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Exploiting second-order advantage from mathematically modeled voltammetric data for simultaneous determination of multiple antiparkinson agents in the presence of uncalibrated interference

Ghobad Mohammadi[a], Khodabakhsh Rashidi[b], Majid Mahmoudi[b], Hector C. Goicoechea[c], Ali R. Jalalvand[b,*]

[a] Department of Pharmaceutics, School of Pharmacy, Kermanshah University of Medical Sciences, Kermanshah, Iran
[b] Research Center of Oils and Fats, Kermanshah University of Medical Sciences, Kermanshah, Iran
[c] Laboratorio de Desarrollo Analítico y Quimiometría (LADAQ), Catedra de Química Analítica I, Universidad Nacional del Litoral, Ciudad Universitaria, CC242 (S3000ZAA), Santa Fe, Argentina

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ABSTRACT

In this work, we are going to develop an efficient electroanalytical methodology based on generation of second-order differential pulse voltammetric (DPV) data at different pulse heights to exploit second-order advantage for simultaneous determination of levodopa (LDP), carbidopa (CDP), methyldopa (MDP), benserazide (BA), tolcapone (TOL) and entacapone (ENT) in the presence of dopamine (DPA) as uncalibrated interference. The recorded data were baseline- and potential shift-corrected by asymmetric least square spline regression (AsLSSR) and correlation optimized warping (COW) algorithms, respectively. After data pre-processing, multivariate curve resolution-alternating least squares (MCR-ALS) and parallel factor analysis 2 (PARAFAC2) were used to develop three-way calibration models and then, the abilities of the developed models to predict analytes' concentrations in the absence and presence of DPA were examined in validation and test sets, respectively. MCR-ALS acted better than PARAFAC2 to predict analytes' concentrations in the absence and presence of DPA as uncalibrated interference. Therefore, MCR-ALS was chosen to predict antiparkinson agents' concentrations in spiked human serum samples as real cases. Fortunately, acceptable results were obtained which were comparable to those obtained by high performance liquid chromatography with UV detection (HPLC-UV) as reference method.

1. Introduction

Parkinson's disease (PD) which mainly affects the motor system is a degenerative disorder of the central nervous system [1,2]. The PD can cause rigidity, depression, anxiety, shaking, thinking and behavioral problems, slowness of movement and difficulty with walking. The PD is caused by a significant decrease at the dopamine (DPA) neurotransmitter level in the brain [1]. The PD has no cure, but medications can save the patient from the symptoms in some extent. The most important drugs which are useful to treat the PD are divided into three groups including levodopa (LDP), DPA agonists and monoamine oxidase B inhibitors [1]. The LDP has been widely used to treat the PD which is converted to DPA by the dopa decarboxylase in the dopaminergic neurons. Carbidopa (CDP) is another drug given to patients with PD in order to inhibit peripheral metabolism of LDP [3]. This property is important for central nervous system effect because allows a larger amount of peripheral LDP to cross the blood-brain barrier. The LDP in combination with CDP is used to improve motor function in

Abbreviations: PD, Parkinson's disease; DPA, dopamine; LDP, levodopa; carbidopa, CDP; MDP, methyldopa; BA, benserazide; TOL, tolcapone; ENT, entacapone; COMT, catechol-O-methyltransferase; HPLC-DAD, high performance liquid chromatography with diode array detection; LC-ATR-FTIR, liquid chromatography-attenuated total reflectance-Fourier transform infrared spectroscopy; LC-DAD-MS, liquid chromatography-diode array detection-mass spectrometry; FIA-DAD, flow injection analysis-diode array detection; COW, correlation optimised warping; AFOM, analytical figure of merit; NAS, net analyte signal; LOD, limit of detection; DPV, differential pulse voltammetry; CV, cyclic voltammetry; SCCD, small central composite design; MCR-ALS, multivariate curve resolution alternating least squares; PARAFAC2, parallel factor analysis 2; AsLSSR, asymmetric least squares spline regression; COW, correlation optimised warping; RMSEP, root mean square error of prediction; REP, relative error of prediction; PARAFAC, parallel factor analysis; PBS, phosphate buffered solution; DDW, doubly distilled water; AFOM, analytical figure of merit; lof, lack of fit; GE, gold electrode.

* Corresponding author.
E-mail address: ali.jalalvand1984@gmail.com (A.R. Jalalvand).

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the patients with the PD [4], however, treatment with LDP/CDP causes several untoward effects [5]. Methyldopa (MDP) is a major metabolite of LDP and its elevated blood levels are associated with the occurrence of LDP-induced dyskinesias in patients with the PD. Some research groups have claimed that the MDP levels or MDP/LDP ratios in human plasma can be used as predictive indicators of the long-term response to LDP therapy [6,7]. Benserazide (BA) is a dopa decarboxylase inhibitor which in combination with LDP is used to manage the PD [8]. Tolcapone (TOL) with commercial name "Tasmar" is a selective nitrocatechol-type inhibitor of the enzyme catechol-O-methyltransferase (COMT) which is used to treat the PD [9]. Entacapone (ENT) with the commercial name "Comtan" is a drug which commonly in combination with other medications is used to treat the PD [10]. Application of the medications to cure the PD affects the DPA levels therefore, DPA must be also determined when the anti-Parkinson drugs are used. Therefore, DPA can be regarded as an uncalibrated interference in determination of the drugs mentioned above. Generally, these medications are determined separately or simultaneously by chromatographic methods which are too expensive and time-consuming. Therefore, developing novel analytical methods for determination of these drugs which are fast and low-cost is highly required.

Multi-way calibration which acts based on several instrumental signals per sample is organized into a mathematical object with more modes than a vector, *e.g.*, as a data matrix [11,12]. The most important practical aspect of multi-way calibration is determination of the analyte(s) of interest in the presence of uncalibrated interference, this property is known as second-order advantage. Multi-way calibration increases the sensitivity due to the measurement of redundant data which decreases the relative impact of the noise in the data and selectivity is also increased because each new instrumental mode contributes positively to the overall selectivity [13,14]. Furthermore, multi-way calibration enables the analytical chemist to obtain more qualitative information about the chemical phenomena than with univariate or first-order data. Several techniques such as fluorescence excitation-emission [15], high performance liquid chromatography with diode array detection (HPLC-DAD) [16], liquid chromatography-attenuated total reflectance-Fourier transform infrared spectroscopy (LC-ATR-FTIR) [17], liquid chromatography-DAD-mass spectrometry (LC-DAD-MS) [18], flow injection analysis-DAD (FIA-DAD) [19], DAD-kinetics [20] and pH–DAD [21] have been used to obtain second-order data. Although these techniques are accurate and reliable but suffer from several disadvantages such as high-cost and complexity of their instruments. Therefore, new techniques are highly required for the inexpensive quantification of analytes in complex matrices. Among the available analytical methods, electrochemical methods with low-cost instruments and applicability to miniaturization are a good choice for accurate, fast and reliable determination of the analyte(s) of interest in interfering media [22–28]. The use of chemometrics in analytical electrochemistry was scarce for many years in comparison to the other techniques especially spectroscopic techniques and this may be related to the lack of linearity between the current and concentration. But, development of non-linear methods and pre-processing methods have increased applications of chemometrics to analytical electrochemistry during the last years [29–35].

In this study, we are going to record second-order differential pulse voltammetric (DPV) data at different pulse heights which help us to obtain three-way voltammetric data arrays for calibration model building by multivariate curve resolution-alternating least squares (MCR-ALS) and parallel factor analysis 2 (PARAFAC2). The developed calibration models will be used to predict concentrations of six anti-Parkinson agents in validation samples and after evaluating their performance, they will be applied to predict concentrations of anti-Parkinson agents in the presence of dopamine (DPA) as uncalibrated interference to choose the best algorithm for the analysis of human serum samples. Finally, the results of the best algorithm applied to the analysis of serum samples will compared with those of obtained by high performance liquid chromatography with UV detection (HPLC-UV) as reference method. The schematic representation of the methodology developed in his work is shown in Scheme 1.

2. Theoretical and experimental considerations

2.1. Theoretical considerations

2.1.1. Recording second-order DPV data

In our work, the pulse height as an instrumental parameter in DPV method was changed for obtaining second-order DPV data. Here, a brief description of the mathematical aspects of the proposed procedure will be given. The signal intensity in DPV can be described by the use of following equations [36]:

$$\delta_i = \frac{nFAD_O^{1/2}C_O^*}{\pi^{1/2}(\tau-\tau')^{1/2}}\left[\frac{P_A(1-\sigma^2)}{(\sigma+P_A)(1+P_A\sigma)}\right] \quad (1)$$

$$P_A = \xi\exp\left[\frac{nF}{RT}\left(E+\frac{\Delta E}{2}-E^{0'}\right)\right] \quad (2)$$

$$\sigma = \exp\left(\frac{nF}{RT}\frac{\Delta E}{2}\right) \quad (3)$$

$$\xi = \left(\frac{D_O}{D_R}\right)^{1/2} \quad (4)$$

where, ΔE is referred to the pulse height, τ is referred to pulse duration and other symbols are well-known and have their conventional meanings. For an electrochemical reaction, a vector can be produced by scanning the potential at constant ΔE and τ. Different data vectors can be produced by applying different ΔEs and scanning the potential at the constant τ. Therefore, by sweeping the potential and applying different ΔEs at a constant τ non-bilinear second-order DPV data will be obtained.

2.1.2. Second-order algorithms

MCR-ALS: The theory of MCR-ALS is based on that the overall voltammetric landscape for a sample could be decomposed into the concentration profile and voltammograms of the species [37]. This means that MCR-ALS is able to separate the corresponding voltammetric landscape of two analytes with overlapping signals into the concentration profile and voltammograms for the two chemical species. Mathematically, if **X** is an unfolded three-dimensional data array, it can be decomposed into two matrices containing the concentration profile and voltammograms of the species, **C** and **V**, respectively, according to:

$$\mathbf{X} = \mathbf{C}\mathbf{V}^{\mathbf{T}} + \mathbf{E} \quad (5)$$

where **E** is a residual matrix and its iterative least squares minimization is used as a criterion for decomposition of matrix **X**. Here, a column-wise augmented matrix is created by unfolding a three-dimensional data array along the pulse height mode. This could be performed by placing sample matrix and the unknown matrix on top of each other [37]. Decomposition is started by supplying the estimated voltammograms of the various species which is applied to estimate $\hat{\mathbf{C}}$:

$$\hat{\mathbf{C}} = \mathbf{X}\mathbf{V}^{T+} \quad (6)$$

where '+' refers to the pseudo-inverse. Then, **V** will be re-estimated according to the Eq. (7):

$$\mathbf{S} = \left(\hat{\mathbf{C}}+\mathbf{X}\right)^{\mathrm{T}} \quad (7)$$

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