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A speedy method for simultaneous determination in tablet active content by NIR and UV-Vis spectrophotometry: Comparison of PLS-1 and ICA-ANN models

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Highlights

- Our goal is to bring a new perspective to drug analyses.
- Calibration methods were not calculated by a subroutine.
- Each procedure was calculated with all available sub-procedures.

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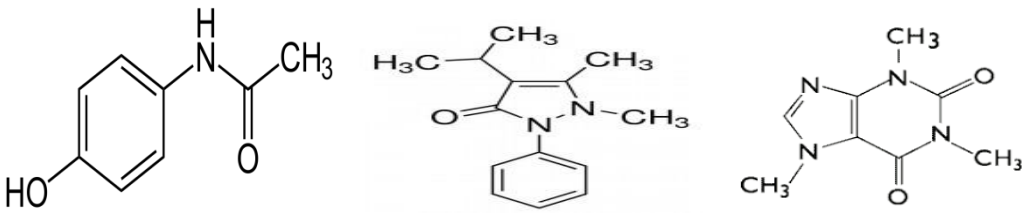
Abstract

In this study, the Near-infrared (NIR) and Ultra-violet visible (UV-Vis) spectroscopy methods, which are frequently used in pharmaceutical industry, were applied to the environments where Paracetamol, Propyphenazone and Caffeine active substances are present, and the spectroscopic data obtained were evaluated comparatively with Independent Component Analysis – Artificial Neural Network (ICA-ANN) and Partial Least Squares-1 (PLS-1), which are powerful chemometric methods. When using solid agents in NIR method, liquid solutions equivalent to them were used in UV-Vis method. Following the application of both methods, spectral data were evaluated as chemometrics and in both spectroscopic methods ICA-ANN method yielded more accurate results than PLS-1. High recovery rates and relatively low standard deviations were found in the applied methods and recommended for use in the pharmaceutical industry.

1. INTRODUCTION

Paracetamol (PAR), Propyphenazone (PRO) and Caffeine (CAF) tablets appear to be the most preferred combination for pain relief. This mixture increases the analgesic effect of CAF, PAR and PRO, causing the prostaglandin effect to decrease, and also resolves headaches, novelties, neuralgia, back pain and other similar pains [1]. The chemical structures of the analytes studied are seen in Figure 1.



(a) (b) (c)

Figure 1. *Studied structures of substances a) Paracetamol b) Propyphenazone c) Caffeine*

Therefore, the interest in developing concurrent non-developed analysis methods a suitable pre-separation phase for common pharmaceutical analysis is justified. Various methods, UV spectrophotometry [2], derivatives ratio spectra for the determination of the compounds above individually or together binary

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mixtures or other drugs-zero crossing spectrophotometry [3] and various High-Pressure Liquid Chromatography (HPLC) methods [4-6] are available. In the literature survey, NIR method of this combination was not found.

Near-infrared spectroscopy and ultra-violet visible spectrophotometric methods have proven being a very powerful analytical tool used to identify samples in agriculture, food, medicine and many other areas [7-10]. Particularly for the quantitative analysis of drug tests, the use of spectroscopy has seen a significant increase over the last decade. In today's studies, the use of pharmaceutical analytical methods, which often require dissolution, is widely applied to separate and identify such components. On the other hand, NIR and UV techniques are very important quantitative analytical techniques that enable rapid identification of samples without the need for any reagents. Compared to conventional analytical methods, the NIR and UV-VIS methods not only attract the pharmaceutical industry, but also attract more attention in research and development. Qualitative and quantitative analysis, ANN's have been increasingly applied over the last few years [11-16]. In this study, we have created a stronger method by adding the ICA method to the neural network's method.

The aim of this research is to develop a new and fast method for PAR, PRO and CAF determinations found in drug samples as infrared and UV spectrophotometric methods and to evaluate them with multivariate calibration techniques. The importance of the study is that there is no need to analyze each component in the synthetic sample in triplicate. Because of the absence of direct quantitative analysis due to the spectral interferences of the compounds in the same region in which there are more than one active substance in the same region, it is possible to analyze only after a separation. The fact that a validated IR and UV-Vis method for the simultaneous analysis of substances in the aforementioned triple combination was not found in the references led us to this study.

2. MATERIAL AND METHODS

2.1. Apparatus and Software

An absorbance measurement was performed using a UV – 1700 model SHIMADZU UV visible spectrometer (Shimadzu, Kyoto, Japan) accoutered with 1 cm compatible quartz cells and used for spectrometric measurements. The NIR spectra were restrained by SHIMADZU IR Prestige-21 FT-IR spectrophotometer (Shimadzu, Kyoto, Japan) within the range 4000-400 cm^{-1}, using KBr disc pellets. Chemometric calculations were executed using software MATLAB R2017a.

2.2. Merchant Product

A merchant pharmaceutical product (Minoset Plus ® Oral tablet, Bayer Pharmaceutical Industry., Istanbul, Turkey; Parol tablet and Panalgine tablet Atabay Pharmaceutical Industry., Istanbul, Turkey) were buy and tested from regional sources.

2.3. UV Measurements

In the concentration ranges shown in Figure 4, a symmetrical calibration set was prepared in the same solvent and studies were continued. In order to minimize calibration errors during the study, symmetric calibration set was preferred. We used an independent set to control the validation methods of CAF, PAR and PRO synthetic mixing solutions recommended in the mentioned concentration ranges. The regulations were fixed in a cool (<25^{o}C) and left in a frozen place for the coldest two weeks.

2.4. Recording of NIR Spectra

All scans were performed in reflection mode using 10 scans at 2 nm intervals between 400 - 4000 nm wavelength range. The input slit used NIR spectrophotometer was 10 nm. All the calculations were performed within the wavelength range of 1700 - 2800 nm. Some areas were thrown out because of some noise.

2.5. Procedure for Dosage Forms

We have used as a reference method to determine the amount of caffeine, paracetamol and propyphenazone, was the state drug standard. The entire contents of the commercial drug were weighed and analyzed by turning it into a fine powder. An exact equivalent of the average tablet weight was diluted in 0.1 m HCl and transformed into a 100 ml calibrated bottle volume. The suspension, which was taken into the bottle, was mechanically shaken and a membrane of 0.45 mm filtered into a 100 ml volumetric bottle. These arrangements moved aliquots to the progression of 10 mL volumetric jars. Each system was linked to the final arrangement, and all investigations were completed by spectrometric method. The NIR and UV absorption spectra of these sample solutions were stored and continued for the implementation of PSL-1 and ICA-ANN calibrations.

2.6. PLS-1

The PLS-1 is a process that combines multiple regression features in addition to Principial Component Analysis (PCA) [17]. Present method is particularly beneficial for estimating dependent variable sets when the point of arguments is too large. PLS-1 is a type of linear regression; however, it reflects dependent and independent variables in a new field. The PLS-1 uses hidden variables with few orthogonal factors. Furthermore, PLS-1 selects these hidden variables to achieve the maximal correlation probable with the sequence of dependent variables.
A multivariate PLS-1 model is expressed as:

$$X = T P^T + E$$
$$Y = U Q^T + F$$

where $X_{N \times M}$ is the monitored data matrix, $Y_{N \times A}$ is the repercussions vector matrix, $T_{N \times L}$ and $U_{N \times L}$ are transformation matrices, $P_{M \times L}$ and $Q_{M \times L}$ are orthogonal vector matrices, and $E_{N \times M}$ is the residual matrix. N is the number of monitoring and M is the number of spectral factors.
To illustrate the predicted force of PLS-1 analysis, Q^2 is more commonly used than other pointers. The Q^2 value, which is very close to 1, shows an excellent version. As a result of this process, the parameter factor model is found to be better than random selection. Defined as a cross validation parameter:

$$Q^2 = \frac{s_y^2 - PRESS}{s_y^2}.$$

Here, s_y is the root mean square aberration of the mean for y's training set.

2.7. ICA

It is the basis of ICA to separate the multivariate signals from the factors or the ones that make them with minimal loss of information. Components contain hidden variables that cannot be found directly makes this powerful method different from other methods. Because of this, ICA is referred to as blind source separation [18]. The following is an expression of the error-free ICA model.

$$X = WS,$$

where X symbolize the acquired data matrix, S symbolize the independent components, and W is the coefficient matrix.
Many ICA algorithms are unusual to process analytical chemistry data. For example, rapid ICA, Infomax ICA, common approximate diagonalization of core matrices (Jade), approximate diagonalization of core ICA (KICA), and mean ICA (MF-ICA). In this study, fast-ICA algorithm was chosen because the calculation was robust and fast.

2.8. ANN

ANNs have the ability to approximate any nonlinear mathematical function, which is especially useful when the relationship between variables is unknown or complex. Due to its ability to detect and resolve complex nonlinear relationships between inputs (targeted) and outputs (investigated) variables, ANNs have been successfully implemented in different fields, from mathematics to medicine.

The real advantage of artificial neural networks is that both linear and nonlinear relationships and their power to represent learning abilities using directly modeled data. The optimal topological neural network is performed for the calibration set to provide high recovery results with small relative error.

3. RESULTS AND DISCUSSION

The original NIR and UV-visible spectra for different concentration samples were shown in Figures 2 and 3. As shown in Figures 2 and 3, both spectra consist of large, low absorption bands, which are non-characteristic, overlapping, which prevent their widespread use for multivariate calibration methods. It was developed with the withdrawal of analytical information.

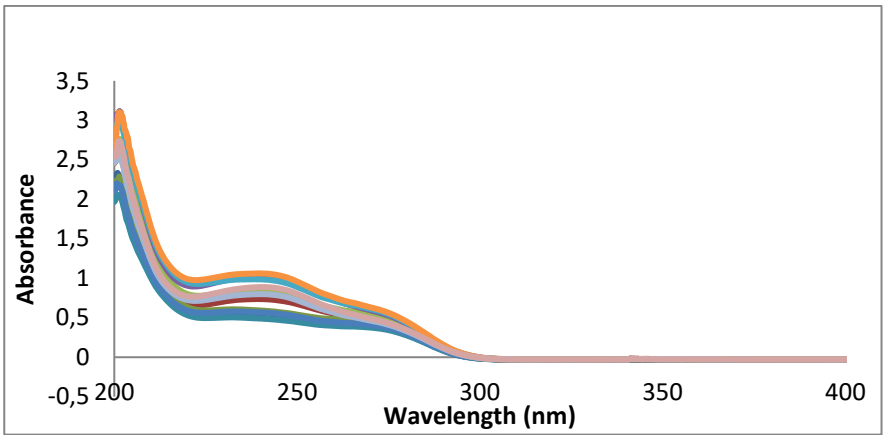

Figure 2. *Absorption spectra of compound PAR, PRO and CAF mixtures in solvent*

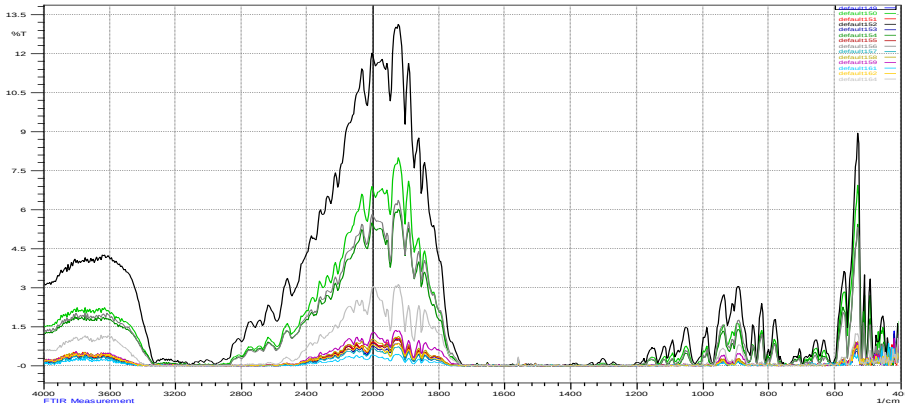

Figure 3. *NIR reflectance spectra of compound PAR, PRO and CAF mixtures*

3.1. PLS-1 Method, Calibration and Validation

To produce two chemometric alignments, a different set of mixtures was arranged, as seen in Figure 4.

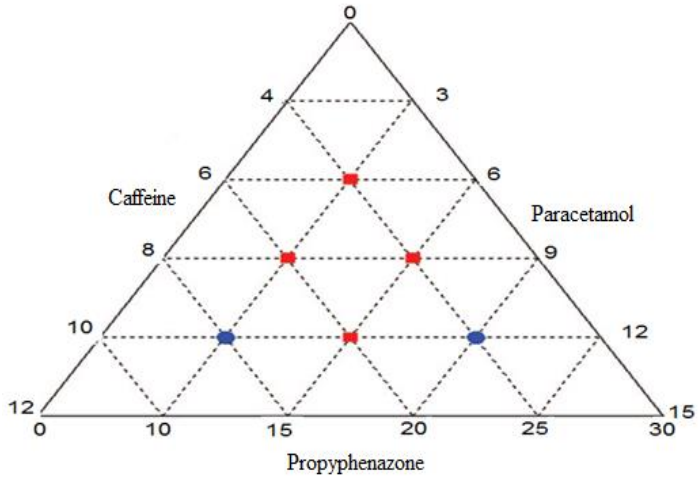

Figure 4. *Concentration set design used for calibration studies*

In the first step of the development of the PLS-1 model, a data set and a calibration set of 16 samples have been created to consider the different concentration ratios of the analytes and to cover the range commonly found in commercial drug samples.

The full cross-validation method recommended by Haaland and Thomas [19] was used to correctly select the optimum number of factors. This consists of taking one sample at a time from the calibration stage and performing the calibration by the remaining samples. The concentration of an extracted sample is expected to be with the model obtained. This step was repeated for each sample evaluated.

The spectra of the prepared compounds were measured in the spectral zone of 220-280 nm and at intervals of $\Delta\lambda$=0.1 nm. The concentration set and absorption data are designed as y-block (25x3) x-block (25x600) for calibrating the applied chemometric methods. The current alignment of the three strategies using absorption information indices has been used to foresee convergence in blending PAR, PRO and CAF uncertain predictions.

The suitability of a given model can be clarify in several ways. Thus, the results can be quantified. According to the literature opinion, one of the most important of these ways is that squares are no longer the sum of errors predicted (PRESS). We need to use Equation (1) to calculate the PRESS value. In this equation n is the number of samples in the calibration set and $C_{i,added}$ and $C_{i,found}$ are the actual and predicted concentration of analyte in the i_{th} sample, respectively [20]

$$\text{PRESS} = \sum_{i=1}^{n} (C_i^{added} - C_i^{found})^2 \ . \tag{1}$$

Clearly, because not all data sets contain an equal number of samples, PRESS values are not the only way to normalize results. If PRESS values for clusters containing different samples are compared, these values should be converted to the standard estimated error (SEP) value given in Equation (2).

$$\text{SEP} = \sqrt{\frac{\sum_{i=1}^{n} (C_i^{added} - C_i^{found})^2}{n}} \ . \tag{2}$$

Where n is a parameter denoting the total number of synthetic mixtures. As a result, the performance of the SEP calibration model is a good parameter for how good it is. However, it should also be noted that the performance varies depending on the analyte concentration of the model.

The developed PLS-1 model was then applied to an independent test set, including 16 artificial samples that were not used during calibration. The experimental and estimated concentration of each analyte can be seen in Table 2.

3.2. ICA-ANN Method

In the second part of this study, spectral data of each analyte was used to develop a neural network model. Thus, fast ICA was used for data preprocessing in the above data sets and initially, input data was measured using the fixed-point toolbox in STATISTICA. Two new matrices, M^{ICA} (n x I) and M^{ICA} unknown (n x I), with matrices (calibration) and unknown (verification), and then N, calibrate or predict the sample set (representing fixed numbers).

Network parameters are determined for this purpose. These parameters contain the number of input layers, the number of latent layers, the number of neurons, n in each layer, the output layer. In this study, numerous hidden layers with different neurons were tested with logistic functions.

Neural network education is believed to be more efficient if some pre-processing steps are implemented for raw input and target data. Random and normalizing data are the most common applications of preprocessing data. The normalization procedure usually makes the model more efficient because it prevents the learning algorithm from mixing different variables with the unequal size and consequently neglecting them with smaller sizes. Training and test data sets should be normalized in the 0.1-0.9 range. The input and output data sets are normalized as shown in Equation (3) given below

$$X_N = 0.1 + \frac{0.8(X - X\,\min)}{(X\,\max - X\,\min)}. \tag{3}$$

Here X_N is normalized, the network input or network output value, x is the original value of a variable, and x_{max} and x_{min} are the maximum and minimum original values of the variables. To produce sufficient data to train and test the model shown in Figure 5, 16 different standard solutions were prepared using different analytical concentrations and each standard solution was exposed to IR determination.

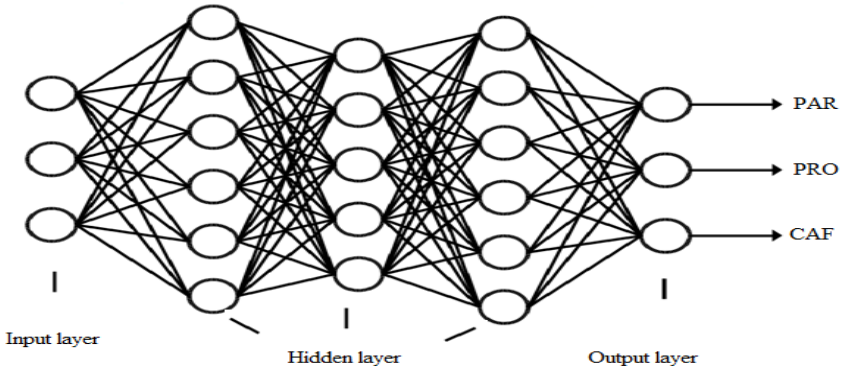

Figure 5. *Demonstration of multi-layer forward feed neural network architecture used in the study*

The neural network was used to train 156 randomly selected pairs of data from this 1869 data pair. In order to test the accuracy of the test results of neural network models, root mean square error (RMS) values were calculated from the following equation

$$RMS = \sqrt{0.5N^{-1}\sum_{i=1}^{N}(X_1^{'} - X_1)^2}\ . \quad (4)$$

where N is the number of test data and the targeted value.
The advanced model, which was trained in the previous stage, was further simulated with a test set of 16 unknown data. The results obtained with the ICA-ANN method are listed in Table 1 together with those predicted by the other method examined in this study and will be discussed later.

Table 1. *Composition of test set and predicted values for CAF, PAR and PRO by PLS-1 and ICA-ANN regression. Concentration values are expressed as ppm*

Mixtures added (µg/mL)			**Recovery (%)**					
			ICA-ANN			**PLS-1**		
PAR	PRO	CAF	PAR	PRO	CAF	PAR	PRO	CAF
2.00	0.00	4.00	99.98	99.98	100.02	99.88	99.64	99.82
4.00	1.00	5.00	100.00	99.98	99.98	100.02	100.00	100.04
6.00	3.00	6.00	100.02	100.00	100.00	101.30	100.04	100.00
8.00	5.00	7.00	99.96	100.02	99.96	98.88	98.96	99.58
10.00	7.00	8.00	100.02	100.14	99.88	100.04	101.02	99.84
12.00	9.00	0.00	99.56	100.00	99.98	99.12	100.16	99.68
0.00	11.00	9.00	99.88	99.86	99.84	99.56	99.28	98.88
14.00	13.00	10.00	100.04	99.98	99.94	98.98	99.84	100.14
16.00	15.00	11.00	100.00	99.88	100.02	98.68	99.86	100.16
18.00	17.00	12.00	99.98	100.02	100.04	100.24	100.14	100.84
20.00	19.00	13.00	99.96	100.04	100.02	99.82	99.94	99.94
22.00	21.00	14.00	100.02	100.02	99.98	100.00	98.88	99.86
24.00	23.00	15.00	99.88	99.98	100.00	98.98	99.66	99.82
26.00	25.00	16.00	99.96	100.04	100.04	98.92	100.02	100.00
28.00	27.00	17.00	99.88	100.00	100.00	99.96	100.14	100.18
30.00	29.00	18.00	100.00	99.98	99.98	99.68	100.06	99.98
Mean			99.94	99.95	99.98	99.62	99.85	99.92
RSD[a]			0.1151	0.0630	0.0546	0.6285	0.5106	0.3946

RSD[a] : Relative Standard Deviation

3.3. Comparison of the Predictive Abilities of Proposed Methods

After the optimum number of factors was found, the final calibration was performed using all calibration samples with an optimum number of calibration factors. As mentioned earlier, a number of independent test data sets that have not been previously used for calibration were modeled using PLS-1 and ICA-ANN methods. The predicted values of each component can be seen in Table 1 with reference values.

Table 2, estimating coefficient (R^2_{pred}, Equation (5)) relative estimation error (REP, Equation (6)) and root mean square estimation error (RMSEP, Equation (7)) shows some important statistical parameters such as

$$R^2_{pred} = 1 - \frac{\sum_{i=1}^{n}(C_{i,act} - C_{i,pred})^2}{\sum_{i=1}^{n}(C_{i,act} - \bar{C})^2}\ , \quad (5)$$

$$REP\ \% = 100\ x \sqrt{\frac{\sum_{i=1}^{n}(C_{i,act} - C_{i,pred})^2}{\sum_{i=1}^{n}(C_{i,act})^2}}\ , \quad (6)$$

$$RMSEP = \sqrt{\frac{\sum_{i=1}^{n}(C_{i,act} - C_{i,pred})^2}{n}}\ . \quad (7)$$

where $C_{i,act}$ and $C_{i,pred}$ is the actual and predicted concentration of a component in the *i*th sample, respectively. $\bar{C}$ is the mean of actual concentrations in a particular set and n is the number of samples in the test set.

Table 2. *Statistical parameters calibration and test set by PLS-1 and ICA-ANN regression for three analytes*

	PAR		**PRO**		**CAF**	
Parameters	**PLS-1**	**ICA-ANN**	**PLS-1**	**ICA-ANN**	**PLS-1**	**ICA-ANN**
RMSEP	**0.2800**	**0.1670**	**0.5320**	**0.3802**	**0.1964**	**0.1140**
R^2pred	**0.9654**	**0.9998**	**0.9984**	**0.9988**	**0.8899**	**0.9888**

3.4. Validation of the Method

PAR, PRO and CAF standards were added to the tablet solutions and the selectivity of the methods were tested. This process is repeated five times for each level. No additives of the excipient's formulation were reported during the process. For all these reasons, the chemometric methods proposed in the study are considered to be suitable for the identification of PAR, PRO and CAF compounds in tablets. Recovery results are presented in Table 3.

According to the results, ICA-ANN method gives more accurate and accurate results than PLS-1 method.

Table 3. *Recovery values of chemometric methods applied with standard additive technique*

			Recovery (%)					
Added to tablet (µg/mL)			**ICA-ANN**			**PLS-1**		
PAR	PRO	CAF	PAR	PRO	CAF	PAR	PRO	CAF
4.00	10	6.00	100.00	99.98	100.00	100.02	100.00	99.98
8.00	15	12.00	99.98	99.98	99.96	98.98	98.88	100.02
12.00	20	18.00	100.04	100.00	99.98	99.68	99.84	99.56
Mean			100.00	99.98	99.98	99.56	99.57	99.85
RSD			0.0305	0.0115	0.0200	0.5302	0.6057	0.2548

3.5. Analysis of Commercial Pharmaceuticals

In Parol, Minoset and Panalgine tablets shown in Table 4, the findings obtained from the chemometric methods were used to calculate the amounts of PAR, PRO and CAF. As can be seen from Table 4, the results acquire from the applied chemometric methods are well sufficient. Additionally, the suggested chemometric methods can accurately determine drug content when administered to the drug.

Table 4. *Test results for the commercial pharmaceutical formulation (mg/tablet)*

	ICA-ANN			**PLS-1**		
Drug	PAR	PRO	CAF	PAR	PRO	CAF
Parol	250.02±0.04	149.88±0.02	49.86±0.08	251.12±0.04	148.88±0.12	49.86±0.10
Minoset	248.88±0.08	150.05±0.02	50.12±0.04	248.84±0.12	149.18±0.26	49.88±0.12
Panalgin	150.28±0.02	298.52±0.26	30.04±0.08	149.68±0.18	298.48±0.28	29.98±0.06

4. CONCLUSION

Successfully applied at the same time, partial least squares calibration and independent component analysis-artificial neural network methods, synthetic solutions and pharmaceutical formulation drugs were able to identify. For all the data obtained as a result of the studies, high correlation coefficients and low estimation errors highlight the high linear relationship between estimation and actual concentrations. The results obtained from the triple mixtures in drugs and the ratios of their concentrations show the very accurate estimation ability of the applied methods.

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CONFLICTS OF INTEREST

No conflict of interest was declared by the authors.

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