Application of multivariate curve resolution alternating least squares to biomedical analysis using electrochemical techniques at a nanostructure-based modified sensor

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Application of multivariate curve resolution alternating least squares (MCR-ALS), for the resolution and quantification of two sulfonamide drugs containing sulfamethizole (SMT) and sulfapyridine (SPY) with a very high degree of overlapping voltammograms, is described. A simple and sensitive carbon nanocomposite electrode has been developed for the electrochemical trace determination of SMT and SPY in Britton-Robinson (B-R) buffer solution. This sensor was designed by incorporation of multi-walled carbon nanotubes (MWCNTs) into the carbon paste electrode (CPE). Response surface methodology (RSM) using central composite rotatable design (CCRD) model was used to optimize effective parameters on differential pulse voltammetry (DPV) response of the two analytes. A 4-factor-5-level CCRD of RSM was applied to model linear, interaction and quadratic effects of chemical and instrumental variables. After potential shift correction, MCR-ALS has been applied to data collected from DPV analysis of the oxidation process of SMT and SPY in different pulse heights. Quantitative voltammetric analyses of SMT and SPY were performed in the concentration range of 0.1-180.0 and 0.5-165.0 μM, and it was found that the detection limits were 50.0 and 60.0 nM, respectively. The method was applied for simultaneous determination of SMT and SPY in spiked human serum and urine samples.

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1. Introduction

The sulfonamide group ($-SO_2NH-$) is often used in medicinal chemistry for the development of new drugs with advanced pharmacological characteristics. In spite of the long history of sulfonamides (sulfa drugs) development, the peak of their patenting covers the years 2008-2014 [1–3]. In fact, the sulfonamides constitute an important group of drugs, with several types of pharmacological agents possessing antibacterial [4], hypoglycemic [5], antitumor [6], anti-carbonic anhydrase [7], diuretic [8], antithyroid [9] or protease inhibitor [10,11] activity among others. The chemical structures of the two sulfa drugs studied here are shown in Scheme 1. Owing to concern over the analytical determination of sulfonamides, various methods have been applied, including high-performance liquid chromatography (HPLC) [12,13], gas chromatography (GC) [14,15] and capillary electrophoresis [16,17].

These techniques have proven to be suitable and sensitive for sulfonamide determination. But, few electrochemical methods have been reported for the quantification of sulfonamide compounds [18,19], most probably due to issues related to electrode deactivation or fouling. Despite this drawback, electroanalytical methods offer certain advantages, such as not being time-consuming, not requiring sample preparation and offering a sensitivity and dynamic range comparable to other analytical methods. However, conventional electrochemical methods cannot provide the necessary information to resolve a system with severe voltammograms overlap. Chemometric methods for extraction of analytical information from multivariate data have been proposed. Multivariate curve resolution-alternating least squares (MCR-ALS) is able to resolve different sources of variance in a particular data set, and it allows to determine two or more components in a mixture with intense overlapping peaks [20–24].

Objectives of this study are to use a nanocomposite electrode based on multi-walled carbon nanotubes (MWCNTs) incorporated into the carbon paste (MWCNTs/CPE) for simultaneous determination of sulfamethizole (SMT) and sulfapyridine (SPY) with very high overlapping peaks in differential pulse voltammetry (DPV). A strategy based on response surface methodology (RSM) in conjunction

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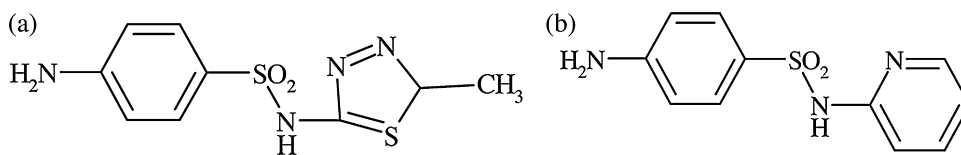
Scheme 1. Chemical structure of (a) sulfamethizole (SMT) and (b) sulfapyridine (SPY).

with central composite rotatable design (CCRD), which requires fewer tests than a full factorial design, to establish the functional relationships between four operating variables on voltammetric responces of the two analytes was used. These relationships can then be used to determine the optimal operating parameters. In the following sections, a MCR-ALS method was carried out to obtain information about the two analytes with very high overlapping voltammograms, for simultaneous voltammetric determination of them in 0.2 M Britton-Robinson (B-R) buffer solution for the first time. The analytical application of the developed method has been shown by simultaneous determination of SMT and SPY in biological samples with complex matrices.

2. Experimental

2.1. Reagents

All reagents were of the analytical grade and deionized water was used during the experiments. SMT, SPY and other chemicals were supplied from Merck. Carbon graphite powder (Merck, Darmstadt, Germany), MWCNTs with outer diameter: 10-20 nm; length: 1-2 μm and with >95% purity (Chinese Academy of Science) and paraffin oil (Merck) were used for the fabrication of working electrode. Also, for more purification of MWCNTs an acid treatment was used. All chemicals for preparation of buffers and supporting electrolytes, such as H_3PO_4, H_3BO_3, CH_3COOH and NaOH were purchased from Merck.

2.2. Apparatus

Electrochemical measurements were performed using a Sama 500 potentiostat (Isfahan, Iran). The three electrode system is employed in all experiments contained a MWCNTs/CPE as working, an Ag/AgCl (KCl 3 M, Metrohm, Switzerland) as reference and a platinum wire (Metrohm, Switzerland) as counter electrode with a standard one-compartment three-electrode cell of 100 mL capacity. All potentials were measured and reported vs. the Ag/AgCl reference electrode.

The pH was measured by a pH meter Model 691 (Metrohm) equipped with a combined glass electrode calibrated using standard buffer solutions of the conventional activity scale. Deionized water was formed with an ultra pure water system (smart 2 pure, TKA, Germany). An ultrasound bath (Bandelin Sonorex, Germany), operated at a constant frequency of 35 kHz was used for the experiment.

Scanning electron microscopy (SEM, KYKY-EM3200) was used to observe the morphological characteristics of the electrodes operating at an accelerating voltage of 26 kV.

Experimental data were analyzed using Minitab ® Release 16, developed by Minitab Inc. (USA). The computations were carried out in the MATLAB 2010 environment using a MCR-ALS user-friendly interface tool [25]. A correlation optimized warping (COW) routine written in MATLAB [26] was used for alignment of electrochemical signals.

2.3. Preparation of the working electrode

Unmodified CPE was prepared by mixing of 0.50 g of graphite powder with 0.2 mL of paraffin oil. The MWCNTs/CPE was prepared according to the following procedure. At first, different amount (2.00, 4.00, 6.00, 8.00 and 10.00 mg) of MWCNTs was dispersed in 5.0 ml deionized water by an ultrasound bath for 30 minutes and then was added into 0.50 g graphite powder in a small mortar. After vaporizing water, 0.2 ml of paraffin oil was added to the mixture. Then, the paste was packed into the end of a glass tube (2 mm diameter and 15 cm long). A copper wire inserted into the carbon paste provided the electrical contact. When necessary, a fresh surface was obtained by pushing an excess of the paste out of the tube and polishing with a weighing paper.

2.4. Experimental design for the RSM and CCRD

RSM developed by Box and Wilson [27] in 1951, is a collection of mathematical and statistical methods that are practical for designing experiments, building models, estimating the effect of factors and searching for optimum conditions for desirable responses [28]. The response surface can be expressed as Eq. 1:

$$y = f(x_1, x_2, \cdots x_n) \tag{1}$$

where y is the response and x_i's are the operating parameters of the process.

Among different RSM experimental designs, the CCRD has been widely applied because it gives sufficient information as compared to a factorial design. Therefore, RSM with CCRD was used to determine the optimum conditions of pH (X_1), MWCNTs amount (X_2), scan rate (X_3) and step potential (X_4) for simultaneous determination of SMT and SPY. The number of experiments (N) required for the CCRD is calculated by Eq. 2:

$$N = 2^k + 2k + r \tag{2}$$

where k is the number of operating variables, 2^k is factorial design (with its origin at the center), 2k is points fixed axially at a distance α from the center to generate the quadratic terms and r is replicate tests at the center. Replicates of the test at the center are very important as they present an independent estimate of experimental errors. α-values depend on the number of variables and can be calculated as $\alpha = \pm 2^{f/4}$.

The correlation of the operating parameters and the responses based on the CCRD is fitted to a quadratic polynomial equation using the least-square method (Eq. 3) of the form:

$$Y = b_0 + \sum_{i=1}^{k} b_i X_i + \sum_{i=1}^{k} b_{ii} X_i^2 + \sum_{i=1}^{k} \sum_{j>i}^{k} b_{ij} X_i X_j + \varepsilon \tag{3}$$

where Y is the responses, b_0 the constant, b_i the linear coefficients, b_{ii} the quadratic coefficients, b_{ij} the interaction coefficients, X_i and X_j are the dimensionless coded variables and ε is the residual (error) term.