Materials Science and Engineering C 76 (2017) 425–430

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

# A simple and sensitive methodology for voltammetric determination of valproic acid in human blood plasma samples using 3-aminopropyletriethoxy silane coated magnetic nanoparticles modified pencil graphite electrode

Abedin Zabardasti [a],*, Hossein Afrouzi [a], Rasoul Pourtaghavi Talemi [b]

[a] Department of Chemistry, Faculty of Science, Lorestan University, Khorramabad, Iran
[b] Faculty of Chemistry, Kharazmi University, Tehran, Iran

ARTICLE INFO

Article history:
Received 23 October 2016
Received in revised form 11 December 2016
Accepted 24 February 2017
Available online 27 February 2017

Keywords:
Valproicacid
Magnetic nanoparticles
Pencil graphite electrode
Electrochemicalimpedance spectroscopy
Differential pulse voltammetry
Plasma

ABSTRACT

In this work, we have prepared a nano-material modified pencil graphite electrode for the sensing of valproic acid (VA) by immobilization 3-aminopropyletriethoxy silane coated magnetic nanoparticles (APTES-MNPs) on the pencil graphite surface (PGE). Electrochemical studies indicated that the APTES-MNPs efficiently increased the electron transfer kinetics between VA and the electrode and the free $NH_2$ groups of the APTES on the outer surface of magnetic nanoparticles can interact with carboxyl groups of VA. Based on this, we have proposed a sensitive, rapid and convenient electrochemical method for VA determination. Under the optimized conditions, the reduction peak current of VA is found to be proportional to its concentration in the range of 1.0 (±0.2) to 100.0 (±0.3) ppm with a detection limit of 0.4 (±0.1) ppm. The whole sensor fabrication process was characterized by cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS) methods with using $[Fe(CN)_6]^{3-/4-}$as an electrochemical redox indicator. The prepared modified electrode showed several advantages such as high sensitivity, selectivity, ease of preparation and good repeatability, reproducibility and stability. The proposed method was applied to determination of valproic acid in blood plasma samples and the obtained results were satisfactory accurate.

## 1. Introduction

Nano-materials are used in a variety of sensor and biosensor applications [1–5] because they exhibit good electro-catalytic properties, high surface-to-volume ratio, high stability, widely available, and provide fast electron transfer rates.

Magnetic nanoparticles (MNPs) are important to various biomedical applications such as magnetic separation, cell labeling, targeted drug delivery, and hyperthermia treatment of solid tumors and contrast agents for magnetic resonance imaging (MRI) [6–10]. Recently, we used functionalized magnetic nanoparticles for modification of electrode surface [11,12]. APTES-MNPs, due to their basic groups of amino and hydroxyl anchored on the external surface, can be used in many technological applications such as in decontamination of effluents produced by industries and nuclear power plants and in various bioprocesses, molecules or drugs [13].

Due to the simple sample preparation, low-cost instrumentation, high sensitivity, selectivity, accuracy and precision of electrochemical methods, they have been used widely in biological and environmental analysis [14–23].

Valproic acid with the chemical name of 2-propylvaleric acid was first approved as an anticonvulsant in the United States in 1978. VA is used in the treatment of primary seizures, partial seizures, myoclonic seizures, bipolar disorders, prophylaxis of migraine headache, febrile convulsions, and brain tumor [24]. Other investigations have proposed to use VA in the treatment of anxiety, alcoholism, schizophrenia and borderline personality disorders [25].

After oral administration of VA, the drug is rapidly adsorbed from the gastrointestinal tract, getting maximum blood levels one to four hour and binds to human plasma proteins (90%). Mainly, metabolism occurs in the liver (95%).

Therapeutic drug monitoring (TDM) is an aid in the clinical management of patients of seizure disorders, which use anticonvulsant drugs including carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone and valproic acid. Therapeutic concentration of VA is 50–100 ppm or 346–693 μmol/L [26]. But there are reports of fatal

---

* Correspondence author.
E-mail address: zabardasti.a@lu.ac.ir (A. Zabardasti).

http://dx.doi.org/10.1016/j.msec.2017.02.140
0928-4931/© 2017 Published by Elsevier B.V.

intoxication caused by overdose of VA [27–29]. Several analytical techniques have reported in literature for determination of VA in biological fluids, including immunological assay [30], high performance liquid chromatography (HPLC) [31–33], LC–MS/MS [34–36], gas chromatography [37–41]. VA has poor UV absorption. So most HPLC methods have low detection wavelengths (210 nm) which are not sensitive, because of increased noise at lower wavelengths especially when using complex matrices such as biological fluids. Other methods such as derivatization methods, GC and LC–MS techniques are time consuming or expensive.

Present method described in this paper has only one derivatization process and has no any other time consuming or expensive step and is applicable for fast, accurate and precise method for monitoring and determination of VA in human plasma. In this work, pencil graphite electrode (PGE) was first modified with a (3-aminopropyl) triethoxysilane (APTES) functionalized magnetic nanoparticles (MNPs). Then, the APTES-MNPs/PGE was directly applied for determination of VA in citrate buffer solution with pH 3.5. The APTES-MNPs, increased the surface area of pencil graphite electrode, accelerated the electron transfer between VA and electrode and interacted with VA. Electrochemical studies showed that the APTES-MNPs/PGE possesses an excellent sensing performance for detecting VA with a linear range from 1.0 (±0.2) to 100.0 (±0.3) ppm and a limit of detection (LOD) as low as 0.4 (±0.1) ppm based on S/N = 3. The analytical feasibility of the approach is examined by measuring the VA content in human plasma real samples and the results show that it is useful.

## 2. Material and methods

### 2.1. Reagents

Valproic acid was prepared from the Daroupakhsh Pharmaceutical Company (Tehran, Iran). Sodium citrate, citric acid, potassium ferrocyanide, ($K_4Fe(CN)_6$), potassium ferricyanide ($K_3Fe(CN)_6$), glycerol, and ammonia solution were purchased from Merck (Darmstadt, Germany). All chemicals were of analytical reagent grade and double distilled water (DDW) was used throughout.

### 2.2. Instrumentation

Voltammetric and electrochemical impedance spectroscopy (EIS) measurements were carried out on an Autolab 302 electrochemical workstation (Metrohm, The Netherlands) as our previous works [42–44]. A conventional three-electrode system was used with a working electrode (un-modified or modified), a 3.5-M KCl Ag/AgCl reference electrode, and a platinum wire counter electrode (Azar Electrode, Iran). A TESCAN (Brno, Czech Republic) scanning electron microscope (SEM) was used to obtain SEM images and a Metrohm-827 pH/mV meter (Herisau, Switzerland) was used for pH adjustments. The measurements were carried out at room temperature.

### 2.3. Preparation of 3-aminopropyletriethoxy silane coated magnetic nanoparticles (APTES-MNPs)

The magnetic nanoparticles were prepared according to our previous work [11]. Briefly, 11.68 g of $FeCl_3 \cdot 6H_2O$ and 4.3 g $FeCl_2 \cdot 4H_2O$ were dissolved in 200 mL deionized water under nitrogen atmosphere with vigorous stirring at 80 °C. Then 45 mL of aqueous ammonia solution (25%) was added. The color of the solution was turned from dark orange to the black immediately. The precipitates were washed three times with deionized water and twice with 0.02 mol $L^{-1}$ sodium chloride. The prepared magnetite suspension was placed in 250 mL round flask and allowed to settle to remove the supernatant. Then 80 mL aqueous solution of 10% (v/v) APTES and 40 mL glycerol were added to the mixture and heated at 90 °C for 2 h under nitrogen atmosphere with stirring. After cooling to room temperature the suspension was washed sequentially with 200 mL deionized water (three times), 100 mL methanol (five times), and 200 mL deionized water (three times). The prepared silane coated MNPs were stored in deionized water.

### 2.4. Sensor fabrication

First, the pencil graphite electrode (PGE) was polished with 10–50 μm alumina slurry and was washed with ethanol and double distilled water. Prior to modifying the PGE surfaces, the APTES-MNPs were prepared as described above. A bare PGE was then immersed in the test tube containing APTES-MNPs and incubated for 24 h to prepare APTES-MNPs/PGE.

## 3. Result and discussion

VA can be reduced on the modified pencil graphite electrode at −0.2 and −0.8 V in the citrate buffer solution with pH 3.5. The mechanism for VA reduction was suggested by Acar et al. as follow [45]:

$$C_7H_{15}COOH + H^+ + e^- \Leftrightarrow C_7H_{15}C(OH)_2(ads)$$
$$C_7H_{15}COO^- + e^- \Leftrightarrow C_7H_{15}C(OH)O \rightarrow C_7H_{15}C(OH)_2(ads)$$

In our experiments, the better analytical characteristic such as sensitivity, wider linear range and lower detection limit were obtained when we considered the second equation that correspond to the reduction peak at −0.8 V. As a result, we perform electrochemical investigation only for this peak and the experimental data for this peak were discussed. The whole sensor fabrication process was schematically presented in Fig. 1.

### 3.1. Microscopic characterization of APTES coated magnetic nanoparticles

Typical SEM micrographs of naked MNPs before and after coating with APTES are shown in Fig. 2. It can be seen from Fig. 2A that naked MNP are spherical in shape with an average size of about 23 nm. Obviously, the dispersing behavior of APTES-MNPs (Fig. 2B) have been improved in comparison with that of naked MNP which might be related to the coated APTES enhancing the repulsion of magnetite particles. With this improved dispersibility, we can expect better repeatability and reproducibility from APTES-MNPs rather than naked MNPs.

### 3.2. Electrochemical characterization of differently modified electrodes

Cyclic voltammograms of different modified electrodes in 1.0 mmol $L^{-1}$ $[Fe(CN)_6]^{3-/4-}$ solution were recorded and shown in

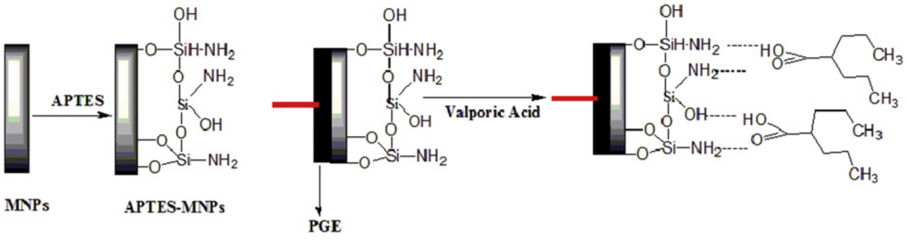

Fig. 1. Schematic illustration of the fabrication steps of the voltammetric VA sensor.