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A disposable electrochemical sensor for the rapid determination of levodopa

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Abstract

Levodopa (L-dopa), the biological precursor of catecholamines, is the most widely prescribed drug in the treatment of Parkinson's disease. The present work presents a proposal for the application of a gold screen-printed electrode an electrochemical sensor for monitoring L-dopa in stationary solution and a flow system. Using the electrooxidation of L-dopa at +0.63 V in acetate buffer pH 3.0 on a gold screen-printed electrode it is possible to obtain a linear calibration curve from 9.9×10^{-5} to 1.2×10^{-3} mol L^{-1} and a detection limit of 6.8×10^{-5} mol L^{-1}. Under amperometric conditions (E_{app} = 0.8 V; flow rate = 14.1 mL min^{-1}; pH 3.0), an analytical calibration graph for L-dopa was obtained from 1.0×10^{-6} mol L^{-1} 6.6×10^{-4} mol L^{-1} with a detection limit of 9.9×10^{-7} mol L^{-1}. The method was successfully applied to the determination of L-dopa in commercial dosage forms without any pre-treatment.

Keywords: L-Dopa; Screen-printed gold electrode; Amperometric determination; Flow system

1. Introduction

The development of screen-printing techniques for the fabrication of versatile, inexpensive and disposable electrodes has been a boon to electroanalytical chemistry for various applications [1–3]. Screen-printed electrodes are planar devices, based on different layers of inks printed on a plastic, glass or ceramic substrate. Many ink-type substrates have been used for sensor construction, where the most successful have included carbon and the noble metals as Au, Pt, Ag, etc. The main advantage of this kind of electrode system is associated with their modest cost, potential portability, simplicity of operation, reliable, and the small instrumental arrangement containing the working electrode, auxiliary and reference electrodes. In addition, its disposable characteristics permit the avoid one of electrode poisoning from repeated reuse of the same electrode surface for successive analyses. Therefore, screen- printing electrodes can be manufactured in bulk at relatively low cost, and their effective performance has gained consideration in environmental, biomedical, occupational hygiene monitoring and all the major fields of analytical chemistry [1–9].

Levodopa (L-dopa), 3 (3,4-dihydroxyphenyl)-L-alanine, the medication of choice for the treatment of Parkinson's disease, is principally metabolized by an enzymatic reaction (*dopa-descarboxilase*) to dopamine compensating for the deficiency of dopamine in the brain [10]. Parkinson's disease is a progressive neurological disorder that occurs when the brain fails to produce enough dopamine. This condition causes tremor, muscle stiffness or rigidity, slowness of movement (bradykinesia) and loss of balance. Dopamine cannot be administered directly because it cannot penetrate the blood–brain barrier. Therefore, L-dopa, which can be orally administered, is used to provide a source of dopamine, and is used in the treatment of Parkinson's disease to provide symptomatic relief to most patients at the initial stages of the disease.

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In order to support the evaluation of L-dopa in pharmaceutical formulations and biological fluids many methods have been developed for its determination. The literature has reported several techniques for their analysis in pharmaceutical formulations and biological fluids, especially spectrophotometry [11–13] and high-performance liquid chromatography [14–18].

Electrochemical methods are powerful techniques to follow the oxidation of catecholamines [19]. The two hydroxyl groups present in L-dopa can be electrochemically oxidized at a glassy carbon electrode and this is the basis for its determination. In agreement with the literature [20] L-dopa under very acidic conditions, is oxidized on glassy carbon electrodes by a quasi-reversible two-electron process to an open-chained quinone at potential of around +0.61 V (H_2SO_4 1 mol L^{-1}). In neutral solution the electrooxidation process is an irreversible electrochemical process (E_p = +0.31 V) followed by a chemical reaction, where dopaquinone cyclizes to cyclodopa, leading to the generation of new electroactive product assigned as dopachrome. In the reverse scan the voltammograms show two peaks attributed to reduction of the remaining dopaquinone and reduction of dopachrome to cyclodopa generated after a fast chemical reaction. Although the electrochemical behavior of L-dopa on glassy carbon electrodes is complex, its determination by voltammetric and amperometric methods are reported in the literature [21–27]. Nevertheless, may methods require the use of reagents clean up of the electrode surface and complicated steps involving modified electrode construction. The use of a simple and rapid method based on a screen-printed electrode could be a good strategy for L-dopa determination.

This paper reports on the application of a gold screen-printing electrode as an amperometric sensor for L-dopa determination. Taking into consideration that under flow analysis conditions, it is possible to add amplification of the amperometric signal, simplification of manifolds features and rapidity of analysis, a microflow cell system adapted to the screen-printed electrode was developed. The influence of several parameters (potential, pH and interference) besides the parameters of the flow system was studied and the method optimized for determining L-dopa in pharmaceutical formulations using a gold screen-printed electrode is described.

2. Experimental

2.1. Apparatus

Voltammetric and amperometric measurements were carried out with an AUTOLAB PGSTAT-30 (EcoChimie) connected to a microcomputer for data acquisition and experimental control. The measurements were performed in an conventional electrochemical cell and a microflow cell system (BVT Technologies, Czhec Republic) where the screen-printed gold electrode (BVT Technologies, Mod. AC1.W1.R1) has coupled.

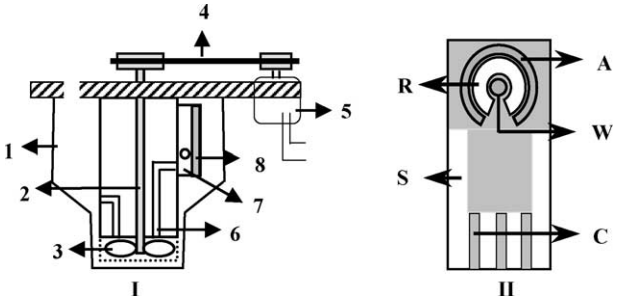

Fig. 1. Schematic diagram of the electrochemical microflow cell (I) and screen-printed gold electrode (II) used in the voltammetric and amperometric measurements.

The design of the gold screen-printed gold electrode used in all there electrochemical experiments is showed in Fig. 1II. The electrode is based on an alumina ceramic base(s) 26 mm long, 7 mm wide and 0.65 mm of thick. On to this surface the working (W), reference (R) and the auxiliary (A) electrodes were applied. The working and auxiliary electrodes were made of Au/Pd (98:2%) and the reference of Ag/AgCl (60:40%). At the end of the sensor was a contacting field, connected with the active part by the silver conducting parts that are covered by a dielectric protection layer. The sensor was connected with a cable to the potentiostat.

The arrangement of the microflow cell system is illustrated in Fig. 1I. A driving shaft (2) was located in the center of a conventional electrochemical vessel (1) carrying the body of the microflow insert (7). The driving shaft was connected to a pump rotor (3). The chamber located above the rotor (4) was connected to the electrode cell containing the three electrodes (8) via a capillary (6). The thin capillary was located in the bulk solution guided the fluid coming from the rotor to the electrode cell (7) where the screen-printed electrode was positioned. The capillary fulfilled the function of stabilizing the flow of liquid before it entered the electrode cell. Following its passage through the cell the liquid was mixed into the bulk content, repeating the cycle several times as necessary. The sensor placed in the cell responds to the sample liquid and this response was recorded as either amperometric or voltammetric mode on the suitable potentiostat.

Cyclic voltammograms under static conditions were recorded after immerging the gold screen-printed electrode directly into the conventional voltammetric cell containing 10 mL of supporting electrolyte and the analyte using a cable with banana plugs as termination. The potential was scanned from −0.2 to 1.2 V at a scan rate of 50 mV s^{-1}.

Under flow conditions, the amperometric and voltammetric measurements were performed recording the electrochemical signal obtained with the solution of L-dopa flowing through the gold screen-printed electrode using linear sweep voltammetry (ν = 3 mV s^{-1}, flow rate = 7.7 mL min^{-1}) and chronoamperometry (E = 0.8 V, t = 50 s and flow rate of 14.1 mL min^{-1}). The parameters were controlled by a GPES 4.9 software (EcoChimie).

2.2. Reagents and solutions

Stock solutions of 0.01 mol L^{-1} L-dopa were prepared daily by direct dissolution of the pure sample (L-3,4-dihydroxyphenyalanine, 99,5%) purchased from BDH (Poole, Dorset, UK) in demineralized water, purified in a Milli-Q system (Millipore). All chemicals were of analytical reagent grade and used without further purification. Acetate buffer solutions 0.1 mol L^{-1} were used as the supporting electrolyte in all experiments.

2.3. Preparation and analysis of pharmaceutical samples

The proposed method was tested to determine L-dopa in two pharmaceutical formulations, commercialized the tablets Sinemet® and Prolopa®, using the following procedure: the contents of three tablets were weight and the fine powder dissolved in 0.1 mol L^{-1} acetate buffer pH 3.0 using an ultrasonic bath for 10 min. The solution obtained after filtration was transferred quantitatively into a calibrated flask and diluted to a final volume of 100 mL of acetate buffer. All the test solutions were obtained by direct dilution of this stock solution with the supporting electrolyte. The amperometric measurements were recorded using an applied potential of 0.8 V and a flow rate of 14.1 mL min^{-1}. The L-dopa content was determined using standard addition method. The same solution was also analyzed by an official method, based on the spectrophotometric characteristics of catecholamines at 280 nm [28].

3. Results and discussion

3.1. Electrochemical behavior

Fig. 2b shows a typical cyclic voltammogram of a solution of 1.0×10^{-3} mol L^{-1} L-dopa in 0.1 mol L^{-1} acetate buffer pH 3.0 on a conventional gold electrode (diameter of 4 mm) with Ag/AgCl (3 mol L^{-1} KCl) as the reference electrode under these conditions, L-dopa was oxidized at E_p = +0.64 V following an irreversible electrochemical process complicated by a well established cyclization reaction [20,29,30] leading to cyclodopa as an intermediate product and then the generation of dopachrome as the final form in the oxidation process. The corresponding reduction of dopachrome to cyclodopa occurs at +0.28 V. Therefore, the fast cyclization reaction suppress as the peak intensity at +0.53 V (Fig. 2b), attributed to reduction of the remaining dopaquinone, suggesting that on gold electrode the chemical reaction of cyclization is faster than for glassy carbon electrode cyclization [20].

In Fig. 2a the electrochemical profile of the some solution on a gold screen-printed electrode (diameter of 0.8 mm), using an external Ag/AgCl reference electrode, is shown. All the voltammograms were recorded from −0.25 to +0.80 V. No interference from oxide formation was observed, estimated

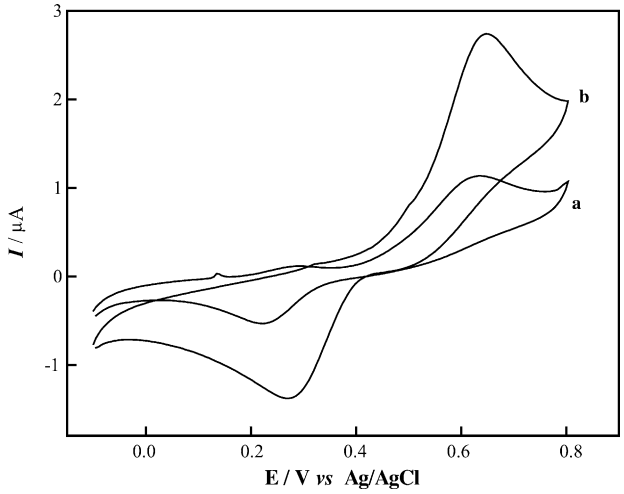

Fig. 2. Cyclic voltammograms obtained for the oxidation of a solution of 1×10^{-3} mol L^{-1} L-dopa in 0.1 mol L^{-1} acetate buffer at pH 3.0 on a conventional gold electrode (a) and a gold screen-printed electrode (b). Scan rate (ν) = 50 mV s^{-1}. Reference electrode = Ag/AgCl.

by using acetate buffer pH 3.0 as blank. The cyclic voltammograms obtained for both electrodes indicates a very similar behavior, except for smaller peak current due to the small geometric area of the electrode. When the external Ag/AgCl reference electrode is not used the cyclic voltammogram is essentially the same but it is observed a shift of around 50 mV to less positive potential on the screen-printed electrode, which was constant in all the voltammograms recorded. In addition, we verified that despite the fact that the screen-printed electrodes are commercialized as disposable electrochemical sensors, the cyclic voltammograms recorded successively for L-dopa in acetate buffer at pH 3.0 showed negligible change for the anodic peak for up to 20 repetitions.

The effect of pH on the oxidation of L-dopa (1.0×10^{-4} mol L^{-1}) on screen-printed electrodes was investigated over a pH range between 3.0 and 5.0. Although L-dopa presented a well-defined peak at more acidic conditions than pH 3.0, studies at lower pH values were not conducted because of the potential deletion effects on the material used to construct the electrode cell. In addition, pH values higher than 7.0 were avoided since the oxidation of L-dopa occurs very close to the electrolyte/electrode discharge on the gold screen-printed electrode and the cyclic voltammogram loses resolution. The anodic peak potential obtained for L-dopa in acetate buffer at pHs of 3.0, 3.5, 4.0, 4.5, 5.0 and 5.5 showed a shift of 60 mV of the peak potential to more positive values, indicating that the electrode process is influenced by protonation reactions [20]. The optimum pH for L-dopa detection was 3.0.

The effect of potential scan rate on the voltammetric response on concentration of 1.0×10^{-4} mol L^{-1} L-dopa oxidation on the gold screen-printed electrode was investigated between 5 and 100 mV s^{-1}. The anodic peak current varied linearly with the square root of the scan rate, equation: ip (μA) = 0.0330 + 0.0970$\nu^{1/2}$ (ν, mV s^{-1}), R = 0.9997, n = 5, suggesting that L-dopa oxidation follows a

diffusion-controlled mechanism. From these results, a scan rate of 50 mV s^{-1} was chosen for further studied.

After optimizing the best operating conditions (pH 3.0 and scan rate 50 mV s^{-1}) the gold screen-printed electrode was tested for L-dopa determination in static conditions. The anodic peak current was linearly dependent on the L-dopa concentration on the range 9.9×10^{-5} to 1.2×10^{-3} mol L^{-1} following the equation: ip (μA) = 0.01043 + 0.89157C (C, mmol L^{-1}), $R = 0.9998$, $n = 10$. The relative standard deviation at 5×10^{-4} was around 4.0% with three different electrodes and around 3.2% using the same electrode (five repetitions). A detection limit of 6.8×10^{-5} mol L^{-1} was determined. The screen-printed electrode for L-dopa determination showed some advantages, including low analysis costs, fast response time, accuracy and simplicity, but the method was not useful for low concentrations of L-dopa.

3.2. Flow analysis conditions

In order to improve the sensitivity of the screen-printed electrode for the determination of L-dopa studies were conducted utilizing hydrodynamic conditions.

Fig. 3 shows typical voltammograms for the oxidation of a solution of 1×10^{-3} mol L^{-1} of L-dopa in acetate buffer at pH 3.0 on a gold screen-printed electrode under hydrodynamic conditions using a constant flow rate of 7.7 mL min^{-1}. Owing to the decrease of the diffusion layer at the electrode surface the hydrodynamic voltammogram presents a higher limiting current since there is a consequent increase in the diffusion current [31]. Therefore, the anodic peak obtained in the flow cell is five times higher than when using the gold screen-printed electrode under stationary condition. The maximum current response obtained from a hydrodynamic voltammogram for L-dopa obtained under flow conditions using acetate buffer as carrier electrolyte was constant at least for 10 voltammograms recorded successively, indicating great analytical potentiality.

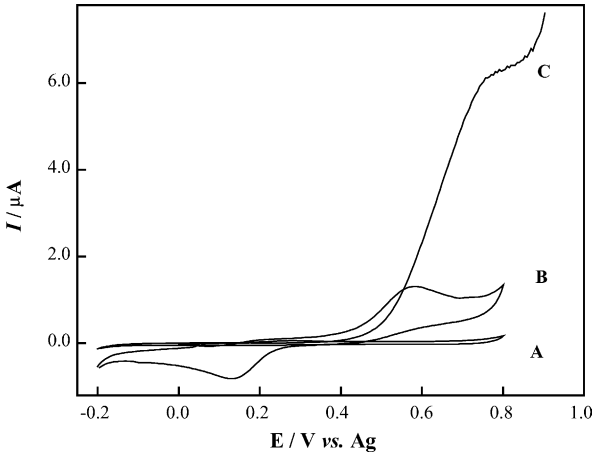

Fig. 3. Cyclic voltammograms (B) of the oxidation of a 1.0×10^{-3} mol L^{-1} solution of L-dopa in 0.1 mol L^{-1} acetate buffer solution at pH 3.0 on a gold screen-printed electrode in stationary (B) conditions, with a scan rate of 50 mV s^{-1}. Linear sweep voltammograms (C) obtained for the oxidation of 1.0×10^{-3} mol L^{-1} solution of L-dopa on a gold screen-printed electrode in the flow cell (hydrodynamic conditions), flow rate = 7.7 mL min^{-1}, curve C, at a scan rate 3 mV s^{-1}, Out (A) supporting electrode on hydrodynamic conditions.

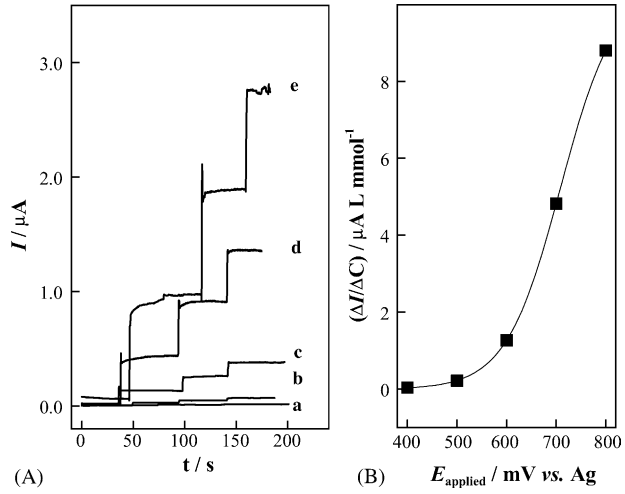

Fig. 4. Effect of the applied potential in the amperometric response (A) and normalized current variation (B) obtained for the oxidation of 9.9×10^{-5}, 2.0×10^{-4} and 2.9×10^{-4} mol L^{-1} solution of L-dopa in acetate buffer at pH 3.0.

Taking into consideration that the gold screen-printed electrode, polarised at positive potentials in acetate buffer at pH 3.0, seems to be a viable amperometric detector for on-line flow-through analysis some parameters were investigated in order to optimize detection.

Fig. 4A shows the effect of the applied potential from 0.40 to 0.80 V on the amperometric curve taken for L-dopa at concentration of 9.9×10^{-5}, 2.0×10^{-4} and 2.9×10^{-4} mol L^{-1} in 0.10 mol L^{-1} buffer acetate at pH 3.0. The electrode response was quite rapid and proportional to the L-dopa concentration at the applied potential (E_{app}) higher than 0.50 V, but higher current intensity is observed for 0.80 V. This value is in agreement with the potential where maximum current is observed for L-dopa oxidation, measured in voltammetric curves recorded in hydrodynamic conditions. Nevertheless, potentials higher than 0.90 V wear avoided since it was verified that some anomalies on the amperometric signal which were attributed to the oxidation of the gold surface electrode. Fig. 4B shows the influence of applied potential on the sensitivity of the electrode response, normalized by the relationship of $\Delta i/\Delta C$, taken as maximum current response for each concentration value from 9.9×10^{-5}, 2.0×10^{-4} and 2.9×10^{-4} mol L^{-1}. The results confirm that at any concentration the best values are obtained for $E_{app} = 0.80$ V, which was chosen for further experiments.

In order to optimize the flow rate effect on the amperometric response, the L-dopa (1.0×10^{-4} mol L^{-1} in acetate buffer, pH 3.0) oxidation signal at + 0.80 V was investigated from 7.7 to 16.1 mL min^{-1}. The results are shown in Fig. 5. The current value increased linearly with the flow rate increases from 7.7 to 14.1 mL min^{-1} and was nearly constant

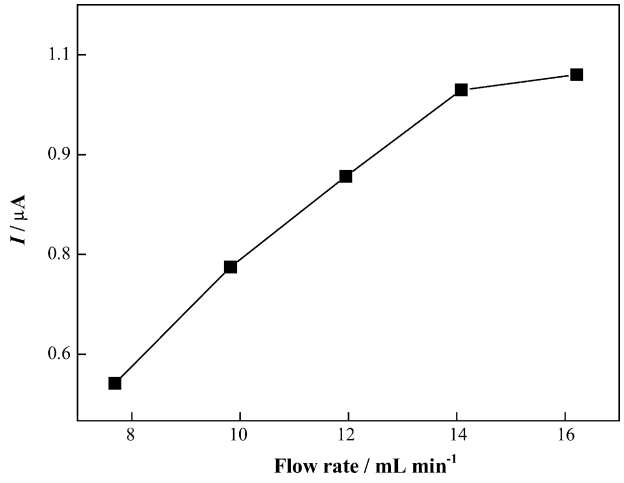

Fig. 5. Influence of the flow rate (mL min^{-1}) on the amperometric response of the gold screen-printed electrode for a 1.0×10^{-4} mol L^{-1} solution of L-dopa (B) in acetate buffer at pH 3.0. E_{app} = 0.80 V.

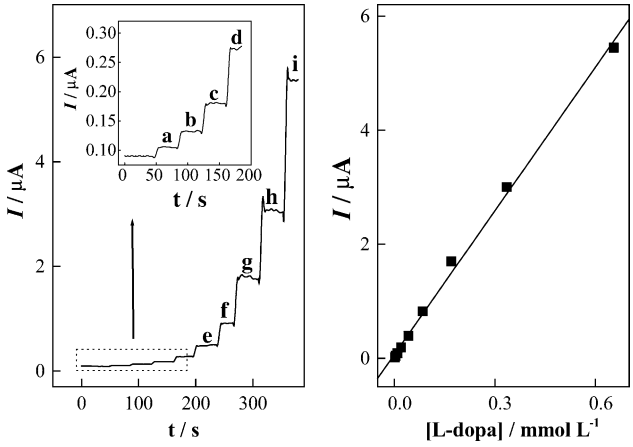

Fig. 6. Amperometric response (A) and analytical curve obtained for L-dopa in acetate buffer at pH 3.0 (B) on the gold screen-printed electrode in a microflow cell operating at E_{app} = 0.8 V, flow rate: 14.1 mL min^{-1}. (a) 1.5×10^{-6}, (b) 4.3×10^{-6}, (c) 9.5×10^{-6}, (d) 2.0×10^{-5}, (e) 4.2×10^{-5}, (f) 8.5×10^{-5}, (g) 1.7×10^{-4},(h) 3.4×10^{-4} and (i) 6.6×10^{-4} mol L^{-1} L-dopa.

at the highest value. With respect to sensitivity, the best value was at a flow rate of 14.1 mL min^{-1}. A critical aspect of sensor performance is the signal stability under the selected amperometric conditions. This was evaluated by verifying the long-term response of the gold screen-printed electrode for a continuous flux of L-dopa, repeated for periods of 50 s. The experiment was carried out for almost 4 h and in the interval between measurements the electrode was maintained, non-polarized, in stationary solution. The sensor response proved to be fairly stable for a series of successive measurements of 1.0×10^{-4} mol L^{-1} L-dopa with a standard deviation of 3.5%, demonstrating its practical utility in routine analysis.

Using the best experimental conditions (E_{app} = 0.8 V; flow rate = 14.1 mL min^{-1}; pH 3.0) an analytical calibration graph was obtained for the L-dopa amperometric response from 1.0×10^{-6} to 1.2×10^{-3} mol L^{-1}. The current values were always sampled during the first 10 s after analyte addition. The current increases in all concentration range investigated, as shown Fig. 6A. A plot of amperometric current as a function of L-dopa concentration yielded straight lines (Fig. 6B) from 1.5×10^{-6} to 6.6×10^{-4} mol L^{-1}, with a sensitivity of 8.4 μA L mol L^{-1}. The detection limit of 9.9×10^{-7} mol L^{-1} was calculated from the standard deviation of signal/slope [32]. The results show that the method using the flow cell coupled to a gold screen-printed electrode markedly increased the sensitivity relative to that obtained at the stationary solution.

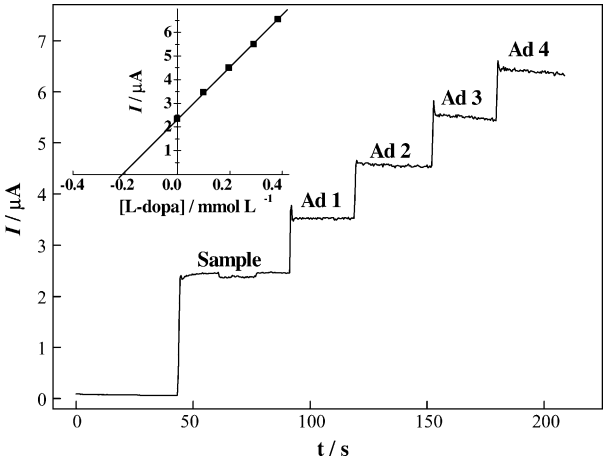

Fig. 7. Amperometric response and standard addition curve (inset curve) obtained for determination of L-dopa in the commercial pharmaceutical formulation (Sinemet®). E_{app} = 0.8 V; flow rate 14.1 mL min^{-1}.

3.3. Analysis of L-dopa in pharmaceutical formulations

The proposed method was applied to the determination of L-dopa in two pharmaceutical formulations commercialized as Sinemet® and Prolopa®, using the standard addiction method. The amperometric response obtained for a claimed concentration of 0.2 mmol L^{-1} of L-dopa in Sinemet is shown

Table 1
Determination of L-dopa in pharmaceutical formulations by amperometric detection on gold screen-printed electrode operating in a flow system at E_{app} = 0.8 V

Sample	Label value (mg)	L-dopa (mg/per tablet or capsule)		E_1 (%)	E_2 (%)
		Official method	Procedure proposed		
Sinemet®	250	255	262	+2, 7	+4, 8
Prolopa®	100	106	108	+1, 9	+8, 0

Flow rate = 14.1 mL min^{-1} and acetate buffer at pH 3.0 electrode and by on official method [33]. E_1 = relative error = amperometric method vs. official method; E_2 = relative error = amperometric method vs. label value; Mean values of three determinations.

in Fig. 7. The corresponding graph obtained is also shown in the inset of Fig. 7. Recoveries of 104 ± 4% and 108 ± 8% of L-dopa, respectively wee obtained for the two pharmaceutical formulation samples ($n = 3$). Table 1 gives the results obtained using both, the official method [33] and the amperometric method, as well as the label values of the samples analyzed. The statistical calculations for the assay results suggested good precision for the amperometric method. The results obtained were also compared by applying the F-test and t-test at 95% confidence level [34]. In the case did the calculated F and t values exceed the theoretical values ($F_{4.4} = 6.39$, $t_8 = 2.306$), confirming that there were no significant differences between both methods.

4. Conclusions

The gold-screen-printed electrode is a promising tool for direct L-dopa determination and can be used for direct applications in real samples without prior chemical/electrochemical treatment. The good analytical performance of the amperometric detector has been demonstrated in a continuous-flow assembly, the results being in agreement with those found by an alternative method. The detection limit, sensitivity and the stability of the screen-printed electrode, and the absence of poisoning of the electrode surface, have shown better results than conventional electrodes and are adequate for monitoring the catecholamine in pharmaceutical formulations. In addition, some advantages of the screen-printed electrode can be also taken into consideration such as: low cost, easy construction and storage, potential for miniaturization, facility of automation and construction of simple and portable equipment.

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