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Chemometrics resolution and quantification power evaluation: Application on pharmaceutical quaternary mixture of Paracetamol, Guaifenesin, Phenylephrine and p-aminophenol

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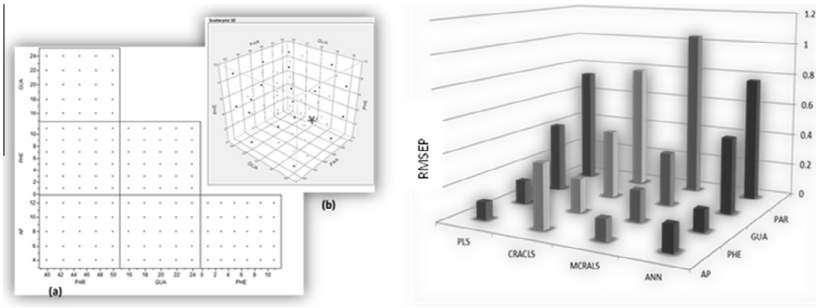
HIGHLIGHTS

- Advanced chemometric models used for the analysis of challenging quaternary mixture.
- The analytical performance of CRACLS, MCR-ALS and PCA-ANN was compared and benchmarked to that of classical PLS-Calibration.
- Individual calibration provides better result with lower RMSEC than the general calibration model.
- Using PCA-ANN instead of ANN allows higher prediction concentrations with lower RMSEC and RMSEP.
- The proposed methods effectively detected the cited drugs in their pharmaceutical dosage form.

GRAPHICAL ABSTRACT



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ABSTRACT

Three advanced chemmometric-assisted spectrophotometric methods namely; Concentration Residuals Augmented Classical Least Squares (CRACLS), Multivariate Curve Resolution-Alternating Least Squares (MCR-ALS) and Principal Component Analysis-Artificial Neural Networks (PCA-ANN) were developed, validated and benchmarked to PLS calibration; to resolve the severely overlapped spectra and simultaneously determine; Paracetamol (PAR), Guaifenesin (GUA) and Phenylephrine (PHE) in their ternary mixture and in presence of p-aminophenol (AP) the main degradation product and synthesis impurity of Paracetamol. The analytical performance of the proposed methods was described by percentage recoveries, root mean square error of calibration and standard error of prediction. The four multivariate calibration methods could be directly used without any preliminary separation step and successfully applied for pharmaceutical formulation analysis, showing no excipients' interference.

1. Introduction

It has been always an analytical interest to simultaneously determine the wide range of active ingredients present in different cough, cold and flu formulations [1–3]. Paracetamol (PAR); [N-acetyl-p-aminophenol] is usually a common agent in these formulations and used as analgesic and antipyretic agent [4]. Guaifenesin (GUA); [(R,S)-3-(2-methoxyphenoxy)-propane-1,2-diol] is an expectorant drug, it assist the bringing up of phlegm from the airway in acute respiratory tract infections, also used for sinusitis, pharyngitis, and bronchitis [5] Phenylephrine (PHE);

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[(R)-3-[-1-hydroxy-2-(methylamino)ethyl]phenol] is a decongestant; it reduces the congestion and the production of mucus, helping the relief of a blocked nose [6].

Several techniques have been proposed in the literature for the determination of PAR [1,7–13], GUA [2,14–17] and PHE [3,11,18–20] even in single or in combination with other drugs. On the other hand, the literature survey revealed that there is no reported methods for simultaneous determination of the ternary mixture of PAR, GUA and PHE in their pharmaceutical formulation, along with p-aminophenol (AP) which is the reported main degradation product and synthesis impurity of Paracetamol [21]. The chemical structures of the studied components are presented in Fig. 1a.

Although Partial Least Squares (PLS) has been regularly employed for many years, new and more advanced approaches for multivariate calibration have been developed and implemented over the past decade like; Concentration Residuals Augmented Classical Least-Squares (CRACLS), that could be expressively used for a broader range of applications in resolving complex mixtures [22]. Also, Multivariate Curve Resolution-Alternating Least Squares (MCR-ALS); which considered the proper choice for solving overlapping bands and high interference. MCR-ALS works by applying constraints during the ALS optimization. A "correlation constraint" proposed by Antunes et al. [23] could be functionally used in the concentration profiles, when compounds' quantification is the main objective of the analysis.

Nowadays, Artificial Neural Networks (ANNs) is more applied, owing to the greater power and progressive capabilities of computers. ANN is more challenging to use, as for most of the multivariate calibration techniques. Moreover, reducing the number of inputs to a network by the mean of Principal Component Analysis (PCA) could reduce both the training time and repetition in the input data, where all the relevant information is usually contained in the first principal component even if there is some non-linearity in the data set [24]. In PCA-ANN data were compressed into scores and used as inputs to the network, therefore noise filtered data which contained only the significant independent variables were responsible for the quantitative determination of the drugs.

The aim of the present study is to show the ability of chemometrics in finding solutions for the quantitative analysis of commercial tablet formulations containing; PAR, GUA and PHE, along with AP, using cheap and simple instrument like the UV spectrophotometer with minimum requirements of solvents. Besides, the work goals to investigate and compare the performance of the presented multivariate calibration methods with different algorithm, namely; PLS, CRACLS, MCR-ALS and PCA-ANN, for their quantitative analysis. Additionally, evaluation of the resolution power of the advanced multivariate techniques for qualitative analysis was tested as well.

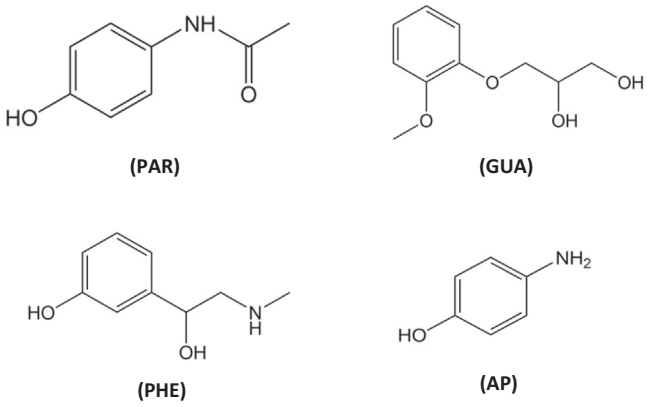

Fig. 1a. Chemical structures of the studied components.

2. Brief theoretical background and model optimization

2.1. PLS

Partial Least Squares (PLS) is considered one of the most prevalent, well established methods for building multivariate calibration models [2,25]. It involves a data compression step and followed by a regression step. Within the data compression step (Eq. (1)), the matrix of spectral measurements **X** is decomposed into a matrix of latent variables scores **T** and a matrix of loadings **P**

$$\mathbf{X} = \mathbf{TP} + \mathbf{Ex} \tag{1}$$

where **Ex** is matrix of spectral residuals.

The next step is a regression step (Eq. (2)), in which the scores of the latent variables are used in the regression equation as a substitute of the original variables.

$$\mathbf{c} = \mathbf{Tq} + \mathbf{ec} \tag{2}$$

where **c** is a vector of concentrations, **ec** is a vector of concentration residuals and **q** is a vector of regression coefficients.

The original variables are compressed into a smaller number of factors (latent variables) or principal components (PCs) and therefore, a model for the prediction of the component concentrations of new samples, is built by using new matrices constituted by scores and loadings. The number of PCs must be optimized as the prediction error lessens with the number of PCs used, until reaching an optimum value.

2.2. CRACLS

The core idea of CRACLS calibration is to outspread the classical CLS method to manipulate the cases, where not all the pure components are of known concentration. CRACLS calibration; iteratively augments the calibration matrix of reference concentrations with concentration residuals estimated during CLS prediction [25–27].

The CRACLS model is presented in Eq. (3):

$$\mathbf{X} = \mathbf{CK} + \mathbf{E} \tag{3}$$

X is a matrix of measured absorbance, **C** is a concentration matrix, **K** is a matrix of the estimated absorptivity and **E** is the regression error.

CRACLS is an alternative method that estimates absorptivity matrix (**K**) by a process of repetitive approximation. In another words, the residual or error term **E** is calculated by difference between predicted and original concentrations, then this **E** matrix can be factor-analyzed by PCA, yielding a matrix of loadings $\mathbf{P}_E$. Thus, by merging the columns of **K** and $\mathbf{P}_E$, a new matrix of absorptivity is generated which is more representative, this iterative approximation proceeds until no further improvement in prediction is recorded.

2.3. MCR-ALS

Factor analysis derived methods like MCR, was successively applied to resolve chemical problems associated with analysis of mixtures [23]. MCR solutions have physical meaning which is not present in PCA. MCR assumes a bilinear model which is the multi wavelength extension of Beer's–Lambert law as described in the following expression;

$$\mathbf{D} = \mathbf{CS}^{\mathrm{T}} + \mathbf{E} \tag{4}$$