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Strategies for solving matrix effects in the analysis of sulfathiazole in honey samples using three-way photochemically induced fluorescence data

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Abstract

A widely employed compound for honey treatment, sulfathiazole (ST), was determined in commercial honey samples, employing a combination of photochemically induced fluorescence excitation–emission matrices (EEMs) and chemometric processing of the recorded second-order data. Parallel Factor Analysis (PARAFAC) and Self-Weighted Alternating Trilinear Decomposition (SWATLD) methods were used for calibration. An appropriately designed calibration with a set of standards composed of 18 samples, coupled to the use of the second-order advantage offered by the applied chemometric techniques, allowed quantitation of sulfathiazole in spiked commercial honey samples. No previous separation or sample pretreatment steps were required. The results were compared with other calibration methods such as N-PLS and PLS-1 that produced good results on synthetic samples but not on the investigated commercial honey samples.

Keywords: Honey; Sulfathiazole; Photochemically induced fluorescence; Pararell factor analysis (PARAFAC); Self-weighted alternating trilinear decomposition (SWATLD)

1. Introduction

Sulfonamides constitute a group of drugs which are widely used in veterinary and medical practice. Thus, residues of these drugs may remain in food of animal origin. Different methods of analysis of these drugs in foods and feeds have been reported [1,2]. In this context, the most investigated foods have been milk, honey, meat, fish and eggs [3–6]. The main part of the proposed methods are based on liquid chromatography with UV [6–8] or fluorimetric [3,9] detection. Spectrofluorimetric [10] and capillar electrophoresis [11] methods have been also established. For the determination of sulfonamides in honey HPLC [9,12,13] methods have been mainly proposed and only one photometric method has been established [14]. The European Legislation does not fix Maximum Residue Limits (LRM) for antibiotics in honey.

Sulfathiazole (ST), 4-amine-*N*-(2-tiazolil) benzenesulfonamide is used for the treatment of honey and the analysis of its residues is of interest. Total ST has been determined after acid hydrolysis and fluorimetric detection coupled to HPLC was performed by derivatization with fluorescamine [4–16]. Sulfathiazole such as the *N*-1-substituted sulfonamides, are weakly fluorescent compounds, but fluorescence emission of these drugs can be photoinduced by UV irradiation [10,17]. Because sulfonamides are polar compounds, severe matrix influences usually occur resulting in complicated clean-up procedures and low recoveries in food analysis.

Multivariate calibration is gaining acceptance for the determination of analytes in complex mixtures. Full-spectrum multivariate calibration methods offer the advantage of speed in the determination of the components of interest, avoiding separation steps in the analytical procedure. Partial

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least-squares (PLS) has become the usual first-order multivariate tool because of the quality of the obtained calibration models, the ease of implementation and the availability of software. An interesting characteristic of PLS is that calibration can be performed by ignoring the concentrations of all other components except the analyte of interest. However, all first-order methods, including PLS, are sensitive to the presence of unmodeled interferents. This situation is encountered when dealing with natural samples of complex composition, such as the presently studied honey samples.

A good alternative to the problem of unexpected interferents is to move to second-order data [18]. Examples of bilinear second-order data are LC–UV, GC–MS and excitation–emission fluorescence matrices (EEMs). Interestingly, the decomposition of a three-way data array (obtained when second-order data for a set of samples are grouped) is often unique, allowing relative concentrations and spectral profiles of individual sample components to be extracted directly. This permits correction for uncalibrated sample constituents, a property which has been named the "second-order advantage" [19]. It is fully exploited by the parallel factor analysis PARAFAC [20] and self-weighted alternating trilinear decomposition SWATLD [21] models, which operate in a three-step mode: (1) trilinear decomposition of the spectral cube formed by stacking the calibration matrices together with that of the unknown sample, (2) calibration of the concentration scale by linear regression and (3) prediction by inter or extrapolation of the unknown in the pseudo univariate graph. The PARAFAC algorithm is based on a least-squares minimization, whereas SWATLD uses a procedure known as alternating trilinear decomposition. EEMs have been used in combination with these chemometric methods for quantitative analysis of biological compounds. In this context, quantification of chlorophylls and pheopigments [22], antitumoral [23], anti-inflamatory [3] and anticonvulsant [23] drugs and antibiotics [4,24] have been proposed. On the other hand, the PARAFAC application to food samples has been scarce [5,6].

In this paper, PARAFAC and SWATLD methods have been applied to determine ST in honey using, for the first time, photochemically induced fluorescence excitation–emission matrices (PIF-EEMs). The results were compared with three-way matrix calibration data analysed by *N*-way partial least-squares regression (N-PLS), and two-way calibration data analysed by partial least-squares regression (PLS-1). The method allows to obtain ST concentration in complex honey sample matrices without interference from the matrix components.

2. Theory

2.1. Three-way trilinear data theory

When a sample produces a $J \times K$ data matrix as it is the case of PIF-EEMs (J = number of excitation wavelengths and K = number of emission wavelengths) the obtained set stacking the training matrices is a cube. For I samples the cube dimensions are $I \times J \times K$. Provided the data follow a trilinear model, the cube can be written as a sum of tensor products of three vectors for each fluorescent component. When $\mathbf{a}_n$, $\mathbf{b}_n$ and $\mathbf{c}_n$ collect the relative concentration ($I \times 1$), excitation ($J \times 1$) and emission ($K \times 1$) profiles for component n, respectively, the data cube $\underline{\mathbf{F}}$ can be written as [25,26]

$$\underline{\mathbf{F}} = \sum_{n=1}^{N} \mathbf{a}_n \otimes \mathbf{b}_n \otimes \mathbf{c}_n + \mathbf{E}$$

In this expression $\otimes$ indicates the tensor product, $\mathbf{E}$ is a residual error term with the same dimensions as $\underline{\mathbf{F}}$ and N is the total number of responsive components. The column vectors $\mathbf{a}_n$, $\mathbf{b}_n$ and $\mathbf{c}_n$ are collected into the three loading matrices $\mathbf{A}$, $\mathbf{B}$ and $\mathbf{C}$. An interesting characteristic of $\underline{\mathbf{F}}$ is that it can be decomposed giving access to spectral profiles $\mathbf{B}$ and $\mathbf{C}$, and relative concentration $\mathbf{A}$, of individual components in the I samples whether there are chemically known or not. In theory this characteristic should allow to obtain the concentration of calibrated components in the presence of any number of uncalibrated components.

We have used underlined bold capital letter for cubes; bold capital letter for matrices; bold lowercase for vectors and italics for scalars.

We have applied PARAFAC and SWATLD to obtain ST concentration in the presence of the uncalibrated components of the honey matrix. These two methods are becoming more and more employed by chemometricians for analyzing three-way data, and the software required for its implementation is easily available on the Internet [27]. Issues relevant to the application of the models are: (i) how to establish the number of components, (ii) how to identify specific components from the information provided by the array decomposition and (iii) how to calibrate the model in order to obtain absolute concentrations for a particular component in an unknown sample.

Bro [20] suggested obtaining the number of responsive components (N) by consideration of the internal parameter known as core consistency, which is a measure of how well a given model is able to reproduce the so-called Tucker core of a cube of data [28]. The core consistency is calculated as a function of a trial number of components. It remains near a value of 100 when the number is less than or equal to the optimum; for higher component numbers it drops below 50%.

Identification of the chemical constituent under investigation is done with the aid of the profiles $\mathbf{B}$ and $\mathbf{C}$, as extracted by PARAFAC and SWATLD, and comparing them with those of a standard solution of the analyte of interest.

Absolute analyte concentrations are obtained after proper calibration, since only relative values ($\mathbf{A}$) are provided by decomposing the three-way data array. Experimentally, this is done by using the information for the set of standards of known composition. The calibration procedure involves decomposing an array formed by joining the matrices for the I training samples with that for the unknown.

2.2. Figures of merit

Figures of merit furnished are the sensitivity (SEN), selectivity (SEL) and analytical sensitivity (γ). For an analyte SEN is defined as the net signal at unit concentration; SEL is the ratio between SEN and the total signal, as suggested by Kalivas and co-workers [29]. The analytical sensitivity (γ), as in univariate calibration, is the ratio between SEN and the spectral noise which is calculated by replicate blank measurements. The inverse (γ^{-1}) establishes the minimum concentration difference that can be appreciated by the method, regardless of the specific technique, equipment and scale employed [30]. The limit of detection (LOD) [31,24] is calculated as LOD = 3.3 S(o), where S(o) is the standard deviation in the concentration estimated for different blank samples.

2.3. Software

All calculations were done using MATLAB 5.3 [32]. A routine for PLS-1 was used following a previously known algorithm [24]. Those for N-PLS and PARAFAC are available on the Internet [27] although a useful MATLAB graphical interface was developed for easy data manipulation and graphics presentation [24]. This interface provides a simple mean of loading the data matrices into the MATLAB working space before running PARAFAC, SWATLD and N-PLS.

The calculated excitation and emission profiles provided by the former two are separately plotted, in order to allow users to identify the analyte of interest. The pseudo-univariate calibration graph [33] corresponding to this particular component is then displayed. Once this is done, the results are conveniently shown in terms of predicted concentration and analytical figures of merit.

3. Experimental

3.1. Apparatus and reagents

Fluorescence measurements were carried out on an Aminco Bowman Series 2 spectrofluorophotometer equipped with a 150 W Xe lamp, connected to a PC Pentium III microcomputer running under Windows 98 (through a GPIB IEEE-488 interface). Data acquisition and analysis were performed by the use of AB2 software. In all cases, 1.00 cm quartz cells were used.

An Osram 200 W HBO high pressure mercury lamp with an Oriel model 8500 power supply was used for irradiating ST solutions. The photochemical set-up included a light-box consisting of a fan, a mercury lamp and a quartz lens. A standard Hellma 1.00 cm quartz fluorescence cuvette was placed on an optical bench at 30 cm from the mercury lamp. The solutions were magnetically stirred during the UV irradiation.

Sulfathiazole is a non-fluorescent sulfonamide. The UV irradiation of its solutions induced a fluorescent emission (PIF) at 342 nm, when exciting at 251 nm. The emission signal is maximum in an ethanol:water (20:80)(v/v) and weakly acid medium. The pH is fixed with acetic/acetate buffer solution of pH 4.75, and the optimal irradiation time is 5 min. Under these conditions a linear relation PIF-ST concentration is found between 0.30 and 3.00 $\mu g\,mL^{-1}$.

The photochemically induced fluorescence excitation–emission matrices (PIF-EEMs) were measured every 5 nm in the excitation range comprised between 200 and 300 nm and every 1 nm in the emission range comprised between 300 and 400 nm. The ST photochemically induced fluorescence (PIF) emission spectrum was recorded between 300 and 400 nm, exciting at 251 nm.

All experiments were performed with analytical-reagent grade chemicals. Stock solutions consisted of 100 $\mu g\,mL^{-1}$ of ST (Sigma). Standard solutions of ST were obtained by suitable dilutions. Buffer solutions consisted of acetic acid/sodium acetate 0.5 M of pH 4.75.

Five honey samples from different countries were used: Spain, Germany, Belgium, Canada and Switzerland.

3.2. Recommended procedure for ST determination in honey

3.2.1. Honey samples

Honey of 10 g were weighed, and then contaminated by spiking known volumes of a concentrated ST aqueous solution. The samples were left at room temperature during 20 min and then diluted with deionised water to 100 mL in a volumetric flask. A suitable volume of this solution was placed in a 25 mL volumetric flask, and 3 mL of 0.5 M buffer solution, 5 mL of ethanol and deionised water were added to final volume.

3.2.2. Calibration and test sets

For calibration, six samples by triplicate set, making a total of 18 samples, was built (Cal1–Cal18). Sulfathiazole concentrations were comprised between 0 and 3 $\mu g\,mL^{-1}$. A suitable volume of this solution was placed in a 25 mL volumetric flask, and 3 mL of 0.5 M buffer solution, 5 mL of ethanol and deionised water were added to final volume. Honey and calibration samples were irradiated for 5 min. Additionally, six samples (Val1–Val6) were built with analyte concentrations different from those employed for calibration but within their corresponding calibration range. Table 1 summarize the used

Table 1
Calibration and test sets

Sample	Sulfathiazole ($mg\,L^{-1}$)	Sample	Sulfathiazole ($mg\,L^{-1}$)
Cal1	0.0	Val1	0.4
Cal2	0.5	Val2	0.8
Cal3	1.0	Val3	1.6
Cal4	2.0	Val4	1.8
Cal5	2.5	Val5	2.2
Cal6	3.0	Val6	2.6

concentration in calibration and test set. Emission spectra and EEMs were measured in random order.

4. Results and discussion

Fig. 1 shows the PIF-EEMs corresponding to a standard ST sample in wide spectral emission and excitation ranges, showing the presence of Rayleigh scattering. To avoid the presence of signals that are uncorrelated with the target concentrations of the studied analyte, EEMs were in all cases recorded in the sensible excitation and emission ranges shown in Fig. 2A and B, where only the analyte contributes to the overall fluorescence intensity, that is, emission from 300 to 400 nm at 1 nm intervals and excitation from 210 to 290 nm at 5 nm intervals. It can be observed that the fluorescent components of honey show signal overlapping with the ST signal. Thus, if the second-order advantage is not used the analysis is not possible. In this context, PARAFAC and SWATLD methodologies have been applied to obtain higher spectral information and a greater spectral differentiation between the honey components and the analyte.

4.1. Test set results

Unidimensional fluorescence emission data recorded for the calibration samples (at the compromise excitation wavelength of 251 nm) were first analyzed using the PLS-1 method. Leave one out cross-validation was applied to the set of calibration samples leading to an optimum number of factors equals to 2, as estimated according to Haaland's criterium [34]. Prediction on the six test samples using this PLS-1 model led to good recoveries. Three-way EEM data for the test set of six samples were also analyzed by N-PLS, PARAFAC and SWATLD. Specific details on the implementation of PARAFAC and SWATLD methods will be given below in connection with the study of honey samples. Indeed, these models give comparably good results, for the set of artificial samples, composed of only sulfathiazole, as summarized in Table 2.

4.2. Honey samples results

The results obtained for honey samples contaminated with ST clearly illustrate the meaning and usefulness of the second-order advantage. On the basis of models trained with the calibration samples Cal1–Cal18, neither PLS-1, nor N-PLS (modelled with unidimensional emission spectra and EEMs, respectively) was able to produce acceptable results on honey samples. Specifically, relative errors of prediction (REP) were unacceptably large in all cases. The results obtained with N-PLS and PLS-1 are collected in Table 3. This is due to the presence of fluorescent honey components whose influence has not been taken into account in the calibration set. These components not only exhibit emission intensities that overlap with the fluorescence signal from the analyte (Fig. 2A) but are also intrinsically variable and,

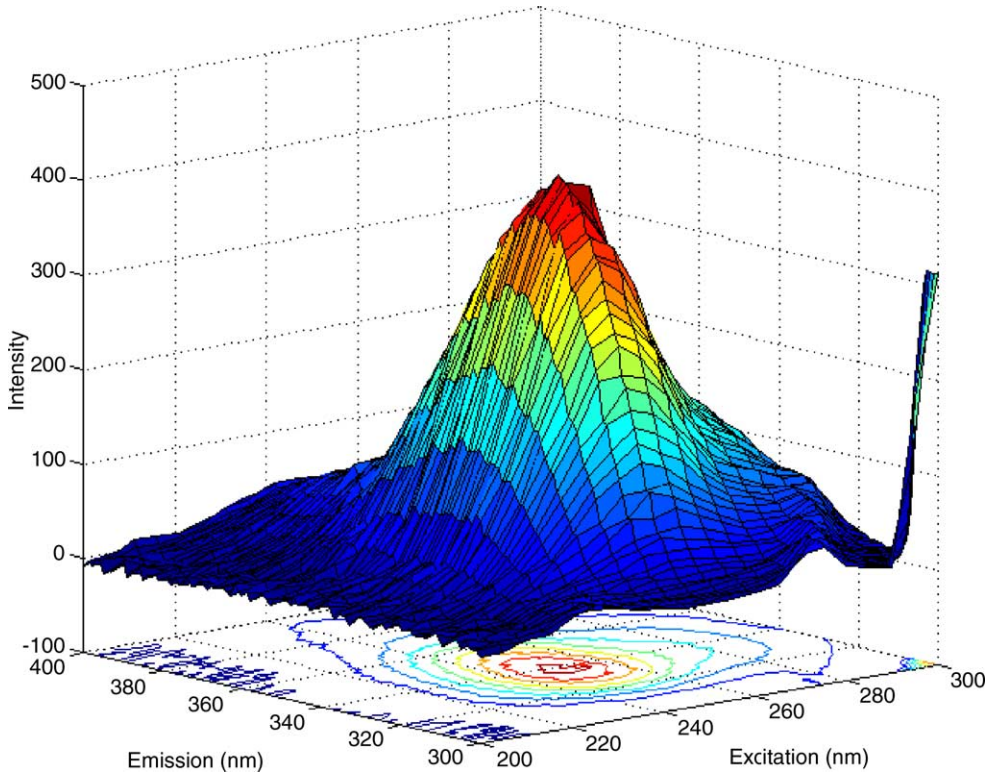

Fig. 1. Three-dimensional plot of the EEM for standard sample of ST, showing the presence of Rayleigh scattering.

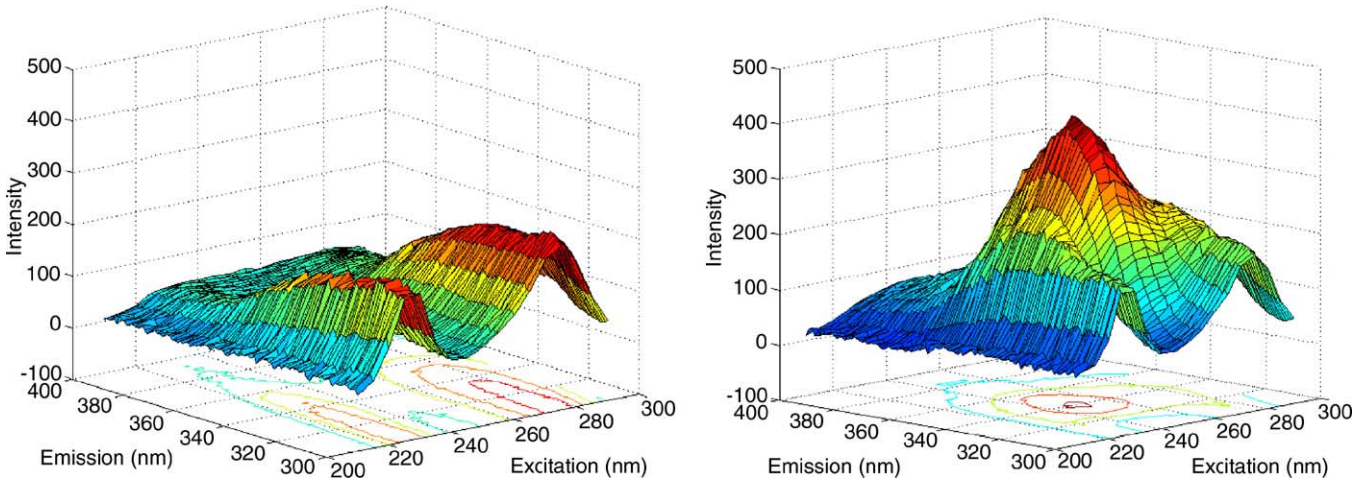

Fig. 2. Three-dimensional plot of the EEM for honey sample recorded in restricted excitation and emission wavelength ranges. EEM (A) for an uncontaminated sample and (B) for a contaminated sample.

Table 2
Predictions in artificial samples applying different calibration methods

Component	Method							
	PLS-1		N-PLS		PARAFAC		SWATLD	
	REP (%)	%R[a]	REP (%)	%R[a]	REP (%)	%R[a]	REP (%)	%R[a]
Sulfathiazole	2.8	104 (2)	3.0	104 (2)	2.8	103 (2)	2.6	103 (2)

REP (%): relative error of prediction; %R: average recovery.
[a] Values between parentheses correspond to the standard deviations computed for the recoveries of the six test samples.

thus, difficult to model if the second-order advantage is not employed.

Although N-PLS is an efficient way of handling three-way data such as those presently employed, this regression model cannot be trained by including the unknown sample into the calibration data cube, since concentration information is unavailable for unknowns. For reasons explained above, N-PLS do not allow obtaining information on uncalibrated interfering agents, such as honey.

PARAFAC and SWATLD were applied, separately for each type of honey, to data cubes formed by PIF-EEMs for six calibration samples, prepared by triplicate (Cal1–Cal18), together with a honey sample. The concentrations of these samples are comprised into the range of linearity above mentioned in the PIF method.

For selecting the number of spectral components for each honey sample the core consistency analysis has been applied [28]. Fig. 3 shows the value obtained for the 18-sample cube when studying the honey sample from Spain. As can be seen, the core consistency drops to a very low value when using

Table 3
Results obtained when applying PLS-1 and N-PLS analysis to honey samples contaminated with sulfathiazole

Added	Predicted (PLS-1/N-PLS)[a]				
	Spain	Germany	Belgium	Canada	Switzerland
–	0.20/0.90	0.10/0.51	0.30/1.39	0.09/0.50	0.43/1.22
0.10	0.60/0.96	0.21/0.60	0.58/1.49	0.20/0.62	0.48/1.33
0.30	0.95/1.28	0.70/0.95	0.75/1.70	0.50/0.70	0.75/1.60
0.70	1.15/1.48	0.90/1.25	1.02/1.95	0.8/1.10	1.18/1.87
1.70	2.06/2.26	1.85/2.14	1.86/2.60	1.80/2.09	1.92/2.66
RMSEP	0.2/06				
REP (%)	26.8/73.5				

RMSEP: root-mean-square error of prediction; REP (%): relative error of prediction.
[a] Sulfathiazole concentration (μg mL^{-1}) predicted. In all cases, the number of spectral components is 2.

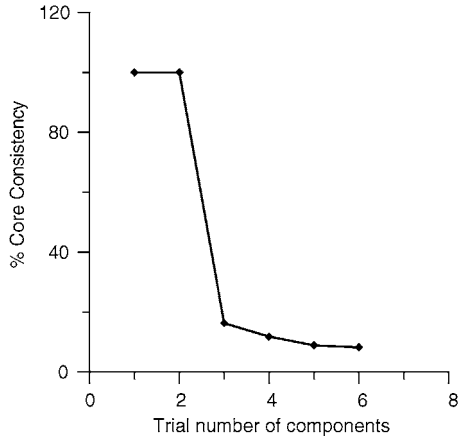

Fig. 3. Plot of the PARAFAC core consistency values as a function of the trial number of components, for the cube composed of the EEM for the sample of honey from Spain, and the 18 calibration EEMs.

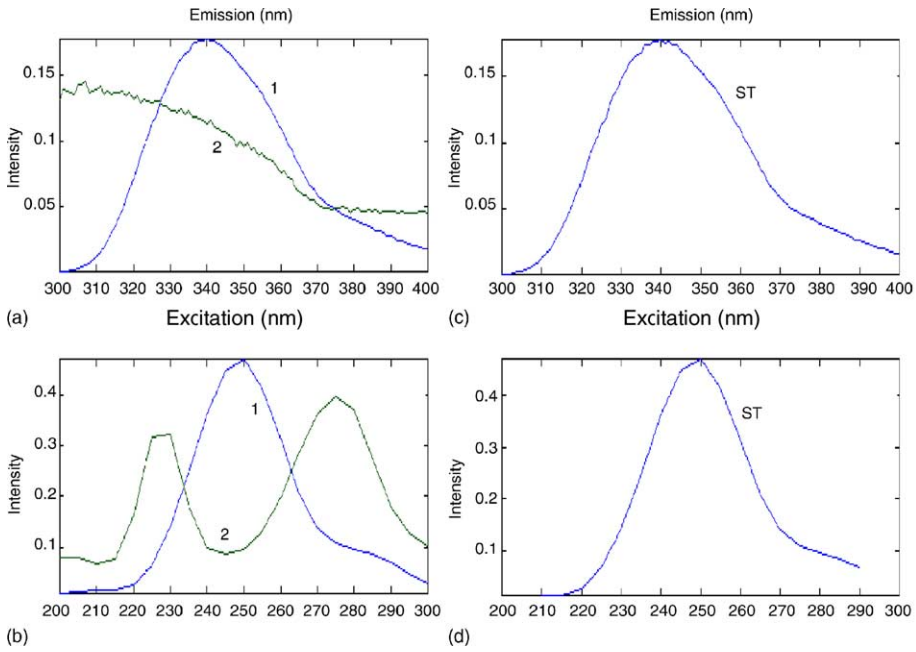

Fig. 4. (a) Emission profiles provided by a two components PARAFAC model (**B** matrix) used to process the cube formed by sample honey from Spain and the 18 calibration samples. The components are labeled according to the contribution of the overall variance. (b) Excitation profiles (**C** matrix). (c) Normalized experimental emission spectra for the one studied analyte, using λ_{exc} = 250 nm. (d) Normalized experimental excitation spectra (λ_{em} = 340 nm).

three spectral components to model the cube, suggesting that $N = 2$ is a sensible choice. The same number of factors was also found for the remaining honey samples, showing that although the calibration samples were built starting from the one pure analyte, the presence of honey adds new fluorescent components to the data cube, collectively considered as a single extra component by PARAFAC and SWATLD.

Fig. 4 shows the plot of loading matrices provided by PARAFAC when processing the honey sample from Spain, together with the calibration set, excitation and emission spectral profiles **B** and **C** (Fig. 4a and b). The components have been labelled with the order assigned by the model. In this case, analyte appears in the first place because it is the origin of the main fluorescence intensity. PIF-emission and PIF-excitation experimental spectra of pure standard ST (Fig. 4c and d), have been compared allowing to assign component 1 to ST and component 2 to matrix honey.

The prediction results for the honey samples are listed in Tables 4 and 5. Honey samples contaminated with 10, 30, 70 and 170 $\mu g\,ST\,g^{-1}$ of honey that are equivalent, according to the sample procedure, to ST concentrations of 0.10, 0.30, 0.70 and 1.70 $\mu g\,mL^{-1}$ into the 25 mL volumetric flacks, respectively, were used. The statistical analysis shows mean prediction errors for sulfathiazole determination that are comparable to those found in the artificial samples.

4.3. Figures of merit

The study based on PARAFAC and SWATLD pseudo-univariate calibration also furnishes figures of merit. The standard errors in predicted concentrations have been reported in Tables 4 and 5. The root-mean-square error of prediction, $\mathrm{RMSEP} = [1/(I-1)\sum_1^I (C_{act} - C_{pred})^2]^{1/2}$, where

Table 4
Results obtained when applying PARAFAC analysis to honey samples contaminated with sulfathiazole

Added	Predicted				
	Spain[a]	Germany[a]	Belgium[a]	Canada[a]	Switzerland[a]
–	0.001 (0.01)	–	0.002 (0.01)	–	–
0.10	0.091 (0.01)	0.089 (0.01)	0.089 (0.006)	0.088 (0.007)	0.09 (0.01)
0.30	0.29 (0.01)	0.28 (0.01)	0.29 (0.01)	0.28 (0.01)	0.28 (0.01)
0.70	0.65 (0.02)	0.70 (0.02)	0.69 (0.01)	0.64 (0.01)	0.72 (0.02)
1.70	1.56 (0.06)	1.69 (0.06)	1.65 (0.06)	1.58 (0.07)	1.57 (0.06)
RMSEP	0.03				
REP (%)	4.2				

RMSEP: root-mean-square error of prediction; REP (%): relative error of prediction.
[a] Sulfathiazole concentration ($\mu g\,mL^{-1}$) predicted. Standard deviation in parentheses. In all cases, the number of spectral components is 2.

Table 5
Results obtained when applying SWATLD analysis to honey samples contaminated with sulfathiazole

Added	Predicted				
	Spain[a]	Germany[a]	Belgium[a]	Canada[a]	Switzerland[a]
–	–	–	–	–	–
0.10	0.10 (0.01)	0.10 (0.01)	0.09 (0.01)	0.089 (0.007)	0.09 (0.01)
0.30	0.29 (0.01)	0.29 (0.01)	0.30 (0.01)	0.28 (0.01)	0.28 (0.01)
0.70	0.66 (0.02)	0.70 (0.02)	0.69 (0.01)	0.64 (0.01)	0.72 (0.02)
1.70	1.58 (0.05)	1.70 (0.06)	1.67 (0.06)	1.58 (0.05)	1.55 (0.06)
RMSEP	0.02				
REP (%)	2.8				

RMSEP: root-mean-square error of prediction; REP (%): relative error of prediction.
[a] Sulfathiazole concentration ($\mu g\,mL^{-1}$) predicted. Standard deviation in parentheses. In all cases, the number of spectral components is 2.

Table 6
Analytical figures of merit

	PARAFAC	SWATLD
Sensitivity (SEN), FU ($L\,mg^{-1}$)	1.77	1.72
Selectivity (SEL)	0.85	0.86
γ^{-1} ($L^{-1}\,mg$)	0.005	0.005
LOD ($mg\,L^{-1}$)	0.02	0.02

FU: fluorescence units (arbitrary).

I is the number of prediction samples, C_{act} and C_{pred} are the actual and predicted concentrations, respectively; and relative error of prediction REP (%) $= (100/\bar{c}) \times$ RMSEP, where $\bar{c}$ is the average component concentration, are included.

The standard deviation in the concentration (S(o)) was estimated for nine different blank samples. The analytical figures of merit for both methods are collected in Table 6.

In order to gain further insight into the accuracy of these methods, linear regression analysis of nominal versus found concentration values was applied for each procedure. The estimated intercept and slope ($\hat{a}$ and $\hat{b}$, respectively) were compared with their ideal values of 0 and 1 using the elliptical joint confidence region (EJCR) test [35]. Fig. 5 shows the EJCRs for the two employed modes when either PARAFAC or SWATLD are applied. As can be seen, the ellipses contain the theoretical ($a = 0$, $b = 1$) point, but the elliptic size corresponding to the PARAFAC algorithm mode is significantly larger. From the inspection of Fig. 5 it can be concluded on improvement in the predictive ability of SWATLD compared to PARAFAC.

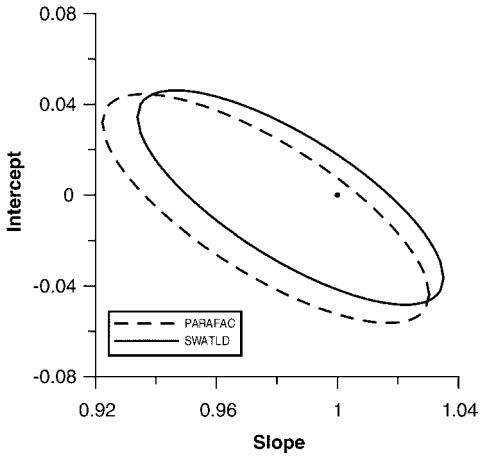

Fig. 5. EJCRs for the slope and intercept corresponding to regressions of predicted vs. added concentrations of sulfathiazole applying PARAFAC and SWATLD. The black circle mark the theoretical ($a = 0$, $b = 1$) point.

5. Conclusions

The fluorimetric determination of sulfathiazole (ST) using second-order multivariate calibration techniques is demonstrated to be feasible. A photoinduced previous process drastically increases the native ST fluorescence. The application of the second-order advantage by using the three-dimensional excitation–emission matrices, allows the ST determination in the presence of unknown interferences in ST spiked honey samples. Slightly better results in the honey samples analysis are obtained by application of SWATLD calibration compared to PARAFAC. Adequate recovery values are obtained in all cases when several honeys from different countries are analyzed. The proposed methodology has demonstrated to be adequate for routine analysis in the control of contamination of sulfathiazole in honey.

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