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Cyclic and differential pulse voltammetry investigations of an iodine contrast product using microelectrode of BDD

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Abstract: This work deals with the electrochemical behavior and detection of an iodine contrast product using microelectrode. For this, cyclic voltammetry and differential pulse were used for behavior study and detection, respectively. In this work, a boron-doped diamond (BDD) microelectrode was used. Cyclic voltammetry showed that the oxidation peak of iohexol (IHX) appeared at a potential of 1.655 V/MSE in H₂SO₄ medium (0.1 M). The electrooxidation process of IHX is irreversible, controlled by diffusion combined by adsorption, and can undergo direct and/or indirect oxidation. In addition, using the differential pulse voltammetry technique, the peak oxidation current shows a linear relationship with the IHX concentration between 4 μmol/L and 74.35 μmol/L. The calculated limit of detection (LOD) and limit of quantification (LOQ) are 1.953 μmol/L and 6.511 μmol/L, respectively. Recovery rates ranging from 95% to 99% in the presence of interfering compounds (inorganic compounds with concentrations 300 times higher than that of IHX). In addition, the DDB successfully recovered the concentration (20 μmol/L) of IHX dissolved with paracetamol concentrations ranging from 31 μmol/L to 149.66 μmol/L. These results suggest that the BDD can be used as a practical sensor to detect and quantify trace amounts of IHX.

Keywords: Iohexol; electrochemical; differential pulse voltammetry; BDD electrode.

1. Introduction

Medicines represent more than 4000 molecules, spread over almost 10,000 marketed pharmaceutical specialties. Many pharmaceutical molecules are increasingly consumed globally, particularly in Côte d'Ivoire, and are likely to contaminate environmental waters (surface water, groundwater, etc.). A literature review has shown that pharmaceutical products are present in different aqueous matrices such as influent and effluent from wastewater treatment plants, surface water, groundwater, marine water, and drinking water^{1,2}. Among the pharmaceuticals present in the waters, omnipaque is an iodine contrast product commonly known as iohexol. Iohexol, like most contrast media, is not biodegradable. The iohexol (C₁₉H₂₆I₃N₃O₉), highly soluble in water, neutral and acidic medium³. The osmolality of iohexol ranges from 322 mOsm/kg, about 1.1 times that of blood plasma, to 844 mOsm/kg, almost three times that of blood. Despite this, it is still considered to be a low osmolality contrast medium. Iohexol is an iodinated X-ray contrast media member, a class of drugs mainly used to enhance soft tissue imaging in diagnostic tests⁴. Consumption of iodinated X-ray contrasts can reach 3.5 million kilograms in one year worldwide⁵. Humans can process up to 200 g per

day⁶. Humans cannot digest iodinated X-ray contrasts in a short time, and most of them are eliminated via urine and faeces. All this information proves that iohexol is one of the highly persistent products⁷. Persistent products are a danger to the aquatic environment and our environment in general. Duirk et al. showed in a study in 2011 that iodine contrasts were frequently detected in raw water at a concentration of 2.7 μg/L⁶. Due to its preference in clinical practice, iohexol will be increasingly present in the aquatic environment. To protect this environment, iohexol must be detected, quantified, and then degraded before being discharged into the aqueous environment (wastewater, groundwater, etc.).

Liquid Phase Chromatography (HPLC/UV)⁸⁻¹⁰, Liquid Chromatography/Mass Spectrometry (LC/MS)¹¹, and Capillary Electrophoresis (CE) are the most commonly used clinical methods for the detection and quantification of iohexol. The use of all these methods requires very expensive and difficult to handle the equipment. New approaches such as electrochemical methods allow the quantification and detection of pharmaceutical residues in the environment. Electrochemistry is a more straightforward, faster, less laborious method and

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provides values as accurate as those provided by the previous methods. The performance of this method is due to the use of electrochemical sensors such as DSA (Dimensionally Stable Anodes), platinum, carbon electrode, boron-doped diamond (BDD), and several other electrodes. BDD electrode has been widely studied for its interesting electrochemical properties, including high thermal conductivity, high hardness, chemical inertness, wide electrochemical potential window in both aqueous and non-aqueous media, very low capacitance, and very low capacitance high electrochemical stability¹². In addition, this material is highly resistant to corrosion. BDD electrode has been used as an electrochemical sensor to detect and quantify paracetamol^{13,14}. The BDD is a better electrochemical sensor as it has been used as an anode to quantify and detect paracetamol and caffeine simultaneously, with a detection limit of $4.9 \cdot 10^{-7}$ mol/L and $3.5 \cdot 10^{-8}$ mol/L, respectively¹⁵. To detect and quantify dopamine with a detection limit of 54 nmol/L¹⁶ and the DPV allowed the quantification of theobromine with a detection limit of 0.42 μ mol/L¹⁷.

In this paper, we will use the conditions already established in the laboratory for the quantification and selective determination of iohexol using a BDD microelectrode (pre-treated to -2 V/SCE or -2.39 V/MSE)¹⁴. In fact, in our literature searches, electrochemical degradation and detection work of omnipaque (iohexol) is very scarce. One of the few works found relates to detecting iohexol by the cyclic voltammetric method¹⁸. In addition, to our knowledge, studies on the detection and quantification of Iohexol on the DDB electrode have not yet been the subject of scientific publication from Côte d'Ivoire (Ivory Coast). The results obtained by the electrochemical method will be compared with the work of other researchers.

2. Experimental method

2.1. Electrochemical measurements

The voltammetric measurements were performed using an Autolab PGSTAT 20 (Ecochemie) connected to a potentiostat equipped with USB electrochemical interface. This system is connected to a three-electrode single compartment glass cell, a data storage and processing computer. GPES 4 software was employed to record voltammograms. The glass electrochemical cell consisted of mercurial sulfate electrode (MSE) and platinum wire as the reference and counter electrode. BDD electrode with a surface of 14.28 mm² was used as the working electrode. All pH values were measured with a pH meter (HI2211).

2.2. Chemicals

The sulfuric acid (H₂SO₄, 95-98%) was purchased from Panreac, Germany, and the KClO₄ (potassium perchlorate) solution was obtained from SIGMA-ALDRICH (99%), USA. Iohexol (Omnipaque™ 300 mg I/mL, C₁₉H₂₆I₃N₃O₉) was supplied by laboratory GE Healthcare (France). A stock solution of 1 mM of

iohexol was prepared by dissolving an accurate mass of the drug in an appropriate volume of H₂SO₄ and KClO₄. The working solutions for the voltammetric investigations were prepared by dilution of the stock solution. All solutions were protected from light and used within 24 h to avoid decomposition. 0.1 M of H₂SO₄ and 0.1 M of KClO₄ were used for the supporting electrolyte solutions. Distilled water was used to prepare supporting electrolytes. The pH was adjusted by adding appropriate amounts of sodium hydroxide solution (NaOH, 2M) and sulfuric acid (H₂SO₄, 2M).

2.3. Experimental process

Analytical curves in the supporting electrolyte (H₂SO₄) were constructed and then used to produce a calibration curve. The DPV measurements were carried out for iohexol concentrations between 0 and 74.35 μ mol/L.

Boron doped diamond (BDD) electrodes was prepared by hot filament chemical vapor deposition (HF-CVD) on low resistivity (1-3 m Ω cm) p-Si wafers (siltronix, diameter 10 cm, thickness 0.5 mm). The process gas was a mixture of 1 % CH₄ in H₂ containing trimethylboron. The film was grown at a rate of 0.24 μ m h⁻¹. The film thickness was about 1 μ m.

Before the experiments, the BDD electrode was electrochemically pre-treated in a 0.5 mol/L H₂SO₄ solution. For this pre-treatment, an anodic pre-treatment (+2V, 15 s) is followed by a cathodic pre-treatment (-2 V, 90 s). This way, the BDD surface was first cleaned of all impurities and then rendered mainly hydrogen¹⁹.

An adequate volume of pure iohexol (omnipaque), corresponding to 1 mmol/L, was taken and transferred to a 100 mL volumetric flask. The volume was adjusted with 0.1 M H₂SO₄ or KClO₄. The contents of the flask were shaken to ensure complete homogeneity and then diluted with the same electrolyte. CV and DPV were used to study the electrochemical behavior and quantification of IHX. Analytical curves were obtained by adding small volumes of iohexol (IHx) stock solution to the electrolyte (HClO₄ or KClO₄). The limit of detection (LOD) and the limit of quantification (LOQ) were calculated from the following equations: LOD = 3*SD/b and LOQ = 10*SD/b with SD the standard deviation, and b is the slope of the calibration curve.

3. Results and discussion

3.1. Cyclic voltammetry investigations of iohexol (IHx) on the micro-BDD

3.1.1. Electrochemical behavior of Iohexol (IHx)

In this study, cyclic voltammetry was used to evaluate the electrochemical behavior of iohexol on the BDD microelectrode. We chose the sulfuric acid medium (0.1M) to know the potential at which the peak related to the oxidation of iohexol would appear.

Figure 1 shows the cyclic voltammograms of BDD in the absence and the presence of iohexol (IHX) in H_2SO_4 (0.1M). In the absence of the drug, no oxidation peaks are observed in the electroactive

region of the diamond. On the other hand, in the presence of iohexol (1mM), a modification of the voltammogram is observed.

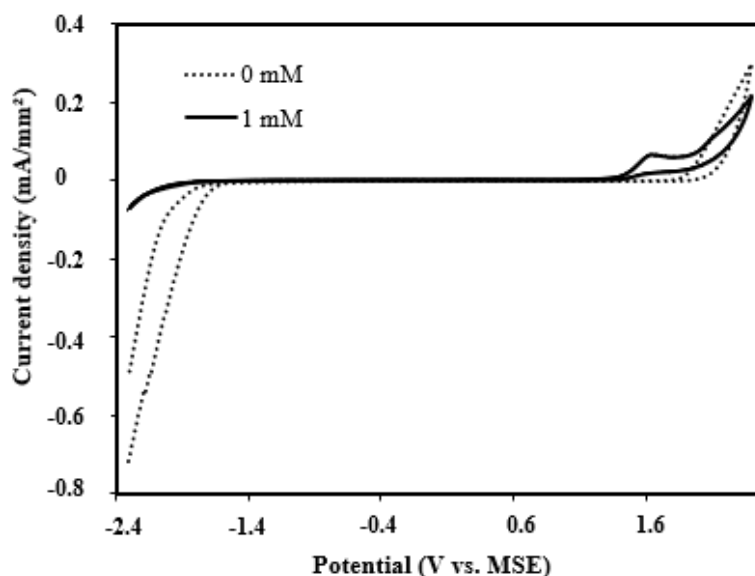


Figure 1. Cyclic voltammograms of BDD at 50mV/s in H_2SO_4 (0.1M) containing 0 and 1 mM IHX; T = 25°C, WE: BDD, CE: wound platinum wire, ER: MSE

An oxidation peak appeared at a potential of 1.655 V/MSE and a current of 0.925 mA in the domain of BDD electroactivity. This shows that the oxidation of the omnipaque takes place by direct electronic exchange at the surface of the electrode. The addition of the IHX also resulted in a decrease in the oxygen release current and an increase in the O_2 release onset potential. In the absence of IHX, the release of O_2 starts at 1.883 V/MSE, but in the presence of IHX, the release of O_2 starts at 2.011 V/MSE. The decrease in the current in the

high potential range attests to the participation of oxidative species such as hydroxyl radicals in the oxidation of the organic compound. In the presence of IHX, there is no peak in the return direction of the scan, indicating that the oxidation process of omnipaque is irreversible on the BDD micro-electrode. The voltammograms in Figure 1 obtained in the absence and presence of omnipaque were performed at 50 mV/s, in the potential range from -2.3 V to 2.4 V/MSE, on the BDD.

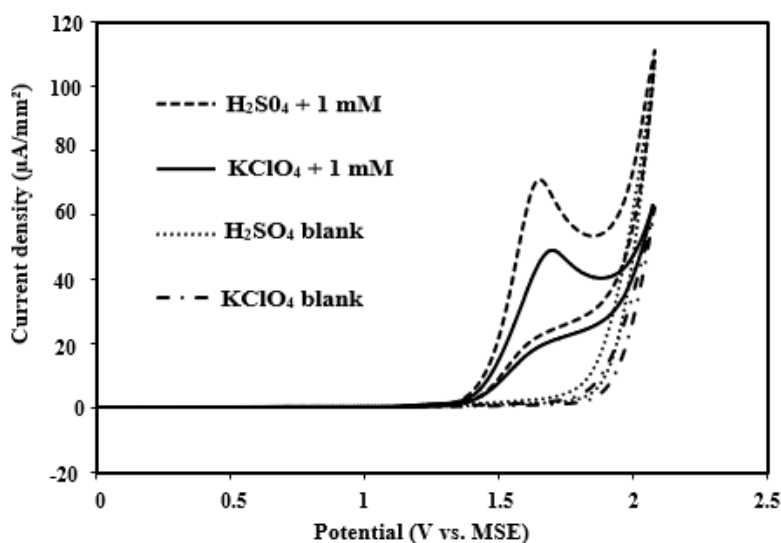


Figure 2. Cyclic voltammetry of micro-DDB in H_2SO_4 (0.1 M) and KClO_4 (0.1 M) in Blank and then containing 1 mM iohexol; WE: BDD; CE: wound platinum wire, ER: MSE. Scanning rate = 50mV/s, T = 26°C

3.1.2. effect of the supporting electrolyte

The electrolyte medium is one of the crucial parameters in an electrochemical process. Therefore, we performed cyclic voltammetry of the same concentration of omnipaque (1mM) in two electrolytes (H_2SO_4 (0.1M) and KClO_4 (0.1M)) to evaluate the effect of this parameter. This study was done in the potential range from 0V to 2.1V/MSE at a rate of 50 mV/s in the potential range from 0 V to 2.1 V/MSE.

Figure 2 shows the influence of the support medium on the detection of IHX. This figure shows that the best response in terms of the peak is obtained in sulfuric acid medium since the H_2SO_4 medium (0.1M) gives a better resolution of the IHX oxidation peak than the potassium perchlorate medium. The best peak intensity is obtained in an acidic environment. This phenomenon would be due to the presence of proton because in a study conducted by A. A Ensafi *et al.* showed that the change in pH of the reaction medium of morphine and codeine influences the potential and the oxidation peaks. This behavior was due to the

participation of protons in the oxidation mechanism of both products²⁰. For these reasons, the sulfuric acid medium will be used as the supporting electrolyte for the rest of our work.

3.1.3. effect of the pH

In order to understand the effect of the pH of the medium on the oxidation of iohexol, voltammetric measurements were made while varying the pH of the electrolytic medium, i.e., sulfuric acid (0.1M). Figure 3 shows the cyclic voltammograms obtained from different pH values (0.97; 3.52; 6.99; 8.89; 12.02). There is a significant difference in the intensity of the IHX oxidation peak obtained with pH 0.97 than the other selected pH values. This could be attributed to the presence of protons in the very acidic medium, which would contribute significantly to the oxidation of IHX²⁰. We find that as the pH of the solution increases, the oxidation peak potentials shift to the left (decrease as shown in Table 1).

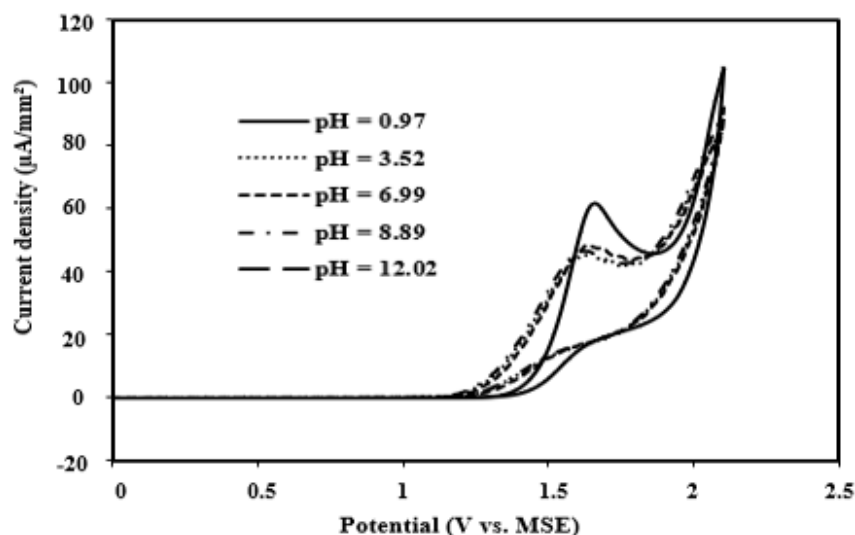


Figure 3. Influence of the pH of the reaction medium (H_2SO_4 (0.1 M)), on the oxidation of 1 mM IHX; WE: BDD; CE: Coiled Pt, ER: MSE. Scanning rate = 50mV/s, T = 26°C

Table 1. Potentials associated with the oxidation peak of iohexol for each PH.

pH	0.97	3.52	6.99	8.89	12.02
E _{pa} (V) of IHX	1.660156	1.650391	1.635742	1.616211	1.616211

The observation of all these remarks allows us to say that the most suitable pH for the determination of omnipaque is the very acidic pH (pH = 0.97). This pH will be retained for the rest of our work.

3.1.4. Effect of IHX concentration on BDD

In the presence of various concentrations of IHX in the electrolyte solution, measurements were made in the same potential range (0 V to 2.1 V/MSE) at a rate of 50 mV/s. The voltammograms obtained are shown in Figure 4. In this figure, it can be seen that the concentration of IHX increases with the oxidation

peak. This reflects direct oxidation of the drug product in the stability range of the supporting electrolyte on the BDD. The inset curve in Figure 4 plots the current density of the different oxidation peaks as a function of the concentration of IHX introduced into the support medium. The proportionality ($R^2 = 0.9971$) between the current density of the oxidation peak and the concentration of IHX confirms that this peak is related to the oxidation of IHX. Thus, during the oxidation of IHX, there is an increase in the current, which suggests that there is an electronic transfer to the electrode surface.

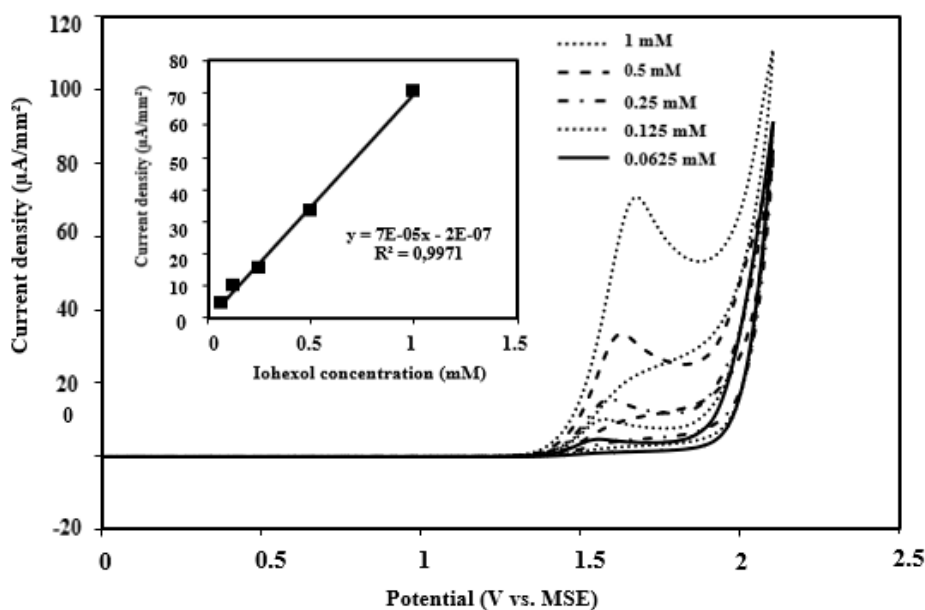


Figure 4. Cyclic voltammogram for different concentrations of Iohexol in a sulfuric acid solution (0.1 M); Inset: Evolution of J_p currents from iohexol oxidation as a function of IHX concentration. WE: BDD, CE: Coiled Pt, ER: MSE. Scanning rate: 50mV/s

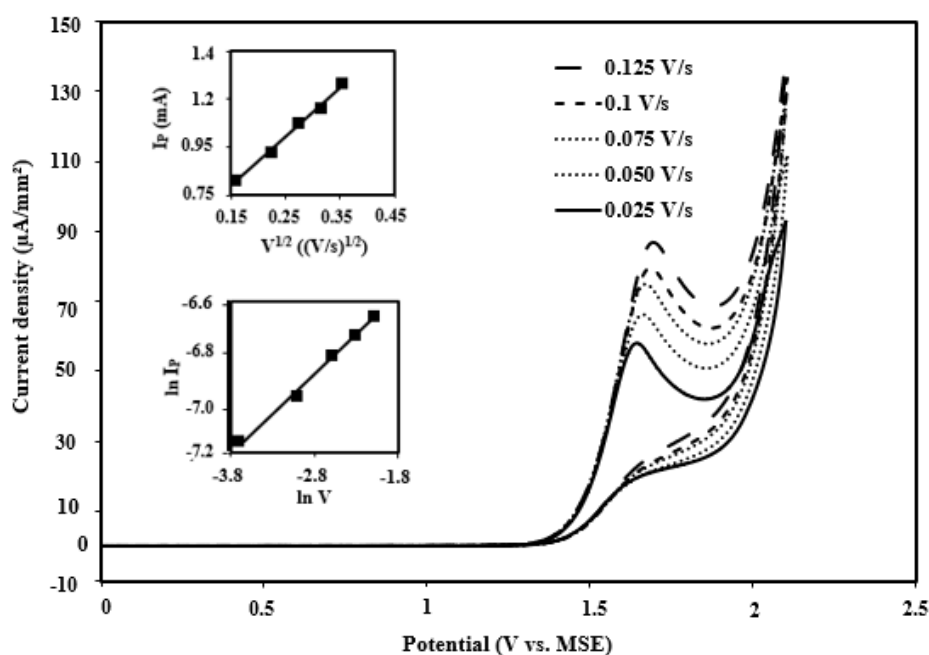


Figure 5. Cyclic voltammogram of BDD electrode in H_2SO_4 (0.1M) containing 1 mM IHX at different scan rates. The dependences I_p against $v^{1/2}$ and $\ln I_p$ against $\ln v$ are displayed in the insets, $T = 26^\circ C$, WE: BDD, CE: Coiled Pt, ER: MSE

3.1.5. effect of the potential scan rate

Figure 5 shows the voltammetric response of the BDD at different scan rates (from 25 to 125 mV/s) and for a concentration of 1mM iohexol. These curves show that the intensity of the current oxidation increases with the scan rates. The peak currents for each scan rate observed at 1.655 V/MSE were determined and plotted as a function of the square root of the scan rate (inset in Figure 5). In addition, the neperian logarithm of I_p was plotted against the neperian logarithm of the applied rate (inset in Figure 5). The purpose of plotting both curves is to determine the kinetic

regime and the kinetic regime (adsorption or diffusion) that the oxidation of the IHX has on the electrode surface²¹.

The recorded oxidation peak current was plotted against the square root of the scan rate (inset of Figure 5). The curve obtained is a straight line described by the equation $I_p = 0.002V^{1/2} + 0.0005$ with a determination coefficient $R^2 = 0,993$, which is very close to 1. This straight line does not intercept the origin of the axes, which is why we deduce that the reaction can be controlled by adsorption²²⁻²⁴. However, Figure 5 describes a line whose equation is

In $I_p = 0.2342 \ln V - 6.261$ and the coefficient $R^2 = 0.993$. Looking at the equation from the second box, we notice that the slope is 0.2342 less than 0.5, so the electrooxidation process of the iohexol is limited by diffusion^{25,26}. This result indicates that an adsorption-diffusion phenomenon occurs during the

electrooxidation reaction of IHX²¹.

3.2. Detection and quantification of iohexol (IHx) by DPV method

The DPV investigations were carried out under the optimal conditions determined by Koffi *et al.*¹⁴.

Table 2. Quantification parameter for pharmaceuticals¹⁴.

Parameters	Iohexol
Pretreatment potential (V)	-2
Pretreatment time (s)	90
Modulation amplitude (V)	0.1
Modulation time (s)	0.05
Step de potential (mV)	0.007

Figure 6 shows the voltammogram obtained in our experiment. These voltammograms are obtained for different concentrations of iohexol, the values of which are between 0 $\mu\text{mol/L}$ and 74.35 $\mu\text{mol/L}$. A slight shift of the peak potential towards the positive values of the potential as the IHX concentration increases is observed. This could be linked to the inter-electrode distances between the working electrodes, counter-electrode, and the reference. It should be noted that the peak of appearance of the omnipaque is from 1.41 V/MSE to 1.45 V/MSE. In this figure, we can see that the peak current density

increases with the concentration of the IHx. The calibration curve (inset in Figure 6) was obtained for different concentrations of IHx ranging from 4 μM to 74.35 μM . The curve obtained is a straight line with a correlation coefficient R^2 of 0.9985, which is very close to 1. This reflects the excellent linearity of the method for this chosen concentration range. The limits of detection and quantification are 1.953 μM and 6.511 μM , respectively, using the equations $\text{LOD} = 3 \cdot \text{SD}/b$ and $\text{LOQ} = 10 \cdot \text{SD}/b$ for their determination; SD is the standard deviation and b is the slope of the straight line in the inset of Figure 6²⁷.

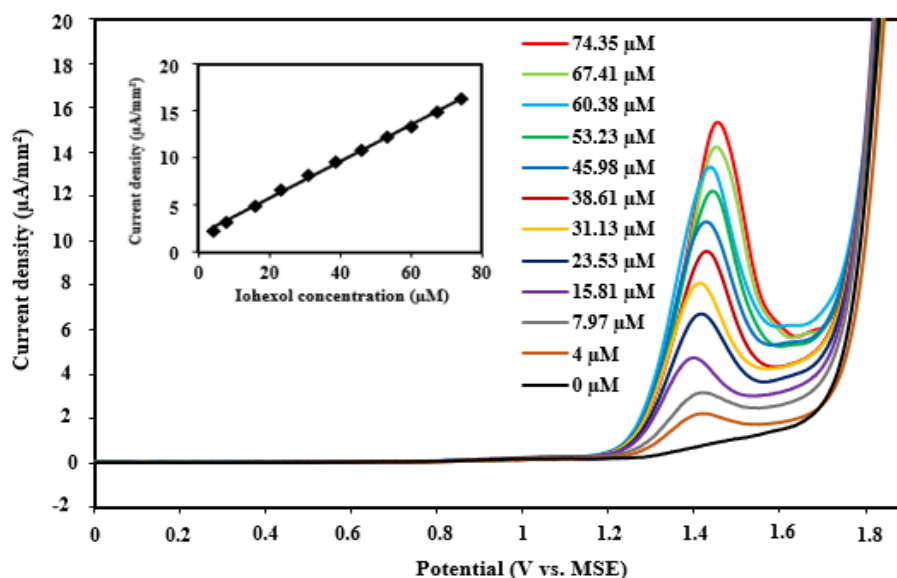


Figure 6. Differential pulse voltammograms of different iohexol concentrations ranging from 0 μM to 74.35 μM , Inset: Calibration curve of the method, $T = 26^\circ\text{C}$, WE: BDD, CE: wound platinum wire, ER: MSE

The recovery rate was determined to show the reliability and precision of the method. For this purpose, three independent measurements of six theoretical concentrations of IHx were carried out.

The results obtained are shown in Table 3. The experimental concentration $[\text{IHx}]_{\text{exp}}$ was calculated with the obtained calibration curve for each of the six (06) concentrations of iohexol used.

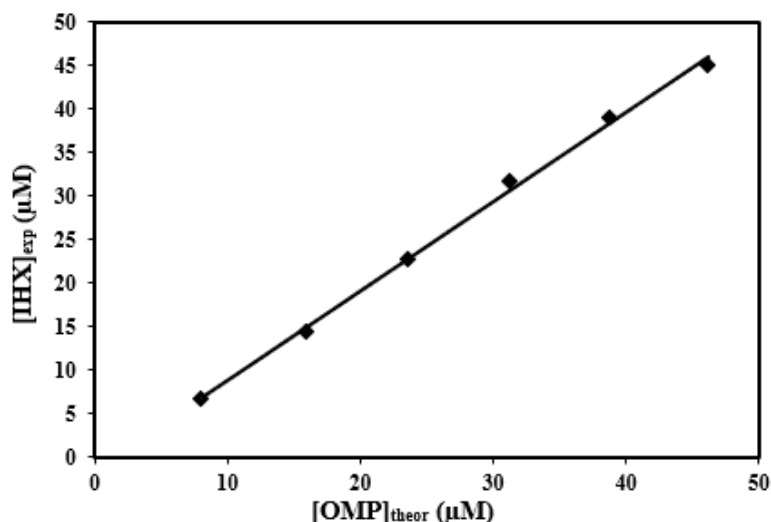


Figure 7. Curve of the experimental iohexol concentration versus the theoretical concentration; T = 26°C, WE: BDD, CE: wound platinum wire, ER: MSE

Plotting the experimental concentration against the theoretical concentration of iohexol (Figure 7) gives a straight line with the following equation: $[IHX]_{exp} = 1.0288[IHX]_{theo} - 1.4873$ with $R^2 = 0.9975$. This line has a correlation coefficient of

approximately 1. This would indicate a proportionality between the experimental and theoretical concentration and the reliability of our voltammetric differential pulse analysis method.

Table 3. Recovery rate of the method.

Samples	Introduced concentration (μM)	Resulting concentration (μM)	Recovery rate (%)	± SD
1	8	6.64	82.99	0.06
2	15.87	14.43	90.93	0.09
4	23.62	22.62	95.78	0.15
4	31.25	31.76	101.63	0.07
5	38.76	39.02	100.67	0.24
6	46.15	44.50	96.43	0.02

3.3 Interference study

3.3.1 Influence of some inorganic ions on the detection of IHX by DPV

In general, in the environment and wastewater, there may be the existence of some inorganic ions that can interfere with the detection of iohexol. In this part, the study of inference has been investigated by separately adding the following compounds potassium cyanide (K^+ ; CN^-), hydrated magnesium sulfate (Mg^{2+} ; SO_4^{2-}), and sodium sulfate ($2Na^+$; SO_4^{2-}) to the iohexol solution. Three concentrations (3.846 mM, 7.407 mM, and 10.714 mM) of these different compounds were successfully added. Our study was possible thanks to using a sulfuric acid solution containing a 20 μM concentration of IHX. The addition of these compounds allowed us to record voltammograms by the DPV method. The peak current densities obtained in the presence of the interfering compounds were

deduced from those obtained without the interfering compounds. The formula for calculating the interference for each compound acting on the iohexol detection signal is $X = \left(\frac{I'}{J} \times 100\right) - 100$, where I' is the peak density of the interfered IHX signal and J is the peak density of the non-interfered signal. Table 4 shows the results obtained.

After observing Table 4, we find that the percentage of interference is between ± 0.123% and ± 5.559%. This would mean that the concentration of K^+ , CN^- , Mg^{2+} , SO_4^{2-} , Na^+ ions, 100 times higher than IHX would produce a negligible effect on its peak detection. Thus, the impact of these interferents being little, we can say that there was no interference in detecting IHX. All these results allow us to say that our method can be used to detect and quantify iohexol in an ion medium such as wastewater.

Table 4. Influence of the concentration of inorganic compounds on the oxidation current of the iohexol.

Interfering Compounds	Concentration in mmol/L of the added interferent	% the change in peak current density in DPV: X
KCN	3.846	-0.123
	7.407	3.563
	10.714	-5.559
MgSO ₄ ·7H ₂ O	3.846	2.062
	7.407	-5.745
	10.714	2.117
Na ₂ SO ₄	3.846	-3.810
	7.407	1.763
	10.714	4.194

3.3.2. Interference of an organic compound on the detection of iohexol by DPV

This interference was studied by adding different concentrations of paracetamol (PCM) (31 μ M; 45.8 μ M; 60.15 μ M; 87.59 μ M; 119.72 μ M and 149.66 μ M) to a 0.1 M sulfuric acid solution containing 20 μ M IHX. Subsequently, the current responses corresponding to the IHX peak were recorded as the paracetamol concentration increased,

as shown in Figure 8. From the observation of Figure 8, one could say that there is a fluctuation in the peak intensity of the IHX appearance. This fluctuation may be due to competition at the electrode surface (micro BDD) as both organic compounds. As the changes are not so significant, it can be stated that our proposed voltammetric protocol (DPV) can be considered adequate for the analysis of waters containing other organic compounds than iohexol.

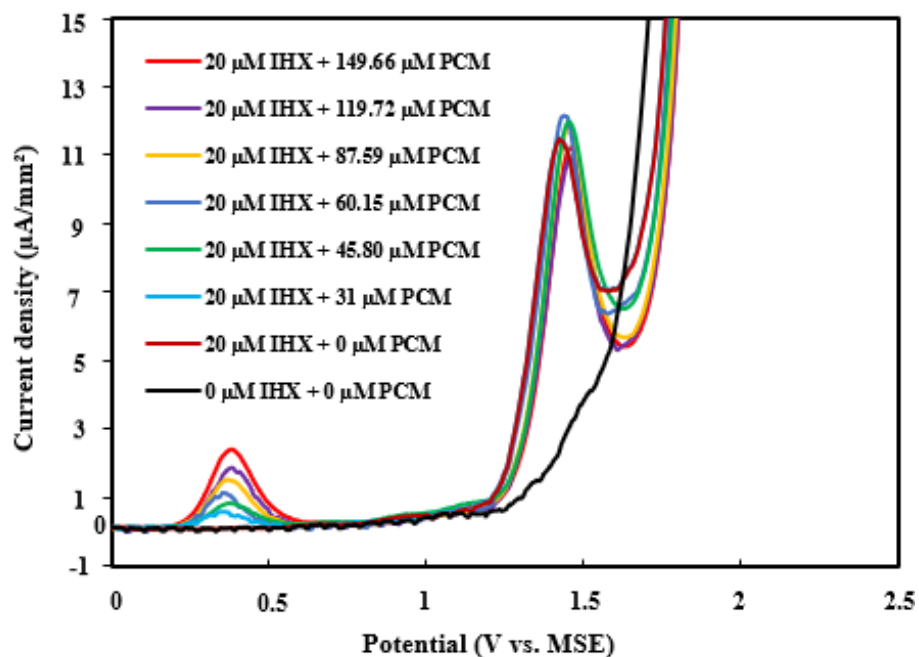


Figure 8. Differential pulse voltammograms of different concentrations of paracetamol in the presence of a fixed concentration of IHX (20 μ M), T = 26°C, WE: BDD, CE: wound platinum wire, ER: MSE

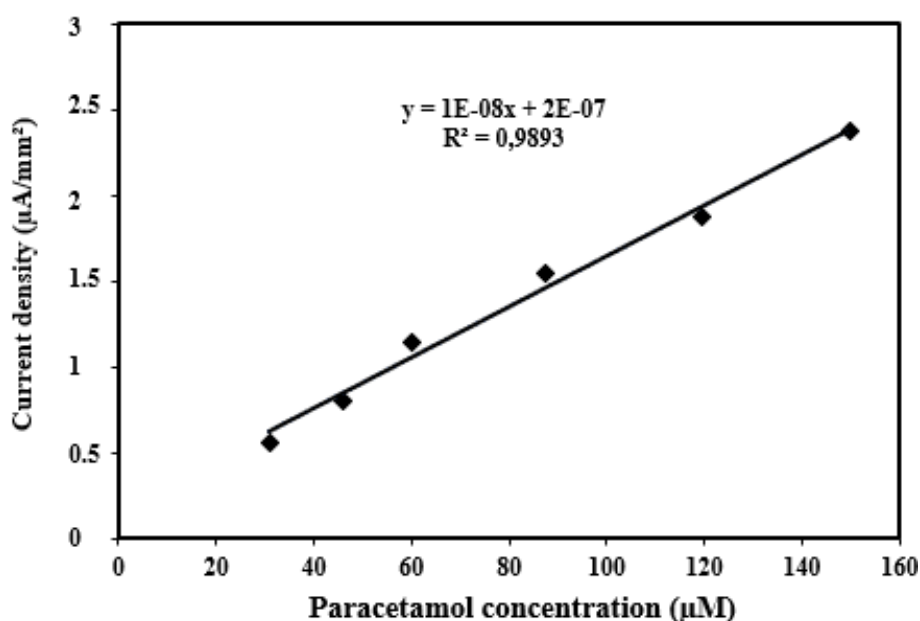


Figure 9. Calibration line for paracetamol in the presence of 20 μM IHX

It was also observed that paracetamol appeared at a potential of 0.379 V/MSE, consistent with the literature ^{28,29}. Therefore, we aimed to detect IHX (20 μM), regardless of the amount of paracetamol introduced into the reaction medium. The successive addition of PCM concentrations to the reaction medium containing 20 μM IHX resulted in a calibration line (Figure 9) with a correlation coefficient of $R^2 = 0.9893$, very close to 1.

3.3.3. Comparison of the electrochemical method with other methods for the detection of iohexol

Table 5 shows that our proposed analytical method is suitable for detecting and quantifying trace iohexol in wastewater. The electrochemical sensor developed (with a miniaturized boron-doped diamond electrode) achieves a trace iohexol detection limit (1.953 μM) or 1.6 μg/mL.

Table 5. Comparison of the effectiveness of some methods in the determination of iohexol.

Method	Medium	Detection range	LOD	References
LC-MS/MS	Sérum	6.8 - 250 μg/mL	10.5 ng/mL	30
HPLC-UV	Plasma	10.4 - 42.9	9.7 ng/mL	31
LC-MS/MS MP Chromatographique	Plasma	4.65 - 85.7 μg/mL	2.8 ng/mL	31
LC-MS/MS	Sérum	10 - 1000 μg/mL	3 μg/mL	32
CE (Capillary Electrophoresis)	Sérum	13 - 305 mg/L	10 - 32 μg/mL	33
HPLC-UV	Rat Plasma	0.05 - 5 μg/mL		34
Electrochimic (DPV)	H ₂ SO ₄ (0,1M)	4 - 74.35 μM	1.953 μM (1.6 μg/mL)	Present work

4. Conclusion

The most commonly used methods for the detection and quantification of iohexol are generally costly. In our study, we have established a simple and less expensive way. The electrochemical DPV method is sensitive and selective for detecting and quantifying iohexol on the miniaturized BDD. Here the BDD is used as an electrochemical sensor for the oxidation of iohexol. During the Cyclic Voltammetry in a sulfuric acid medium (0.1M), the oxidation peak appeared at 1.655 V/MSE. Then in the same medium, during the DPV, the peak occurred at 1.415 V/MSE. Using the parameters already optimized for the detection of

pharmaceuticals on the BDD in our laboratory, we obtained a LOD and a LOQ of 1.953 μM and 6.511 μM, respectively, for a concentration range of iohexol from 4 μM to 74.35 μM. The selectivity of the method was also proven, even in ion media and other pharmaceutical compound. Therefore, the technique would be suitable for the quantification and detection of iohexol.

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