Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Pharmaceutical and Biomedical Analysis
33 (2003) 655–665
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Comparison of multivariate calibration methods to determine simultaneously mebendazole–cambendazole and mebendazole–thiabendazole in pharmaceutical preparations by UV–visible spectrophotometry

Suely R.C. Andrade [a], Ieda S. Scarminio [a,*], Marlene M.F. Nery [b], Aline C. de Oliveira [a]

[a] *Departamento de Química, Universidade Estadual de Londrina, Campus Universitário, 86051-990 Londrina, PR, Brazil*
[b] *Departamento de Tecnologia de Alimentos e Medicamentos, Universidade Estadual de Londrina, Campus Universitário, 86051-990 Londrina, PR, Brazil*

Received 4 February 2003; received in revised form 22 May 2003; accepted 23 May 2003

Abstract

Three multivariate calibration methods, Principal Component Regression (PCR), the K-matrix method and Q-mode factor analysis followed by varimax and Imbrie's oblique rotations were applied to the simultaneous spectrophotometric determinations of mebendazole (MBZ)–cambendazole (CBZ) and thiabendazole (TBZ)–mebendazole in commercial samples of Exelmin and Helmiben. The calibration set concentrations were selected to contain a ±10% variation in the quantity of active ingredients as declared by the manufacturer. The Q-mode factor analysis provides superior results for the two pharmaceutical formulations. The K-matrix method proved to be totally inadequate for these determinations. Almost all Q-mode results have relative errors much smaller than 5% of the active ingredient contents. This investigation shows that PCR and Q-mode factor analysis can be used to determine MBZ–CBZ and TBZ–MBZ in commercial drugs.

Keywords: Multivariate calibration; Spectrophotometry; Simultaneous analysis

1. Introduction

Mebendazole–cambendazole and mebendazole–thiabendazole are important drugs for the treatment of a wide range of helminth infections [1,2]. The pharmaceutical literature contains few references about methods for determining mebendazole (MBZ), cambendazole (CBZ) and thiabendazole (TBZ) individually and in pharmaceutical associated combinations. On the other hand, several methods are available for the determination of drugs in other formulations. Spectrophoto-

* Corresponding author. Tel.: +55-43-3371-4366; fax: +55-43-3328-4440.
E-mail address: ieda@qui.uel.br (I.S. Scarminio).

0731-7085/03/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/S0731-7085(03)00305-4

metric methods provide practical and significant economic advantages over other methods. The main problems with spectrophotometric analysis are limited selectivity, lack of specific chromogenic reactions as well as strong spectral band overlap exhibited by most active ingredients in the ultraviolet region. The latter problem can often be resolved using separation methods for the simultaneous determination of two or more compounds in the same mixture. However the analytical application of UV–visible spectrophotometry has gained momentum in the context of control analysis due to changes both in instrumentation, e.g. the advent of diode array spectrophotometers [3], and in methodology, with the development of chemometric procedures for processing complex signals. These advances have allowed the simultaneous determination of analytes including even those suffering from extensive band overlap [4,5].

The quantification of multiple analytes in the same sample has long been one of the most interesting fields of chemical analysis. With modern instruments, numerous spectral data can be recorded and easily digitized, and different mathematical approaches have been proposed to deal with these over-determined systems. In this respect, the use of multivariate calibration methods has grown rapidly and is gaining popularity for the determination of mixtures of compounds. These methods show the advantage of using complete spectral information, and allow for a rapid determination of mixture components, often with no need of prior separation or sample treatment. Some common multivariate calibration methods are multiple linear regression (MLR) [6], partial least-squares (PLS) [7,8], principal component regression (PCR) [9–11], and the K-matrix method (sometimes referred to as classical least squares, CLS) [8,12,13]. Up to now, many multicomponent calibration methods have been developed, and undoubtedly new methods will be developed in the future. Although it is necessary to introduce new methods, it is often more important to use existing methods appropriately. It is very difficult to generalize about the superiority of one method over another, because their relative performance is often dependent on the particular data set analysed.

In general the application of multivariate calibration methods requires a calibration step where the relationship between the spectra and component concentrations is deduced from a set reference samples. This is followed by a prediction step in which the results of the calibration are use to determine unknown component concentrations from sample spectra.

Recently Scarminio et al. [14] proposed a multivariate method to determine the chemical compositions of complex mixtures based on Q-mode factor analysis followed by varimax and Imbrie's oblique rotations. This method does not require an extensive calibration set, as do the PCR, PLS, and K-matrix methods since only standard spectra or the spectra of the pure absorbing species are necessary.

In this work the aim is to compare the results of Q-mode factor analysis followed by varimax and Imbrie's oblique rotations with the results of PCR and K-matrix methods for the simultaneous analyses of mebendazole (MBZ), cambendazole (CBZ) and thiabendazole (TBZ) in both their pure forms and in pharmaceutical formulations. In this way no prior separation step is necessary in the analytical procedure.

2. Experimental

2.1. Apparatus and software

An Ocean Optics miniature fiber optic CHEM2000-UV–vis spectrophotometer equipped with a deuterium tungsten light source with an integrated cuvette holder, a 300 μm solarization-resistent optical fiber, and an OOIChem operating software that provides a real-time interface to a variety of spectral-processing functions connected to an IBM computer was used for all the absorbance measurements and statistical data treatment. The FORTRAN programs used for the PCR, K-matrix and Q-mode factor analysis, varimax and Imbrie's oblique rotations calculations were developed in our laboratory.

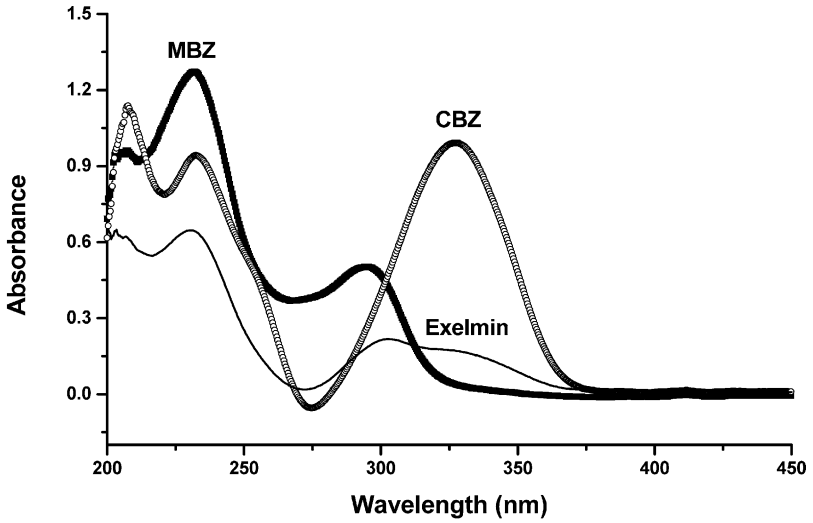

Fig. 1. Absorption spectra of: (a) 12.9 μg l^{-1} MBZ; (b) 12.9 μg l^{-1} CBZ and (c) Exelmin tablet (9.38 μg l^{-1} MBZ and 3.52 μg l^{-1} CBZ).

2.2. Pharmaceutical formulations

Two commercial products, Exelmin tablets (produced by the Ucifarma Laboratory, nominally containing 200 mg of mebendazole and 75 mg of cambendazole per tablet) and Helmiben tablets (produced by Eurofarma Laboratory, nominally containing 200 mg of mebendazole and 332 mg of thiabendazole per tablet) were acquired in a local pharmacy.

Mebendazole, cambendazole and thiabendazole standards were kindly donated by Sanofi Winthrop Farmacêutica Ltda.

2.3. Standard solution preparation

Standard stock solutions of cambendazole and mebendazole (645 μg ml^{-1}) and thiabendazole and mebendazole (708 μg ml^{-1}) were prepared separately by exact weighing of the pure standard.

Table 1
Results of simultaneous determinations of mebendazole and cambendazole in the calibration set using the PCR method

	Calibration (μg ml^{-1})		Prediction (μg ml^{-1})		Relative error (%)	
	MBZ	CBZ	MBZ	CBZ	MBZ	CBZ
1	12.90	0.00	12.96	−0.08	0.46	–
2	12.90	0.00	12.94	−0.06	0.31	–
3	0.00	12.90	0.11	12.80	–	−0.77
4	0.00	12.90	−0.01	12.91	–	0.08
5	3.23	9.67	3.24	9.66	0.31	0.10
6	3.23	9.67	3.21	9.68	0.62	−0.10
7	6.45	6.45	6.33	6.55	−1.86	−1.55
8	6.45	6.45	6.41	6.47	−0.62	−0.31
9	9.67	3.23	9.82	3.08	1.55	4.64
10	9.67	3.23	9.57	3.34	−1.03	−3.40
11	9.35	3.48	9.25	3.63	−1.07	−4.31
rms[a]	0.083[b]	0.089[b]				

[a] rms error $= \sqrt{\Sigma(c_{prev} - c_{cal})^2/N}$.
[b] μg ml^{-1}.

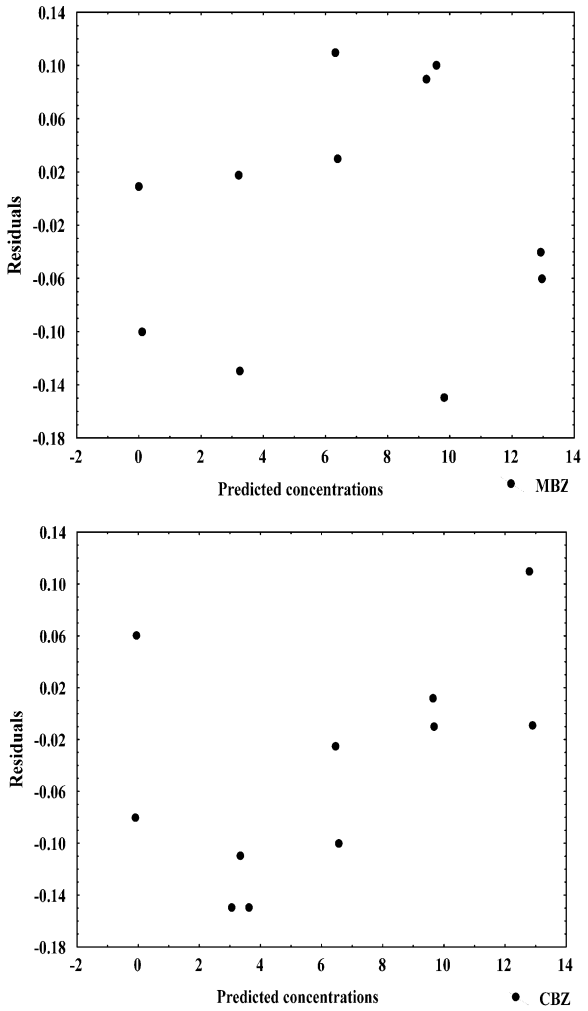

Fig. 2. Plots of the residuals against the predicted concentrations for mebendazole and cambendazole using PCR.

Dissolution in 2% (v/v) H_2SO_4–methanol mixture was promoted by sonicating for a few minutes.

The standard solutions of cambendazole–mebendazole and thiabendazole–mebendazole were prepared by dilution of the stock solutions to obtain final concentrations of 12.90 and 14.16 μg ml^{-1}, respectively. All solvents and reagents were of analytical reagent grade. All experiments were carried out at room temperature.

2.4. Preparation of cambendazole and mebendazole binary mixtures

Binary mixtures of cambendazole and mebendazole were prepared by suitable dilutions of the stock solutions, to obtain final total concentrations of 12.90μ g ml^{-1}. Six synthetic mixtures with different concentrations were chosen in order to include a 90–110% range of the amounts present in the commercial samples as recommended by regulatory agencies and labeled by the manufacturing laboratory. These solutions served as the calibration set. In the test set, three commercial samples prepared according to the procedure described above were used.

2.5. Preparation of mebendazole and thiabendazole binary mixtures

Binary mixtures of thiabendazole and mebendazole were prepared by suitable dilutions of the stock solutions, to obtain final concentrations of 14.16 μg ml^{-1}. Six synthetic mixtures with different concentrations were chosen in order to include a 90–110% range of the amounts present in the commercial samples as recommended by regulatory agencies and labeled by the manufacturing laboratory. These solutions served as the calibration set. In the test set, three commercial samples prepared according to the procedure described above were used.

2.6. Commercial samples

For Exelmin and Helmiben, twenty tablets of each pharmaceutical formulation were weighed individually and to obtain the average weight. The tablets were powdered and homogenized in a mortar. A total of 32.2 and 35.4 mg of Exelmin and Helmiben, respectively, were weighed accurately, dissolved in 2% (v/v) H_2SO_4–methanol by sonication in a 100 ml calibrated flask and filtered through Whatman N^0. 42 filter paper 2-ml aliquots of the filtrate were transferred into 50 ml volumetric flasks with the solvent mixture containing final concentrations of 12.90 and 14.16 μg ml^{-1}, respectively.

Table 2
Results of simultaneous determinations of mebendazole and cambendazole in the calibration set using Q-mode factor analysis followed by varimax and Imbrie's oblique rotations

	Calibration (μg ml^{-1})		Prediction (μg ml^{-1})		Relative error (%)	
	MBZ	CBZ	MBZ	CBZ	MBZ	CBZ
1	12.90	0.00	12.83	0.04	−0.54	–
2	12.90	0.00	12.90	0.00	0.00	–
3	0.00	12.90	0.04	12.86	–	−0.31
4	0.00	12.90	0.00	12.90	–	0.00
5	3.23	9.67	3.22	9.68	−0.31	0.10
6	3.23	9.67	3.10	9.80	−4.02	1.34
7	6.45	6.45	6.45	6.45	0.00	0.00
8	6.45	6.45	6.45	6.45	0.00	0.00
9	9.67	3.23	9.60	3.30	−0.72	2.17
10	9.67	3.23	9.67	3.23	0.00	0.00
11	9.35	3.48	9.54	3.36	2.03	3.45
Rms[a]	0.076[b]	0.060[b]				

[a] rms error $= \sqrt{\Sigma(c_{prev} - c_{cal})^2/N}$.
[b] μg ml^{-1}.

2.7. Spectra acquisition

For Exelmin the absorption spectra of the solutions prepared at different concentrations of CBZ and MBZ and the pure standards were registered between 212 and 364 nm against a blank. In the same way, for Helmiben the absorption spectra of the solutions prepared at different concentrations of CBZ and TBZ and the pure standards were registered between 202 and 400 nm against a blank.

3. Results and discussion

3.1. Simultaneous determination of mebendazole and cambendazole

For the simultaneous determination of MBZ and CBZ in tablet form, a calibration set of six binary mixtures with different concentrations was prepared. The compositions of the mixtures were 75–25, 50–50 and 25–75%, respectively, of MBZ and CBZ. Individual MBZ and CBZ standard solutions and one mixture with a composition as similar as possible to the Exelmin tablet also were included (72.72% MBZ–27.27% CBZ). The spectra for MBZ, CBZ as well as for the commercial sample are showed in the Fig. 1.

3.1.1. PCR analysis results

Two principal components were found to account for 99.7% of the variance in the calibration. Table 1 summarizes the compositions of synthetic mixtures, the predicted concentration values, the relative errors and the root mean squares errors (rms errors) for the calibration step.

The predicted concentrations of MBZ and CBZ in each sample were compared with the known concentrations of this calibration set. The rms error was used as a diagnostic test for examining the errors in the predicted concentrations.

Another diagnostic test was carried out by plotting the residuals against the predicted concentrations, Fig. 2. The residuals appear randomly distributed, indicating an adequate model.

3.1.2. Q-mode factor analysis results

This method does not require an extensive calibration set, as do the PCR and K-matrix methods. Only spectra of the pure absorbing species or standard spectra are necessary. In order to compare the Q-mode results with those of PCR and the K-matrix method it is convenient to

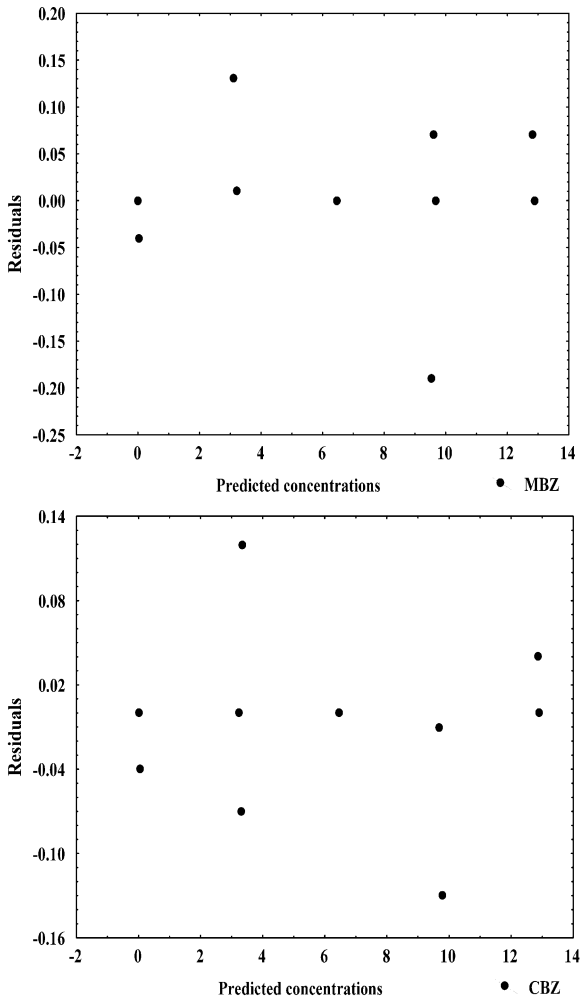

Fig. 3. Plots of the residuals against the predicted concentrations for mebendazole and cambendazole using Q-mode factor analysis followed by varimax and Imbrie's oblique rotations.

maintain the calibration-test set denominations for all methods.

The results of the MBZ and CBZ determinations are given in Table 2. The two pure MBZ and CBZ samples were each measured in 2-fold replicates. Two Q-mode factors explained 99.3% of the total variance. These were subjected to varimax and oblique rotations in order to obtain the final concentrations. As can be seen from the values of the rms errors the results using Q-mode factor analysis are slightly better than those obtained by PCR. Fig. 3 shows the plot of the residuals against the predicted concentrations. The residuals in this case appear randomly distributed and close to zero, indicating a better model for this method.

3.1.3. K-matrix analysis results

The multivariate calibration K-matrix method was also applied to the spectral data. The results are given in Table 3. In order to compare the results of the three methods, the rms errors were calculated between the real and predicted concentrations. These root mean square errors of calibration for the MBZ and CBZ were so high, 1.44 and 0.41 μg ml^{-1} that the method was considered very inferior to the others. The weakness of the K-matrix method predictor is caused by having a larger number of variables (absorbances) than number of samples. Collinearity can cause large problems in the unconditional estimation of the $\hat{\beta}$.

3.1.4. Simultaneous determination of mebendazole and cambendazole in Exelmin tablets

PCR and Q-mode factor analyses were applied to the determination of MBZ and CBZ in a commercial tablet. Three replicate determinations were made. Table 4 shows the results obtained for the MBZ and CBZ determinations in the pharmaceutical preparation, using both methods. As can be seen, Q-mode factor analysis gave more precise predictions for both drugs. The results provided by the two methods are in good agreement with that allowed by legislation, i.e. they were below 10%. However these errors are quite larger than those found in Tables 1 and 2 for the calibration set samples. This might be attributable to uncertainties in the MBZ and CBZ concentration results in the commercial sample. The values presented in Table 4, are nominal values furnished by the manufacturing laboratory, which are labeled in the commercial samples. However, according to the drug regulatory agencies, the MBZ concentration for the commercial samples could be in the range 8.44 and 10.32 μg l^{-1} and for CBZ, 3.17 and 3.87 μg l^{-1}. For the CBZ the differences between the nominal concentration and that one found by using the multivariate calibration method were all

Table 3
Results of simultaneous determination of mebendazole and cambendazole in calibration matrix using K-matrix method.

	Calibration (μg ml^{-1})		Prediction (μg ml^{-1})		Relative error (%)	
	MBZ	CBZ	MBZ	CBZ	MBZ	CBZ
1	12.90	0.00	15.10	0.48	17.05	–
2	12.90	0.00	14.96	0.43	15.96	–
3	0.00	12.90	0.16	12.79	–	−0.85
4	0.00	12.90	0.11	12.95	–	0.39
5	3.23	9.67	4.03	9.90	24.77	2.38
6	3.23	9.67	3.67	9.78	13.62	1.14
7	6.45	6.45	7.42	6.83	15.04	5.89
8	6.45	6.45	7.45	6.73	15.50	4.34
9	9.67	3.23	11.80	3.67	22.02	13.62
10	9.67	3.23	11.88	4.10	22.85	26.93
11	9.35	3.48	10.65	3.95	13.90	13.50
rms[a]	1.44[b]	0.41[b]				

[a] rms error $= \sqrt{\Sigma(c_{prev} - c_{cal})^2/N}$.
[b] μg ml^{-1}.

higher than 10% which one is the legally imposed limit.

Since MBZ and CBZ there is no standard reference methodology for simultaneous analysis, we applied the Beer's law for mixture to the spectra set. As the results showed concentration values far from the accepted range, we consider that this method was inadequate to this analysis, and therefore these results were not included in the manuscript.

3.2. Simultaneous determination of thiabendazole and mebendazole

For simultaneous determination of TBZ and MBZ in tablet form, a calibration set of seven binary mixtures with different concentrations was prepared. The compositions of mixtures were 75–25, 50–50, 40–60 and 25–75%, respectively, of TBZ and MBZ. Individual TBZ and MBZ standard solutions and one mixture with a composi-

Table 4
Comparison of results of simultaneous determinations of mebendazole and cambendazole in an Exelmin tablet by applying PCR and Q-mode factor analysis followed by varimax and Imbrie's oblique rotations

	Exelmin (μg ml^{-1})		PCR (μg ml^{-1})		Q-mode factor analysis (μg ml^{-1})	
	MBZ[a]	CBZ[a]	MBZ	CBZ	MBZ	CBZ
12	9.38	3.52	8.42	4.34	8.77	4.13
13	9.38	3.52	8.45	4.30	8.77	4.09
14	9.38	3.52	8.55	4.18	9.03	3.87
rms[b]			1.11[c]	0.93[c]	0.66[c]	0.64[c]

[a] Nominal values.
[b] rms error $= \sqrt{\Sigma(c_{prev} - c_{nom})^2/N}$.
[c] μg ml^{-1}.

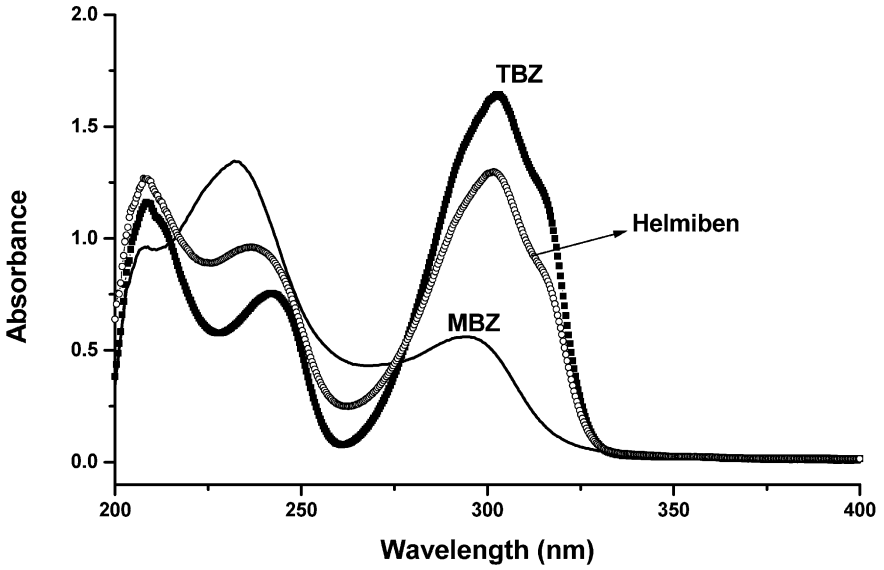

Fig. 4. Absorption spectra of: (a) 14.16 μg l^{-1} MBZ; (b) 14.16 μg l^{-1} CBZ and (c) Helmiben tablet (8.84 μg l^{-1} TBZ and 5.32 μg l^{-1} MBZ).

tion as similar as possible to that of the Helmiben tablet also were included (62.4% TBZ–37.6% CBZ) in the set. The spectra for TBZ, MBZ as well as for the commercial sample are showed in the Fig. 4.

3.2.1. PCR analysis results

Two principal components were found to account for 99.6% of the variance in the calibration. Table 5 summarizes the compositions of the synthetic mixtures, the predicted concentration

Table 5
Simultaneous determinations of thiabendazole and mebendazole in the calibration set using PCR

	Calibration (μg ml^{-1})		Prediction (μg ml^{-1})		Relative error (%)	
	MBZ	CBZ	MBZ	CBZ	MBZ	CBZ
1	14.16	0.00	14.03	0.14	−0.92	–
2	14.16	0.00	13.97	0.19	−1.34	–
3	0.00	14.16	−0.05	14.21	–	0.35
4	0.00	14.16	−0.19	14.36	–	1.41
5	3.54	10.62	3.64	10.53	2.82	−0.85
6	3.54	10.62	3.55	10.61	0.28	−0.09
7	7.08	7.08	7.29	6.88	2.97	−2.82
8	7.08	7.08	6.86	7.30	−3.10	3.11
9	10.62	3.54	10.66	3.50	0.38	−1.13
10	10.62	3.54	10.72	3.45	4.52	−7.52
11	5.66	8.54	5.75	8.41	−0.22	0.37
12	8.54	5.66	8.75	5.42	1.81	−3.01
rms[a]	0.15[b]	0.15[b]				

[a] rms error $= \sqrt{\Sigma(c_{\text{prev}} - c_{\text{cal}})^2/N}$.
[b] μg ml^{-1}.

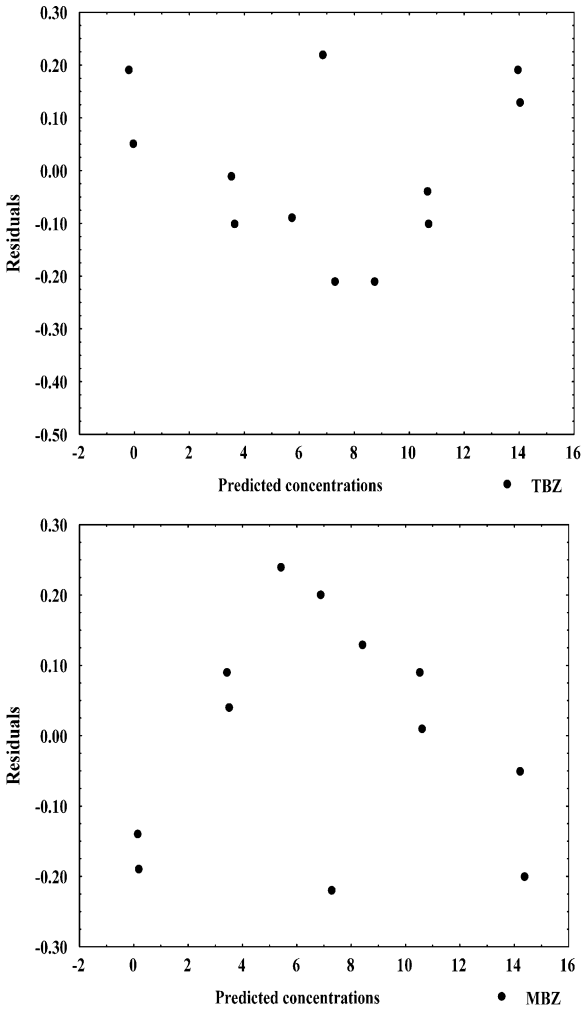

Fig. 5. Plots of the residuals against the predicted concentrations for thiabendazole and mebendazole using PCR.

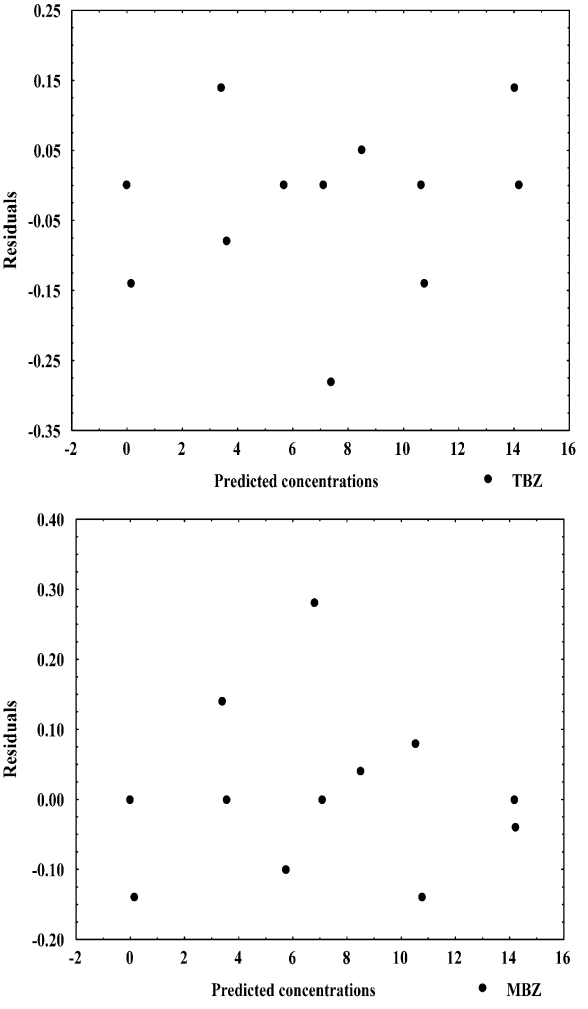

Fig. 6. Plots of the residuals against the predicted concentrations for thiabendazole and mebendazole using Q-mode factor analysis followed by varimax and Imbrie's oblique rotations.

values, the relative errors and the rms errors for the calibration step.

The predicted concentrations of TBZ and MBZ in each sample were compared with the known concentrations in this calibration set. Fig. 5 shows the plot of the residuals against the predicted concentrations. The residuals do not appear randomly distributed, showing systematic curvature and probably indicating an inadequate model.

3.2.2. *Q-mode factor analysis results*

The results for the TBZ and MBZ determinations are given in Table 6. The two pure TBZ and MBZ samples were each measured in twofold replicates. Two Q-mode factors explained 99.6% of the total variance. These were subjected to varimax and oblique rotations to obtain the final concentrations. It can be seen from the values of the rms errors that the results are slightly more precise by using Q-mode factor analysis than using PCR. Fig. 6 shows the plot of the residuals against the predicted concentrations. The residuals in this case are randomly distributed, close to zero, indicating a better fitting model for this method.

Table 6
Simultaneous determinations of thiabendazole and mebendazole in the calibration set using Q-mode factor analysis followed by varimax and Imbrie's oblique rotations

	Calibration (μg ml^{-1})		Prediction (μg ml^{-1})		Relative error (%)	
	MBZ	CBZ	MBZ	CBZ	MBZ	CBZ
1	14.16	0.00	14.02	0.14	−0.99	–
2	14.16	0.00	14.16	0.00	−0.00	–
3	0.00	14.16	0.14	14.20	–	0.28
4	0.00	14.16	0.00	14.16	–	0.00
5	3.54	10.62	3.62	10.54	2.26	−0.75
6	3.54	10.62	3.40	10.76	−3.95	1.32
7	7.08	7.08	7.36	6.80	3.95	−3.95
8	7.08	7.08	7.08	7.08	0.00	0.00
9	10.62	3.54	10.62	3.54	0.00	0.00
10	10.62	3.54	10.76	3.40	1.32	−3.95
11	5.66	8.54	5.66	8.50	0.00	−0.47
12	8.54	5.66	8.49	5.76	−0.58	1.77
rms[a]	0.12[b]	0.11[b]				

[a] rms error $= \sqrt{\Sigma(c_{\text{prev}} - c_{\text{cal}})^2/N}$.
[b] μg ml^{-1}.

3.2.3. K-matrix analysis results

The multivariate calibration K-matrix method was also applied to the spectral data. The rms calibration errors for TBZ and MBZ were very high, 0.33 and 5.14 μg ml^{-1}, indicating the inadequacy of the method for this application.

3.2.4. Simultaneous determination of thiabendazole and mebendazole in Helmiben tablet

PCR and Q-mode factor analysis were applied to the determinations of TBZ and MBZ in a commercial tablet. Three replicate determinations were made. Table 7 shows the results obtained for each TBZ and MBZ determination in the pharmaceutical preparation, using both methods. As can be seen, Q-mode factor analysis gave a better prediction for both drugs. The results provided by both methods are in good agreement with that allowed by legislation, in this case below 10%. However using PCR these errors are substantially larger than those found in Table 5 for the calibration set samples.

4. Conclusions

PCR and Q-mode factor analysis methods both provide simultaneous analytical determinations of

Table 7
Simultaneous determinations of thiabendazole and mebendazole in a pharmaceutical formulation using PCR and Q-mode factor analysis followed by varimax and Imbrie's oblique rotations.

	Helmiben (μg ml^{-1})		PCR (μg ml^{-1})		Q-mode factor analysis (μg ml^{-1})	
	TBZ[a]	MBZ[a]	TBZ	MBZ	TBZ	MBZ
13	8.84	5.32	8.95	4.92	8.84	5.32
14	8.84	5.32	8.52	5.34	8.76	5.40
15	8.84	5.32	8.71	5.16	8.84	5.32
rms[b]			0.24[c]	0.30[c]	0.06[c]	0.06[c]

[a] Nominal values.
[b] rms error $= \sqrt{\Sigma(c_{\text{prev}} - c_{\text{nom}})^2/N}$.
[c] μg ml^{-1}.

MBZ–CBZ and TBZ–MBZ in synthetic mixtures and commercial tablets with precisions well within those required by current legislation. The Q-mode factor results are somewhat better than those obtained using PCR but the differences in precision are probably not statistically significant. However the Q-mode analysis has one very big advantage over PCR for analytical determinations in commercial drug products. No extensive calibration set need be investigated. Instead only the spectra of the pure ingredients or standard spectra need be used. This results in faster analysis results at a lower price. Q-mode factor analysis has a very promising future for the routine analysis of drugs for which simultaneous analyte determinations are necessary for pharmaceutical mixture preparations.

Acknowledgements

The authors are grateful to the Fundação Araucária for financial support.

References

[1] M.H. Ross, Parasitololoy 114 (1997) 137–144.
[2] T.N.Z. Barragry, Vet. J. 32 (1984) 161–164.
[3] M.L. Fernández de Córdova, P. Ortega Barrales, A. Molina Díaz, Anal. Chim. Acta 369 (1998) 263–268.
[4] M.L. Luis, J.M.G. Fraga, F. Jiménez, A.I. Jiménez, J.J. Arias, Talanta 53 (2001) 761–770.
[5] E. Dinç, F. Onur, Anal. Chim. Acta 359 (1998) 93–106.
[6] P. Geladi, B.R. Kowalski, Anal. Chim. Acta 185 (1986) 1–17.
[7] K.D. Zissis, R.G. Brereton, S. Dunkerley, R.E.A. Escott, Anal. Chim. Acta 384 (1999) 71–81.
[8] A. Muñoz de la Peña, A. Espinosa-Mansilla, M.I. Acedo Valenzuela, H.C. Goicoechea, A.C. Oliviere, Anal. Chim. Acta 463 (2002) 75–88.
[9] M. Forina, M.C. Casolino, C. de la Pezuela Martinez, J. Pharm. Biomed. Anal. 18 (1998) 21–23.
[10] C. Demir, R.G. Brereton, Analyst 123 (1998) 181–189.
[11] J.M. Lemus Gallego, J. Pérez Arroyo, Anal. Chim. Acta 460 (2002) 85–97.
[12] D.M. Haaland, G. Easterling, D.A. Vopicka, Appl. Spectrosc. 39 (1985) 73–84.
[13] S.-Q. Liu, W.-W. Wang, Chemom. Intell. Lab. Syst. 45 (1999) 131–145.
[14] I.S. Scarminio, W.J. Barreto, D.N. Ishikawa, E.L. Paczkowski, Anal. Sci. 16 (2002) 1337–1340.