



Original scientific paper

A novel electrochemical sensor for differential pulse voltammetric determination of droxidopa

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Abstract

This study prepares a voltammetric sensor for determining droxidopa (DXP). A carbon paste electrode (CPE) modified with ZnO-CuO nanoplates (ZC/CPE) was used to create the voltammetric sensor. DXP was determined using the ZC/CPE sensor and differential pulse voltammetry. ZC/CPE's anodic current response showed a linear correlation with the DXP concentration between 0.1 and 300.0 μM under ideal experimental conditions, indicating a sensitivity of 0.181 $\mu\text{A } \mu\text{M}^{-1}$. The ZC/CPE sensor's limit of detection for measuring DXP was 0.06 μM . The technique was used to measure DXP in human urine and water samples.

Keywords

Neurotransmitters; Parkinson's disease; synthetic amino acid; modified electrode

Introduction

Analytical examination of bulk drug materials, intermediates, drug products and drug formulations is crucial in pharmaceutical research. For this reason, many phases of quality assurance and control in the pharmaceutical industry depend on the development of analytical techniques [1]. Parkinson's disease develops when degenerative problems of the central nervous system occur [2].

Movement-related symptoms, such as slowness, rigidity, and trouble walking and gaiting, are evident in the early stages of the illness [2]. Droxidopa (DXP) is a synthetic amino acid precursor and psychoactive medication that functions as a prodrug to neurotransmitters [3].

DXP was initially developed to treat hypertension. To sustain blood flow throughout the body when standing, DXP raises norepinephrine and adrenaline levels in the peripheral nervous

system (PNS), causing tachycardia and hypertension. DXP has been demonstrated to alleviate orthostatic hypotension symptoms resulting from a number of illnesses, such as Parkinson's disease [4,5].

Increased blood pressure, nausea, and headache are the most often reported adverse medication responses with DXP, according to data from clinical trials and post-marketing surveillance programs carried out in Japan. Data from clinical trials to date indicate that droxidopa is an effective and well-tolerated norepinephrine precursor [6].

Droxidopa may have an analgesic impact on those with chronic pain, according to preclinical and clinical research. An analgesic effect has been shown to correlate with elevated norepinephrine levels in the central nervous system (CNS). It is theorized that DXP can reduce pain in fibromyalgia patients by raising norepinephrine levels in the central nervous system [7].

Liquid chromatography with mass spectrometry [8], high-performance liquid chromatography-tandem mass spectrometry [9] and electrochemical sensing systems [10,11] are some of the studies that have been reported for a simple, inexpensive, quick, sensitive, and accurate method for determining DXP (alone or in combination with other species) [10,11].

As flexible chemical techniques, electrochemical methods offer unique benefits, including excellent precision, cost-effectiveness, and a wide linear dynamic range [12]. Low limit of detection (LOD), direct analyte determination, ease of sample preparation, significant selectivity, quick reaction, simplicity and gentle procedures are just a few benefits of electrochemical methods [13]. Because of electrode surface contamination, sluggish electron transfer rates, and adsorption of reaction products, electrochemical approaches for detecting a target analyte on a bare electrode may reduce selectivity, stability, and sensitivity [14].

Modifying inert substrate electrodes with modifiers is one way to address this issue. This approach offers substantial benefits for electrochemical sensor development, and several modified electrodes have been created for this purpose [15]. Because of their broad potential windows, low cost, and low electrical resistance, carbon paste electrodes (CPEs) are among the most often used electrodes [16]. In unaltered electrodes, the oxidation peaks of most electroactive chemicals overlap significantly. Resolving the signals is essential for improved selectivity [16].

Electrodes could be modified to address this issue [13]. The use of modifiers to modify electrodes is an intriguing area of analytical chemistry [13]. One of the most significant benefits of any modifier is the lowering of overpotential, which improves the method's sensitivity and selectivity [13]. Many efforts have focused on developing modified electrodes using different materials and nanostructures [15]. Nanomaterials offer high specific surface area, superior conductivity, many surface-active sites, and potent catalytic activity. These characteristics can greatly improve sensor stability and sensitivity [15]. Additionally, they can speed up electrochemical reactions and improve electron transport efficiency by acting as catalysts. The joining of two metal oxide semiconductors of the p- and n-type enhances stability and catalytic activity in addition to forming a heterojunction by dividing charge carriers. ZnO is a cheap inorganic compound with a wide band gap, high mobility, and minimal toxicity [17].

CuO, a stable, accessible p-type semiconductor with a modest band gap [18], can be combined with ZnO to form a hybrid nanostructure that enhances electrochemical sensing through the synergistic effects of binary metal oxides. Thus, ZnO-CuO nanocomposites can greatly improve substrates' electrocatalytic capabilities [19].

In electroanalysis, these nanocomposites can also increase reaction rates, reduce overpotential, and improve repeatable electrode responsiveness. Electrodes treated with nanocomposites show increased response for identifying various important biological and clinical species [18,19].

This work describes a sensor for enhanced DXP detection using ZnO-CuO nanoplates. The ZC/CPE sensing platform outperformed unmodified CPE in electrochemical performance for DXP detection because of its higher electrical conductivity and larger active surface area. Quantitative investigations showed that the proposed sensor had strong electrochemical sensing capabilities for DXP measurement, with a low limit of detection (LOD) and high sensitivity across a wide linear detection range. Additionally, this study evaluated the modified electrode's analytical performance in identifying DXP in actual samples.

Experimental

Materials and instruments

Merck and Sigma-Aldrich supplied analytical-grade chemicals of the highest purity, which were used without further purification. Orthophosphoric acid and its salts were used to prepare buffer solutions with pH values between 4.0 and 12.0. The Autolab potentiostat-galvanostat (PGSTAT 12N, Metrohm (Netherlands)) was used for the electrochemical methods. An Ag/AgCl electrode served as the reference electrode, a Pt wire served as the counter electrode, and unmodified and modified CPE served as the working electrodes in a three-electrode setup. The solution was adjusted to the required pH with phosphate buffer (PBS) using a 710-Metrohm type digital pH meter.

Synthesis of ZnO-CuO nanoplates

CuCl₂ (0.001 M) and ZnCl₂ (0.05 M) solutions were prepared at pH 11.7 to initiate the formation of ZnO-CuO nanoplates. The solution was maintained at 70 °C for 2 hours. Ammonia solution (25 %) was used to adjust the pH of the mixture. The temperature was raised to 95 °C for three hours to complete the synthesis. After ZnO-CuO nanoplate preparation and precipitation, the precipitate was centrifuged for 20 minutes at 16000 rpm. Methanol and water were used to wash the separated precipitate three times, respectively. Lastly, it was dried for two hours at 70 °C.

Fabrication of modified carbon paste electrode

The ZnO-CuO nanoplate and graphite powder (4:96 wt/wt%) were combined with a suitable quantity of paraffin oil in a mortar and mashed with a pestle to create a homogenous ZnO-CuO nanoplate paste during the initial ZC/CPE preparation step. To create a uniform surface, the homogenous ZnO-CuO nanoplate paste was then crushed into the glass tube's end and smoothed with soft paper. To create electrical connectivity, a copper wire was lastly placed inside the glass tube. Without ZnO-CuO nanoplate paste, the unaltered CPE was built using a similar process.

Preparation of real samples

Urine sample was centrifuged for 10 min at 3000 rpm. Next, different quantities of DXP solution were added to a 25 mL volumetric flask containing 5 mL of filtrate, which was then diluted with PBS (pH 7). This solution was used for the measurements in the next step.

Results and discussion

Electrochemical response of bare carbon paste electrode and carbon paste electrode modified with ZnO-CuO nanoplates to droxidopa

DPVs of DXP (100.0 µM) in PBS with varied pH values (from pH 2.0 to 9.0) were recorded to assess the impact of PBS pH value on the response of ZC/CPE toward DXP. A notable rise in the anodic peak current (I_{pa}) during DXP oxidation was observed when the pH was raised from 2.0 to 7.0. On the other hand, DXP's I_{pa} steadily decreased as the pH value increased. According to this investigation, pH 7.0 was considered the ideal pH value.

Next, using cyclic voltammetry (CV), the electrochemical behaviour of DXP (100.0 μM) at bare CPE and ZC/CPE was measured (Figure 1). The obtained CVs at bare CPE and ZC/CPEs revealed the oxidation peak of DXP, as shown in Figure 1. Additionally, no reduction peak appeared in the DXP reverse scan, indicating irreversible oxidation of DXP. The response of bare CPE to DXP oxidation was demonstrated by the weak I_{pa} (8.58 μA) for DXP at 700 mV in the bare CPE (CV a). These results showed that the modified electrode oxidizes DXP well, owing to the good properties of the manufactured ZnO-CuO nanoplates.

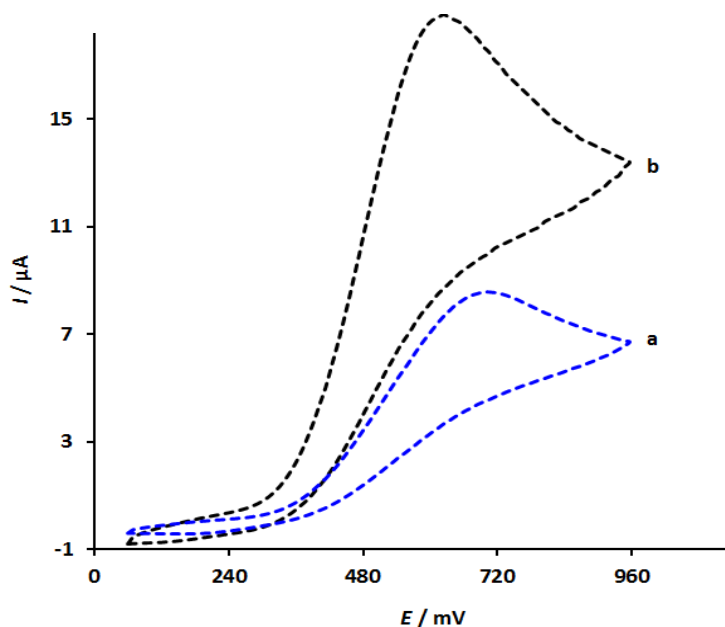


Figure 1. CVs of (a) bare CPE and (b) ZC/CPE for DXP (100.0 μM) at 50 mV s^{-1}

The impact of scan rate on droxidopa oxidation at carbon paste electrode modified with ZnO-CuO nanoplate

As shown in Figure 2, CV tests were carried out at different scan rates to assess the impact of scan rate on DXP oxidation at ZC/CPE.

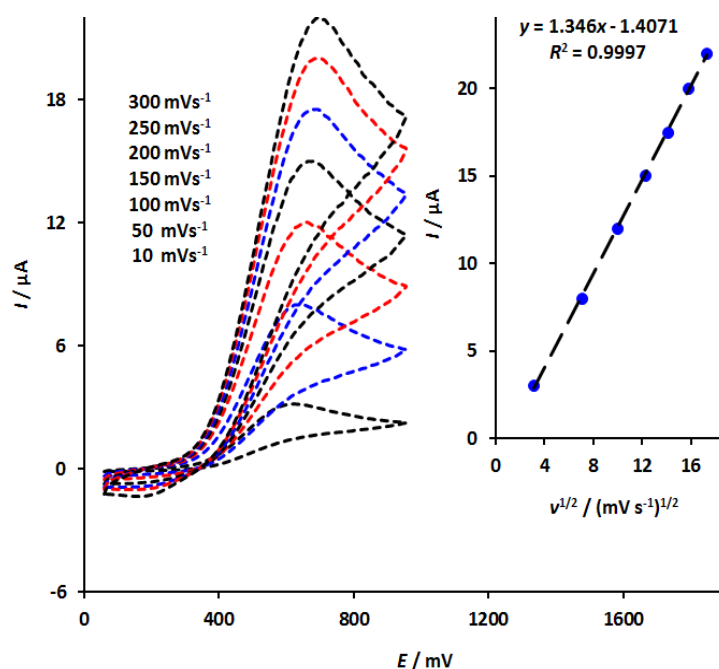


Figure 2. CVs recorded for DXP (40.0 μM) on ZC/CPE at variable scan rates. Inset: Plot of I against $v^{1/2}$ for DXP electrooxidation

The oxidation of DXP is diffusion-controlled, as the relationship between I and the square root of the scan rate ($v^{1/2}$) was linear (Figure 2 (Inset)). Additionally, increasing scan rates shift the anodic peak potential (E_{pa}) toward more positive values, indicating irreversible DXP oxidation.

Chronoamperometric studies

By setting the working-electrode voltage to 690 mV, we obtained DXP chronoamperograms at various concentrations (Figure 3). Graphing I vs. $t^{-1/2}$ allowed the linear curves for different DXP concentrations to be recovered from the chronoamperometric traces (Figure 4A). The DXP concentration was then plotted against the slope of the generated plots (Figure 4B). This slope and Cottrell's equation were then used to calculate D , which was $1.83 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$.

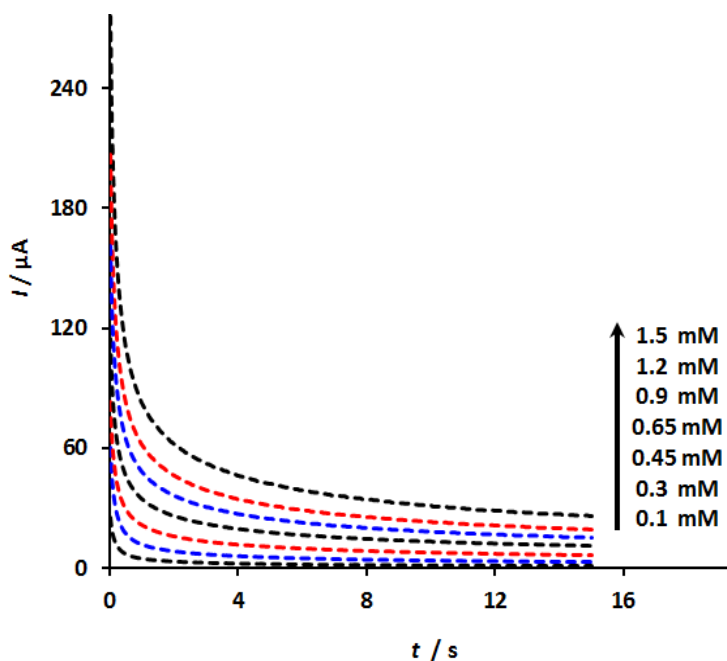


Figure 3. Chronoamperograms acquired for the ZC/CPE during exposure to variable DXP concentrations

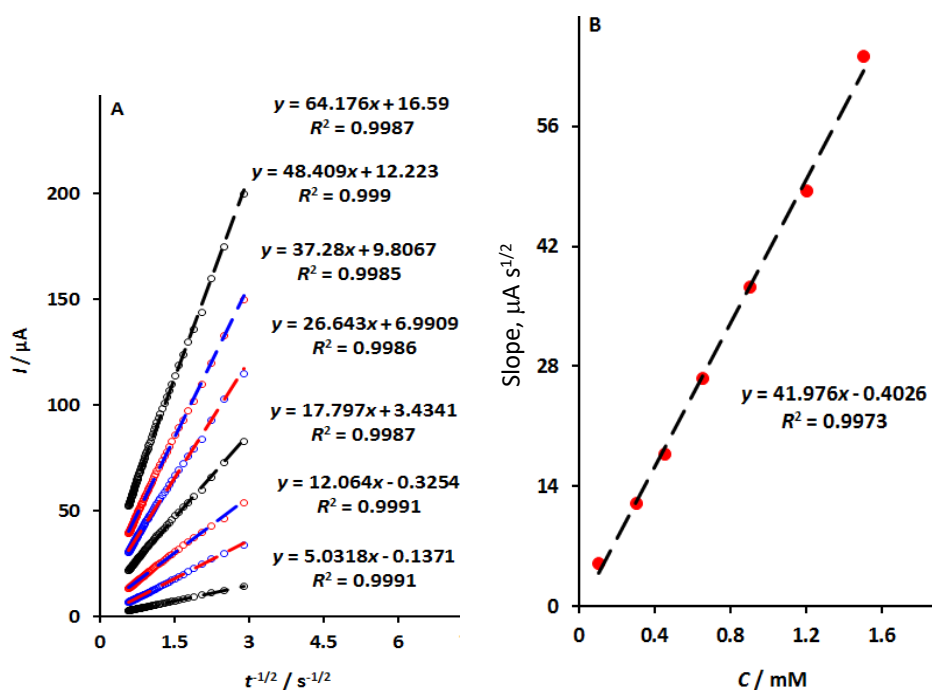


Figure 4. A: Plots of I vs. $t^{-1/2}$ and B: Plot of slope vs. DXP concentration

Calibration plot and limit of detection

Using a DPV experiment with various DXP doses, the linearity of the DXP oxidation peak current on the ZC/CPE was evaluated (Figure 5). The calibration curve showed linearity between 0.1 and 300.0 μM , $I = 0.181c + 0.6282$, where $c / \mu\text{M}$ is the DXP concentration and $I / \mu\text{A}$ is the peak current. Based on three times the blank's standard deviation (3σ), the limit of detection was 0.06 μM .

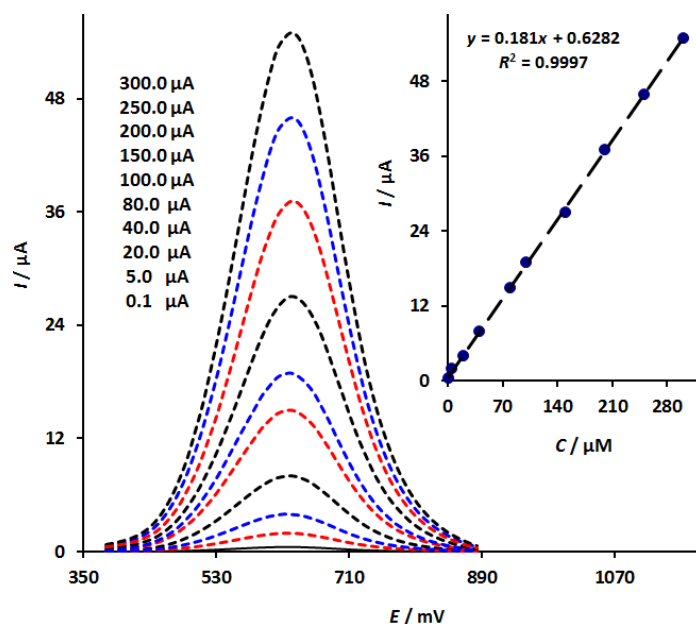


Figure 5. DPVs acquired for the ZC/CPE during exposure to variable DXP concentrations. Insets: Relationships between the I and concentration of DXP

Repeatability, reproducibility and stability of carbon paste electrode modified with ZnO-CuO nanoplate

6 test solutions containing DXP (30.0 μM) were produced and tested using one ZC/CPE to investigate the repeatability of ZC/CPE. The repeatability of ZC/CPE was verified, as the RSD obtained in this assessment was 3.5 %. 6 test solutions containing DXP (30.0 μM) were prepared and tested using six ZC/CPE to assess its reproducibility. The reproducibility of ZC/CPE was demonstrated, as the RSD obtained in this assessment was 4.3 %.

A test solution containing DXP (30.0 μM) was prepared and tested using ZC/CPE to verify its stability. This electrode was used to measure DXP after being stored in a desiccator for 21 days. We conclude that ZC/CPE is stable because the electrooxidation current of DXP fell to 95.0 % of the initial current, while the oxidation potential remained unchanged.

Interference study

Under optimized experimental parameters, using 50.0 μM DXP in a solution adjusted to pH 7.0, the influence of different compounds that could potentially interfere with the quantification of DXP was evaluated. The tested species were selected from compounds that are frequently present alongside DXP in pharmaceutical formulations and/or biological samples. For each possible interferent, the maximum allowable concentration that caused less than a 5% deviation in the DXP response was considered as the tolerance threshold.

The findings indicated that several compounds and ions, including glucose, l-lysine, l-asparagine, l-serine, l-cystine, glycine, l-threonine, methionine, fructose, citric acid, methanol, N-acetyl cysteine, l-cysteine, ethanol, tryptophan, histidine, lactose, sucrose, l-proline, benzoic acid, phenylalanine, glutathione, urea, Fe^{2+} , Mg^{2+} , Al^{3+} , Fe^{3+} , SO_4^{2-} , NH_4^+ , CO_3^{2-} , Ca^{2+} , F^- and S^{2-} did not noticeably affect

the measurement of DXP. In contrast, ascorbic acid, norepinephrine, levodopa, and epinephrine showed measurable interference during DXP analysis. Although ascorbic acid interfered with the assay, this effect can be minimized, when necessary, by applying ascorbate oxidase, an enzyme known for its strong specificity toward the oxidation of ascorbic acid.

Real sample analysis

To avoid matrix effects, the proposed sensor (ZC/CPE) was used to measure DXP in human urine and water samples using the conventional addition approach. For this purpose, the prepared samples in PBS were mixed with DXP standard solutions at specific concentrations, and their DPVs were recorded. By extending the figure, one can ascertain the amount of undefined DXP present in actual samples.

The recovered values, which ranged from 96.4 to 104.5 %, were deemed adequate after reporting the data in Table 1. The findings demonstrated that the additional analyte could be quantitatively extracted from the actual samples. The results showed that the developed sensor is a dependable and effective sensing platform for determining DXP in actual samples. Additionally, the mean RSD demonstrated the method's repeatability.

Table 1. Determination of DXP in real samples using ZC/CPE (n=5).

Sample	Amount, μM		Recovery, %	RSD, %
	Added	Found		
Urine	5.0	5.1	102.0	3.2
	7.0	6.9	98.6	2.1
	9.0	8.9	98.9	2.0
	11.0	11.5	104.5	2.9
Tap water	5.5	5.3	96.4	2.8
	7.5	7.6	101.3	3.5
	9.5	9.4	98.9	1.7
	11.5	11.9	103.5	2.4

Conclusions

For simultaneous DXP detection, a straightforward ZnO-CuO nanoplate was developed. Combining ZnO-CuO nanoplates with CPE improves mass transport, electron transfer, and electrocatalytic activity. Under ideal experimental conditions, the linear calibration curve for DXP spanned 0.1 to 300.0 M, with a linear regression analysis LOD of 0.06 μM . Additionally, good recovery for DXP detection in actual samples was obtained, indicating that the voltammetric approach is appropriate for analysis.

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