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Multiway calibration strategy with chromatographic data exploiting the second-order advantage for quantitation of three antidiabetic and three antihypertensive drugs in serum samples

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ABSTRACT

This paper proposes a multiway calibration strategy implementing the modeling with MCR-ALS and U-PLS/RBL of second-order chromatographic data for quantitation of six analytes: gliclazide, glibenclamide, glimepiride, atenolol, enalapril and amlodipine in serum samples, in an analysis time of 3 min.
The performance of both algorithms was compared in terms of predictive ability, showing relative error of prediction values below 10% in all cases. LOD values calculated are below 30 ng mL^{-1} for all the studied drugs, which allow detection in human serum in patients under treatment. U-PLS/RBL has higher sensitivity and better detection and quantification limits for all the studied analytes; however results obtained by MCR-ALS enable its usage as well. Both methods provide comparable results for glibenclamide, glimepiride and gliclazide. With this multiway calibration strategy, the presence of enalapril, amlodipine and atenolol could be quantitated with high accuracy. Run time was reduced by 50% considering previous reports, as well as reduction of solvents, in accordance with green chemistry principles.

1. Introduction

Diabetes is a disease affecting 9% of the Argentinian population [1]. Type II diabetes is the most common form of diabetes in which cellular resistance to insulin and insufficient pancreatic secretion derive in hyperglycemia. In order to diagnose and treat type II diabetes properly, it is mandatory to develop analytical methods for management and pharmacological treatment monitoring.

Sulfonylureas are oral antidiabetic drugs that increase insulin release form pancreatic beta cells. Gliclazide, glibenclamide and glimepiride are second generation sulfonylurea drugs used as initial treatment of type II diabetes in patients who cannot control hyperglycemia with diet and exercise [2].

Diabetic patients also have a high prevalence of hypertension. Pharmacological therapy frequently combines antihypertensive and antidiabetic drugs [3]. Atenolol belongs to the beta blocker drug group; enalapril is an angiotensin-converting enzyme inhibitor; and amlodipine is a calcium channel blocker, all of these with antihypertensive action. Usual seric concentration of the three antihypertensive and the three antidiabetic analyzed drugs are: atenolol 0.30–0.70 μg mL^{-1}; amlodipine 0.004–0.017 μg mL^{-1}; enalapril 0.l5–0.30 μg mL^{-1}; gliclazide 2.00–8.00 μg mL^{-1}; glibenclamide 0.14–0.35 μg mL^{-1}; and glimepiride 0.20–0.31 μg mL^{-1} [4].

In a previous work, we developed a novel dispersive liquid–liquid micro extraction (DLLME) procedure and a HPLC–UV method, optimized and fully validated for the determination of gliclazide, glibenclamide and glimepiride in serum, in the presence of atenolol, enalapril and amlodipine. The advantages of the latter method are simplicity of operation, rapidity, low cost, high–recovery, high enrichment factor, and environmental benignity fitting the requirements of green analytical chemistry [5].

Multivariate calibration strategies are quickly gaining attention in analytical chemistry, given the possibility of quantifying analytes in complex matrixes in the presence of interferents. If one calibrates with pure analyte standards, matrix data is recorded and sufficient selectivity is present in the various data modes; it is possible to predict analyte concentration in any future sample, no matter how many signal-overlapping constituents. This is referred to as the "second order advantage", the signal from unexpected constituents can be modeled and mathematically removed, in such a way that their effect is negligible [6].

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An important number of algorithms have been used in order to exploit the second-order advantage: generalized rank annihilation (GRAM) [7], direct trilinear decomposition (DTLD) [8], self-weighted alternating trilinear decomposition (SWATLD) [9], alternating penalty trilinear decomposition (APTLD) [10], parallel factor analysis (PARAFAC) [11], multivariate curve resolution alternating least squares (MCR–ALS) [12], bilinear least squares (BLLS) [13], unfolded partial least squares/residual bilinearization (U–PLS/RBL) [14] and artificial neural networks followed by residual bilinearization (ANN/RBL) [15].

In this paper, a multiway calibration strategy implementing two well-known algorithms (MCR-ALS and U-PLS/RBL) are proposed for quantitation of gliclazide, glibenclamide, glimepiride, atenolol, enalapril and amlodipine in serum samples, in a shorter analysis time than that previously reported [5].

2. Theory

2.1. MCR-ALS

This algorithm works on a data set by optimizing initial estimates in an ALS way within each iterative cycle under the action of suitable constraints until a convergence criterion is fulfilled [16].

Each HPLC-DAD chromatographic run of a single sample provides a data matrix, indicated as $\mathbf{D}$ ($J \times K$), where the J rows representing the UV spectra recorded at the different elution times and the K columns representing the chromatographic elution profiles recorded at the different wavelengths. This corresponds to a bilinear model based on the multi wavelength extension of Beer's absorption law:

$$\mathbf{D} = \mathbf{C}\mathbf{S}^{\mathrm{T}} + \mathbf{E} \tag{1}$$

where $\mathbf{C}$ ($J \times N$) is the matrix of elution profiles of the analyzed compounds and $\mathbf{S}^{\mathrm{T}}$ ($N \times K$) is the matrix of their pure spectra. N is the number of components.

Multiset structures are obtained combining several chromatographic runs. These structures are organized appending the $\mathbf{D}_i$ data matrices (the index i indicates a chromatographic run for a specific sample) one on top of each other. The resulting $\mathbf{D}_{\mathrm{aug}}$ (column-wise augmented) multiset can be decomposed into the $\mathbf{C}_{\mathrm{aug}}$ matrix, which contains the $\mathbf{C}_i$ submatrices of the resolved elution profiles for the single chromatographic runs, $\mathbf{S}^{\mathrm{T}}$ the matrix of pure spectra common to all chromatograms analyzed and $\mathbf{E}_{\mathrm{aug}}$, the difference between the raw data and the reconstructed data by the $\mathbf{C}_{\mathrm{aug}}\mathbf{S}^{\mathrm{T}}$ model, i.e., the experimental error not explained by the bilinear model. This bilinear model assumes that the components in the $\mathbf{D}_i$ data matrices included in the column-wise augmented data matrix share the same pure spectra, whereas they can have different concentration profiles.

The MCR-ALS algorithm calculates $\mathbf{C}_{\mathrm{aug}}$ and $\mathbf{S}^{\mathrm{T}}$ from the sole information in the experimental data, $\mathbf{D}_{\mathrm{aug}}$. The first step is to determine the number of eluted compounds present in a particular cluster of peaks, i.e., the "chemical rank" associated with the data matrix. This determination is performed with a principal component analysis on the $\mathbf{D}_{\mathrm{aug}}$ matrix. Then, an initial estimate of the $\mathbf{S}^{\mathrm{T}}$ matrix is obtained with techniques based on the detection of purest variables [17]. These initial spectral estimates are iteratively optimized with a constrained alternating least squares regression procedure.

The iterative optimization is performed until the results agree with the convergence criterion, which often means that the difference in lack of fit between two consecutive iterations is below a predefined threshold (0.01% change in standard deviation). The lack of fit (%LOF) and the explained variance (EV) express the fitting quality of the resolution results; they are used to choose the best MCR-ALS model for each chromatographic segment.

Several constraints can be applied to confer chemical meaning to the profiles obtained by MCR-ALS in the analysis of a single HPLC-DAD run, such as non-negativity, unimodality, spectral normalization and component correspondence in order to reduce the effects of rotational ambiguity.

Finally, the areas under the matrix $\mathbf{D}_{\mathrm{aug}}$ are used to build a pseudounivariate plot relating them with the nominal concentrations of the standards. This plot is then used to predict the analyte concentration in the unknown sample.

2.2. U-PLS/RBL

Unfolded partial least-squares (U–PLS) is a powerful algorithm for processing vectorial signals per sample, it provides multiway data processing with enough flexibility to face calibration protocols based on complex data [16]. It is complemented by residual bilinearization (RBL) which models the residues of U-PLS for the test sample as a sum of bilinear contributions from the unexpected components.

The first step in U-PLS calibration is to convert the calibration data arrays into vectors. This will produce a $JK \times 1$ vector from a $J \times K$ data matrix. A new calibration matrix $\mathbf{X}_{\mathrm{cal}}$, suitable for the application of PLS regression, is built by placing all column vectors adjacent to each other. The latter $\mathbf{X}_{\mathrm{cal}}$ matrix can therefore be of size $JK \times I$ (I = number of calibration samples) for second-order data, and is subjected to the classical PLS regression analysis.

As it is well-known for PLS, a set of loadings $\mathbf{P}$ and weight loadings $\mathbf{W}$ ($JK \times A$, where A is the number of latent variables) as well as regression coefficients $\mathbf{v}$ (size $A \times 1$) are obtained after the calibration step. Usually, the leave-one-out cross-validation procedure is implemented for selecting the parameter A [18]. Subsequently, $\mathbf{v}$ is employed to estimate the analyte concentration through the following equation:

$$y_{\mathrm{u}} = \mathbf{t}_{\mathrm{u}}{}^{\mathrm{T}}\mathbf{v} \tag{2}$$

where $\mathbf{t}_{\mathrm{u}}$ (size $A \times 1$) is the test sample score, obtained by projection of the (unfolded) data for the test sample $\mathbf{X}_{\mathrm{u}}$ [vec($\mathbf{X}_{\mathrm{u}}$)] of size ($JK \times 1$) onto the space of the A latent factors:

$$\mathbf{t}_{\mathrm{u}} = \left(\mathbf{W}^{\mathrm{T}}\mathbf{P}\right)^{-1}\mathbf{W}^{\mathrm{T}}\mathrm{vec}(\mathbf{X}_{\mathrm{u}}) \tag{3}$$

If the sample contains unexpected components, the scores given by Eq. (3) are not suitable for analyte prediction using Eq. (2), generating abnormally large residuals in comparison with the typical instrumental noise assessed by replicate measurements.

RBL intends to model the residuals assuming that they can be arranged into a bilinear matrix. This procedure fits the sample data to the sum of two contributions: 1) the portion of the test data, which can be explained by the calibration PLS loadings, and 2) the contribution from the potential interferents modeled by a certain number of principal components (N_{RBL}). The complete U-PLS/RBL modeling equation involves a residual error term to be minimized by least squares:

$$\mathbf{X}\mathrm{u} = \mathrm{reshape}(\mathbf{P}\mathbf{t}_{\mathrm{RBL}}) + \mathbf{B}_{\mathrm{RBL}}\mathbf{T}_{\mathrm{RBL}}{}^{\mathrm{T}} + \mathbf{E}_{\mathrm{RBL}} \tag{4}$$

The product ($\mathbf{B}_{\mathrm{RBL}}\mathbf{T}_{\mathrm{RBL}}^{\mathrm{T}}$) is the principal component analysis (PCA) model for the residual matrix [($\mathbf{X}$u–reshape($\mathbf{P}\mathbf{t}_{\mathrm{RBL}}$)] with N_{RBL} principal components, with "reshape" meaning the transformation $JK \times 1$ vector into a $J \times K$ data matrix. Minimization of $\mathbf{E}_{\mathrm{RBL}}$ allows one to retrieve the final score vector $\mathbf{t}_{\mathrm{RBL}}$. Initially, the residual matrix contains contributions from both the calibrated analytes and the potential interferents. Modeling this latter matrix with PCA extracts N_{RBL} bilinear components; the more these bilinear components resemble the unexpected contributions, the better the product is able to model the behavior of the analytes in the test sample, leading to a continuous decrease in the residuals.

Generally RBL can be carried out by a Gauss-Newton minimization. Once the residuals $\mathbf{E}_{\mathrm{RBL}}$ are minimized in Eq. (4), the output is a final $\mathbf{t}_{\mathrm{RBL}}$ vector which represents the true contribution of the calibrated

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