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Two simple and fast electrochemical methods for simultaneous determination of promethazine and codeine



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ABSTRACT

Two new analytical procedures for fast and simultaneous determination of promethazine (PRO) and codeine (COD) have been developed. One method is based on batch injection analysis with multiple pulse amperometric detection (BIA–MPA) and the other is based on capillary electrophoresis with capacitively coupled contactless conductivity detection (CE–C⁴D). Both methods are simple, robust, precise (RSD < 1.6 %, $n = 10$), present high analytical frequency (~ 80 injections h^{-1}) and generate reduced volume of waste. The BIA–MPA procedure provides linear range from 5 to 25 mg L^{-1} and 8 to 40 mg L^{-1} (for PRO and COD, respectively) and limits of detection of 0.065 and 0.135 mg L^{-1} (for PRO and COD, respectively). The CE–C⁴D procedure provides linear range from 58 to 290 mg L^{-1} and 122–610 mg L^{-1} (for PRO and COD, respectively) and limits of detection of 20 and 28 mg L^{-1} (for PRO and COD, respectively). The results obtained with the CE–C⁴D and BIA–MPA methods were compared to those obtained by HPLC and similar results were obtained (95% confidence level).

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1. Introduction

Promethazine (PRO) or N,N-dimethyl-1-phenothiazin-10-ylpropan-2-amine is an antihistaminic with sedative, antipsychotic, analgesic and anticholinergic properties. However, PRO may also cause adverse effects, such as endocrinal, cardiac and reproductive alterations [1]. Codeine (COD) or 7,8-didehydro-4,5 α -epoxy-3-methoxy-17-methyl morphinan-6 α -ol is used as an effective analgesic and also as an agent against cough [2–4]. The overdose with COD can cause serious adverse effects such as diarrhea, nausea, vomiting, constipation, dry mouth, itching, confusion, sedation and respiratory depression. Furthermore, COD can be used as an abuse drug, but much less often than other opioids [5]. PRO and COD are combined in the ratio of 1:1.6 (w/w) in pharmaceutical formulations (syrups). The synergistic activity between both compounds is commonly used for treating of colds or allergic symptoms such as runny nose, sneezing and coughing.

There are some analytical methods in the literature which focus on simultaneous determination of PRO and COD, such as capillary zone electrophoresis with amperometric detection [6], micellar electrokinetic chromatography [7], thin-layer chromatography

[8], and UV spectrometry [8]. However, most of these methods show high costs, requiring sample pretreatment and long time of analysis.

Capillary electrophoresis with capacitively coupled contactless conductivity detection (CE–C⁴D) has recently been used as an alternative for simultaneous determination of a large variety of ionic compounds, such as inorganic and organic ions [9,10], drugs [11,12], sugars [13], amines [14], amino acids [15] and other species [16]. The C⁴D is constituted of two cylindrical electrodes positioned around the capillary column without any direct contact with the electrolytic solution. It can be easily positioned anywhere along the capillary [17–20]. CE–C⁴D usually presents low cost of operation, short analysis time, high separation efficiency, versatility and low consumption of reagents and samples [11].

Batch injection analysis (BIA) is a non-flow injection technique introduced by Wang and Taha [21]. Recently, a new application of the BIA system was demonstrated based on its coupling with multiple pulse amperometry (MPA). The use of MPA as detection mode made possible the simultaneous determination of two analytes with a single injection and using a single working electrode [17,20]. This approach renders several desirable characteristics, such as the need of small sample volumes (typically 1–150 μL), high sampling rate, low cost, and possible use in laboratories with minimum of infrastructure or for on-site analysis [21–24]. BIA systems with amperometric detection can be easily used in on-site analysis (portable system) because its components (electronic

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pipette, potentiostat and laptop computer) are commercially available with internal battery power source. In addition, after positioning of the three electrodes (working, auxiliary and reference or pseudo-reference) and filling the BIA cell with electrolyte, the system provides more than two hundred injections without replacement of any component of the system.

Recently, an option of working electrode which is being increasingly used is boron-doped diamond (BDD) because it presents advantages over conventional solid electrodes in terms of high stability (low adsorption of organic molecules), chemical inertness, wide potential window, good sensitivity and low background current [25,26].

The proposal of this work is the simultaneous determination of PRO and COD using BIA-MPA on bare boron-doped diamond electrode and capillary electrophoresis with capacitively coupled contactless conductivity detection. Results were validated in relation to linearity, repeatability (intra-day and inter-day studies), detection and quantification limits, recovery studies, and by comparison with the results from HPLC analysis.

2. Experimental

2.1. Reagents and samples

Promethazine (PRO) hydrochloride and codeine (COD) phosphate were purchased from Henrifarma (São Paulo, SP, Brazil) and Galena (Campinas, SP, Brazil), respectively. Carboxymethyl cellulose, sorbitol, tween 80, sodium benzoate and sucralose were purchased from All Chemistry (São Paulo, SP, Brazil). All solutions were prepared with deionized water (Millipore Direct-Q3) with a resistivity not less than 18 MΩ cm. Reagents were of analytical grade and were used without further purification. For amperometric experiments, acetic acid/acetate buffer (0.1 mol L⁻¹; pH 4.7) was used as the supporting electrolyte. A buffer solution containing 10 mmol L⁻¹ oxalic acid and 1.8 mmol L⁻¹ triethanolamine (pH 8.4) was used as the background electrolyte (BGE) in CE analyses. Lithium hydroxide (internal standard) was purchased from Sigma-Aldrich (Milwaukee, WI, USA).

Pharmaceutical formulation (syrup) containing PRO and COD was obtained from local drugstore. For the analyses, an aliquot of the syrup was diluted to an adequate concentration in electrolyte for subsequent injection in the BIA-MPA system or in water if injected in the CE-C⁴D system. Before the injection on CE-C⁴D system, all samples and standard stock solutions were kept under sonication for 10 min and the resulting solutions were filtered with a membrane filter (pore size of 0.45 μm).

2.2. Instruments and apparatus

Electrochemical measurements were performed with a μAuto-lab Type III potentiostat (Metrohm Autolab B.V.) controlled by GPES 4.9.007 software. For multiple-pulse amperometry (MPA) measurements, a mini Ag/AgCl saturated with KCl [27] and platinum wire were employed as the reference and auxiliary electrodes, respectively. A thin film (around 1.2 mm) of boron-doped diamond (BDD) with a doping level of 8000 ppm, on a polycrystalline silicon wafer (Adamant Technologies SA, La Chaux-de-Fonds, Switzerland) was used as the working electrode. Prior the first use, the BDD electrode was anodically pretreated by applying 0.01 A for 1000 s in 0.04 mol L⁻¹ Britton-Robinson buffer solution and then cathodically pretreated by applying -0.01 A for 1000 s in a 0.1 mol L⁻¹ H₂SO₄ solution. This pretreatment is similar to that used in previously published works [28,29]. After the first pretreatment, the BDD electrode was treated only cathodically once at the beginning

of the workday. If the electrode is not used for a few days, both pretreatments (anodic and cathodic) are again required.

BIA measurements were carried out using a homemade cell as previously described [30]. All experiments were carried out with the solution under stirring. A micro DC-motor was adapted to the BIA cell and used in the solution stirring [23]. The stirring rate can be easily changed by varying the voltage from a universal AC/DC voltage regulator (3–12 V). All studies were performed at a constant stirring rate of 1395 ± 10 rpm (with the application of 5 V). The injection of solutions (samples or standards) was performed with a motorized electronic micropipette (Eppendorf multipette® stream) with a constant distance between the working electrode and the multipette® combitip® (≈2 mm), as recommended in a previous work [24].

The electrophoretic analyses were performed using homemade equipment with two compact and high-resolution capacitively coupled contactless conductivity detectors (CE-C⁴D) [31,32]. A fused silica capillary with dimensions of 50 μm inner diameter, 375 μm outer diameter, 40 cm long, and effective length of 10 cm (Agilent, Folsom, CA, USA) was used. Before analyses, the capillary was preconditioned with 0.1 mol L⁻¹ NaOH solution (15 min), deionized water (10 min) and background electrolyte (10 min). The samples were injected hydrodynamically for 0.6 s at 25 kPa and the separation potential adopted was 25 kV.

Results for the simultaneous determination of COD and PRO by BIA-MPA and CE-C⁴D were compared to those obtained by using high performance liquid chromatography (adapted from [33]). A Hitachi pump L-2130, Hitachi LC-4250 UV-VIS detector and, a Shim-pack CLC-ODS column (25 mm × 4.6 mm; Shimadzu) was used. The mobile phase was composed of methanol/water (60:40, v/v; pH adjusted to 2.35 with phosphoric acid), and the flow rate was 1.0 mL min⁻¹. The detector was fixed at 250 nm. The retention times were 2.63 and 5.57 min for COD and PRO, respectively.

3. Results and discussion

3.1. BIA-MPA

Fig. 1 shows cyclic voltammograms obtained at BDD electrode using acetic acid/acetate buffer as the supporting electrolyte (0.1 mol L⁻¹; pH 4.7) before (—) and after addition of PRO (---) or COD (----).

Under this condition, 2 mols of COD are oxidized to bis-COD at about +1.10 V involving the transfer of two electrons and two protons [34–36]. No cathodic peak was observed in the reverse scan,

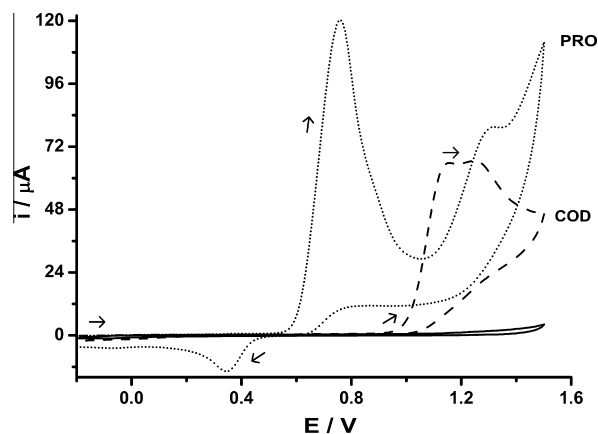


Fig. 1. Cyclic voltammograms of BDD working electrode in 0.1 mol L⁻¹ acetate buffer before (—) and after addition of 203 mg L⁻¹ COD (----) or 160 mg L⁻¹ PRO (---). Scan rate: 50 mV s⁻¹; step potential: 5 mV.

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