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Flow injection simultaneous determination of acetaminophen and tramadol in pharmaceutical and biological samples using multiple pulse amperometric detection with a boron-doped diamond electrode

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ABSTRACT

An analytical procedure was developed for the simultaneous determination of acetaminophen (ACP) and tramadol (TRA) by flow injection analysis with multiple pulse amperometric detection (FIA–MPA) using a cathodically pretreated boron-doped diamond electrode (BDDE). The proposed method was applied to the simultaneous determination of ACP and TRA in pharmaceutical samples and synthetic biological fluids. The obtained results are in acceptable levels, the proposed method presents low RSD values (<2.70 and 4.70% for intra- and inter-day, respectively), linear ranges from 1.0 to 100 μmol L^{-1} for ACP and from 0.08 to 10 μmol L^{-1} for TRA, limits of detection of 0.03 and 0.04 μmol L^{-1} for ACP and TRA, respectively, elevated analytical frequency (approximately 85 injections h^{-1}) and adequate accuracy (confirmed by comparison with HPLC results).

1. Introduction

Tramadol (TRA) ((±)-cis-2-(dimethylaminomethyl)-1-(3-methoxyphenyl) cyclohexanol hydrochloride) has been used since 1977 like other narcotics applied for treatment of moderate surgical pain, surgical pain in children, cancer pain control, obstetric pain and chronic pain [1,2]. It is similar to codeine, differing only by a methyl substitution on the phenolic moiety of the morphine structure.

TRA is classified as an opioid, once binds to receptors in the brain (opioid receptors) and inhibits reuptake of norepinephrine and serotonin and enhances the release of these neurotransmitters, also is a synthetic analog of codeine and is not currently classified as a controlled substance [3–5]. This opioid, like other narcotics, cannot be abused. Its therapeutic plasma concentration ranges from 100 to 300 mg L^{-1} [4]. TRA is rapidly and almost completely absorbed after oral administration but its absolute bioavailability is only 65–70% due to first-pass metabolism [6]. About 10–30% of the drug is excreted unmetabolized in the urine [7].

Acetaminophen (ACP) (N-acetyl-p-aminophenol) (also known as paracetamol) is a well establish medicine and widely used as analgesic antipyretic drug that has actions similar to aspirin and can be an effective substitute for patients with allergy to aspirin, also there are plenty of medicines for cold and influenza which use it as a major ingredient. It is commonly used for the relief of fever, headaches, other minor aches, and pains and the management of more severe pain [8,9]. It is considered a safe medicine in therapeutic doses, however an overdose can cause a plethora of problems because an accumulation of toxic metabolites can occur, which cause acute and sometimes fatal hepatoxicity and nephrotoxicity [10]. Other intoxications problems can cause a plethora of undesirable effects such as skin rashes, inflammation of the pancreas and liver disorders. All these problems are related to abuse of large doses, chronic use or concomitant use with alcohol or other drugs [11].

Considering a complementary mechanism action of ACP and TRA, the combination of these drugs in tablets tends to enhance the analgesic effectiveness and reducing side effects [12,13]. However, their overdose can be toxic to organism and the improper or uncontrolled use can lead to serious health complications. The determination of the levels that these compounds present in pharmaceuticals and biological fluids is important to prevent overdoses leading to undesirable effects or intoxication. For this reason, it is extremely important to develop a sensitive, selective, rapid and simple method for the simultaneous determination of these drugs.

Some methods have been applied for the simultaneous determination of these drugs [14–16]. However, these methods may consume a long time for analysis, and can be expensive and often it needs a pretreatment step of sample. The ACP and TRA are electroactive

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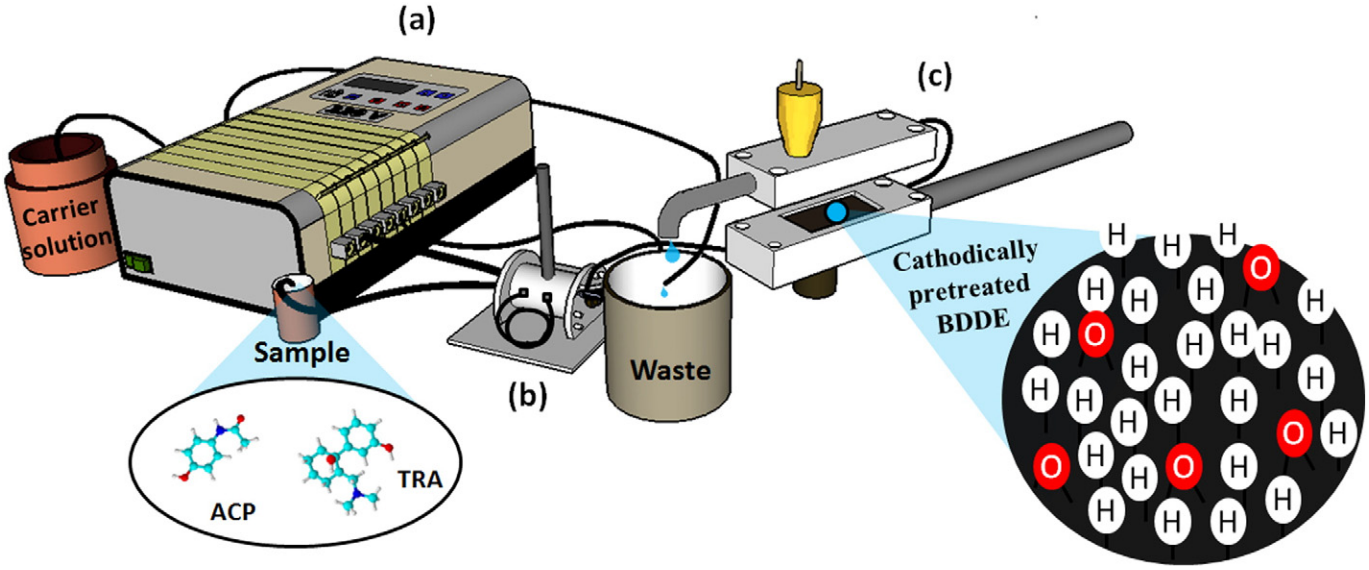

Fig. 1. Diagram of a system used in flow injection analysis (FIA), (a) peristaltic pump, (b) manual injector and (c) electrochemical detector with an Ag/AgCl (3.0 mol L^{-1} KCl) electrode as the reference electrode, a stainless steel tube as the auxiliary electrode and a cathodically pretreated BDDE.

compounds and can be oxidized electrochemically. Electrochemical methods have shown great advantages in analysis of pharmaceutical samples and synthetic biological fluids [17–19]. These advantages are mainly due to simplicity of this method, its selectivity, low cost and relatively short analysis time as compared to chromatography.

Flow injection analysis with amperometric detection of analyte has been widely reported since 1980 [20] and a pulse amperometric flow injection method for measurement of atmospheric hydrogen peroxide was proposed by the first time by Huang et al. [21]. However, there are a few reports in the development of new methods applying flow injection techniques with a multicomponent analysis [22–24]. A common method is the application of two or more sensors using different constant potentials for each proposed electrode, therefore, obtaining analytical signals, which are analyzed by multivariate calibration method. Another strategy rarely employed is the use of multiple pulse amperometry (MPA) and FIA for simultaneous determinations of different classes of analytes [25,26]. This procedure also allows a better selectivity and accuracy, by the possibility of inclusion of a potential pulse constant, which promotes electrochemical cleaning or the use of internal standard method [27,28].

Boron-doped diamond electrodes (BDDE) are carbon-based materials widely used in electroanalysis due to their excellent electrochemical properties, such as low and stable background current in aqueous solutions, wide potential window, low adsorption, and long-term stability of the response [29,30]. Studies of electrochemical BDDE properties were recently published by our research group, in which we calculate the electroactive area and the heterogeneous electron transfer rate constant [31].

In the present work, the advantages of using a cathodically pretreated BDDE combined with FIA—MPA for the simultaneous analytical determination of TRA and ACP are presented. The proposed method is compared and contrasted with other works described in the literature [32–35], besides being independently compared with a HPLC method for the simultaneous determination of TRA and ACP in pharmaceutical commercial products and it also subsequently analyzed directly synthetic biological fluids, with good agreement.

2. Experimental

2.1. Apparatus

The voltammetric and MPA measurements were performed using an Autolab PGSTAT—30 (EcoChemie) potentiostat/galvanostat controlled by the GPES 4.9 software. Voltammetric measurements and the working electrode pretreatment were carried out in a three electrode borosilicate glass cell, with an Ag/AgCl (3.0 mol L^{-1} KCl) electrode as the reference electrode, a platinum wire as the auxiliary electrode and BDDE as the working electrode. The BDDE consisted of a BDD film with a doping level of 8000 ppm (B/C) (NeoCoat SA, La Chaux—de—Fonds, Switzerland) (For details on its preparation and characteristics of the BDDE, please see Hupert et al. [36]). The MPA measurements were performed using a system developed by Richter et al. [37], a stainless steel tube was used as counter electrode, along with a miniaturized Ag/AgCl (3.0 mol L^{-1} KCl) reference electrode and the working electrode was a BDD film. The FIA system was composed with polyethylene tubing of 1.0 mm i.d and the flow rate of 3.8 mL min^{-1} was controlled by a peristaltic pump (Fig. 1).

The BDDE (0.69 cm^2 exposed area) was anodically or cathodically pretreated in a 0.5 mol L^{-1} H_2SO_4 by applying 0.04 A cm^{-2} or −0.04 A cm^{-2} during 30 s or 180 s, respectively.

TRA and ACP determinations using high performance liquid chromatography comparative method were adapted from Karunakaran

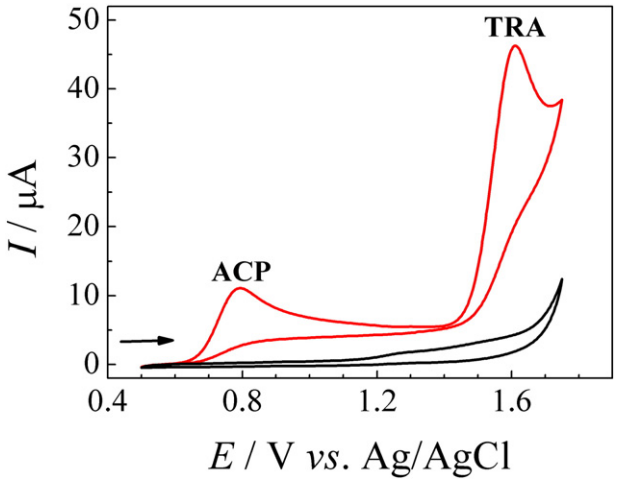

Fig. 2. Cyclic voltammograms obtained in the absence (—) and in the presence (—) of 0.2 mmol L^{-1} ACP and TRA in 0.04 mol L^{-1} Britton–Robinson buffer (pH 2.0) with a cathodically pretreated BDDE and scan rate, $v = 50$ mV s^{-1}.