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Original Research Article

The Simultaneous Spectrophotometric Determination of Acetaminophen, Celecoxib, Diazepam, and Famotidine in Environmental Samples by Partial Least Squares

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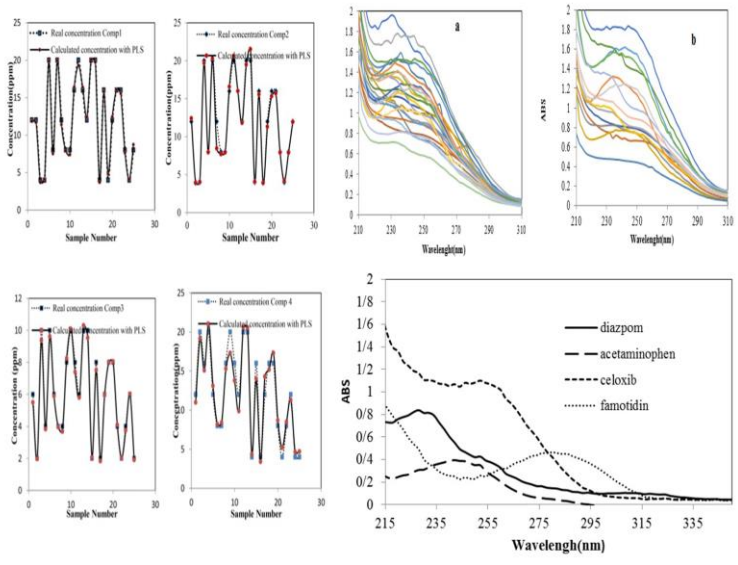
ABSTRACT

In this study, the application of a partial least squares algorithm (PLS) was proposed for simultaneous spectrophotometric determination of acetaminophen, celecoxib, diazepam, and famotidine in hair, wastewater, and urban water samples. Although the determination of these drugs is very important in biological and pharmaceutical samples, spectrophotometric measurements were reported at the same time due to the spectral overlap. The results of applying PLS showed that acetaminophen, celecoxib, diazepam, and famotidine could be simultaneously determined within the concentration ranges of 4-20 ppm, 4-20ppm, 2-10 ppm, and 4-20 ppm respectively in calibration set, prediction set, and real samples. The proposed method does not require spectral correction and chemical pretreatment for quantitative analysis of the mentioned drugs.

GRAPHICAL ABSTRACT



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Introduction

Acetaminophen (paracetamol, AC) is a widely used anti-fever and analgesic drug, considering children and adults [1, 2]. Also, it is a substitute for aspirin [3]. Nevertheless, AC metabolism in the liver produces toxic metabolites. If AC exceeds the therapeutic dose, it will cause liver toxicity and bloating [4,5]. Celecoxib is a non-steroidal anti-inflammatory COX2 drug that improves arthritis and rheumatoid arthritis. It is an analgesic and anticancer drug, though it is ineffective in the dosage proposed for platelet aggregation [6] whose brand name is Selberx [7]. On the other hand, diazepam is a medicine from the family of benzodiazepine. Benzodiazepines have anticonvulsant and sedative effects and are generally used to treat epileptic seizures, anxiety, insomnia, and depressions. The serious point about diazepam is that its overdose can lead to death [8]. If mixed with alcohol, the effect of its sedative will be potentiated [9]. Finally, famotidine is used to improve gastrointestinal ulcers caused by excessive gastric acid secretion. It is the most commonly used drug for treatment of acid reflux and its contents to the esophagus as well as the throat and stomach. This drug is actually an antihistamine that acts on acid-secreting cells in the stomach and prevents acid secretion [10]. After taking medicine, most of it is excreted unchanged through the urine. Famotidine has basic properties and two structures. This drug can create an ion-pair complexion. Note that nitro ethanol sulfate guanidine, sulfur monohydrate and amine groups are found in its molecular structure, which can cause the transfer of metal ions and the formation of ion-coupled complexes [11]. So, measuring these drugs is very important and essential. Many instrumental and electrochemical methods are used to measure the effects of diazepam, celecoxib, acetaminophen, and famotidine, either alone or in combination with other drugs or their metabolites. These methods include fluorescence spectrophotometric [12], chromatography [13], hyphenated technique [14-20], and electrochemical methods such as voltammetry [21-33], spectro electrochemical [34], etc. So far, the simultaneous determination of the four drugs through spectrophotometry has not been reported because of the spectral overlapping of these drugs. In recent years, multivariate calibration methods have been considered for analysis in multi-component systems [35-37]. Among the multivariate calibration methods, partial least squares (PLS) regression has received much attention in the chemometrics literature. This technique is a powerful multivariate statistical tool successfully and commonly applied to analytical procedures, because of its ability to overcome the problems such as poor selectivity, collinearity, band overlaps and interactions, and ease of implementation due to the easily available statistical software [38]. In the present work, for simultaneous determination of ternary mixtures of celecoxib, acetaminophen, famotidine, and diazepam, a spectrophotometric method was used via partial least squares (PLS) method [39-44].

Material and methods

All absorbance spectra were recorded using a Varian Cary 300 Bio UV-Visible Spectrophotometer equipped with a 1.00 cm path length quartz cells. The data analysis was performed using MATLAB and PLS-Toolbox.

Acetaminophen, celecoxib, diazepam, and famotidine were purchased from Sigma-Aldrich.

Preparation of stock and working standard solutions

Stock solutions of acetaminophen, celecoxib, diazepam, and famotidine (100 mg/L) were prepared individually, weighed and dissolved in methanol. Appropriate aliquots of the stock solutions were diluted with the water to obtain the suitable working standard solutions according to the linear calibration range for each drug.

Construction of calibration and validation sets

Individual calibration curves were obtained with several points as absorption versus acetaminophen, celecoxib, diazepam, and famotidine concentrations within the ranges of 1-40 ppm, 4-30 ppm, 2-20 ppm, and 4-50 ppm, respectively, and were evaluated by linear regression. The absorption spectra were scanned from 210 to 310 nm at one nm wavelength interval. The calibration procedure for simultaneous determination was performed with 40 standard samples (25 samples as calibration set and 15 samples as prediction set) in aqueous media from different mixtures of acetaminophen, celecoxib, diazepam, and famotidine.

Analysis of acetaminophen, celecoxib, diazepam, and famotidine in spiked hair, urban water, and hospital wastewater

Hair samples were cut into pieces (2-4 cm) and washed several times to remove external contaminants with distilled water. The samples were then dried and powdered. Different amounts of drugs were spiked to powdered specimens. The drugs trapped in the powdered hair sample were extracted by vortexing in an ultrasonic bath with 2 ml methanol (120 second). These samples were centrifuged at 4000 rpm for 20 minutes and filtered using Whatman filter paper No. 2. The absorbance spectra of the solution were recorded from 210 to 310 nm. Water and wastewater samples were collected in plastic bottles. Prior to spectrum recording, different amounts of drugs were spiked to them. In order to remove the particles, the solutions used in this study were filtered through 0.45-µm Millipore membrane filter (Billerica, MA).

Results and Discussion

Spectrophotometric measurements

Figure 1 displays a pure absorbance spectrum of the four compounds in the aqueous Solution. As shown, the spectrum of these four compositions reveals a strong overlapping, which is difficult to be measured simultaneously by conventional spectrophotometry. Thus, to overcome this problem, it is necessary to apply suitable and multivariate analysis methods, offering a good recovery, with PLS regression as one of these practical methods.

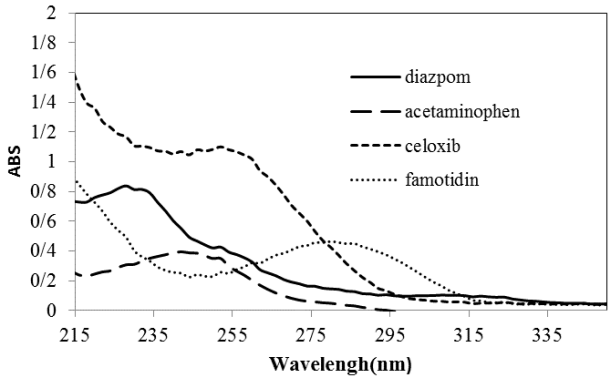

Figure 1: Absorption spectra of acetaminophen, celecoxib, diazepam and famotidine

Validation of the method

The PLS regression was applied for determining the concentrations of analyses. The calibration procedure consisted of a complete experimental design with five concentration levels for acetaminophen, celecoxib, diazepam, and famotidine. The two-set synthetic mixture solution was prepared to contain combinations of the concentration levels (4 to 20 ppm of acetaminophen, celecoxib and famotidine and 2 to 10 ppm of diazepam). One set (25 samples) was applied for training to develop the calibrated model (Figure 2a) and the other set (15 samples) was applied to the validation set for predicting the unknown concentration of mixtures (Figure 2b). Table 1 shows the values of acetaminophen, celecoxib, diazepam, and famotidine concentrations used as calibration and prediction solutions.

Table 1: values of acetaminophen, celecoxib, diazepam and famotidine concentrations used as calibration and prediction solutions

Solution calibration set	Acetaminophene (ppm)	Celecoxib (ppm)	Diazepam (ppm)	Famotidine (ppm)
1	12	12	6	12
2	12	4	2	20
3	4	4	10	16
4	4	20	4	20
5	20	8	10	12
6	8	20	6	8
7	20	12	4	8
8	12	8	4	16
9	8	8	8	20
10	8	16	10	16
11	16	20	8	12
12	20	16	6	20
13	16	12	10	20
14	12	20	10	4
15	20	20	2	16
16	20	4	8	4
17	4	16	2	12
18	16	4	6	16
19	4	12	8	16
20	12	16	8	8
21	16	16	4	4
22	16	8	2	8
23	8	4	4	12
24	4	8	6	4
25	8	12	2	4
Prediction Set				
1	10.5	5	2.5	19
2	5	19	4	19
3	19	8	9	10.5
4	8	19	6	8
5	10.5	8	4	17
6	8	8	7	19
7	8	17	9	17
8	17	19	7	10.5
9	17	10.5	9	19
10	10.5	19	9	5.5
11	19	19	2.5	17
12	5	17	2.5	10.5
13	17	5	6	17
14	5	10.5	7	17
15	17	8	2.5	8

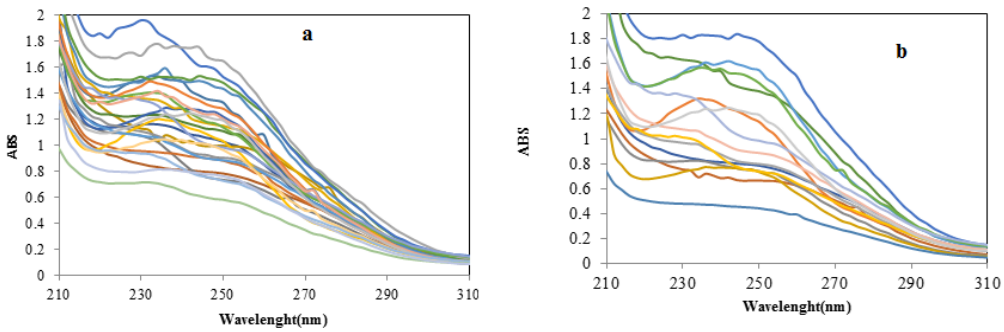

Figure 2: Absorption spectra of synthetic mixture solution of drugs (a) calibration set (b) prediction set

Choosing the number of factors and optimized PLS models

PLS is a popular method used as a predictive model. It needs designation of the number of factors to retain when generating a predictive model. Selection of the optimum number of factors in the PLS algorithm is estimated by the cross-validation method, leaving out one sample at a time. The prediction error was calculated for each component for the prediction set, which were the samples not participating in the construction of the model. 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 the first variable, which helped develop the PLS modeling in the calibration step. Then, another latent variable added for the model and the PRESS was re-calculated. This process was repeated for one to 10 latent variables, used in the PLS modeling. Figure 3 shows the plots of PRESS versus the number of factors PLS models for acetaminophen, celecoxib, diazepam, and famotidine. According to these figures, the significant factors were five, three and four for acetaminophen, celecoxib, diazepam, and famotidine, respectively. Further, the second method was trial and error in which case we chose different factors and ran the PLS program for each selected factor. Based on the minimum error factor, the significant factors were obtained as five for the four compounds (Table 2).

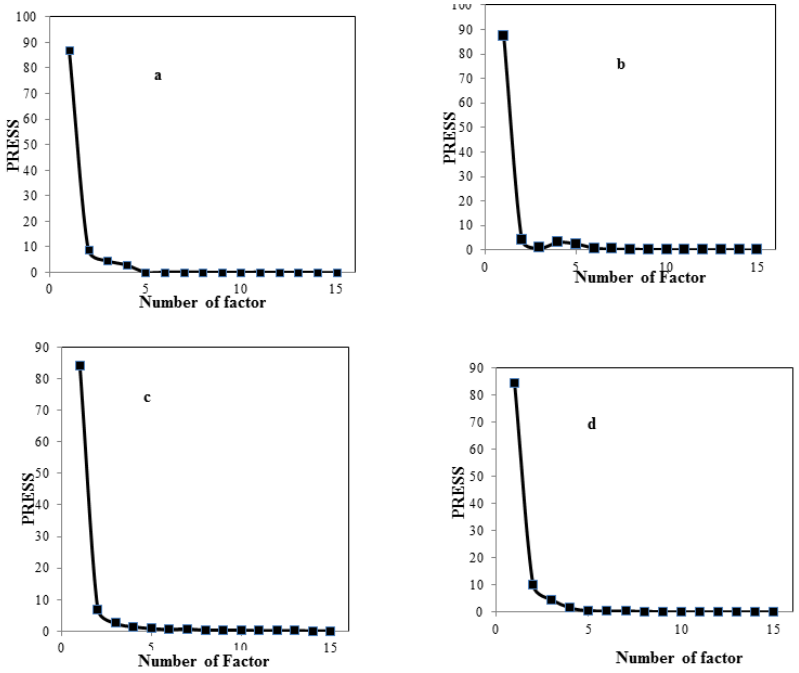

Figure 3. Plots of predictive residual error sum of squares (PRESS) versus number of factors by PLS model, acetaminophen (a), celecoxib (b), diazepam (c) and famotidine (d)

Table 2. Statistical parameter for acetaminophen, celecoxib, diazepam and famotidine in validation set of PLS model

	RMSD [a]	RED [b]	Recovery %	R2 [c]
acetaminophen	0.013	2.38	92.5	0.990
celecoxib	0.040	5.80	91.6	0.982
diazepam	0.014	5.00	93.3	0.984
famotidine	0.021	4.06	95.4	0.978

[a] RMSD calculated according to: RMSD= ((sum(Creal−Cfound) 2)/sum(Cfound) 2) 1/2.
[b] REP calculated according to: REP = 100 × ((sum(Creal−Cfound) 2)/n) 1/2.
[c] Correlation coefficient for plotting the Creal versus C found

Simultaneous determination of acetaminophen, celecoxib, diazepam, and famotidine in spiked real samples

To assess the applicability of the optimized model in practice, we further simultaneously determined the content of acetaminophen, celecoxib, diazepam, and famotidine in spiked hair, urban water, and hospital wastewater (Table 3 and Figure 4).

Table 3: Acetaminophen, celecoxib, diazepam and famotidine in spiked real samples by PLS

sample	Added Comp (ppm)	Found Comp1 (ppm)	Added Comp2 (ppm)	Found Comp2 (ppm)	Added Comp3 (ppm)	Found Comp3 (ppm)	Added Comp4 (ppm)	Found Comp4 (ppm)
Hair samples	10	8.10 (±0.55)	10	12.5 (±1.4)	10	9.7 (±0.1)	10	8.96(±1.4)
wastewater	5	5.41 (±0.46)	5	6 (±0.5)	5	4.5 (±0.3)	5	4.90(±0.44)
water	2	2.40 (±0.31)	10	9.9 (±2.2)	2	2.1 (±0.5)	10	11.1 (±0.9)

Comp1: Acetaminophen, Comp2: Celecoxibe, Comp3: Diazepam, Comp4: Famotidine

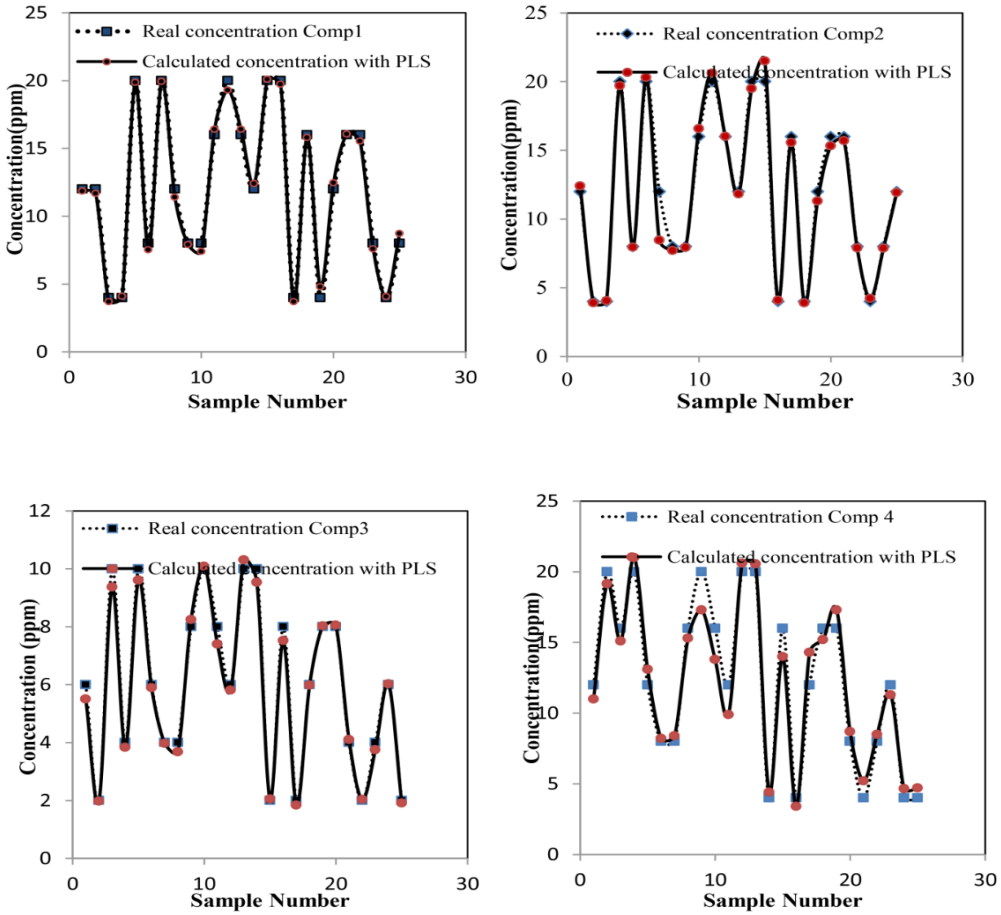

Figure 4: Real concentration versus calculated concentration by PLS for Comp1 (acetaminophen), Comp2 (celecoxib), Comp3 (diazepam) and Comp4 (famotidine)

Conclusion

Spectrophotometry method provides a simple and fast procedure for determining four currently used drugs in environmental and other real samples. The mixture of acetaminophen, celecoxib, diazepam, and famotidine is a complex system due to its high spectral overlapping between the absorption spectra of their individual component. Resolution of the mixture is accomplished by PLS.

Conflict of Interest

We have no conflicts of interest to disclose.

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