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Carbon Paste Electrode Modified with $BiVO_4$ to Sense Metformin

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A new method for determining 3-(diaminomethylidene)-1,1-dimethylguanidine (Metformin) content in pharmaceuticals was developed using an $BiVO_4$ modified carbon paste electrode. The study was carried out using the cyclic voltammetry technique. Under the experimental conditions applied, the electrode senses Metformin by detecting a quasi-reversible process corresponding to the oxidation of the imino group of the guanidino group and the reduction of the resulting product. To increase the peak currents associated to this redox process, potential sweep runs were performed with the modified carbon paste electrode at switching potentials between 1200 mV and 900 mV vs Ag, AgCl(s). In addition, the effect of applying a static potential during different times before performing the potential sweep runs was investigated. Finally, the effect of pH on the electrode selectivity to MET was also evaluated. The best results were obtained by applying during 20 s a static potential of 1300 mV vs Ag, AgCl(s) at pH 10 with a carbonate buffer. Under these conditions, the anodic peak current of the imino group in guanidino group of Metformin at 0.668 V was significantly increased. The peak current was proportional to MetforminMET concentration in the range of $7x10^{-4}$ to $6 x 10^{-3}$ M. The detection limit was $4x10^{-4}$ M. The method was tested for determining Metformin in pharmaceutical samples. The results were similar to those obtained with the conventional method of analysis, which is more complex. The catalytic effect of Cu(II) ion toward the oxidation of metformine (MET) have been observed in NH3·H2O–NH4Cl buffer (pH 8.9; 0.1 M). The oxidation peak current of imino-group in guanidino-group of MET at 0.95 V at carbon paste electrode (C/PE) in the presence of 2.0 × 10−4 M Cu(II) ion was increased by about 20 times and the peak potential was unchanged compared with that in the absence of Cu(II) ion. Moreover, the oxidation peak current of MET at multiwalled carbon nanotube paste electrode (MWCNT/PE) was further increased by about three times compared with that at C/PE in the same medium. Based on the catalytic oxidation peak of MET by Cu(II) ion at MWCNT/PE, a voltammetric method for the determination of MET is developed. The peak current of the catalytic oxidation peak was proportional to MET concentration in the range of 2.0 × 10−7× 10−5 M. The detection limit was 6.7 × 10−8 M.

Keywords: Metformin, Modified electrodes, $BiVO_4$, Cyclic voltammetry.

1. INTRODUCTION

Emerging contaminants are a group of compounds that are strong candidates for future regulation due to their potential toxicity; some drugs are part of this group of pollutants, such as Metformin (MET). This drug is widely used in many countries to control Type II Diabetes, and also to reduce cholesterol and triglycerides. However, MET has side effects, such as causing gastrointestinal complications and lactic acidosis by inhibiting gluconeogenesis [1-2]. MET is not metabolized in the body, so that approximately 70% is excreted unchanged; therefore, significant drug concentrations are found in wastewater. For example, water effluents have been reported to have MET concentrations of 3.5-88 μg/L in Virginia and 110-129 mg/L in Germany [3].

Various analytical techniques are applied for determining MET content in biological fluids. HPLC with UV detector [4], HPLC/MS/MS [5], UV-Vis diffuse reflectance spectroscopy [6], and voltammetry are some of these techniques [7].

Different electrode types have been used for MET quantification. For example, chemically modified electrodes (CME) using nickel oxide (NiO) with Cu (II) ions (immobilized or free in the solution) have been reported. Gold microelectrodes, hanging mercury drop electrodes, and potentiometric electrodes prepared with β-cyclodextrin derivatives have also been used [8-17].

In recent years, TiO_2 particles have been used for modifying electrode surfaces. The electrochemical behavior of these modified electrodes has been studied for determination of organic compounds in aqueous media, such as captopril, hydrazine, paracetamol, buzepide methiodide, D-penicillamine, and tryptophan [18-22]. $BiVO_4$ is a promising semiconductor material. A wide variety of applications have been developed for $BiVO_4$ powders, such as photocatalysis [23], gas sensing [24], ionic conductors [25], pigments [26] and photovoltaic devices [27]. To our best knowledge, no studies have been reported on the fabrication of carbon paste electrodes modified with $BiVO_4$ particles.

In this paper, we describe a method for determining MET in pharmaceutical samples using a new electrochemical sensor based on the incorporation of $BiVO_4$ particles into a carbon paste matrix.

2. EXPERIMENTAL

2.1. Reagents and apparatus

The MET hydrochloride standard (99%) was provided by REACTIMEX. Electrode preparation was carried out with graphite powder (BAS Inc.), and nujol (Plought Inc.). $BiVO_4$ was used as modifier agent; it was sintethized by a co-precipitation method following the procedure described previously by our group [28]. NaH_2PO_4 (99%, Alfa-Aesar) and potassium biphthalate (HACH) were used for preparing the supporting electrolyte solution.

The voltammetric determinations were performed in an Epsilon E2 potentiostat, using a modified carbon paste electrode (mCPE) as working electrode, Ag/AgCl as reference electrode, and Pt

as auxiliary electrode. The MET spectroscopic determination was performed in a Cary 100 UV-VIS spectrophotometer. The pH measurements were performed using a Oakton 1100 pH-meter.

2.2. Preparation of the mCPE

To prepare the mCPE, we weighed graphite powder, $BiVO_4$ and nujol in several proportions. The mix was homogenized in an agata mortar during 10 min. The obtained paste was introduced in a teflon tube (3 mm I.D.) and the electrical contact was provided with a copper wire placed inside the teflon tube.

2.3. Electrochemical caracterization of the mCPE

Cyclic voltammetry was performed using the mCPE in solutions with and without MET. The supporting electrolyte was a phosphate buffer (pH 7.2). The potential sweep cicle started at the open circuit potential, rised to 1300 mV, returned to −800 mV, and rised again to 1000 mV; the scan rate was 200 mV/s.

2.4 Electrolysis with the mCPE at 1300 mV

Potential sweep runs were performed with the mCPE changing potential program, reducing the switching potential from 1200 mV to 900 mV to evaluate its effect on the redox processes.

2.5 Effect of pH

Potential sweeps were applied to MET solutions (4 mM) at different pH values, using potassium biphthalate, monobasic sodium phosphate and bicarbonate as supporting electrolytes, adjusted with NaOH or HCl as appropriate.

2.6 Calibration curve

MET solutions with concentrations from 0.1 mM to 10 mM at pH 10 were prepared to produce a calibration curve, evaluate its linearity, and determine the detection and quantification limits.

2.7 MET analysis in pharmaceuticals

Commercial tablets were milled in a mortar. 0.5 g of powder was dissolved in 25 mL of distilled water to prepare the MET solution. Dilutions of this solution were made in carbonate buffer (pH 10) and methanol to perform voltammetry and spectrophotometry analyses, respectively.

3. RESULTS AND DISCUSSION

3.1 MET electrochemical response with mCPE

The behavior of the electrode in the presence of MET is shown in Fig. 1. Two processes occur: an oxidation process (668 mV), and a reduction process (−243 mV). These processes are well defined and take place at potentials significantly different from those of the solvent redox processes. The oxidation process is only observed in the second scan in the positive direction, which suggests that, at more positive potentials, MET forms an oxidized, reducible species. The formation of this reducible species, observed in the negative sweep, generates a reduced, oxidizable species, which is observed in the second scan in the positive direction. The process observed at 0.668 V is associated to oxidation of the imino group in guanidino group to a N-hydroxy imino group, and the oxidized form obtained is reduced at −0.243 V. Under the described experimental conditions, these processes are quasi-reversible.

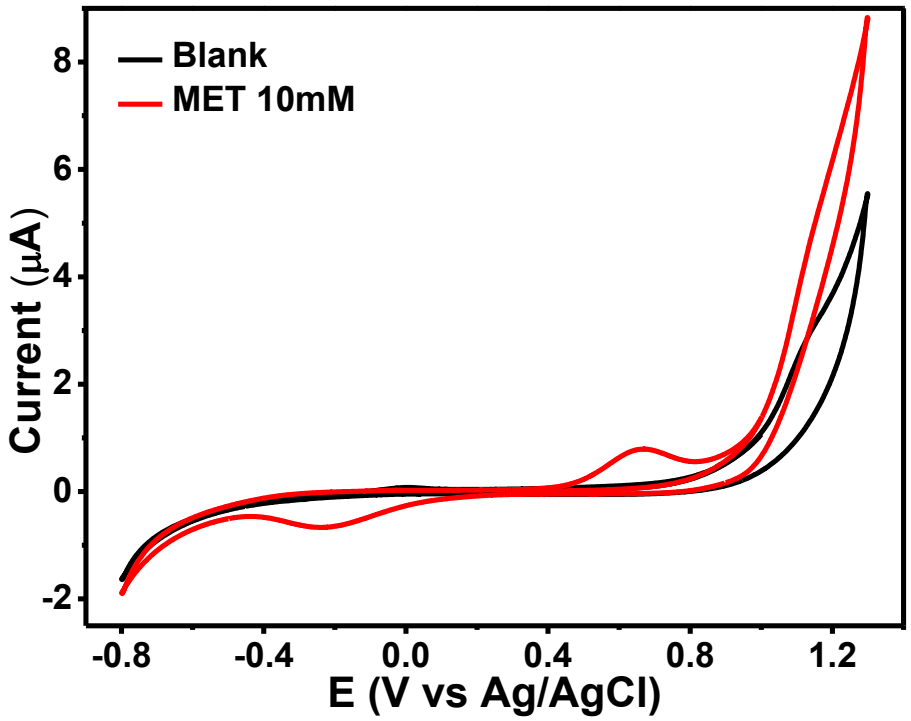

Figure 1. Cyclic voltammetry of MET on the mCPE (pH 7.2, 200 mV/s scan rate).

Fig. 2 shows that the peak current increases with the scan rate. This increase is proportional to $\upsilon^{1/2}$ in the oxidation and reduction processes, which indicates that both processes are controlled by MET diffusion from the bulk solution to the electrode surface.

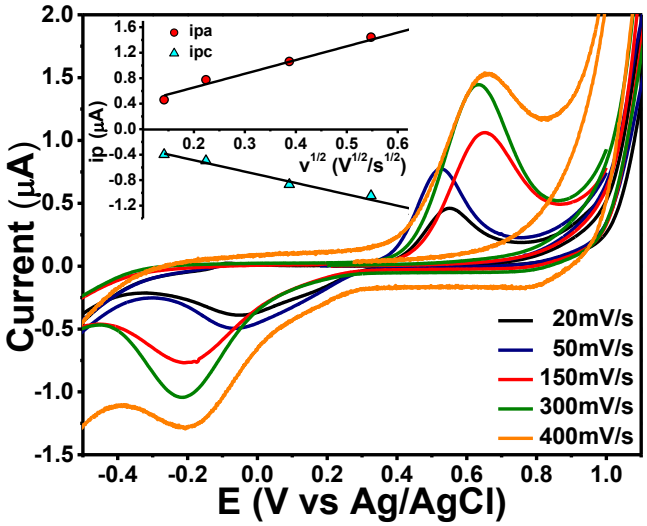

Figure 2. Cyclic voltammetry of 10 mM MET at pH 7.2 with phosphate buffer at different scan rates. The insert shows an ip vs $\upsilon^{1/2}$ graph.

3.2. Potential program

With the objective of better defining the redox processes associated to MET, different potential programs were applied by varying the switching potential. Fig. 3 shows the resulting oxidation and reduction processes for potential sweeps reaching values up to 1200 mV. This study shows the convenience of using a 1200 mV switching potential for the cyclic voltammetry because at this potential the MET redox processes are favored (the peak currents increase).

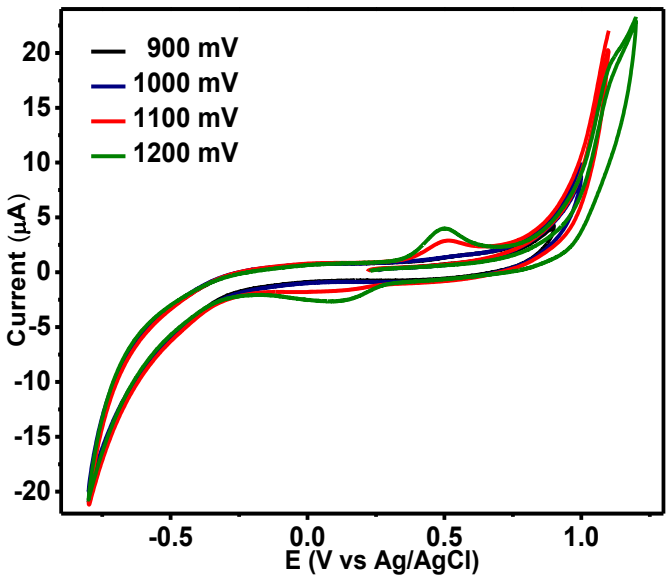

Figure 3. Cyclic voltammetry of 10 mM MET with variable switching potentials from 900 mV to 1200 mV and 200 mV/s scan rate.

In order to increase the method sensibility and obtain greater peak currents, a 1300 mV initial static potential was selected. In addition, this constant potential was applied for periods of 2 s to 60 s before performing the potential sweep runs. The results are depicted in Fig. 4, which shows that the peak current increases with the time of the constant potential application. No significant differences exist between application times of 50 s and 60 s. For times above 50 s, the reduction process is slightly affected by an overlapping with the oxygen reduction process. For this reason, we decided to use 20 s as the potential application time prior to the potential sweep runs.

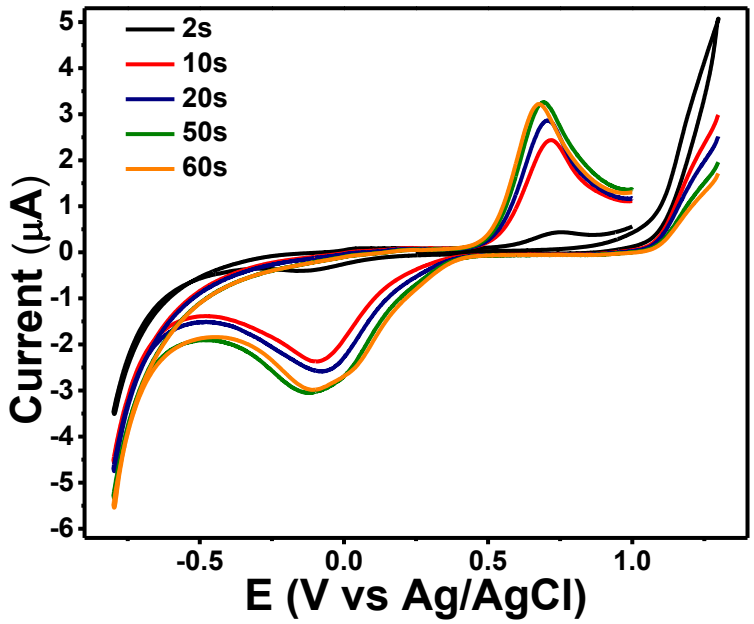

Figure 4. Cyclic voltammetry of 10 mM MET at 200 mV/s scan rate, for different times (2 s to 60 s) of application of a 1.3 V potential before the potential sweep run.

3.4. Effect of pH

Fig. 5 depicts the voltammograms of MET 4 mM solutions for pH values of 3, 4, 5, 6, 7.2, 8, 8.7 and 10. The figure shows that the processes are not detectable or exhibit very small currents in most cases. The process with the highest current occurs at pH 10. Increasing the pH shifts the reduction peak potential to more negative values, which affects the process thermodynamic viability. However, the oxidation process is less affected than the reduction process and the anodic peak potential is not a linear function of pH. Fig. 5 shows the linear dependency of the cathodic Ep with pH. This dependency of Ep with pH for the cathodic process could be attributed to reactions involving oxhydryl groups according to the electrode process for MET reported in [12]. Given the increase of the kinetic viability of both processes at pH 10, we selected this pH value for the next studies.

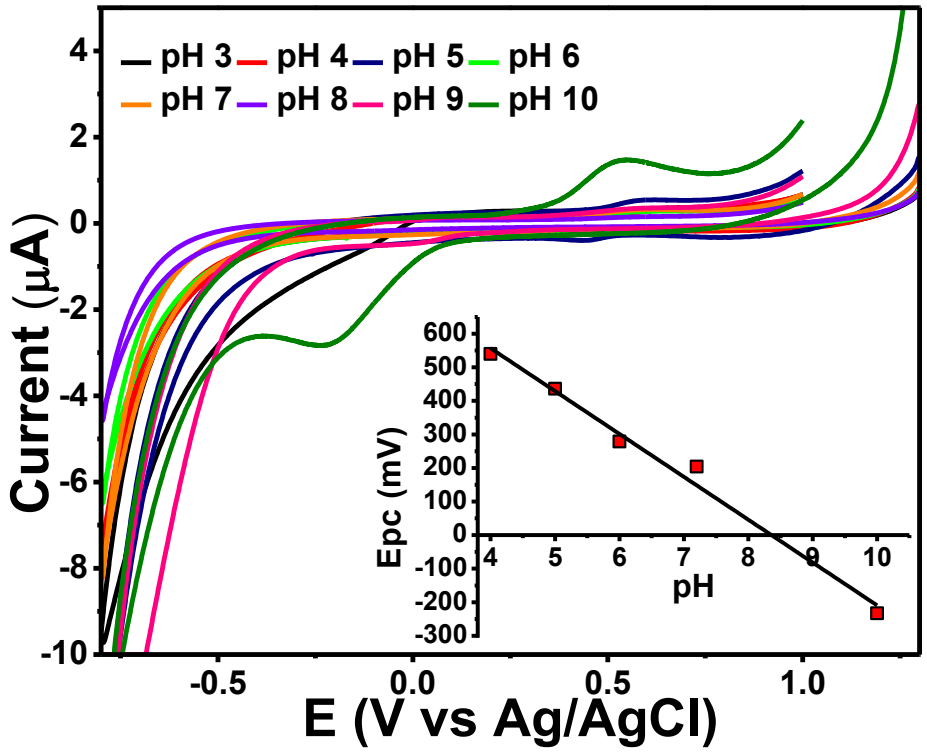

Figure 5. Cyclic voltammetry of 4 mM MET at different pH values and 200 mV/s scan rate.

3.5. Calibration curve

Fig. 6 shows the voltamogramms corresponding to MET solutions at pH 10. Given that oxidation is well defined at this pH value, even for a 0.1mM concentration, we selected this process to obtain the calibration curve and evaluate the effect of MET concentration.

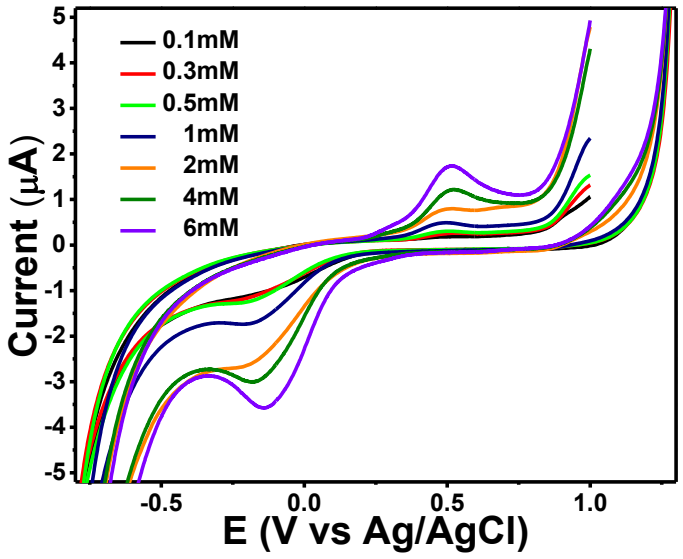

Figure 6. Cyclic voltammetry of MET in different concentrations, at pH 10 and 200mV/s scan rate.

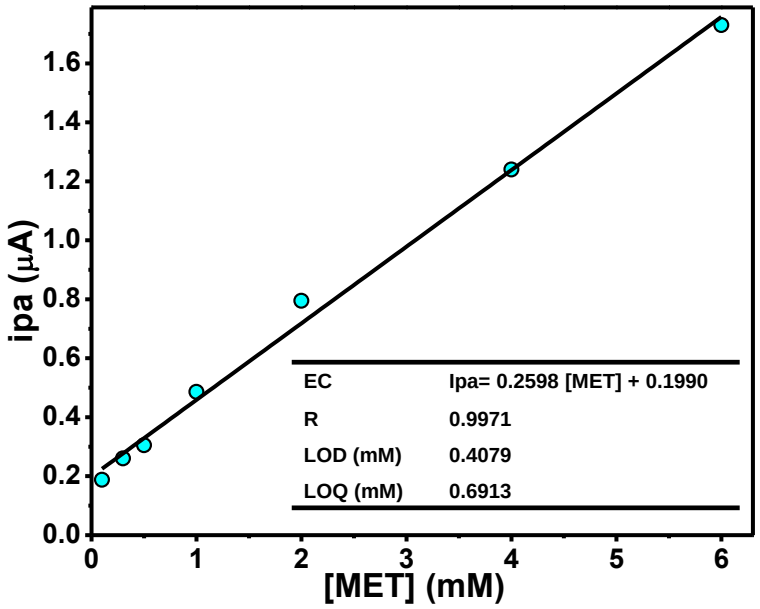

Figure 7. Calibration curve of MET with mCPE at pH 10.

Fig. 7 depicts the calibration curve of MET, obtained with the mCPE. The curve shows the linear range of the electrode response (R = 0.9971). The statistical analysis resulted in a detection limit of 0.4 mM and a quantification limit of 0.7 mM. The electrode response was not linear for MET concentrations higher than 6 mM. However, this curve can be used for determining MET in pharmaceutical samples (using proper dilution in order to perform the analysis in the linear response range).

3.6 MET analysis in pharmaceuticals

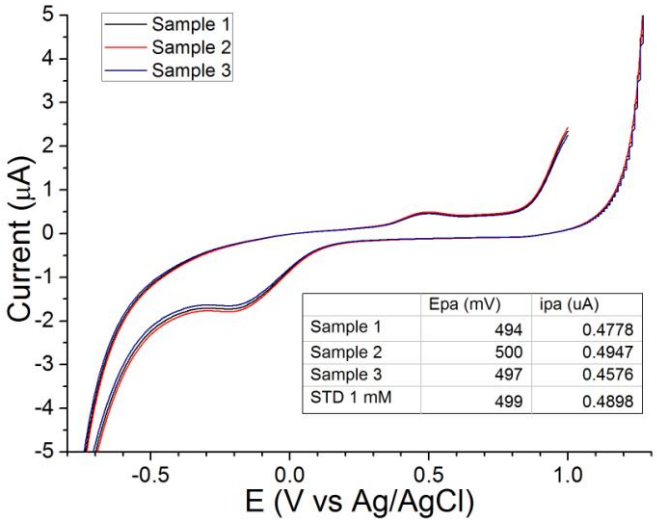

Figure 8. Cyclic voltammetry of solutions of pharmaceutical samples (1 mM MET) in phosphate buffer (pH 10, 200 mV scan rate).

Fig. 8 shows the voltammograms of tablet samples (1 mM MET) dissolved in carbonate buffer at pH 10. The shape of these voltammograms is very similar to that of the voltammogram shown in Fig. 5 for pH 10. Fig. 8 also shows that the voltammograms for different samples are very similar, which indicates good reproducibility.

The same tablet samples were analyzed with the spectrophotometry UV method normally used to determine MET. Table 1 shows a comparison of the results obtained with this method and the mCPE method proposed in this paper. No significant difference was observed between the spectrophotometric method and the proposed method using a carbon paste electrode modified with $BiVO_4$. According to this result, this method can be used for analizing MET in pharmaceutical samples.

Table 1. Comparison of the proposed method with the UV method

Method	Linear range	Solvent	% Recovery	%VC
mCPE	$1x10^{-4}$ – $6x10^{-3}$ M	Carbonate buffer (pH 10)	102.2	3.89
UV (237 nm)	$6x10^{-6}$ - $1.3x10^{-4}$ M	Metanol	102.6	0.26

4. CONCLUSIONS

The carbon paste electrode modified with $BiVO_4$ has the ability to sense MET. The best pH value for the electrode to work as a sensor is 10. The electrochemical processes were found to be quasi-reversible. These processes are controlled by the MET diffusion to the electrode surface. The electrode response depends linearly on MET concentration. This paper also shows that carbon paste electrode modified with $BiVO_4$ has the ability of sensing MET in pharmaceuthical samples with detection limit of 0.4069 mM and quantification limit of 0.6913 mM.

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