhanced sensitivity, low detection limits, and a broad linear response range. The proposed approach highlights the potential of BDDP-based electrochemical sensors as simple, cost-effective, and efficient tools for pharmaceutical analysis and environmental monitoring. Furthermore, this study contributes to the development of sustainable and accessible analytical technologies aligned with the United Nations Sustainable Development Goals, particularly SDG 3 (Good Health and Well-being) and SDG 6 (Clean Water and Sanitation), (WHO, 2023).

1. Materials and methods

1.1 Chemicals and reagents

All chemicals and reagents used in this study were of analytical grade and were employed without any further purification. Graphite powder (71–90 μm, ≥99.9%) was obtained from Alfa Aesar (Thermo Scientific, USA), while paraffin oil was supplied by Zeta Farmaceutici (Italy). Boron-doped diamond powder (BDDP) with different particle size ranges were synthesized and provided by the Tokyo University of Science according to the procedure reported by Kondo (2021). Azithromycin (AZI) stock solutions were freshly prepared in ethanol and stored at 4 °C until use. Working solutions were obtained by appropriate dilution of the stock solution immediately before the experiments (Cenolli et al., 2024).

1.2 Preparation of carbon paste electrodes

Carbon paste electrodes (CPEs) were prepared by thoroughly mixing graphite powder and paraffin oil in an agate mortar for approximately 1 h to obtain a homogeneous paste (Kulla et al., 2024; Ameda et al., 2024). To evaluate the effect of boron-doped diamond powder (BDDP) particle size on the electrochemical response, three BDDP materials with different average particle sizes were investigated: BDDP1 (150 nm), BDDP2 (350 nm), and BDDP3 (650 nm) (Luong et al., 2009). For each material, modified carbon pastes containing 1–20% (w/w) BDDP were prepared. The components were carefully homogenized to ensure a uniform distribution of BDDP particles throughout the carbon paste matrix. The resulting pastes were stored at 4 °C for 24 h prior to use. Subsequently, the paste was packed into plastic syringe bodies to form electrodes with an effective length of approximately 1 cm. Electrical contact was established by inserting a copper wire into the paste-filled syringe (Cenolli et al., 2026).

1.3 Electrochemical measurements

Electrochemical experiments were carried out using a PalmSens 4 potentiostat/galvanostat (PalmSens, The Netherlands) connected to a conventional three-electrode cell system. An Ag/AgCl electrode (3 M KCl) served as the reference electrode, a platinum wire was employed as the counter electrode, and either an unmodified CPE or a BDDP-modified CPE was used as the working electrode. Square wave voltammetry (SWV) was selected for the electrochemical determination of azithromycin. Measurements were performed in 0.1 M acetate buffer solution at pH 5.0, which served as the supporting electrolyte. To obtain the best analytical performance, SWV parameters such as equilibration time, potential step, modulation amplitude, and frequency were optimized. The final measurements were conducted at an operating frequency of 10 Hz.

1.4 Analytical performance evaluation

The analytical characteristics of the developed sensors were evaluated using calibration curves obtained by successive additions of standard AZI solutions. The relationship between oxidation peak current and analyte concentration was examined by linear regression analysis. The performance of the electrodes was assessed in terms of sensitivity, linearity (R^2), limit of detection (LOD), and repeatability. Repeatability was expressed as the relative standard deviation (RSD%) of replicate measurements, while the LOD was determined

from the calibration data. These parameters were used to compare the different BDDP-modified electrodes and to identify the optimal sensor configuration for azithromycin determination.

1.5 AZI in environmental water samples

A total of 36 environmental water samples, from different rivers and lakes, were prepared and analysed for the determination of AZI (Nuro et al., 2024). Standard AZI solutions (3 mM) were prepared for analytical measurements. Prior to analysis, each water sample was mixed with 0.2 M acetate buffer solution (pH ~ 5) in a 1:1 (v/v) ratio, using 15 mL of environmental water sample and 15 mL of acetate buffer. Electrochemical measurements were performed by square wave voltammetry (SWV) using the following parameters: potential range from 0 to 1.8 V, step potential of 10 mV, pulse amplitude of 100 mV, and frequency of 5 Hz. The peak currents obtained under these conditions were recorded and used for the analysis of all 36 samples.

2. Results and discussion

2.1 Effect of BDDP type on the electrochemical response of AZI

The electrochemical response of azithromycin (AZI) was initially evaluated using carbon paste electrodes modified with three boron-doped diamond powders (BDDPs) differing in their average particle size: BDDP1 (150 nm), BDDP2 (350 nm), and BDDP3 (650 nm). Measurements were carried out in 0.1 M acetate buffer solution (pH~ 5) using square wave voltammetry (SWV) under preliminary optimized experimental conditions. The obtained voltammograms revealed notable differences in the oxidation response of AZI depending on the type of BDDP incorporated into the carbon paste matrix. Among the tested materials, BDDP1 generated the most intense and well-defined oxidation peaks, indicating a more favorable electrochemical behavior toward AZI oxidation. In contrast, electrodes modified with BDDP2 and BDDP3 produced lower peak currents and less pronounced voltammetric signals. These results suggest that particle size and surface characteristics of the boron-doped diamond powder significantly influence the electrochemical performance of the modified electrodes. Consequently, BDDP1 was selected for further optimization studies.

2.2 Optimization of BDDP content

To determine the optimal amount of modifier, BDDP1 was incorporated into the carbon paste matrix at concentrations ranging from 1 to 20% (w/w). The

electrochemical response of each electrode composition was evaluated under identical experimental conditions. Among the tested formulations, the electrode containing 4% BDDP1 exhibited the highest oxidation signal and the most favorable analytical characteristics. Lower modifier contents produced less intense responses, whereas higher percentages did not result in further signal enhancement and, in some cases, led to a decrease in peak intensity. The observed behavior may be attributed to the balance between the beneficial effect of BDDP on electron transfer and the possible disruption of the conductive carbon network at higher modifier loadings. Therefore, 4% BDDP1 was selected as the optimal electrode composition for subsequent studies.

2.3 Analytical characteristics of the optimized sensor

The analytical performance of the optimized CPE@4%BDDP1 sensor was evaluated through calibration experiments performed under optimized SWV conditions. A linear relationship between the oxidation peak area and AZI concentration was observed over the concentration range of 0.1–600 µM.

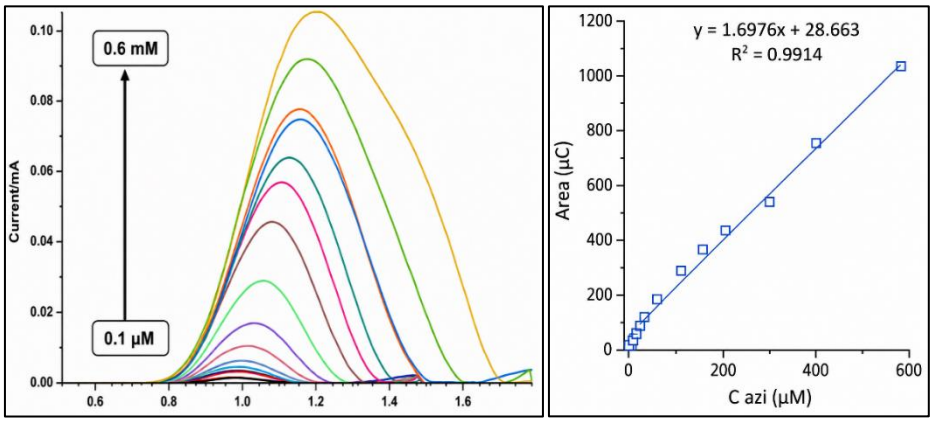

Figure 1 SWV voltammograms obtained using the CPE modified with 4% BDDP1 together with the corresponding calibration curve for AZI concentrations ranging from 0.1 to 600 µM in 0.1 M acetate buffer (pH 5.0).

The calibration plot showed excellent linearity with a correlation coefficient (R^2) of 0.9914. The sensor exhibited a sensitivity of 1.6976 µC*µM^{-1} and a limit of detection (LOD) 74.8 ppb. In addition, replicate measurements demonstrated good repeatability, confirming the stability of the electrochemical response. Based on these results, the CPE modified with 4%

BDDP1 was selected for further application in the determination of AZI in real samples.

2.4 Validation of AZI in environmental water samples

The applicability of the developed CPE@4%BDDP1 sensor was evaluated through the determination of azithromycin in environmental water samples using the standard addition method. Calibration curves obtained for the investigated samples exhibited good linearity throughout the studied concentration range, as demonstrated by the high correlation coefficient (R^2) values. The observed linear relationship between the analytical signal and the added AZI concentration confirms the suitability of the proposed sensor for quantitative analysis in complex aqueous matrices.

Minor differences in calibration parameters among samples may be attributed to matrix-related effects, including variations in dissolved organic matter and the presence of naturally occurring constituents. Nevertheless, the overall linear behavior indicates good stability of the electrochemical response and reliable analytical performance.

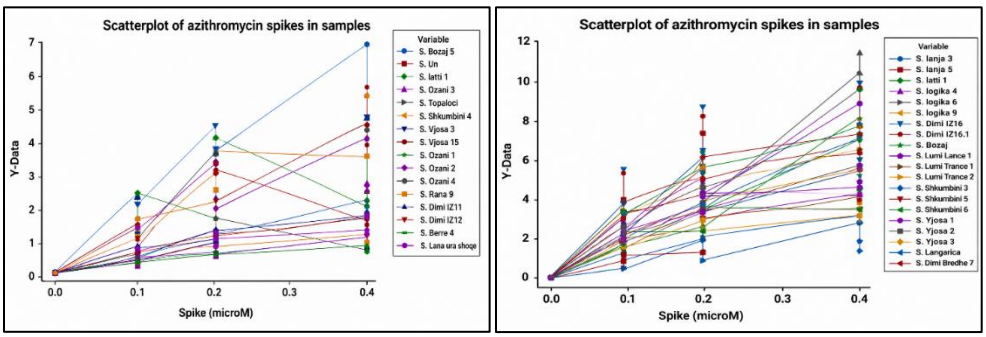

Figure 2 Calibration curves obtained for azithromycin in environmental water samples.

The accuracy of the method was further assessed through recovery experiments performed at different standard addition levels. Recovery values showed greater variability at the lowest concentrations (0.1 and 0.2 µM), whereas more consistent results were obtained at higher fortification levels. The addition of 0.4 µM AZI produced recovery values closest to 100%, indicating improved signal reproducibility and reduced matrix influence. Overall, the obtained recovery values confirm the applicability of the developed sensor for the determination of azithromycin in environmental water samples. The combination of satisfactory linearity and acceptable

recoveries demonstrates that the proposed method is suitable for quantitative analysis in complex environmental matrices.

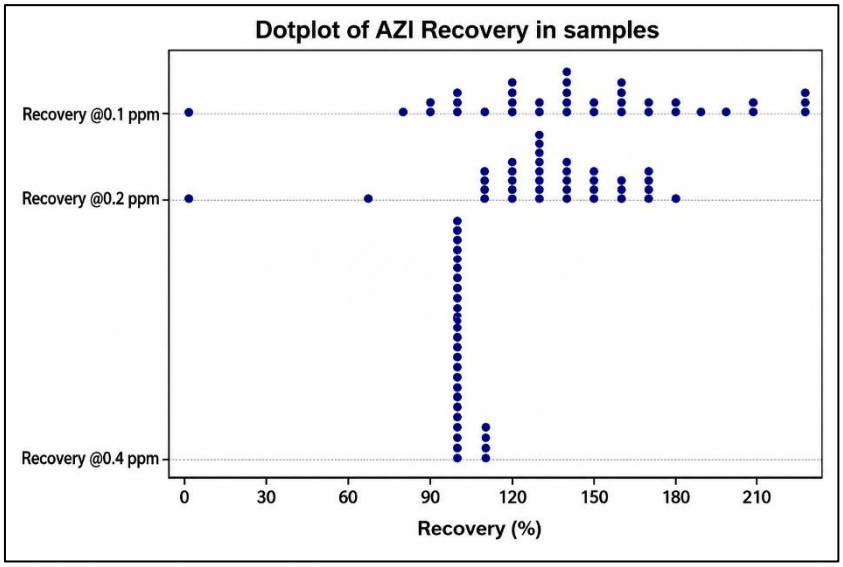

Figure 3. Recovery values obtained for azithromycin standard additions in environmental water samples.

The validation results indicate that the selected BDDP-modified carbon paste electrode provides adequate sensitivity, good repeatability, and satisfactory analytical performance for the determination of azithromycin in real water samples.

2.5 Determination of AZI in environmental water samples

The developed CPE@4%BDDP1 sensor was applied to the analysis of environmental water samples collected from different river systems in Albania. Quantification for some of these samples was performed using the standard addition method, and the corresponding calibration equations are summarized in Table 1. For all analysed samples, the estimated azithromycin concentrations were below the method detection limit. Calculated concentrations ranged from 0.002 to 0.079 µM; however, these values should be considered indicative only, as they fall below the validated quantification range of the method. Consequently, the presence of azithromycin in the analyzed samples could not be confirmed with sufficient analytical confidence. Despite the absence of quantifiable concentrations above the detection limit, the obtained results suggest that if azithromycin is present in

the investigated water bodies, it occurs at very low concentration levels. The highest estimated values were observed for Drini i Zi 7 (0.079 µM), Erzeni 4 (0.078 µM), Moglica 9 (0.077 µM), and Lumi i Tiranës 2 (0.067 µM), although all remained below the analytical detection limit. One sample (Pogradeci) produced an anomalous calibration result and was therefore classified as an outlier. This observation may be associated with matrix effects, experimental uncertainty, or local environmental conditions and should be further investigated in future studies. To further evaluate the applicability of the proposed sensor in real matrices, recovery experiments were performed using spiked environmental samples. Recovery values ranged from 86% to 107%, with relative standard deviations below 20%, demonstrating satisfactory accuracy and repeatability. These results confirm that the developed BDDP-modified carbon paste electrode is suitable for the determination of azithromycin in environmental water samples and can be applied for monitoring purposes when analyte concentrations fall within the validated analytical range.

Table 1. Calibration equations and estimated azithromycin concentrations obtained for some of the environmental water samples.

Sample	Equation	AZI (µM)
Erzeni 4	y = 1.4021x + 0.1088	0.078
Shkumbini 5	y = 19.7724x + 0.8607	0.044
Mat 1	y = 9.4057x + 0.4867	0.052
Vjosa 3	y = 12.9390x + 0.5483	0.042
Osumi 2	y = 3.4625x + 0.0891	0.026
Lumi i Lanes 1	y = 12.3143x + 0.4833	0.039
Lumi i Tiranës 2	y = 12.6600x + 0.8520	0.067
Drini i Zi 7	y = 17.7714x + 1.4100	0.079
Lin	y = 7.5247x + 0.1864	0.025
Pogradeci	y = 3498.0837x - 271.2594	Outlier
Banja FS	y = 9.7295x + 0.5340	0.055
Moglica 9	y = 7.4419x + 0.5693	0.077

Conclusions

A boron-doped diamond powder modified carbon paste electrode (CPE@BDDP) was successfully developed and optimized for the electrochemical determination of azithromycin (AZI). Among the investigated materials and compositions, the electrode containing 4% BDDP1 exhibited the best analytical performance, providing high sensitivity, good linearity over a wide concentration range (75 ppb-449 ppm) and a low limit of detection (LOD) of 74.8 ppb. Electrochemical characterization confirmed the successful incorporation of boron-doped diamond particles within the carbon paste matrix and revealed a heterogeneous surface morphology with increased roughness and porosity, features that are favorable for electrochemical applications.

The modified electrode demonstrated enhanced voltammetric responses compared to the unmodified carbon paste electrode, highlighting the beneficial effect of BDDP on electron-transfer processes. The applicability of the developed sensor was evaluated using environmental water samples collected from different aquatic systems in Albania. Although the estimated azithromycin concentrations were below the analytical detection limit, the obtained calibration curves and recovery studies demonstrated satisfactory analytical performance in complex environmental matrices. Recovery values ranging from 86% to 107% confirmed the accuracy and reliability of the proposed methodology. Overall, the results demonstrate that the BDDP-modified carbon paste electrode represents a simple, low-cost, and effective platform for the electrochemical determination of azithromycin. The developed sensor shows promising potential for environmental monitoring applications and may serve as a useful tool for the rapid screening of pharmaceutical contaminants in aquatic environments.

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