PARAFAC AND PLS APPLIED TO DETERMINATION OF CAPTOPRIL IN PHARMACEUTICAL PREPARATION AND BIOLOGICAL FLUIDS BY ULTRAVIOLET SPECTROPHOTOMETRY

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Summary – A new ultraviolet spectrophotometric method has been developed for the direct qualitative determination of captopril in pharmaceutical preparation and biological fluids such as human plasma and urine samples. The method was accomplished based on parallel factor analysis (PARAFAC) and partial least squares (PLS). The study was carried out in the pH range from 2.0 to 12.8 and with a concentration from 0.70 to 61.50 μg ml^{-1} of captopril. Multivariate calibration models PLS at various pH and PARAFAC were elaborated from ultraviolet spectra deconvolution and captopril determination. The best models for this system were obtained with PARAFAC and PLS at pH = 2.04 (PLS-PH2). The applications of the method for the determination of real samples were evaluated by analysis of captopril in pharmaceutical preparations and biological (human plasma and urine) fluids with satisfactory results. The accuracy of the method, evaluated through the root mean square error of prediction (RMSEP), was 0.58 for captopril with PARAFAC and 0.67 for captopril with PLS-PH2 model. Acidity constant of captopril at 25 °C and ionic strength of 0.1 M have also been determined spectrophotometrically. The obtained pK_a values of captopril are 3.90 ± 0.05 and 10.03 ± 0.08 for pK_{a1} and pK_{a2}, respectively.

INTRODUCTION

Captopril, (2S)-1-[(2S)-3-mercapto-2-methylpropanoyl] pyrrolidine-2-carboxylic acid, whose structure is shown in Figure 1, is an orally active inhibitor of the angiotensin-converting enzyme and is widely used for the treatment of hypertensive diseases on its own or in combination with other drugs.[1,2] This compound can also be used to treat congestive heart failure. Various methods have been reported for the determination of captopril in several samples. These include titrimetry,[3] spectroscopy,[4-6] electroanalytical methods,[7-9] chromatography[10] and flow injection system.[11,12] Nevertheless, the literature is lacking studies concerning the spectrophotometrically determination of captopril in both pharmaceutical preparations and biological (plasma and urine) fluids.

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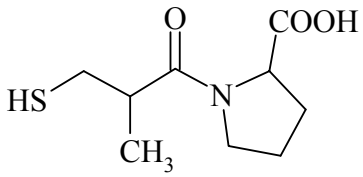

FIGURE 1. - Chemical structure of captopril.

Three-way array may be obtained by collecting data tables with a fixed set of objects and variables under different experimental conditions, such as pH, sampling time, temperature, etc. The tables collected under various conditions can be stacked providing a three-dimensional arrangement of data. In some situation, even higher dimensional arrays may be considered. These methods can be applied for exploratory analysis, curve resolution analysis of variance, and calibration purposes using spectrophotometric, spectrofluorimetric, chromatographic, flow injection, sensory analysis, or experimental design data and kinetic procedures.[13-15]

Parallel factor analysis (PARAFAC), is a multi-way method originating from psychometrics.[13] It is gaining more and more interest in chemometric and associated areas for many reason: simply increased awareness of the method and its possibilities, the increased complexity of the data dealt with in science and industry, and increased computational power. PARAFAC, one of several decomposition methods for *N*-way data, is a generalization of principal component analysis (PCA)[13] to higher orders. A PARAFAC model of a three-way array is given by three loading matrices, **A**, **B** and **C**, with elements a_{if}, b_{jf} and c_{kf} (Eq. (1)), respectively (f=1-F principal components). The tri-linear model is found to minimize the sum of squares of the residues, e_{ijk} in the model,[16] which is represented as follows:

$$X_{ijk} = \sum a_{if} b_{jf} c_{kf} + e_{ijk} \qquad (1)$$

where a_f, b_f and c_f are the *f*th columns of the loading matrices **A**, **B** and **C**, respectively. An important difference between the two-way PCA and multi-way PARAFAC is that the PARAFAC model is not nested. This fact means that the parameters of an *F*+1 component model are not equal to the parameters of an *F* component model plus one additional component. The reason for this is that the components are not required to be orthogonal, hence independent. Therefore, every model has to be calculated specifically with all its components. The algorithm used to solve the PARAFAC model is alternating least squares (ALS).[17,18] ALS successively assumes the loadings in two modes and then estimates the unknown set of parameters of the last mode. The algorithm converges iteratively until the relative change in fit between two iterations is below a certain value (the default is 1×10^{-6}). It is initialized by either random values or values calculated by a direct tri-linear decomposition based on the generalized eigenvalue problem.[17] Constraining the PARAFAC solution can sometimes be helpful in terms of the interpretability or the stability of the model. The fit of a constrained model will always be lower than the fit of an unconstrained model, but if the constrained one is more interpretable and realistic, this may justify the decrease in fit. The most often used constraints are orthogonality and non-negativity. The resolution of spectra used to require the non-negativity constraint since negative spectral parameters do not make sense.[14,16] Application of PARAFAC in spectrophotometry has been discussed by several reports.[19-24]

The basic principle of the multivariate calibration is the simultaneous utilization of many independent variables, $x_1, x_2, \ldots, x_n$, to quantify one or more dependent variables of interest, y. The partial least squares (PLS) regression analysis[25,26] is the most widely used method for this

purpose, and it is based on the latent variable decomposition relating two blocks of variables, matrices X and Y, which may contain spectral and concentration data, respectively. These matrices can be simultaneously decomposed into a sum of f latent variables, as follows:

$$X = TP^T + E = \sum t_f p'_f + E \qquad (2)$$

$$Y = UQ^T + F = \sum u_f q'_f + F \qquad (3)$$

in which T and U are the score matrices for X and Y, respectively; P and Q are the loadings matrices for X and Y, respectively, E and F are the residual matrices. The two matrices are correlated by the scores T and U, for each latent variable, as follows:

$$u_f = b_f t_f \qquad (4)$$

in which b_f is the regression coefficient for the f latent variable. The matrix Y can be calculated from u_f, as Eq. (5), and the concentration of the new samples can be estimated from the new scores T^*, which are substituted in Eq. (5), leading to Eq. (6)

$$Y = TBQ^T + F \qquad (5)$$

$$Y_{new} = T^* BQ^T \qquad (6)$$

In this procedure, it is necessary to find the best number of latent variables, which normally is performed by using cross-validation, based on determination of minimum prediction error.[25] Application of PLS in spectrophotometry has been reported by several papers.[27-32].

In this paper, a method for determination of captopril in pharmaceutical formulations and biological fluids (urine and plasma) based on ultraviolet spectrophotometric measurements is proposed. The study was carried out in the pH range from 2.0 to 12.8 and with a concentration range from 0.70 to 61.50 μg ml^{-1}. Partial least squares (PLS) at different pH and PARAFAC were employed for ultraviolet spectra deconvolution and captopril quantitation. During the spectra deconvolution step by PARAFAC, core consistency diagnostic (CORCONDIA) procedure was used to determine the number of different species present in the data set. In PARAFAC quantitation, the sample factor loadings were used to establish a linear relationship with captopril concentration and good results were obtained for samples at low μg ml^{-1} concentrations.

Acidity constants value can be a key parameter for understanding and quantifying chemical phenomena such as reaction rates, biological activity, biological uptake, biological transport and environmental fate. So, we were interested in obtaining acidity constants of captopril and also using their results in pH selection for PARAFAC data manipulation. The protolytic equilibria of captopril at 25 °C and ionic strength of 0.1 M (KNO_3) have been determined spectrophotometrically. DATAN program applied for determination of protolytic equilibria. Output of DATAN program is pK_a values, concentration distribution diagrams and pure spectrum of each assumed species. The theory and application of the physical constraints method (DATAN) was discussed in several papers.[33-40]

EXPERIMENTAL

Reagents

All solutions were prepared with analytical-grade reagents, and doubly distilled water used throughout. Captopril, hydrochloric acid, potassium nitrate and sodium hydroxide were purchased from Merck. Stock standard solution of captopril (1000 μg ml^{-1}) was prepared by dissolving the compound in water.

Instrumentation and software

Spectrophotometric measurements were made on SUV-2120 spectrophotometer (Scinco), which controlled by a computer and equipped with a 1-cm path length quartz cell was used for ultraviolet spectra acquisition. Spectra were acquired between 200 and 300 nm. The pH of the solutions was measured with a Model M-12 (HORIBA). All absorption spectra were digitized at in the wavelength 200-300 nm. The measured data were processed on an AMD 2000 XP (512 Mb RAM) computer with programs in MATLAB 6.5 (MathWork) or for processing by using DATAN program. The *N*-way toolbox, version 2.1, available at http://www.models.kvl.dk/source, was employed for PARAFAC calculations, while PLS calculus was carried out in the PLS-Toolbox, version 2.0 (Eigenvector Technologies).

Procedure

Known amounts of standard solutions of captopril were placed in a 10-ml volumetric flask and completed to the final volume with deionized water and adjusted in pH range from 2.0 to 12.8 by hydrochloric acid and sodium hydroxide. The final concentration of these solutions varied between 0.70 to 61.50 μg ml^{-1} for captopril.

Real samples

For the determination of captopril in pharmaceutical formulations, 10 tables were placed in a 250-ml flask, made to volume with double-distilled water and ultrasonicated for 3 min. An aliquot of 0.2 ml of the resulting solution was transferred into a 25-ml flask and made mark with distilled water.

Urine spiked with captopril was obtained by the following procedure: an aliquot of pure captopril was added into 10 ml urine sample. A 1 ml of the resulting urine solution was mixed with 5 ml (0.2M) sodium carbonate buffer and 10 ml butyl chloride. The mixture was rotated for 30 min and centrifuged at 2500 rpm for 15 min. The butyl chloride layer was separated and then evaporated till dryness. Resultant residue was dissolved in water and pH adjusted (at different pH) into a 10 ml volumetric flask, diluted to the mark.[19]

Plasma spiked with captopril was obtained by diluting aliquots of the stock standard captopril solution with the human plasma. A 1 ml aliquot of this spiked solution was diluted to 5 ml with ethanol in 10 ml centrifuge tube. The precipitated protein was separated by centrifugation for 15 min at 2500 rpm. The clear supernatant layer was filtrated by Whatman filter to procedure protein free-spiked human plasma, and then it was added into 10 ml volumetric flask and diluted to mark (at different pH).[19]

RESULTS AND DISCUSSION

Determination of acidity constants of captopril

The absorption spectra of captopril in water at various pH values at 200-300 nm intervals were recorded. Sample spectra of captopril at different pH values in water are shown in Figure 2.

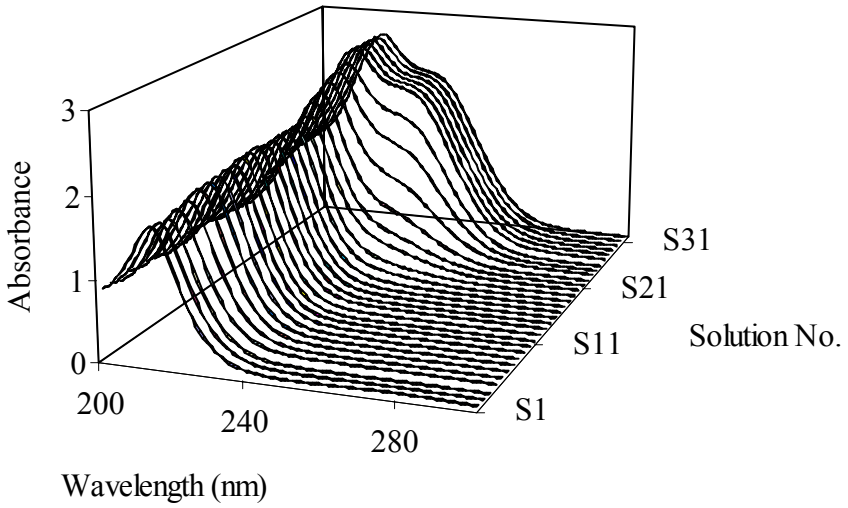

FIGURE 2. - Absorption spectra of captopril at different pH values: (1) 2.00, (2) 2.55, (3) 2.73, (4) 3.02, (5) 3.60, (6) 4.03, (7) 4.40, (8) 4.96, (9) 5.39, (10) 6.00, (11) 6.57, (12) 6.85, (13) 7.35, (14) 7.61, (15) 7.95, (16) 8.17, (17) 8.42, (18) 8.79, (19) 8.98, (20) 9.31, (21) 9.43, (22) 9.69, (23) 10.00, (24) 10.32, (25) 11.00, (26) 11.31, (27) 12.00, (28) 12.14, (29) 12.46, (30) 12.76, (31) 12.82.

The principal component analysis of all absorption data matrix obtained at various pH shown at least three significant factors. This claim is, also, supported by the statistical indicators method that has been recently developed by Elbergali et al.[41] which has predicted three distinguishable components in the samples. These factors could be attributed to the two dissociation equilibria of captopril.

The pK_a values of captopril were investigated spectrophotometrically at 25 °C and ionic strength of 0.1 M (KNO_3). Protolytic equilibria of captopril were evaluated using DATAN program using the corresponding absorption spectra-pH data. Output of DATAN program is pK_a values, number of principal components, concentration distribution diagrams and pure spectrum of each assumed species. In this study, we obtained pK_a values of captopril, 3.90 ± 0.05 and 10.03 ± 0.08 for pK_{a1} and pK_{a2}, respectively. The concentration distribution diagram and pure spectra shows in Figure 3.

Parallel factor analysis (PARAFAC)

The main advantage of three-way multivariate calibration is that it allows concentration information of an individual component to be extracted in the presence of any number of uncalibrated constituents. Therefore, it is highly useful for solving analytical problems involving a complex matrix. Figure 2 shows the experimentally obtained spectra of captopril in different pH. In this study, we selected the pH = 2.04, 4.10, 7.02, 9.10 and 11.00 for three-way data. The data was arranged in a three-way array 22×100×5, composed of 22 solutions, with different captopril concentrations (Table 1), in the rows, 100 wavelengths in the columns and 5 pH values in the slices. No preprocessing (centering or auto scaling) was applied to the data. When using PARAFAC, an initial definition of the number of factors to build the model is necessary.

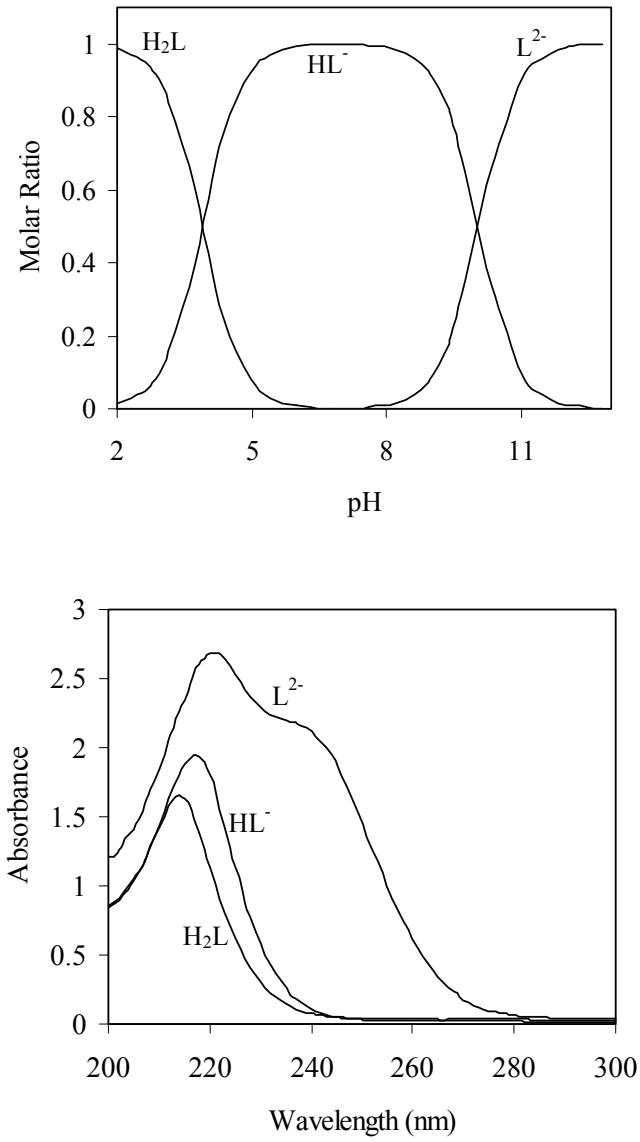

FIGURE 3. - (a) Distribution of different species of captopril as function of pH for the spectral data of Figure 2, (b) The pure absorption spectra of different form of captopril.

Selection of number of factor for PARAFAC

This choice is of fundamental importance because all conclusions about the deconvolution and quantitation results will be related with this number of factors. In PARAFAC, it is possible to use several constraints such as non-negativity, unimodality or orthogonality. In this work an unconstrained model was preferred as more realistic results can be obtained. Unconstrained PARAFAC models of the captopril data at different pH were developed using one to five components and the percentage of fit was used as the initial approach to select the number of factors. The percentage of fit value corresponds to how well the model can reproduce the experimental data and it is given as:

$$fit(\%) = 100 \times \left(1 - \frac{\sum_{i=1}^{I}\sum_{j=1}^{J}\sum_{k=1}^{K}(X_{ijk} - \hat{X}_{ijk})^2}{\sum_{i=1}^{I}\sum_{j=1}^{J}\sum_{k=1}^{K} X_{ijk}^{\ 2}} \right) \qquad (7)$$

where X_{ijk} is the ijk th experimental element and $\hat{X}_{ijk}$ the ijk th element predicted by the model. The results are presented in Table 2. It is possible to note that this parameter is not conclusive for selection of the number of factors, since percentage of fit higher than 99% were obtained using from 2 to 5 factors. This parameter is important to identify if there are factors lacking in the model. Therefore, other more conclusive tools, such as core consistency (CORCONDIA) was used in this study. All data set (22×100×5) was utilized for the core consistency evaluation, using one to five factors, with the values calculated according to Eq. (2). The core consistency diagnostic (CORCONDIA) is defined as:

$$CORCONDIA = 100 \times \left(1 - \frac{\sum_{d=1}^{F}\sum_{e=1}^{F}\sum_{f=1}^{F}(g_{def} - t_{def})^2}{\sum_{d=1}^{F}\sum_{e=1}^{F}\sum_{f=1}^{F} t_{def}^2} \right) \qquad (8)$$

where g_{def} is the calculated element of the core using the PARAFAC model, defined by dimensions (d×e×f); t_{def} the element of a binary array with zeros in all elements and ones in the super-diagonal and F is the number of factors in the model. In ideal PARAFAC model, g_{def} is equal to t_{def} and, in this case, CORCONDIA will be equal to 100%. The appropriate number of factors is accessed by the model with the highest number of factors and a valid value of core consistency diagnostic test. The analysis of the core consistency supports that two factors are necessary, because the utilization of more factors leads to a great decrease of the core consistency.[17] Two factors give a CORCONDIA value of 100% (a perfect trilinear model) whilst, when using three or more factors, this value diminishes to values below to 2%. The results are also shown in Table 2.

TABLE 1. - Concentration data of the calibration and prediction set of captopril for PARAFAC and PLS models (μg ml^{-1}).

Calibration	Concentration	Calibration	Concentration	Prediction	Concentration
C1	0.70	C12	34.70	P1	7.30
C2	2.30	C13	31.30	P2	17.00
C3	5.60	C14	37.50	P3	20.20
C4	8.90	C15	40.50	P4	21.80
C5	10.00	C16	46.60	P5	28.10
C6	12.20	C17	49.60	P6	32.80
C7	15.40	C18	52.60	P7	39.00
C8	18.60	C19	54.60	P8	42.10
C9	23.40	C20	55.60	P9	51.10
C10	26.60	C21	58.60	P10	60.00
C11	30.00	C22	61.50		

TABLE 2. - Percentage fit and CORCONDIA values versus the number of components in the PARAFAC model.

Number of factors	1	2	3	4	5
Fit (%)	98.87	99.23	99.25	99.27	99.31
CORCONDIA (%)	100.0	98.3	1.42	0.54	0.08

Deconvolution and calibration

As presented in the above section, two factors for unconstrained PARAFAC model furnished the best model for the deconvolution of the data. The decomposition of the three-way data by PARAFAC gives rise to three loading matrices, one of which, **C**, corresponds to the sample mode. The **C**-loading are the relative concentrations of the captopril in the solutions. In the calibration step, this **C**-loading (which includes two loadings) is regressed against the real concentrations of captopril to get two linear calibrations. Linear regression results and standard deviation of results, line equations and correlation coefficient are summarized in Table 3. In the prediction step, these regression lines can then be used to predict the concentration of captopril in future test samples (Table 4). The results obtained by applying PARAFAC to ten synthetic samples are listed in Table 4. Table 4 also shows the percentage relative error for prediction series of captopril. The prediction results for captopril are very good.

TABLE 3. - Statistical parameters of the linear relationship between the proportion loadings calculated by PARAFAC and the true concentration of captopril.

	First loading of C-Loading (First calibration)	Second loading of C-Loading (Second calibration)
Number of data points	22	22
Intercept	0.0072	0.0178
Standard deviation of intercept	0.0105	0.0188
Slope	0.0041	0.0039
Standard deviation of slope	0.0026	0.0041
Correlation coefficient*	0.9989	0.9941
Standard deviation of regression	0.0381	0.0413

*$P < 0.001$ at 95% confidence level.

TABLE 4. - Added and found results of the prediction set of captopril using PARAFAC models (μg ml^{-1}).

Added captopril	First calibration		Second calibration	
	Found	RE(%)	Found	RE(%)
7.30	7.23	-0.96	7.21	-1.23
17.00	17.12	0.71	17.28	1.65
20.20	20.03	-0.84	19.94	-1.29
21.80	21.48	-1.47	21.28	-2.39
28.10	28.06	-0.14	28.22	0.43

TABLE 4. – (Continued)

32.80	32.78	-0.06	33.8	3.05
39.00	39.95	2.44	39.93	2.38
42.10	42.56	1.09	43.12	2.42
51.10	49.8	-2.54	52.45	2.64
60.00	59.36	-1.07	59.61	-0.65
RMSEP	0.58		0.73	
RSEP	1.64		2.05	
γ (μg^{-1} ml)*	96		121	
LOD (μg ml^{-1})*	0.11		0.17	
LOQ (μg ml^{-1})*	0.33		0.51	

*γ (analytical sensitivity) = SEN/$[V(R)]^{1/2}$ where SEN is the sensitivity (estimated as the net analyte signal) and V(R) is the variance of the instrumental signal [42], LOD (limit of detection) = 3.3 s(0) where s(0) is the S.D. in the predicted concentration of captopril in a blank sample, LOQ (limit of quantification) = 10 s(0) [42].

Partial least squares (PLS)

Calibration and validation

The multivariate calibration is a powerful tool for determinations, because it extracts more information from the data and allows building more robust models. Therefore, it was decided to perform a multivariate calibration using PLS models built for each pH value individually and compare it with PARAFAC model. According to an experimental design (Table 1), twenty two solutions were used to build the models (calibration set), that were tested on ten different solutions (external test set). The models were validated using cross-validation.

Selection of the optimum number of PLS factors is required to avoid overfitting. This is usually done by cross validation employing the leave-one-out procedure, which involves systematically removing one calibration sample at a time and employing the remaining samples for model building. The concentration of the sample left out is then predicted with the model, and the predicted concentrations of all samples are compared with their actual values. The optimum number of factors (latent variables) to be included in the calibration model was determined by computing the prediction error sum of squares (PRESS) for cross-validated models using a high number of factors (half the number of total standard +1), which is defined as follows:

$$PRESS = \sum (y_i - \hat{y}_i)^2 \qquad (9)$$

where y_i is the reference concentration for the *i*th sample and $\hat{y}_i$ represents the estimated concentration. One reasonable choice for the optimum number of factors would be that number which yielded the minimum PRESS. Since there are a finite number of samples in the training set, in many cases the minimum PRESS value causes overfitting for unknown samples that were not included in the model. Also, the F-statistical test can be used to determine the significance of PRESS values greater than the minimum. The maximum number of factors used to calculate the optimum PRESS was selected as 11 and the optimum number of factors obtained by the application of PLS models is summarized in Table 5. In all instances, the number of factors for the first PRESS values whose F-ratio probability drops below 0.75 was selected as the optimum. Figure 4 shows the PRESS obtained by optimizing the calibration set of the absorbance data with PLS at different pH models.

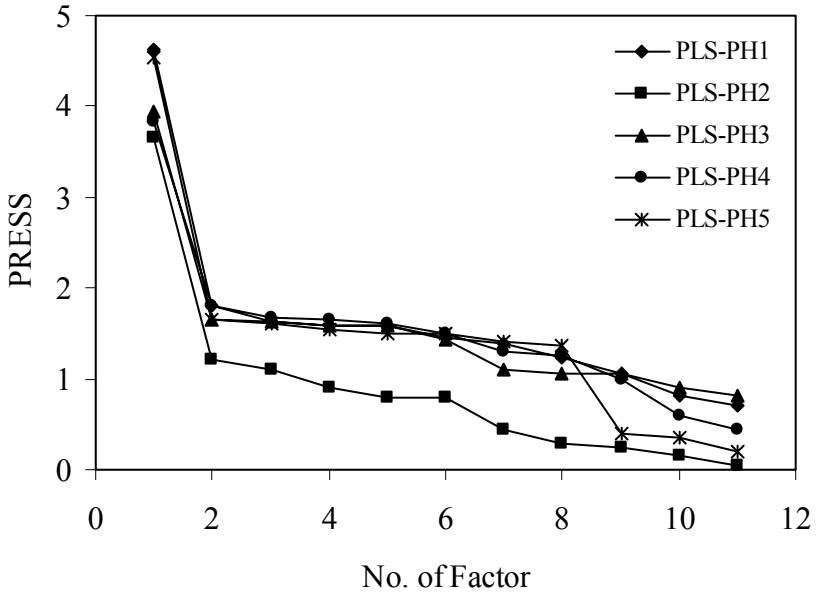

FIG. 4 - Plots of PRESS versus number of factors by PLS at different pH.

Determination of captopril in synthetic solution

The predictive ability of both PARAFAC (Table 4) and PLS models at each pH (Table 5) were determined using ten synthetic solutions. The results obtained by applying PLS at each pH to ten synthetic samples are listed in Table 5. Table 5 also shows the root mean square error of prediction (RMSEP) and relative standard error of prediction (RSEP). As can be seen, PLS model at PH2 is better than other models.

Statistical parameter

For the evaluation of the predictive ability of a multivariate calibration model, the root mean square error of prediction (RMSEP) and relative standard error of prediction (RSEP) can be used:[27]

$$RMSEP = \sqrt{\frac{\sum_{i=1}^{n}(y_{pred} - y_{obs})^2}{n}} \qquad (10)$$

$$RSEP(\%) = 100 \times \sqrt{\frac{\sum_{i=1}^{n}(y_{pred} - y_{obs})^2}{\sum(y_{obs})^2}} \qquad (11)$$

where y_{pred} is the predicted concentration in the sample, y_{obs} is the observed value of the concentration in the sample and n is the number of samples in the validation set. The RMSEP and RSEP(%) results for PARAFAC and PLS models summarized in Tables 4 and 5. Comparison of these results indicates satisfactory results for PARAFAC model.

Figures of merit are regularly employed for method comparison. They are best understood by resorting to the useful concept of net analyte signal (NAS), first developed by Lorber [42]. Theory of NAS described in several papers [43-46]. A summary of validation statistics for PARAFAAC and PLS models are shown in Table 4 and 5, which demonstrates that, in general, the PARAFAC method shows a better analytical performance.

TABLE 5. - Added and found results of the prediction set of captopril using PLS models at different pH (μg ml^{-1}).

Added	PLS-PH1 (pH=2.04)		PLS-PH2 (pH=4.10)		PLS-PH3 (pH=7.02)		PLS-PH4 (pH=9.10)		PLS-PH5 (pH=11.00)	
	Found	RE(%)	Found	RE(%)	Found	RE(%)	Found	RE(%)	Found	RE(%)
7.30	6.99	-4.25	7.31	0.14	7.28	-0.27	7.87	7.81	6.63	-9.18
17.00	17.55	3.24	17.19	1.12	17.07	0.41	17.86	5.06	16.53	-2.76
20.20	19.98	-1.09	20.32	0.59	20.52	1.58	20.2	0.00	19.8	-1.98
21.80	21.5	-1.38	21.41	-1.79	22.08	1.28	21.64	-0.73	21.6	-0.92
28.10	28.11	0.04	28.46	1.28	28.86	2.70	28.36	0.93	28.86	2.70
32.80	33.6	2.44	32.89	0.27	33.82	3.11	34.89	6.37	34.11	3.99
39.00	40.26	3.23	40.12	2.87	40.51	3.87	40.6	4.10	41.24	5.74
42.10	43.96	4.42	42.32	0.52	43.76	3.94	43.81	4.06	44.02	4.56
51.10	51.59	0.96	52.57	2.88	52.42	2.58	52.18	2.11	52.27	2.29
60.00	60.23	0.38	59.98	-0.03	60.75	1.25	60.18	0.30	59.05	-1.58
No. of Factor	3		2		2		3		3	
PRESS	1.64		1.21		1.65		1.68		1.61	
RMSEP	0.80		0.62		0.96		1.10		1.19	
RSEP	2.27		1.74		2.69		3.11		3.38	
γ (μg^{-1} ml)*	141		132		153		168		206	
LOD (μg ml^{-1})*	0.13		0.12		0.14		0.15		0.15	
LOQ (μg ml^{-1})*	0.39		0.36		0.42		0.45		0.45	

*γ (analytical sensitivity) = SEN/$[V(R)]^{1/2}$ where SEN is the sensitivity (estimated as the net analyte signal) and V(R) is the variance of the instrumental signal [42], LOD (limit of detection) = 3.3 s(0) where s(0) is the S.D. in the predicted concentration of captopril in a blank sample, LOQ (limit of quantification) = 10 s(0) [42].

Application

In order to show the analytical applicability of the present methods, PARAFAC and PLS-PH2 (pH 2.04) were applied to determination of captopril in real samples (pharmaceutical formulations) and complex matrices, i.e. urine and human plasma. The results showed that satisfactory recovery for captopril could be obtained (Table 6 and 7) using the recommended procedures. Results of the determination are summarized in Table 6 and 7. The data obtained by these methods reveal the capability of the methods for determination of captopril in pharmaceutical formulations and biological fluids such as urine and plasma without considerable error. The average recoveries in pharmaceutical formulations and biological fluids (urine and human plasma) are summarized in Table 6 and 7, respectively. In synthesis samples, the results of PARAFAC are better than PLS-PH2 with a little difference. But in real samples, PARAFAC shows improve than PLS-PH2.

TABLE 6. - Determination of captopril in pharmaceutical preparations using the PARAFAC and PLS-PH2 models.

Pharmaceutical preparations	Label claim (mg)	Amount Found (PARAFAC)	Recovery (%)	Amount Found (PLS-PH2)	Recovery (%)
Tables 1	25	24.80 ± 0.22	99.2	22.31 ± 0.34	89.2
Tables 2	25	24.70 ± 0.34	98.8	21.83 ± 0.48	87.2

TABLE 7. - Determination of captopril in urine and human plasma using PARAFAC and PLS-PH2 models (μg ml^{-1}).

Type of samples	Added	Amount Found (PARAFAC)	Recovery (%)	Amount Found (PLS-PH2)	Recovery (%)
Plasma sample 1	1.20	1.11 ± 0.08	92.5	0.86 ± 0.15	71.7
Plasma sample 2	25.60	23.80 ± 0.12	92.7	20.33 ± 0.23	79.4
Plasma sample 3	44.00	40.23 ± 0.32	91.4	37.45 ± 0.45	85.1
Urine sample 1	2.00	1.76 ± 0.09	88.0	1.63 ± 0.10	81.5
Urine sample 2	31.00	28.12 ± 0.14	90.7	27.11 ± 0.18	87.5
Urine sample 3	45.20	41.36 ± 0.29	91.5	39.45 ± 0.33	87.3

CONCLUSION

In this work, determination of captopril in pharmaceutical formulations was accomplished based on ultraviolet spectrophotometry using PARAFAC and PLS calibration. The study was carried out in the pH range from 2.0 to 12.8 and with a concentration range from 0.70 to 61.50 μg ml^{-1} of captopril. Multivariate calibration models using PLS at different pH and PARAFAC were elaborated for ultraviolet spectra deconvolution and captopril quantitation. The best models for the system were obtained with PARAFAC and PLS at pH 2.04. The capability of the method for the analysis of real samples was evaluated by determination of captopril in pharmaceutical preparations and biological (urine and plasma) fluids with satisfactory results. Also, the acidity constants of captopril at 25°C and ionic strength of 0.1 M have been determined spectrophotometrically. Finally it can be concluded that the model developed by the PARAFAC method has more prediction ability

especially for real samples with respect to PLS method, which clearly reveals that the tolerance limit of three-way calibration methods for matrix effect is higher than of the two-way methods.

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REFERENCES

1) R.C. Heel, R.N. Brogden, T.M. Speight, G.S. Avery, *Drugs,* **20**, 409 (1980).
2) K. Florey, Analytical Profiles of Drug Substances, vol. 11, Academic Press, New York, 1982, p. 81.
3) The United States Pharmacopeia, 28th ed, USP Convention Inc., Rockville, 2004, p. 338.
4) X.R. Zhang, W.R.G. Baeyens, G. Van der Weken, A.C. Calokerino, K. Nakashima, *Anal. Chim. Acta,* **303**, 121 (1995).
5) S.M. Al-Ghannam, A.M. El-Brashy, B.S. Al-Farhan, *Farmaco,* **57**, 625 (2002).
6) S. Mazurek, S.; Szostak, R.; *J. Pharm. Biomed. Anal.,* **40**, 1225 (2006).
7) J.M.G. Fraga, A.I.J. Abizanda, F.J. Moreno, J.J.A. Leon, *Talanta,* **46**, 75 (1998).
8) A.M. Pimenta, A.N. Arahjo, M.C.B.S.M. Montenegro, *Anal. Chim. Acta,* **438**, 31 (2001).
9) R.I. Stefan, J.F. Van Staden, H.Y. Aboul-Enein, *Anal. Chim. Acta,* **411**, 51 (2000).
10) G. Favaro, M. Fiorani, *Anal. Chim. Acta,* **332**, 249 (1996).
11) A. Economou, D.G. Themelis, G. Theodoridis, P.D. Tzanavaras, *Anal. Chim. Acta,* **463**, 249 (2002).
12) B. Li, Z. Zhang, M. Wu, *Microchem. J.,* **70**, 85 (2001).
13) A. Niazi, Application of Bi-linear and Three-linear Chemometrics Methods to Quantitative Analysis and Equilibria Study, Ph.D. Thesis, Razi University, 2005.
14) R. Bro, Multi-Way Analysis in the Food Industry, Ph.D. Thesis, Amsterdam, 1998.
15) R. Bro, *Chemom. Intell. Lab. Syst.,* **38**, 149 (1997).
16) C.A. Andersson, R. Bro, *Chemom. Intell. Lab. Syst.,* **52**, 1 (2000).
17) R. Henrion, *Chemom. Intell. Lab. Syst.,* **25**, 1 (1994).
18) A.K. Smilde, *Chemom. Intell. Lab. Syst.,* **15**, 143 (1992).
19) R. Bro, *Crit. Rev. Anal. Chem.,* **36**, 279 (2006).
20) A. Niazi, J. Ghasemi, J.; A. Yazdanipour, *Anal. Lett.,* **38**, 2377 (2005).
21) A. Niazi, M. Sadeghi, *Chem. Pharm. Bull.,* **54**, 711 (2006).
22) D. Gimenez, L. Sarabia, M.C. Ortiz, *Anal. Chim. Acta,* **544**, 327 (2005).
23) I. Garcia, L.A. Sarabia, M.C. Ortiz, *Anal. Chim. Acta,* **501**, 193 (2004).
24) J.M.D. Cueva, A.V. Rossi, R.J. Poppi, *Chemom. Intell. Lab. Syst.,* **55**, 125 (2001).
25) J.C.G. Esteves da Silva, C.J.S. Oliverira, *Talanta,* **49**, 889 (1999).
26) H. Martens, T. Naes, Multivariate Calibration, John Wiley, Chichester, 1989.
27) J. Gabrielsson, J. Trygg, *Crit. Rev. Anal. Chem.,* **36**, 243 (2006).
28) J. Ghasemi, A. Niazi, *Talanta,* **65**, 1168 (2005).
29) A. Niazi, *J. Braz. Chem. Soc.,* **17**, 1020 (2006).
30) A. Niazi, *Croatica Chim. Acta,* **79**, 573 (2006).
31) V. Kaur, A.K. Malik, N. Verma, *Annali di Chimica,* **97**, 237 (2007).

32) P.M. Santos, B. Sandrino, T.F. Moreira, K. Wohnrath, N. Nagata, C.A. Pessoa, *J. Braz. Chem. Soc.,* **18**, 93 (2007).
33) R.C. Barthus, L.H. Mazo, R.J. Poppi, *J. Pharm. Biomed. Anal.,* **38**, 94 (2005).
34) M. Kubista, R. Sjoback, J. Nygren, *Anal. Chim. Acta,* **302**, 121 (1995).
35) M. Kubista, J. Nygren, A. Elbergali, R. Sjoback, *Crit. Rev. Anal. Chem.,* **29**, 1 (1998).
36) M. Kubista, I.H. Ismail, A. Forootan, B. Sjogreen, *J. Fluorescence,* **14**, 139 (2004).
37) J. Ghasemi, A. Niazi, M. Kubista, *Spectrochim. Acta Part A,* **62**, 649 (2005).
38) A. Niazi, A. Yazdanipour, J. Ghasemi, M. Kubista, *Collect. Czech. Chem. Commun.,* **71**, 1 (2006).
39) A. Niazi, M. Ghalie, A. Yazdanipour, J. Ghasemi, *Spectrochim. Acta Part A,* **64**, 660 (2006).
40) A. Niazi, A. Yazdanipour, J. Ghasemi, M. Kubista, *Spectrochim. Acta Part A,* **65**, 73 (2006).
41) A. Niazi, A.A. Rezaei, F. Shahhosseini, *Annali di Chimica,* **97**, 199 (2007).
42) A. Elbergali, J. Nygren, M. Kubista, *Anal. Chim. Acta,* **379**, 143 (1999).
43) A. Lorber, K. Faber, B.R. Kowalski, *Anal. Chem.,* **69**, 1620 (1997).
44) J. Ferre, S.D. Brown, F.X. Rius, *J. Chemom.,* **15**, 537 (2001).
45) J. Ferre, N.M. Faber, *Chemom. Intell. Lab. Syst.,* **69**, 123 (2003).
46) A.M. Pena, A.E. Mansilla, M.I.A. Valenzuela, H.C. Goicoechea, A.C. Olivieri, *Anal. Chim. Acta,* **463,** 75 (2002).
47) M.G. Trevison, R.J. Poppi, *Anal. Chim. Acta,* **493**, 69 (2003).