ISSN(PRINT) : 2320 -1967
ISSN(ONLINE) : 2320 -1975

GLOBAL SCIENTIFIC INC.

ChemXpress

ORIGINAL ARTICLE

CHEMXPRESS 5(3), 073-077, (2014)

Spectrometric determination of trazodone and sertralin in tablets by multivariate calibration approach

Nuray Aytekin, A.Hakan Aktaş*

**Süleyman Demirel University, Science and Art Faculty,
Department of Chemistry, Isparta, (TURKEY)
E-mail: hakanaktas@sdu.edu.tr**

Received : 03rd April, 2014 ; Revised : 01st June, 2014 ; Accepted : 06th June, 2014

Abstract : Two multivariate calibration-prediction techniques, principal component analysis (PCR) and partial least squares (PLS) were applied to the spectrometric multicomponent analysis of the drug containing trazodone (TRAZ) and sertralin (SERT) without any separation step. The selection of variables was studied. A series of synthetic solution containing different concentrations of TRAZ and SERT were used to check the prediction ability of the PCR and PLS. The results obtained in this investigation strongly encourage us to apply these techniques for a routine analysis and quality control of the two drugs.

Keywords : Trazodone; Sertralin; Spectrometry; Multivariate calibration.

INTRODUCTION

Depression, whether mild or severe forms, is most widely known psychological disorders. Sertraline and trazodone hydrochloride are selective serotonin reuptake inhibitors which are clinically effective for the treatment of depression. The drugs are chemically known as (1S,4S)-4-(3,4dichlorophenyl)-1,2,3,4-tetrahydro-1-naphtyl(methyl) amine and 2- {3-[4-(3-chlorophenyl)-1-piperazin]propyl}-1,2,4-triazolo[4,3-a]pyridin-3-(2H)-one monohydrochloride (Figure 1).

Several methods have been published for the determination of SERT in pharmaceutical formulations and biological samples including spectrometry[3,8,10,18], voltammetry[17,20], HPLC[6,11,19,22], and gas chromatography[23]. On the other hands, various methods have been used for the determination of trazodone hydrochloride, in pharmaceutical formulations including spectrophotometry[14], gas chromatography[15], HPLC[1,12] and voltammetry[16].

During the last decade the powerful chemometric methods principal component analysis (PCR) and partial least-squares (PLS) were used in spectral data analysis for the mixtures containing two or more compounds with overlapping spectra[4,7,13]. These methods have wide range applications, e.g. spectrometric[2,9], chromatographic[21] and electrochemical[5] quantitative analysis.

The multivariate calibration techniques use full spectrum, full automation, multivariate data analysis and the

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reduction of noise and the advantages of the selection calibration model. In addition these multivariate calibrations do not need any separation procedure, they are very cheap, very easy to apply and very sensitive. For these reasons these multivariate techniques are popular today.

In this study two chemometric methods were applied to analyse the synthetic mixtures and tablets consisting of TRAZ and SERT in the presence of interferences of the absorption spectra. The application of chemometrics allows the interpretation of multivariate data and is vital to the success of the simultaneous determination of the clinical drugs.

EXPERIMENTAL

Apparatus

A Shimadzu (Model UV-1700) UV-Visible spectrometer (Shimadzu, Kyoto, Japan), equipped with 1cm matched quartz cells was used for spectrometric measurements.

Standard solutions

All materials used were of analytical grade. Stock solutions of 100 mg/100 mL TRAZ and SERT were prepared in methanol. The solutions were stable for the least two weeks if they had been stored in a cool (< 25°C) and dark place.

Pharmaceutical preparations

Two commercial preparations; Lustral® tablet (produced by Pfizer Pharm. Ind., Turkey, containing 50 mg sertraline) and Desyrel® tablet (produced by Çınay Pharm. Ind., Turkey, containing 50 mg trazodone) per tablet were analyzed by the proposed chemometric techniques.

Procedure for dosage forms

An accurately weighed pulverized tablets equivalent to 100 mg of the studied drugs was extracted with 10 mL of M Methanol, diluted with water, and sonicated for about 15 min. The extracts were filtered into 100 mL volumetric flasks then washed and diluted to volume with distilled water. Aliquots these solutions were transferred into a series of 10 mL volumetric flasks and the analysis were completed as spectrometric procedure. All the techniques were applied to the final solution.

CHEMOMETRICS METHODS

PCR and PLS

PCR and PLS are factor analysis multivariate statistical tools which have many of the full spectrum advantages and have been successfully applied to spectrophotometric analyses of multicomponent mixtures. PCR and PLS need a calibration step where the models for the spectra and the component concentrations of the unknown are estimated from the sample spectrum. Both of these methods involve spectral decomposition. The PCR decomposition is based entirely on spectral variations without regard for the component concentrations. In PLS, the spectral decomposition is weighted to the concentration. The major difference in

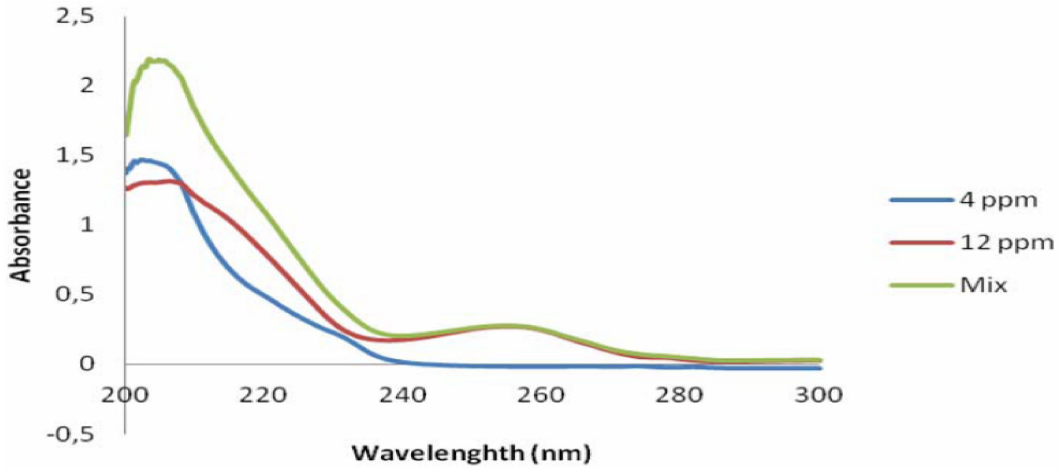

Figure 1 : Original absorption spectra of 4,0 µg/mL SERT 18,0 µg/mL TRAZ and their mixture in methanol

the predictive abilities of these two methods is that PLS seems to predict better than PCR when there are random linear baselines or independently varying major spectral components which overlap with the spectral features of the analysis. The optimal of calibration method depend on the particular experimental conditions. However, PLS seems to a reasonable choice over a wide range of conditions.

RESULTS AND DISCUSSION

Figure 1 shows the absorption spectra for TRAZ and SERT and their mixture in methanol. In order to build the three chemometric calibration, a training set was randomly prepared by using the standard mixture solution containing 4,0-20,0 μg/mL TRAZ and 1,0-5,0 μg/mL SERT in the variable proportions as shown in TABLE 1. The absorbance data matrix were obtained by measuring at the 15 wavelengths with the intervals $\Delta\lambda$ = 5 nm in the 200 – 275 nm spectral region. The prepared calibrations of three techniques using the absorbance data sets were used to predict concentration of the unknown values of TRAZ and SERT in their mixture. Linearity range was 2,0-10,0 μg/mL for TRAZ and 1,0-5,0 g/mL for SERT in the multivariate calibration proposed.

TABLE 1 : Composition of a training set of standard synthetic mixtures containing two drugs

No	SERT (μg/mL)	TRAZ (μg/mL)
1	1	4
2	1	8
3	1	12
4	1	16
5	1	20
6	2	4
7	2	8
8	2	12
9	2	16
10	2	20
11	3	4
12	3	8
13	3	12
14	3	16
15	4	4
16	4	8
17	4	12
18	5	4
19	5	8

A calibration for each technique was computed in the MAPLE 7.0 and PLS Toolbox 4.0 software by using set consisting of two drugs and their absorbance data. The multivariate calibrations of three techniques were used to predict the unknown concentrations of TRAZ and SERT in the samples.

Some statistical parameters were given for the validation of the constructed calibrations for the training set and synthetic binary mixtures of both drugs.

The application competence of a calibration model can be explained in several ways. We can also examine these results numerically. One of the best ways to do this by examining the predicted residual error sum-of-squares or PRESS. To calculate PRESS we compute the errors between the expected and predicted values for all the samples, square them, and sum them together.

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

Strikingly speaking, this is not a correct way to normalize the PRESS values when not all of the data sets contain the same number of samples. If we want correctly compare PRESS values for data sets that contain differing numbers of samples, we should convert to standard error of prediction (SEP), which is given by following formula.

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

Where C_i^{added} the added concentration of drug is, C_i^{found} is the found concentration of drug and n is the total number of the synthetic mixtures. The SEP can provide a good measure of how well, on average, the calibration model performs. Often, however, the performance of the calibration model varies depending on the analyte level.

In the application of two chemometric techniques to the synthetic mixtures containing two drugs in variable compositions, the mean recoveries and relative standard deviations for PCR and PLS were found to be 99.33%, 0.63 and 99.99%, 0.52 respectively for TRAZ and 98.36% and 1.30, 100.09% and 1.65 respectively for SERT (TABLE 2 and 3).

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TABLE 2 : Results obtained for TRAZ and SERT indifferent synthetic mixtures by using PCR technique

Mixture (µg/mL)				Recovery (%)	
SERT	TRAZ	SERT	TRAZ	SERT	TRAZ
1	4	0,98	3,95	98,00	98,75
1	8	0,99	7,95	99,00	99,38
1	12	0,98	11,96	98,00	99,67
1	16	0,94	15,95	94,00	99,69
1	20	0,99	19,98	99,00	99,90
2	4	1,97	3,95	98,50	98,75
2	8	1,96	7,90	98,00	98,75
2	12	1,96	11,98	98,00	99,83
2	16	1,99	15,96	99,50	99,75
2	20	1,95	19,95	97,50	99,75
3	4	2,94	3,91	98,00	97,75
3	8	2,91	7,99	97,00	99,88
3	12	2,98	11,97	99,33	99,75
3	16	2,99	15,96	96,67	99,75
4	4	3,96	3,92	99,00	98,00
4	8	3,97	7,96	99,25	99,50
4	12	3,98	11,96	99,50	99,62
5	4	4,97	3,98	99,40	99,50
5	8	4,91	7,94	98,20	99,25
			$\bar{X}$	98,36	99,33
			RSD*	1,30	0,63

RSD*: Relative standard deviation.

TABLE 3 : Results obtained for TRAZ and SERT indifferent synthetic mixtures by using PLS technique

Mixture (µg/mL)				Recovery (%)	
SERT	TRAZ	SERT	TRAZ	SERT	TRAZ
1	4	1,01	4,04	101,09	101,00
1	8	1,02	7,93	102,52	100,35
1	12	0,96	12,04	96,24	100,21
1	16	1,01	16,03	101,45	100,06
1	20	1,03	20,01	103,50	99,39
2	4	1,98	3,97	99,08	99,74
2	8	1,97	7,97	98,86	100,19
2	12	1,98	12,02	99,19	100,07
2	16	1,96	16,01	98,34	99,62
2	20	2,00	19,92	100,46	100,79
3	4	3,07	4,03	102,34	99,61
3	8	2,99	7,96	99,71	99,74
3	12	2,98	11,96	99,43	99,95
3	16	2,99	15,99	99,90	99,08
4	4	3,95	3,96	98,92	100,67
4	8	4,00	8,05	100,14	100,53
4	12	4,01	12,06	100,42	99,71
5	4	5,01	3,98	100,34	99,17
5	8	4,99	7,99	99,87	99,88
			$\bar{X}$	100,09	99,99
			RSD*	1,65	0,52

RSD*: Relative standard deviation.

According to the added concentration and the concentration found in samples, the SEP and PRESS values of PCR and PLS techniques were calculated 0.0517, 0.0268 and 0.0508, 0.0137 respectively for TRAZ, 0.0432, 0.0383, and 0.0354, 0.0280 respectively for SERT (TABLE 4).

TABLE 4 : Statistical parameters in the calibration-prediction

Parameter	Method	TRAZ	SERT
PRESS	PCR	0.0508	0.0354
	PLS	0.0137	0.0280
SEP	PCR	0.0517	0.0432
	PLS	0.0268	0.0383
R	PCR	1.0000	0.9997
	PLS	0.9999	0.9996
Intercept	PCR	-0.0621	-0.0195
	PLS	0.001	0.001
Slope	PCR	1.0015	0.9937
	PLS	0.9999	0.9996

The linear regression analysis of the added concentration and the concentration found in the synthetic mixtures were realized for each drug and for each calibration technique. In this regression analysis, the correlation coefficient (r), intercept, slope and relative standard deviation values were found satisfactory for the proposed chemometric techniques in TABLE 4. As can be seen, all the statistic values indicated that all techniques are convenient for the determination of two drugs in synthetic mixtures.

TABLE 5 : Assay results for the pharmaceutical formulation (mg/tablet)

Drug	PCR	PLS
TRAZ		
Mean ± SD*	50.02 ± 1.12	50.12 ± 1.18
SERT		
Mean ± SD*	49.68±3.84	48.96±3.70

Results obtained are average of six experiments for each technique; *SD : Standard deviation *

A summary of the assay results for the pharmaceutical formulation is given TABLE 5. The results of all methods were very to each other as well as to the label value of commercial drug formulation.

CONCLUSION

Two chemometric technique in spectrometric analysis, PCR and PLS, were proposed for the simultaneous determination of TRAZ and SERT in their binary mixtures. These techniques were applied with great success to two commercial pharmaceutical tablets. The resolution of highly overlapping drug mixtures was achieved by the use of PCR and PLS techniques. A selection of working wavelength having high correlation values with concentration due to interference coming from matrix sample or additional analytes outside the working range. The proposed chemometric techniques can be applied for the routine analysis of two drugs in the tablet formulation without any a priori chemical separation and without time consuming.

ACKNOWLEDGEMENT

This research work has been supported by research grants from Süleyman Demirel University Scientific Research Project 3681-YL1-13.

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