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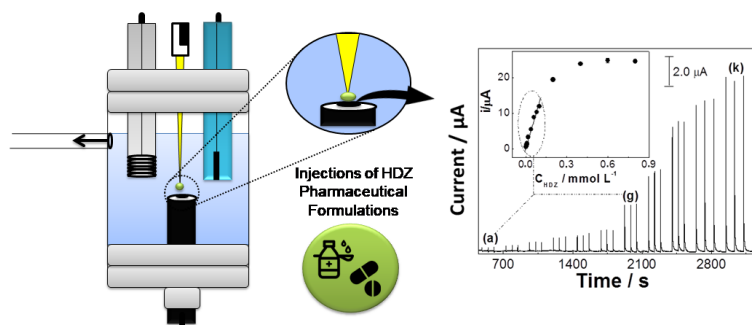
# Development of an Electrochemical Sensor Modified with Dealuminated Zeolite with Citric Acid for Hydroxyzine Determination by BIA-Amperometry

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An electrochemical sensor modified with zeolite dealuminated with citric acid was developed for the determination of hydroxyzine in pharmaceutical products during BIA-amperometry experiments. The modified electrochemical sensor was prepared by mixing powdered graphite with zeolite treated with citric acid homogenized with hexane and mineral oil (60:20:20% w/w/w respectively). The developed sensor

showed reproducible amperometric responses in a linear range of  $1.0 \times 10^{-6} - 2.0 \times 10^{-5} \text{ mol L}^{-1}$  in +1,28 V (vs. Ag/AgCl). The detection limit and detection limit found were  $3.10 \times 10^{-7} \text{ mol L}^{-1}$  e  $1.04 \times 10^{-6} \text{ mol L}^{-1}$ , respectively. The method developed by BIA-amperometry was applied for the determination of the analyte in tablets and commercial syrups and the results found agreement with the nominal values of the commercial samples.

**Keywords:** batch Injection analysis, amperometric sensor, carbon paste electrodes, hydroxyzine, zeolite

## INTRODUCTION

The need to carry out quality control of medicines, foods and other products intended for human consumption in a fast and effective way has contributed to advances in the development of automated analytical systems. These systems have promising characteristics that contribute to the performance of a large number of analyzes in a short time with the sensitivity and selectivity required in the development of

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analytical methods.<sup>1,2</sup> Flow injection analysis (FIA) was the first automated analytical system, developed in 1975 by Ružička and Hansen.<sup>3</sup> FIA systems have advantages related to high analytical frequency, analysis speed, precision and reproducibility, being used in the analysis of food, drugs and chemical contaminants.<sup>3-6</sup> However, the consumption of a large amount of reagents and the use of complex systems with pumps and valves make the analysis in FIA unfeasible and disadvantageous.<sup>1,7</sup>

As an alternative to FIA analysis, batch injection analysis (BIA) was developed by Wang and Taha in 1991.<sup>8</sup> It is a tool which has been explored by some research groups as an alternative to perform quick analysis in a very simplified way. BIA analysis consists of the direct injection of small volumes of samples on the center of the detector immersed in a solution in the absence of the analyte through a motorized micropipette.<sup>1,7,9</sup> Electrochemical detectors are widely combined with BIA, mainly amperometric ones, for the development of sensors capable of performing the determination of a wide range of electroactive analytes.<sup>1</sup>

To improve the sensitivity and selectivity of electrochemical sensors, different materials have been used to modify their surfaces. Generally, these materials give the electrochemical sensor a high surface area and good electronic conductivity.<sup>10</sup> Traditionally, materials such as graphene, carbon nanotubes, metallic nanoparticles and other nanomaterials are used as excellent modifiers.<sup>11-14</sup> Recently, sensors modified with zeolites have been reported in the literature due to high surface area and appreciable physicochemical properties sensors.<sup>15,16</sup> A specific case is dealuminated zeolite with citric acid, which produces changes in the outer layer of zeolite material, conferring a large volume of mesopores to this material.<sup>17</sup> In this perspective, the present work aimed to develop an electrochemical sensor modified with dealuminated zeolite with citric acid for the determination of hydroxyzine (HDZ).<sup>18</sup> During amperometric experiments, this sensor modified with zeolite was associated with a BIA configuration for analyses of pharmaceutical samples.

## MATERIALS AND METHODS

### *Reagents and solutions*

Hydroxyzine Hydrochloride (99,5%) was kindly provided by Medquímica Industria Farmaceutica LTDA., Juiz de Fora, MG, Brazil. Acetic acid, phosphoric acid and boric acid were purchased from Sigma Aldrich (St. Louis, MO, USA). Hexane and dichloromethane were purchased from Merk (Darmstadt, Germany). Acetonitrile was purchased from LiChrosolv (Germany). Powder graphite was purchased from Synth (Brazil). HZSM-5 zeolite (MFI structure) used in this work was supplied by Zeochem (reference n V1148.4) with a Si/Al ratio of 14 and modified with citric acid (CA) by Vieira et al.<sup>17</sup> Zeolite modified with CA will be presented in this paper as MZCA.

The solutions were prepared with ultrapure water from Milli-Q purification system with resistivity 18.2 MΩ cm (Millipore, Bedford, USA). The stock solution of HDZ in the concentration of 0.10 mol L<sup>-1</sup> was prepared by dissolving the solid salt in ultrapure water and stored in a dark flask under refrigeration.

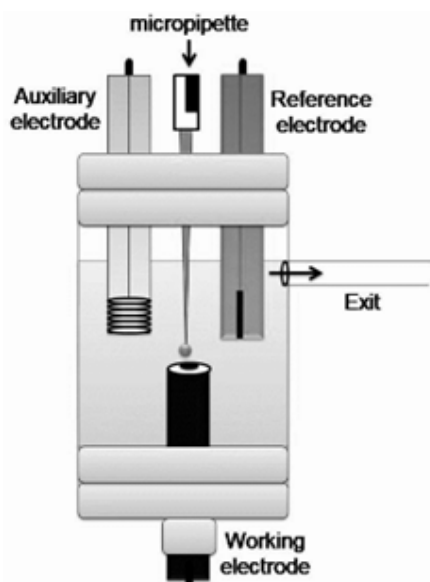
The standard solutions of the analyte were properly diluted with supporting electrolyte just before the measurements. Britton-Robinson (BR) 0.1 mol L<sup>-1</sup> buffers, at different pH values (2.0 – 6.0), were prepared by mixing 0.5 mol L<sup>-1</sup> acetic acid solution to 0.5 mol L<sup>-1</sup> phosphoric acid solution and 0.5 mol L<sup>-1</sup> boric acid solution. A 1.0 mol L<sup>-1</sup> sodium hydroxide solution was used to adjust the desired pH value. The pharmaceutical formulations of the syrup and the pills were purchased in a local drugstore.

### *Instrumentation*

#### *Cyclic voltammetry and amperometry*

All measurements were performed using a potentiostat  $\mu$ -AutoLab Type III (Metrohm). Cyclic voltammetry studies were carried out using a conventional electrochemical cell of 10 mL. The working electrode body was made of 7.0 cm long Teflon<sup>®</sup> coated rod with a small hole 3.0 mm in diameter and depth of 2.0 mm as well as the electric contact was made of a copper wire which was connected to the back of the Teflon<sup>®</sup>. Then, it was filled with carbon paste modified with zeolite. The reference electrode was the Ag/AgCl<sub>(KCl sat)</sub>

built in our lab,<sup>19</sup> and the auxiliary was of platinum wire. The BIA-amperometry experiments were performed in a wall-jet cell capable of 25 mL as shown in Figure 1.



**Figure 1.** Representation of wall-jet cell (length of 6.5 cm and diameter of 3.0 cm).

HDZ standard solutions and drug samples were injected into the system by an automatic electronic micropipette (E4 XLS, model SE4-100XLS+ – Rainin, USA) with the tip centered at 2.0 mm of the working electrode surface.

#### **Preparation of the modified electrode with zeolite**

The preparation of carbon paste modified with zeolite was adapted from the method described by Wang and Walcarius (1996).<sup>15</sup> The zeolite was mixed with the powdered graphite in the proportion of interest and suspended in an organic solvent (10.0 mL of solvent to 1.0 g of the solid mixture). The system was homogenized in a magnetic stirrer at a temperature of 100 °C until complete evaporation of the organic solvent. Mineral oil was added in the desired proportion to the homogeneous solid composed of zeolite and graphite powder to obtain modified carbon paste. In this study, the solvents dichloromethane and hexane were evaluated. Experiments were also carried out without the solvent homogenization step proposed by the method described as a comparison criterion.

#### **Sample preparation**

For HDZ voltammetric analysis, aliquots of 1.50 mL of the syrup of HDZ 2.0 mg mL<sup>-1</sup> were transferred to a volumetric flask of 1.0 L and completed with 0.1 mol L<sup>-1</sup> of phosphate buffer (pH = 4.0).

For the analysis of tablets of HDZ the average mass of 3 tablets was calculated. The tablets were macerated in a pestle mortar. A suitable mass of the homogenized powder was weighed and homogenized with 10 mL of 0.1 mol L<sup>-1</sup> of phosphate buffer (pH = 4.0) and the excipients were removed by filtration. The filtered solution was transferred to a volumetric flask of 25 mL and completed with 0.1 mol L<sup>-1</sup> of phosphate buffer (pH = 4.0). Appropriate aliquots of HDZ were added to the electrochemical cell containing 10 mL of electrolyte solution.

For the performance of HPLC/DAD the syrup and tablet samples were diluted in order to obtain a solution whose hydroxyzine concentration was 100 µg mL<sup>-1</sup> based on methodology described by Brandão and collaborators (2011).<sup>20</sup> First, a tablet was diluted in ultrapure water in a 10 mL volumetric flask, thus obtaining a concentration of 100 µg mL<sup>-1</sup> hydroxyzine solution. In the case of liquid samples, about 250 µL of each syrup sample were diluted in ultrapure water in 5 mL flasks (with calibrated flask volume) to obtain a 100 µg mL<sup>-1</sup> hydroxyzine solution. The solutions were stored in amber vials and kept under refrigeration.

### Comparison technique

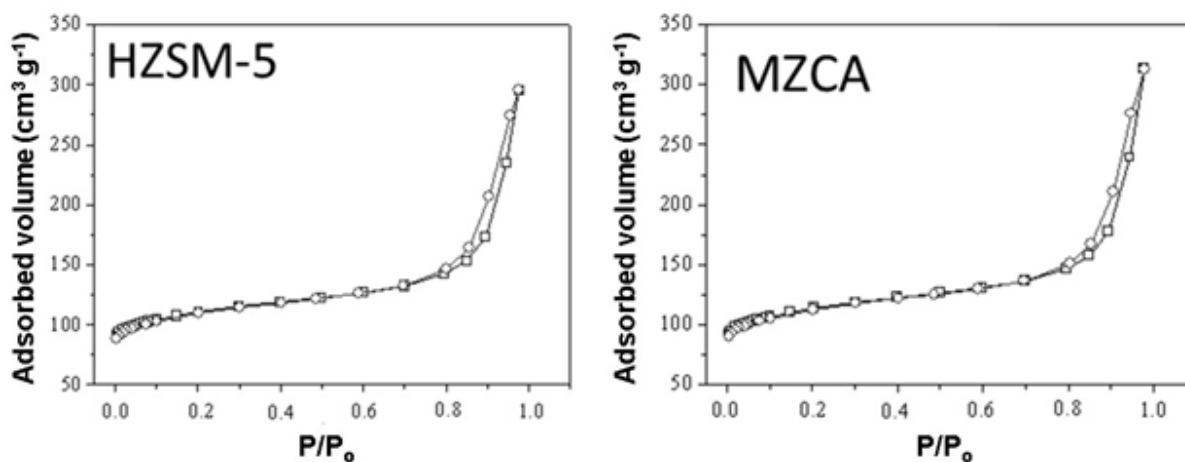
Comparative HDZ analysis was performed in a high-pressure liquid chromatograph (HPLC) (model HP 1100, Germany) equipped with quaternary pump, autosampler, temperature-controlled column compartment and diode array detector (DAD). The software for the operation of the analysis and manipulation of the chromatograms was the ChemStation version Rev.03.2.B. The column used was a Zorbax Elypse Plus C18 (5  $\mu\text{m}$ , 250 x 4.6 mm, Agilent, USA). The chromatographic method was adapted from Brandão and collaborators (2011)<sup>20</sup> and consisted of maintaining the column temperature at 58 °C, wavelength 232 nm, flow rate 0.8 mL/min and acidified mobile phase (pH 4.0) composed of acetonitrile:water (4:6). The analysis time was 9 min and the injected volume of sample and standard was 20  $\mu\text{L}$ .

For the analytical curve, a stock solution of hydroxyzine (3.74 mg mL<sup>-1</sup>) was prepared by diluting the standard in BR buffer (pH = 4.0) and from this, the working solutions were prepared for curve construction (0.80 to 0.120 mg mL<sup>-1</sup>). After the optimization of the method, the curve was made in triplicate and the samples were injected in sextuplicate. The hydroxyzine content in commercial samples was determined from the peak areas corresponding to the analyte of interest in the samples and the linear regression obtained from the calibration curve.

## RESULTS AND DISCUSSION

### Characterization of zeolite modified with citric acid

The MZCA zeolite used as modifier in this work was a HZSM-5 dealuminated with citric acid (CA) in a concentration of 1.0 mol L<sup>-1</sup> under the temperature of 80 °C.<sup>17</sup> Figure 2 shows the adsorption isotherms for HZSM-5 and MZCA zeolites. These isotherms show the simultaneous presence of mesopores that can be evidenced by the presence of a hysteresis loop at higher P/P<sub>0</sub> (close to 1) and micropores (high initial N<sub>2</sub> uptake at P/P<sub>0</sub> < 0.1). Usually, this observation occurs for materials that possess non-rigid slit-shaped pores and has been attributed to the presence of interparticle mesopores created by agglomeration of small crystallites.<sup>21</sup> The adsorption sites may be located on the surface of these mesopores.<sup>17</sup>



**Figure 2.** N<sub>2</sub> adsorption–desorption isotherm obtained for parent HZSM-5 e MZCA sample: being -□- adsorption isotherm and -○- desorption isotherm.

The results obtained in Figure 2 were treated using the t-plot method to determine the external area ( $S_{\text{ext}}$ ), micropore volume ( $V_{\text{micro}}$ ) and pore volume ( $V_{\text{pore}}$ ). They indicated that MZCA material has a large  $V_{\text{micro}}$  (0.15 cm<sup>3</sup> g<sup>-1</sup>) and  $V_{\text{pore}}$  (0.49 cm<sup>3</sup> g<sup>-1</sup>) and  $S_{\text{ext}}$  (73.0 m<sup>2</sup> g<sup>-1</sup>).

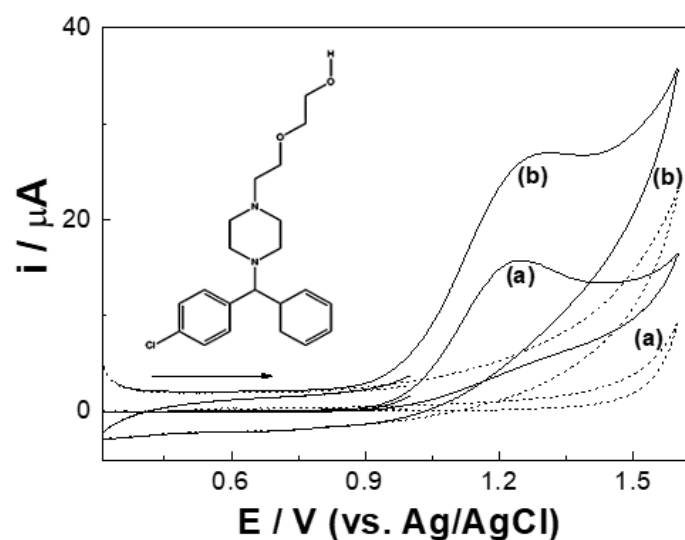
The FTIR data from both materials (Figure 2) indicates the presence of a band in the region of 798 cm<sup>-1</sup> referring to the symmetrical stretching of the Si-O-Si bond of the zeolite lattice structure. The HZSM-5 zeolite has a characteristic absorption band observed in the region between 550 cm<sup>-1</sup> and which can be attributed to the vibrations of the five-membered double rings that make up its structure. For the MCZA material, this band was observed in the region of 547 cm<sup>-1</sup>. Dealumination can cause not only a shift in

the FTIR spectrum bands, but also a thinning of the same, and the small shift in these bands was due to the low dealumination that the citric acid treatment caused.<sup>17</sup> In addition, this treatment decreased the intensity of the band at 3608 cm<sup>-1</sup>, attributed to the Si(OH)-Al groups that are adsorption sites (acidic sites), as well as the OH bands related to extra-framework Al species (3662 and 3780 cm<sup>-1</sup>). It was also observed that Al content (Si/Al ratio) decreased with CA treatment. These results mentioned were published by our research group in 2015.<sup>17</sup>

Anyhow this CA dealumination improved the electronic transfer and the MCZA zeolite was used as modifying agent during construction of working electrode.

### **Voltammetric studies of hydroxyzine using the CPE modified with zeolites**

The electrochemical behavior of HDZ was investigated in carbon paste electrode (CPE) modified with MZCA and CPE in the absence of this zeolite. The voltammetric experiments were performed with 5.0x10<sup>-4</sup> mol L<sup>-1</sup> of the analyte in 0.10 mol L<sup>-1</sup> of BR buffer solution (pH 4.0) and are presented in Figure 3. The electrolyte was initially chosen due to the hydroxyzine oxidation-reduction reaction, which takes place preferentially in an acidic medium, according to the work developed by Lourenção et al. (2017).<sup>22</sup>



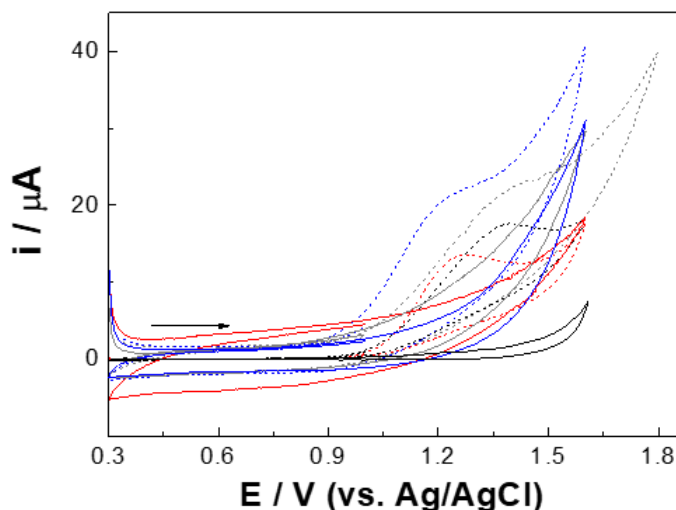
**Figure 3.** Cyclic voltammograms recorded for (a) CPE and (b) CPE + MZCA, both prepared in hexane, in 0.1 mol L<sup>-1</sup> BR buffer solution, pH 4.0 (dashed line) and 5.0 x10<sup>-4</sup> mol L<sup>-1</sup> HDZ solution (solid line). The inset shows the chemical structure of hydroxyzine (HDZ).

The process presented in Figure 3 for both cases (CPE with or without MZCA) corresponds to irreversible electrooxidation ( $E_{pa} = +1.28$  V vs. Ag/AgCl) of the hydroxyl group located on the aliphatic part of the analyte molecule (HDZ or 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]piperazin-1-yl]ethoxy]ethanol).<sup>22,23</sup> No other peaks were observed in the reverse scan direction (considering a potential region from 0.3 to 1.6 V vs. Ag/AgCl), which indicated the irreversible nature of the reaction. The increase in anodic peak current ( $I_{pa}$ ) found in voltammograms b, is related to the presence of MZCA. This material has a large volume of micropore ( $V_{micro} = 0.15$  cm<sup>3</sup> g<sup>-1</sup>) and pore ( $V_{pore} = 0.49$  cm<sup>3</sup> g<sup>-1</sup>) in addition to high external area ( $S_{ext} = 73.0$  m<sup>2</sup> g<sup>-1</sup>) that favor the HDZ multilayer adsorption mechanism on the external surface of the working electrode. The high external area of the MZCA can be attributed to the external acidity (40 μmol g<sup>-1</sup>) obtained from the dealumination of the zeolite with the incorporation of CA.<sup>17</sup> Thus, the CPE with MZCA (CPE/MZCA) was selected for further analysis due to the significant increase of approximately 36.0% in  $I_{pa}$  when compared to the CPE.

The CPE/MZCA was evaluated under different conditions of paste preparation, according to the method proposed by Wang and Walcarius (1996),<sup>15</sup> in which the zeolite was homogenized in graphite by the addition of an organic solvent.<sup>15</sup> The method initially proposed uses dichloromethane as a solvent for the homogenization of graphite with zeolite. Based on the principles of green chemistry, which implies



a reduction in the consumption of toxic organic solvents, clean technology, and reduction at source, the hexane solvent was tested as a less toxic.<sup>24</sup> Analyzes were performed with  $5.0 \times 10^{-4}$  mol L<sup>-1</sup> of the analyte in 0.10 mol L<sup>-1</sup> of BR buffer solution (pH 4.0). In this study, the voltammograms of CPE/MZCA (a) and CPE (b) in the absence solvent, CPE/MZCA in the presence of dichloromethane (c) and CPE/MZCA in the presence of hexane (d) are compared in Figure 4.



**Figure 4.** Cyclic voltammograms of  $5.0 \times 10^{-4}$  mol L<sup>-1</sup> HDZ in 0.1 mol L<sup>-1</sup> BR buffer solution (pH 4.0) (dashed line) and only electrolyte (solid line), under different working electrode preparation conditions: (red line) CPE/MZCA and (black line) CPE in absence of solvent, (gray line) CPE/MZCA in dichloromethane and (blue line) CPE/MZCA in hexane.

The results obtained (Figure 4) demonstrate a significant increase in  $I_{pa}$  when CPE/MZCA is found in the presence of solvents such as dichloromethane and hexane, (gray and blue lines, respectively). Due to the lower toxicity and the significant increase in  $I_{pa}$ , hexane was selected as the homogenizing solvent in the preparation of the working electrode. Thus, subsequent experiments were carried out with CPE/MZCA in the presence of hexane (CPE/MZCA-Hex).

The CPE/MZCA-Hex was evaluated in different proportions of graphite (80 – 50%), zeolite MZCA-Hex (10 – 30%) and mineral oil (20 – 50%). The results indicated that in the proportion of 60:20:20% w/w/w for construction of working electrode, the  $I_{pa}$  presented the significantly increased when compared to the other proportions.

Other voltammetric studies (not presented in this work) were also performed with the solution 0.10 mol L<sup>-1</sup> of BR buffer solution and varying the pH over a range from 2.0 to 6.0. The pH range was evaluated in this range, since at pH above 6.0 there is a decrease in  $I_{pa}$ .<sup>22</sup> The results show that increasing the pH value improves the intensity of  $I_{pa}$  up to pH 4.0. At higher pH,  $I_{pa}$  remains constant and the peak shifts to more positive potentials. Similar results are reported in the work developed by Lourencao and collaborators (2017).<sup>22</sup> In this sense, the 0.1 mol L<sup>-1</sup> of BR buffer solution pH 4.0 was selected for further analysis.

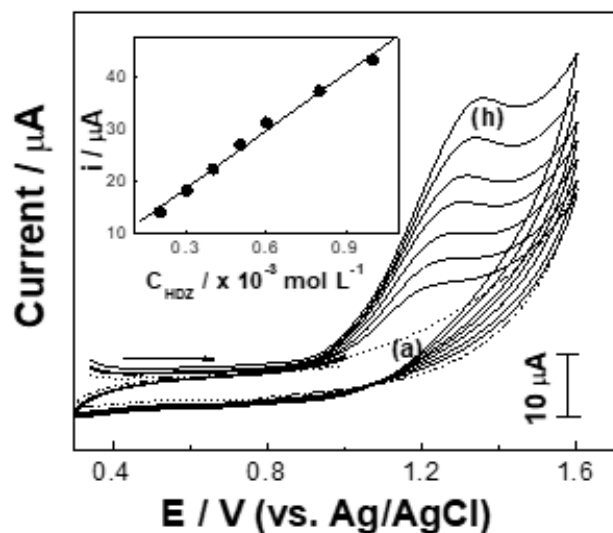
The apparent electroactive surface area of the CPE/MZCA-Hex was evaluated by cyclic voltammetry at different scan rates and using the Randles-Sevcik Equation (Equation 1).

$$i_p = (2,69 \times 10^{-5}) \cdot n^{2/3} \cdot A D_0^{1/2} v^{1/2} C_0 \quad \text{Equation 1}$$

where  $n$  is the number of electrons,  $A$  is the electrode area (cm<sup>2</sup>),  $C_0$  is the concentration of the electroactive species (mol cm<sup>-3</sup>),  $D_0$  is the diffusion coefficient (cm<sup>2</sup> s<sup>-1</sup>) and  $v$  is the sweep speed (V s<sup>-1</sup>).

The voltammetric experiments were performed with 0.1 mol L<sup>-1</sup> K<sub>3</sub>[Fe(CN)<sub>6</sub>] solution in 0.1 mol L<sup>-1</sup> KCl as supporting electrolyte. The scan speed was varied from 50 mV s<sup>-1</sup> to 900 mV s<sup>-1</sup> and the active surface area found for the modified working electrode was of 0.1041 cm<sup>2</sup>.

It still takes into account the cyclic voltammetric experiments, it was possible to observe in the inset of Figure 5 that after successive additions of HDZ (from  $2.0 \times 10^{-4}$  to  $1.0 \times 10^{-3}$  mol L<sup>-1</sup>) in 0.10 mol L<sup>-1</sup> of BR buffer solution, pH 4.0, the current signals were very stable and reproducible with  $r = 0.996$  (scan rate of 100 mV s<sup>-1</sup>).



**Figure 5.** Voltammograms of HDZ standard solutions in 0.1 mol L<sup>-1</sup> BR buffer solution (pH 4.0), using a working electrode constructed from carbon paste + MZCA-Hex + mineral oil (60:20:20%, w/w/w): (a) electrolyte; (b) 2.0; (c) 3.0; (d) 4.0; (e) 5.0; (f) 6.0; (g)  $8.0 \times 10^{-4}$  and (h)  $1.0 \times 10^{-3}$  mol L<sup>-1</sup>. Scan rate: 100 mV s<sup>-1</sup>. Apparent electroactive surface area of 0.1041 cm<sup>2</sup>.

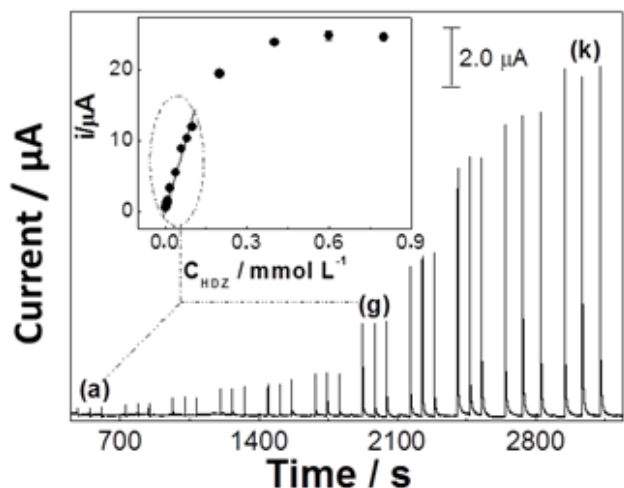
#### **Amperometry Bath Injection Analysis (BIA-Amperometry)**

To establish the best conditions for amperometry in association with bath injection analysis (BIA) in the determination of HDZ, main parameters (distance between the micropipette and the electrode surface, working potential, sample injection volume and injection speed) were investigated using  $1.0 \times 10^{-5}$  mol L<sup>-1</sup> of the analyte in 0.1 mol L<sup>-1</sup> BR buffer solution (pH = 4.0). Amperometric studies under hydrodynamic conditions were performed to obtain the best distance between the micropipette and the electrode surface (from 1.0 to 3.0 mm) as well as the best work potential (from 0.5 to 1.5 V vs. Ag/AgCl). The optimal distance between CPE/MZCA-Hex and the micropipette tip was found to be 2.0 mm, as well as the most favorable work potential was 1.3 V (vs. Ag/AgCl).

The effect of the volume of the sample injected into the system was evaluated from 10 to 100 μL. The experiments showed an increase in  $I_{pa}$  with the increase in sample volume up to 80 μL. For larger volumes, the increase was less significant and the time required for each analysis also increased. In this sense, the volume chosen for carrying out the subsequent experiments was 80 μL.

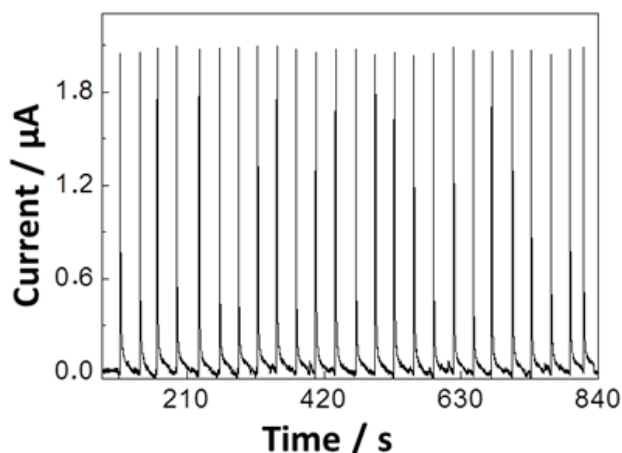
The effect of injection speed was also evaluated in a range from 22.5 to 126.6 μL s<sup>-1</sup>, considering a working potential of 1.3 V and a sample volume of 80 μL. It was possible to observe that  $I_{pa}$  significantly increased up to a velocity of 80 μL s<sup>-1</sup>. At higher speeds, the increase was negligible. For this experiment, the best injection speed selected was of 80 μL s<sup>-1</sup>.

Figure 6 indicates that throughout the investigated range of analyte concentration (from  $1.0 \times 10^{-6}$  to  $1.0 \times 10^{-4}$  mol L<sup>-1</sup>), the behavior of  $I_{pa}$  was only reproducible and linear in  $1.0 \times 10^{-6}$  –  $2.0 \times 10^{-5}$  mol L<sup>-1</sup>. In higher concentration ranges (from  $4.0 \times 10^{-5}$  to  $1.0 \times 10^{-4}$  mol L<sup>-1</sup>) there is a deviation from linearity. The analytical curve constructed in the linear range presented a slope of  $0.13035 \pm 0.0013$  μA mol L<sup>-1</sup> and an intercept of  $1.2841 \times 10^{-7} \pm 1.247$  μA, with a correlation coefficient of 0.992. The estimated detection limit (LOD) was  $2.57 \times 10^{-7}$  mol L<sup>-1</sup> and the calculated quantification limit (LOQ) was  $8.55 \times 10^{-7}$  mol L<sup>-1</sup>.<sup>19</sup>



**Figure 6.** BIA-Amperometric responses of the PCE modified with zeolite for increasing HDZ concentrations in 0.1 mol L<sup>-1</sup> BR buffer solution, pH 4.0: (a) 1.0; (b) 2.0; (c) 4.0; (d) 6.0; (e) 8.0 × 10<sup>-6</sup>; (f) 1.0; (g) 2.0; (h) 4.0; (i) 6.0; (j) 8.0 × 10<sup>-5</sup> and (k) 1.0 × 10<sup>-4</sup> mol L<sup>-1</sup>. Working potential: +1.3 V (vs. Ag/AgCl), injected volume: 80 μL and injection speed: 80 μL s<sup>-1</sup>. The detail shows the analytical curve (a-g).

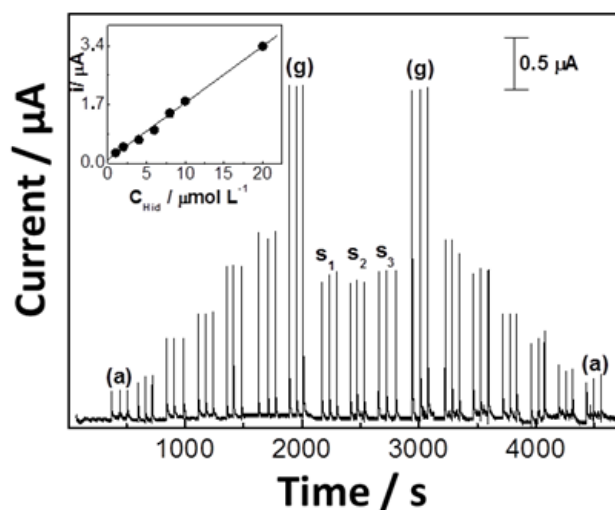
In the work carried out by Lourencao and collaborators,<sup>22</sup> the method applying square-wave adsorptive anodic stripping voltammetry (SWAdASV) presented LOD of 1.0 × 10<sup>-7</sup> mol L<sup>-1</sup>. The work developed by Beltagi et al. a SWAdASV procedure has been developed, presenting LOD of 1,5 × 10<sup>8</sup> mol L<sup>-1</sup>. When compared to the developed method, the LOD of the mentioned works are smaller, however in both cases an adsorption process is used that can improve the LOD, however, it makes the analysis more time consuming.<sup>22,23</sup> Figure 7 shows the responses of 25 successive additions of standard solution at the concentration of 8.0 × 10<sup>-6</sup> mol L<sup>-1</sup> of HDZ in 0.1 mol L<sup>-1</sup> BR buffer solution, pH 4.0. A good repeatability of the analytical signal is observed throughout the experiment, with a relative standard deviation equal to 2.60%. The injection frequency found was 121 per hour.



**Figure 7.** 25 injections of 8.0 × 10<sup>-6</sup> mol L<sup>-1</sup> HDZ in 0.1 mol L<sup>-1</sup> BR buffer solution (pH 4.0) and using PCE modified with zeolite. Working potential: +1.3 V (vs. Ag/AgCl), injected volume: 80 μL and injection speed: 80 μL s<sup>-1</sup>.

Figure 8 shows the results obtained in the BIA-amperometry system for pharmaceutical samples which is preceded by a series of additions of standard HDZ solutions in a range from 1.0 × 10<sup>-6</sup> to 2.0 × 10<sup>-5</sup> mol L<sup>-1</sup>. In this experiment, a linear relationship between  $I_{pa}$  and analyte concentration was also observed, as can be seen in the analytical curve (inset of Figure 8).





**Figure 8.** BIA-Amperometric responses of the PCE modified with zeolite for increasing HDZ concentrations in 0.1 mol L<sup>-1</sup> BR buffer solution (pH 4.0): (a) 1.0; (b) 2.0; (c) 4.0; (d) 6.0; (e) 8.0x10<sup>-6</sup>; (f) 1.0; (g) 2.0x10<sup>-5</sup> mol L<sup>-1</sup> and pharmaceutical samples (S<sub>1</sub>-S<sub>3</sub>). Working potential: +1.3 V (vs. Ag/AgCl), injected volume: 80 µL and injection speed: 80 µL s<sup>-1</sup>. The detail shows the analytical curve (a-g).

The performance of the developed electroanalytical method was compared with the HPLC/UV-Vis proposed by Brandao and collaborators (2011).<sup>20</sup> Table I presents these results accompanied by the corresponding standard deviations calculated from three independent measurements for each sample.

**Table I.** Results obtained for the analysis of hydroxyzine dihydrochloride in 3 pharmaceutical formulations using the proposed BIA-amperometry and HPLC method<sup>20</sup>

Sample	Composition	Nominal value (mg)	Amperometry ± S.D. <sup>a</sup> (mg)	HPLC ± S.D. <sup>a</sup>
S <sub>1</sub>	Sodium benzoate, potassium sorbate, carmellose, sodium cyclamate, sodium saccharin, glycerol, cherry and raspberry essences	2.0	2.10 ± 0.02	1.64 ± 0.02
S <sub>2</sub>	sodium benzoate, potassium sorbate, sorbitol, glycerol, cherry flavor, raspberry essence, povidone, propylene glycol, sucralose, hydrochloric acid, sodium hydroxide	2.0	2.07 ± 0.02	1.81 ± 0.01
S <sub>3</sub>	Starch, lactose monohydrate, copovidone, talc, magnesium stearate	25.0	25.3 ± 0.1	21.34 ± 0.16

<sup>a</sup> n=3

The results obtained by the method proposed using CPE/MZCA-Hex as the working electrode are close to the nominal values of samples (S<sub>1</sub>, S<sub>2</sub> and S<sub>3</sub>) with a percentage difference of 5.0%, 3.5% and 1.2%, respectively, indicating a good performance of the proposed method. The greatest differences are observed in the results obtained by HPLC/UV-Vis (18.0%, 10.0% and 15.0% for S<sub>1</sub>, S<sub>2</sub> and S<sub>3</sub> samples)

compared with labelled values. These results attest that the BIA-amperometry method proved to be more effective due to minor differences in relation to the nominal value.

## CONCLUSIONS

In this study, an BIA-amperometry methodology was developed using a modified carbon paste electrode. The results obtained indicated a good applicability of CPE/MZCA-Hex in the amperometric determination of HDZ in pharmaceutical formulations. The BIA-amperometry method showed reproducible and stable responses during the execution of the experiments. The modification of the working electrode with CPE/MZCA-Hex may have facilitated the oxidation process of HDZ, improving the sensitivity of the method when compared to the electrode without modification (36.0% increase in anodic current value). The proposed method presents a linear response to HDZ concentration in a range of  $1.0 \times 10^{-6}$  to  $1.0 \times 10^{-5}$  mol L<sup>-1</sup>, with an LOD of  $2.57 \times 10^{-7}$  mol L<sup>-1</sup> and a differentiated sampling rate (121 injections per hour).

## Conflicts of interest

The authors declare that there is no conflict of interest.

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