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Application of PLS and PARAFAC in simultaneous spectrophotometric determination of oxytetracycline, tetracycline and doxycycline in honey samples

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Abstract

A simple, sensitive, rapid and precise spectrophotometric method has been developed and validated for simultaneous determination oxytetracycline (OTC), tetracycline (TC) and doxycycline (DXC) in honey samples. Chemometrics methods suitable for overlapping spectra and have resolved successfully the overlapping bands. Two chemometrics techniques parallel factor analysis (PARAFAC) and partial least square (PLS) were applied to the determination of TCs in their ternary mixture and the proposed calibration techniques were validated by analyzing synthetic mixtures consisting of these drugs. The calibration and validation sets were constructed with solutions in the concentration ranges from (0.1-16) μgmL^{-1} for TC, (0.1-30) μgmL^{-1} and (0.1-20) μgmL^{-1} for DXC and OTC. The procedure was repeated at different pH values. Partial least squares (PLS) models were built at each pH and used to determinate a set of synthetic mixtures. The best model was obtained at pH =8.0. The PARAFAC model was applied to a three-way array constructed using all the pH data sets and enable better results. The RMSEP for DXC, OTC and TC with PLS and PARAFAC were 0.123, 0.236, 0.167 and 0.0196, 0.0480, 0.0316 respectively.

Keywords: PLS, PARAFAC, tetracyclines, simultaneous spectrophotometric

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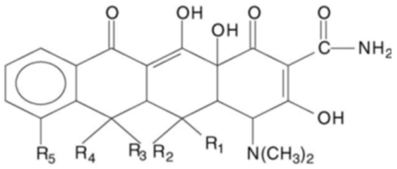
Introduction

Tetracycline (TC), Oxytetracycline (OTC) and Doxycycline (DXC) are members of the tetracycline group of broad-spectrum antibiotics (Goodman & Gilman, 1996), widely are used in human and animals. Fig. 1 shows the chemical structures of tetracycline, oxytetracycline and doxycycline studied in this project. The main applications of tetracyclines in animal husbandry are for preventative treatment of bacterial infections and to increase growth rates (Elmund *et al.,* 1971).



	R_1	R_2	R_3	R_4	R_5
Tetracycline	H^-	H^-	OH-	CH_3^-	H^-
Oxytetracycline	H^-	OH-	OH-	CH_3^-	H^-
Doxycycline	H^-	OH^-	H^-	$CH3^-$	H^-

Fig. 1- Structures of the tetracyclines

Tetracyclines are also prescribed in aquaculture to control infections in salmon, catfish, and lobsters, sprayed onto fruit trees and other plants to treat infection by *Erwinia amylovara*, injected into palm trees to treat *Mycoplasma* infections (lethal yellow), and used to control infection of seeds by *Xanthomonas campestris*. They have also been applied in the treatment of bee livestock to foulbrood disease of the honeybee, which is caused by either *Bacillus larvae or Streptococcuspluton* (Wegener *et al.,* 2007). These substances remain as residues in animals, fish and birds, and are harmful to humans at quite low levels. It is necessary to take into account that the level dosages in animals are higher than in human patients and because of this, considerable amounts of these drugs could be accumulated into alimentary derivatives (e.g. milk, honey, meat, etc.). Analytical control is necessary because of the possible toxic, allergic reactions, liver damage, yellowing of teeth, and gastrointestinal and generally leads to a change in the balance of the intestinal flora (Espinosa-Mansilla *et al*., 1995, Robert, 1996, Ni *et al*., 2011). Most chromatographic methods such as HPLC (Fritz & Zuo, 2007, Biswas *et al.*, 2007), thin layer chromatography (Crecelius *et al.,* 2002), capillary electrophoresis (Wei *et al*., 2003, Casado-Terrones *et al.,* 2007), are employed successfully in the monitoring of TCs in tissue samples with different detection modes such as UV-spectrophotometry, fluorescence, and mass spectrometry in the past (Kennedy *et al*., 1998, Capolongo *et al.*, 2002, Cinquina *et al*., 2003). These methods with, pretreatment have been used in the past, but they involve tedious prior extraction steps. The fast advances in pharmaceutical industry impose the development of more rigorous analytical methods, particularly faster and inexpensive, for the quality control of pharmaceutical products. Spectrophotometric methods are the most widely used for the determination of tetracyclines in bulk and pharmaceutical preparations. They usually form, based on their reaction with different reagents such as cupric chloride (Suha, 1989), Diphenyl-1-Picrylhydrazyl (DPH) (Emara *et al*., 1991), and WO_4^{2-} (Al-Tamrah & Alwarthan, 1992), 4-aminophenazone and hexacyanoferrate (III) (Karlicek & Solich, 1994). In the recent years, the interest in the analytical applications of derivative spectrophotometry has been increasing. The principle advantage of the derivative measurements is the improvement in the detectability of minor spectral peaks. Only few methods are reported in the literature for the derivative spectrophotometric determination of tetracyclines. Derivative techniques

are good tools for the simultaneous resolution of organic compounds in the base of spectroscopic properties, but normally only two compounds can be determined due to considerable spectral overlapping between these drugs. Actually, a more powerful way to treat the ternary and more complex mixtures of organic compounds, which exhibit similar spectral characteristics, is the application of multivariate analysis methods (Espinosa-Mansilla *et al.,* 1995). Chemometrics calibration techniques such as principal component regression, partial least square regression and multiple linear regression (MLR). Various chemometrics methods with different determination techniques have been used for drug and milk analysis (Garcia *et al.,* 2004, Rodriguez *et al.,* 2009). The PARAFAC and N-PLS regression methods are well known chemometrics tools involving factor analysis and have successfully been applied to the spectral data analysis (Murphy *et al.,* 2013). Niazi *et al.* applied PARAFAC and PLS to spectrophotometric determination of tetracycline (Niazi & Sadeghi, 2006). Valverde *et al.* applied a method using photochemically induced fluorescence signals combined with both first and second-order multivariate calibrations, PLS and parallel factor modeling (PARAFAC), N-way partial least-squares (NPLS) and bilinear least squares (BLLS) for analysis of a mixture of three TCs in surface water samples (Valverde *et al*., 2006a,b).

The aim of this work is to develop a very simple and sensitive method for determination of tetracycline, oxytetracycline and doxycycline based on spectrophotometric methods and chemometrics approaches. In this study, two chemometrics techniques PARAFAC and PLS were applied to the determination of TCs in their ternary mixture and the proposed calibration techniques were validated by analyzing synthetic mixtures consisting of these drugs. The methods were subjected to the real samples and successful results were obtained.

Experimental

Reagents

All chemicals were of analytical reagent grade. OTC, TC and DXC antibiotics and obtained from Sigma. Individual stock solutions of TC, OTC, and DXC (0.5 mg/mL) were prepared by dissolving 5mg of the analytical standards in 10mL of methanol and stored in the dark at 20ºC for up to one month. Na_2EDTA-Mcllvaine buffer solution (pH=4.0) was prepared by dissolving 15 g of disodium hydrogen phosphate dehydrate (Merck, Germany), 13 g of citric acid monohydrate (Merck, Germany) and 3.72 g of EDTA (Merck, Germany) in water and diluting to 1 L. Universal buffer solutions in the pH range from 2.0-12.0 were prepared by it mix 0.04 M H_3BO_3, 0.04 M H_3PO_4 and 0.04 M CH_3COOH that has been titrated to the desired pH with 0.2 M NaOH. A solution of trichloroacetic acid (10% w/v) was prepared in water. All the solutions were prepared in deionized water.

Apparatus and Software

A Varian (Cary 100bio) spectrophotometer controlled by a computer and equipped with a 1-cm path length quartz cell was used for UV-Vis spectra acquisition. Spectra were acquired between 220 and 500 nm (1 nm resolution). A Sartorius pb-11 pH-meter furnished with a combined glass saturated calomel electrode was calibrated with at least two buffer solutions at pH 3.00 and 9.00. The N-way toolbox for Matlab 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 4.0 (Eigenvector Technologies).

Procedure

The calibration set was constructed according to a 2^3 + 1 (three factors at two levels plus one central point) experimental design (Table 1). The TC solutions were in the (0.1-16.0) $\mu gmL^{-1}$and DXC solutions were in the (0.1-30.0) μgmL^{-1} and the OTC solutions were in the (0.1-20.0) μgmL^{-1} range. The synthetic mixtures used to validate the model. Known amounts

of standard and validation solutions were placed in a 10 mL volumetric flask and completed to the final volume with buffer at different pH. Absorbances of solutions were read against buffer with different blank.

Honey Samples

A honey sample (5.0 gr), was dissolved in 30 ml water in a beaker, and sonicated for 5 min, until a clear solution was obtained. Then was filtered in order to remove any solid impurities. This solution was transferred to a 50 ml volumetric flask and diluted to the mark with distilled water. 2 mL of this solution was placed in a polypropylene tube and dissolved in 5 mL of

Table 1- 2^3 +1 experimental design for the calibration set

Analyte	Solution								
	1	2	3	4	5	6	7	8	9
DXC	+	+	+	-	-	-	+	-	~
OTC	+	+	-	+	-	+	-	-	~
TC	+	-	+	+	+	-	-	-	~

Na_2EDTA-McIlvaine buffer (pH 4.0). Then spiked with known variable amounts of TCs. The sample solution was shaken for 2 min on a vortex at high speed and then centrifuged for 5 min at 8,000 rpm. The supernatant solution was collected and filtered through a 0.45 µm Micropore filter. This solution was transferred to a 10 ml volumetric flask and diluted to the mark with universal buffers. Blank samples were prepared in the same way as above, but without the compound-spiking step.

Results and discussion

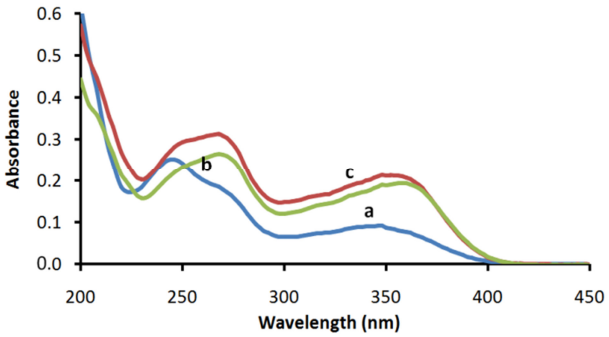


Fig. 2- Absorption spectra of (a) DXC, (b) OTC and (c) TC at pH=8.0

Fig. 2 displays the UV absorption spectra for aqueous solutions of TC, DXC and OTC at pH 8.0. As can be observed, there is a strong overlap among the spectra, which prevents the use of univariate calibration. Their UV spectra show strong absorptions around 270 and 360 nm in neutral and acidic solutions.

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 (Niazi & Yazdanipour, 2007). 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***-loadings are the relative concentrations of the TCs in the mixtures. In the calibration step, these loadings are regressed against the real concentrations of each TCs in the mixtures to get a linear calibration line (Ghasemi & Niazi, 2005). In the prediction step, this regression line can then be used to predict (if any new interference is present) the concentration of each TCs in future test samples. In this study, we selected the pH = 2.0, 5.0, 6.0, 7.0, 8.0 and 11.0 for three-way data. The data were arranged in a three-way array 9×281×6, composed of 9 solutions, with different TCs concentrations (Table 1), in the rows, 281 wavelengths in the columns and 6 pH values in the slices. An important parameter to determine is the number of PARAFAC components, which are necessary to build the data. Several methods can be used to determine this parameter, such as split-half Analysis, investigation of residuals, etc. In this work, the method used is core consistency diagnostic (CORCONDIA).

Core consistency diagnostic (CORCONDIA)

All data sets (9 × 281 × 6) were utilized for the core consistency evaluation, using one of five factors. The core consistency diagnostic (CORCONDIA) is defined as:

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

The core consistency diagnostic (CORCONDIA) is defined as: CORCONDIA where g_{def} is the calculated element of the core using the PARAFAC model, defined by dimensions (d×e×f); t_{def} is the element of a binary array with zeros in all elements and ones in the superdiagonal, and F is the number of factors in the model. In the 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 the core consistency diagnostic test. This diagnostic tool indicated that N=3 was the correct choice. Because the utilization of more factors lead to a great decrease of the core consistency (Trevisan & Poppi, 2003). Three factors give a CORCONDIA value of 100% (a perfect trilinear model) whilst, when using four or more factors, this value diminishes to values below to 1%. The results are also shown in Table 2.

Table 2- Fit values and core consistency diagnostic values in percentages vs. the number of components in the PARAFAC model

Number of factors	1	2	3	4	5
CORCONDIA (%)	100	95.62	86.42	0.56	0.12
Fit (%)	95.61	96.55	99.65	99.66	99.68

Method validation

PARAFAC model was employed to decompose the three-way calibration data set. The first analytical curves were built up by adjusting a linear model between loadings obtained after PARAFAC decomposition against each analyte concentration in the calibration data set to obtain a linear calibration for the measured concentration of the each analyte. The correlation coefficients of the calibration curves equation indicate that a good linear regression between the loadings and the concentrations were established. Linear regression results and standard deviation of results and correlation coefficient are summarized in Table 3. The results obtained by applying PARAFAC to

seven synthetic samples are listed in Table 4. Table 4 also shows the recovery for prediction series of TCs and root mean square error of prediction (RMSEP) and relative standard error of prediction (RSEP). The prediction results for TCs are very good.

Table 3- Statistical parameters of the linear relationship between the proportion loadings calculated by PARAFAC and the true concentration DXC, TC, OTC

	DXC	TC	OTC
Number of data points	9	9	9
Intercept	0.0596	0.0869	0.0412
Standard deviation of intercept	0.0321	0.0238	0.0112
Slope	0.6821	0.5409	0.7412
Standard deviation of slope	0.0271	0.0301	0.0261
Correlation coefficient	0.9982	0.9979	0.9991
Standard deviation of regression	0.0302	0.0192	0.0103

Table 4- Concentration Data of the validation and Prediction Set of TC, DXC, OTC for PARAFAC models (µgmL^{-1})

Validation			Prediction			Recovery%		
DXC	**OTC**	**TC**	**DXC**	**OTC**	**TC**	**DXC**	**OTC**	**TC**
5	8	12	4.98	8.02	12.03	99.6	100.2	100.2
12	2	5	12.01	1.99	5.01	100.1	99.5	100.2
5	16	5	5.02	16.11	5.03	100.4	100.7	100.6
2	2	2	2.01	1.98	2.02	100.5	99.0	101.0
10	10	10	10.02	10.00	10.06	100.2	100.0	100.6
4	6	5	4.03	6.03	4.99	100.7	100.5	99.8
RMSEP			0.0196	0.0480	0.0316			
RSEP%			0.27	1.01	0.429			

PLS analysis

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), 9 solutions were used to construct the models (calibration set) and another six solutions to validate them (validation set). The models were validated using cross validation. The root mean square error of prediction (RMSEP) and relative standard error of prediction (RSEP) values were used as parameters for comparison among the models. 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.

Table 5- Added and found results of the prediction set of DXC, OTC and TC using PLS method at different pH (_µgml^{-1})

Added			PLS-PH1 (pH = 2.0)			PLS-PH2 (pH = 5.0)			PLS-PH3 (pH = 6.0)		
DXC	**OTC**	**TC**	**DXC**	**OTC**	**TC**	**DXC**	**OTC**	**TC**	**DXC**	**OTC**	**TC**
5	8	12	4.78	8.20	12.55	4.81	8.19	12.28	4.82	8.21	12.26
12	2	5	12.18	2.11	5.18	12.29	2.19	5.19	12.26	2.16	5.17
5	16	5	5.26	16.44	5.15	5.36	16.49	5.19	5.31	16.71	5.14
2	2	2	2.21	1.89	1.86	2.26	1.76	1.82	2.19	1.89	1.79
10	10	10	10.24	9.87	10.29	10.26	9.62	10.75	10.24	9.60	10.89
4	6	5	4.14	6.42	4.79	4.16	6.49	4.52	4.26	6.59	4.61
NF			5	5	5	6	6	3	6	6	6
RMSEP			0.212	0.274	0.290	0.26	0.339	0.293	0.373	0.426	0.429
RSEP%			2.87	2.29	2.90	3.50	2.65	2.90	3.36	2.94	3.52

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

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

Determination of TC, DXC and OTC in synthetic solution

The predictive ability of both two- and three-way models at each pH was determined using six synthetic solutions (their compositions are given in Table 5). The results obtained by applying PLS at each pH to six 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 PH5 (pH =8.0) is the best model.

Table 5- continue

PLS-PH4 (pH = 7.0)			PLS-PH5 (pH =8.0)			PLS-PH6 (pH = 11.0)		
DXC	OTC	TC	DXC	OTC	TC	DXC	OTC	TC
4.81	8.19	12.29	4.88	8.16	12.23	4.62	8.23	12.61
12.27	1.66	5.19	12.11	1.92	5.09	12.65	1.85	5.23
5.29	16.78	5.16	5.11	16.48	5.12	5.61	16.95	5.48
2.16	1.91	1.82	2.09	1.94	1.89	2.16	1.76	1.48
10.26	9.75	10.93	10.11	9.81	10.27	10.36	9.64	10.89
4.29	6.61	4.59	4.19	6.18	4.91	4.61	6.78	4.26
5	5	4	5	5	4	6	7	4
0.363	0.448	0.449	0.123	0.236	0.167	0.491	0.543	0.614
4.90	3.01	3.60	1.67	3.85	2.22	3.75	5.95	7.98

Determination of TC, DXC and OTC in honey

In order to show the analytical applicability of the proposed methods, first calibration curve obtained from PARAFAC and PLS model at PH5 (pH =8.0) were applied to determination of for TC, DXC and OTC in real samples (honey). The results showed that satisfactory recovery for TC, DXC and OTC could be obtained (Table 6) using the recommended procedures. Results of the determination are summarized in Table 6. The data obtained by these methods reveal the capability of the methods for determination of TCs in real samples

Table 6- Determination of TC, DXC and OTC in honey using PARAFAC and PLS-PH5 models (µgmL^{-1})

Type of samples		Added (ppm)	Amount Found (PARAFAC)	Recovery (%)	RSD%	Amount found (PLS-PH5 (pH =8.0))	Recovery (%)	RSD%
Honey Sample 1	TC	2	1.91	95.5	0.06	1.74	87	0.21
	DXC	2	1.96	98	0.08	1.62	81	0.19
	OTC	2	2.05	102.5	0.07	2.29	114.5	0.16
Honey Sample 2	TC	4	4.02	100.5	0.05	4.13	103.2	0.17
	DXC	4	4.01	100.2	0.07	3.77	94.2	0.23
	OTC	4	3.97	99.2	0.04	3.76	94	0.15

Conclusion

Most of the methods for the determination of antimicrobials described in Pharmacopoeias recommend analysis by HPLC. The proposed chemometrics techniques are rapid, precise and accurate for the simultaneous quantitative resolution of the veterinary formulation, as well as for the simultaneous analysis of the mixtures containing drugs having overlapped spectra. Multivariate calibration models using PLS at different pH and PARAFAC were elaborated for TCs quantitation. The best models for the system were obtained with PARAFAC and PLS at pH5 (pH =8.0). 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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کاربردPLS و PARAFAC در اندازه‌گیری هم زمان اسپکتروفتومتری اکسی تتراسایکلین، تتراسایکلین و داکسی سایکلین در نمونه‌های عسل

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چکیده

روش ساده، حساس، سریع و دقیق اسپکتروفتومتری برای اندازه‌گیری هم‌زمان تتراسایکلین (TC)، اکسی تتراسایکلین (OTC) و داکسی سایکلین (DXC) در نمونه‌های عسل به‌کارگرفته شد. روش‌های کمومتریکس برای اندازه‌گیری ترکیباتی است که با یکدیگر همپوشانی طیفی دارند. در این تحقیق، دو روش کالیبراسیون کمترین مربعات جزیی (PLS) و آنالیز فاکتورهای موازی (PARAFAC) برای اندازه‌گیری تتراسایکلین‌ها استفاده شد. محدوده خطی کالیبراسیون برای تتراسایکلین ۱۶-۰/۱، اکسی تتراسایکلین ۲۰-۰/۱ و داکسی‌سایکلین ۳۰-۰/۱ میکروگرم بر میلی‌لیتر است. دو سری محلول شامل سری کالیبراسیون و سری پیش‌گویی غلظت‌ها ساخته شده و آزمایش در pHهای مختلف تکرار شد. توسط سری کالیبراسیون مدل PLS در هر pH ساخته شده و سپس این مدل‌ها برای پیش‌گویی غلظت در سری نمونه‌های سنتزی مورد استفاده قرار گرفت. با مقایسه خطای مرحله پیش‌گویی، بهترین مدل در pH= ۸/۰ انتخاب شد. با استفاده از داده‌های طیفی حاصل از pHهای مختلف، مدل ۳ بعدی PARAFAC طراحی شد. RMSEP برای DXC، OTC و TC با PLS و PARAFAC به‌ترتیب ۰/۱۲۳، ۰/۲۳۶، ۰./۱۶۷ و ۰/۰۱۹۶، ۰/۰۴۸۰، ۰/۰۳۱۶ به‌دست آمد. مقایسه RMSEP در دو مدل نشان می‌دهد که مدل حاصل از PARAFAC قادر به پیش‌گویی بهتری نسبت به PLS است.

واژه‌های کلیدی: PLS، PARAFAC، تتراسایکلین‌ها، اندازه‌گیری هم‌زمان

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