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Nano composite system based on coumarin derivative–titanium dioxide nanoparticles and ionic liquid: Determination of levodopa and carbidopa in human serum and pharmaceutical formulations

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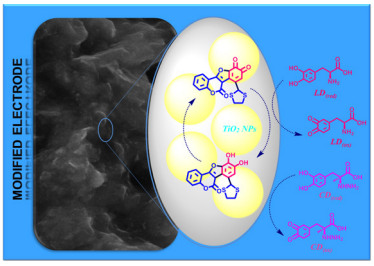
HIGHLIGHTS

- Nanostructured electrochemical sensor based on TiO_2 and ionic liquid was used for the determination of levodopa in the presence of carbidopa.
- Selectivity, reproducibility and low detection limit make the nanostructured modified electrode very useful for accurate determination of levodopa.
- This sensor was applied in determination of levodopa and carbidopa in pharmaceutical formulations, blood serum and urine.

GRAPHICAL ABSTRACT



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ABSTRACT

The combination of coumarin derivative (7-(1,3-dithiolan-2-yl)-9,10-dihydroxy-6H-benzofuro[3,2-c]chromen-6-on), (DC)–titanium dioxide nanoparticles (TiO_2) and ionic liquid (IL) yields nanostructured electrochemical sensor, formed a novel kind of structurally uniform and electrocatalytic activity material. This new ionic liquid–TiO_2 nanoparticles modified carbon paste electrode (IL–CTP) due to its enhanced conductivity presented very large current response from electroactive substrates. The modified electrode was characterized by different methods including a scanning electron microscope (SEM), electrochemical impedance spectroscopy (EIS) and voltammetry. A pair of well-defined quasi reversible redox peaks of coumarin derivative was obtained at the modified carbon paste electrode (DC/IL–CTP) by direct electron transfer between the coumarin derivative and the CP electrode. Dramatically enhanced electrocatalytic activity was exemplified at the DC/IL–CTP electrode, as an electrochemical sensor to study the electro oxidation of levodopa (LD) and carbidopa (CD). Based on differential pulse voltammetry (DPV), the oxidation of LD and CD exhibited the dynamic range between 0.10– 900.0 μM and 20.0–900.0 μM respectively, and the detection limit (3σ) for LD and CD were 41 nM and 0.38 μM, respectively. DPV was used for simultaneous determination of LD and CD at the DC/IL–CTP electrode, and quantitation of LD and CD in some real samples (such as tablets of Parkin-C Fort and Madopar, Sinemet, water, urine, and human blood serum) by the standard addition method.

1. Introduction

Antiparkinsonian drug levodopa is principally metabolized by an enzymatic reaction (dopa-decarboxylase) to dopamine compensating for the deficiency of dopamine in the brain [1]. Parkinson's disease is believed to be related to low levels of the

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neurotransmitter dopamine in the brain. Therefore, the dopamine precursor levodopa [3-(3,4-dihydroxyphenyl)-L-alanine] is employed for its treatment. For better therapeutic effect and lower toxicity, carbidopa is administered in association with levodopa in pharmaceutical formulation containing 10–25% of carbidopa. This catecholamine has inhibition effect on the decarboxylase activity [2]. Therefore, by administering levodopa combined with carbidopa, the concentration of dopamine is controlled at appropriate level and this combination also results in reduction of side effects and improvement of therapy. This is why the development of a method for the simultaneous determination of levodopa and carbidopa has appeared to be of great importance because of their coexistence in pharmaceutical preparations [3,4].

In order to achieve a better medicinal effect and lower toxicity, it is very important to control the content of levodopa and carbidopa in pharmaceutical tablets. Therefore, it is important to establish a simple, inexpensive, fast, sensitive and accurate detection method for the simultaneous determination of these drugs.

Various methods like spectrophotometry [5], gas chromatography (GC) [6], high performance liquid chromatography (HPLC) [7], chemiluminescence [8], amperometric and voltammetric determination [9,10], potentiometry [11], radioimmunoassay [12] and flow injection analysis (FIA) [13] have been described for the determination of levodopa and carbidopa in various biological samples and pharmaceutical preparations. Nevertheless these methods often have diverse disadvantages such as high cost, low selectivity, the use of organic solvents, complex sample preparation procedures or long analysis time. In contrast, electrochemical methods can offer several advantages, for example, an inexpensive and simple analytical method with remarkable detection sensitivity, reproducibility, and ease of miniaturization [14–16], they are superior for use in the analytical determination of levodopa and carbidopa [17–19].

Carbon ionic liquid electrode has been reported as a high performance electrode with many good features and provision of high rates of electron transfer [20]. The acknowledged advantages of these ILs include good chemical and thermal stability, almost negligible vapor pressure, good ionic conductivity, and wide electrochemical windows etc. [21,22]. The improvement of voltammetric signal (overpotential decrease, decrease in the peak-to-peak potentials separation and peak current increase) when mineral oil is replaced by IL was demonstrated [23], perhaps due to better solubility of polar analytes in a binder. Although the increase in the capacitive current may be considered as a disadvantageous, replacement of oil with IL will be larger the magnitude of the faradaic signal and consequently increases the signal to noise ratio. Also, it has been shown that adding the IL to oil binder can improve the signal which is obtained on classic carbon paste (CP) electrode [20,24–26].

The modification of electrodes using redox modifiers is an interesting field in analytical chemistry. Redox modifiers are electroactive compounds that effectively shuttle electrons between the analyte and the electrode. One of the most important effects of any modifier is a reduction of the overpotential required for electrochemical reaction, which enhances the sensitivity and selectivity of the method [27–29].

According to the above points, we used these three important kinds of compounds for the fabricated novel nanostructure modified carbon paste electrode based on coumarin derivative (DC), the unique properties of ionic liquids and TiO_2 nanoparticles. The experimental results indicate that DC/IL–CTP offers several advantages such as high repeatability, good stability and high apparent charge transfer rate constant. To the best of our knowledge, there is no report on the simultaneous determination of levodopa and carbidopa using ionic liquid/TiO_2 nanoparticles carbon paste electrode. Thus, in this paper, we described initially electrocatalytic effect of DC/IL–CTP for the individual and simultaneous determination of levodopa and carbidopa. The proposed method possesses many advantages such as fast response, low detection limit, large dynamic range, and good selectivity. Utilizing the developed method, determination of the two compounds has been carried out in pharmaceutical formulations, water, urine and human blood serum samples.

2. Experimental

2.1. Apparatus and chemicals

The electrochemical measurements were performed with an Autolab potentiostat/galvanostat (PGSTAT-302N, Eco Chemie, The Netherlands). An Ag/AgCl/KCl (3.0 M) electrode, a platinum wire, and the DC/IL–CTP were used as the reference, auxiliary and working electrodes, respectively (reference and auxiliary electrodes from AZAR electrode, Iran). All the potentials are quoted versus Ag/AgCl (3.0 M KCl) reference electrode.

Levodopa, carbidopa and other reagents were analytical grade from Merck (Darmstadt, Germany). Graphite powder and paraffin oil (DC 350, density = 0.88 g cm^{-3}) as the binding agent (Merck, Darmstadt, Germany) were used for preparing the pastes. DC and TiO_2 nanoparticles were synthesized in our laboratory which their synthesis are described in the supplementary data. The 1-butyl-3-methylimidazolium hexafluorophosphate and titanium tetra isopropoxide were purchased from Sigma Aldrich.

2.2. Preparation of the electrode

To obtain the best conditions in the preparation of the DC/IL–CTP, we optimized the ratio of DC, TiO_2 and IL. The results of our studied showed that the maximum peak current intensity of levodopa could be obtained at the surface of DC/IL–CTP with optimum ratio of DC, TiO_2 and IL. The DC-IL/CTP were prepared by dissolving 0.010 g DC in 2 mL chloromethane and then added in 0.900 g graphite powder and 0.010 g TiO_2 with a mortar and pestle. Then, 0.3 mL IL and 0.5 mL of paraffin were added to the above mixture and mixed for 20 min until a uniformly wetted paste was obtained. The paste was then packed into the end of a glass tube.

For comparison, DC modified CP electrode (DC–CP) without TiO_2 and IL, TiO_2 paste electrode (DC–CTP) without IL, IL carbon paste electrode (DC/IL–CP) without TiO_2 and unmodified carbon paste electrode (CP) in the absence of DC, IL, and TiO_2 were also prepared in the same way.

3. Results and discussion

3.1. The surface morphologies of electrodes

Typical SEM images of different electrodes were shown in Fig. 1. The CP electrode is characterized by a surface formed by irregularly shaped flakes of graphite that were isolated and each layer could be clearly distinguished (Fig. 1(a)). Fig. 1(b) shows a SEM image of DC/IL–CTP with more uniform surface topography and no separated carbon layers could be observed. It can be seen that TiO_2 was distributed on the surface of the electrode. A layer of IL is formed on the graphite particles even with the addition of small amount of IL to the graphite. This phenomenon is consistent with literatures [30,31].

The addition of IL to CP electrode is recommended to improve the currents signal obtained on classic CP electrode [32,33]. Shown in Fig. 1(c) and (d) are the comparison of mechanism of electrode reaction of polar reactant at CP electrode and DC/IL–CTP. Increase in the currents of the IL modified electrode compared to CP electrode due to the better dispersion of the graphite powder in this binder