ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
28 (2002) 1091–1100

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

www.elsevier.com/locate/jpba

Simultaneous spectrophotometric determination of mefenamic acid and paracetamol in a pharmaceutical preparation using ratio spectra derivative spectrophotometry and chemometric methods

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Received 25 August 2001; received in revised form 24 November 2001; accepted 2 December 2001

Abstract

Four new methods are described for the simultaneous determination of mefenamic acid (MEF) and paracetamol (PAR) in their combination. In the first method, ratio spectra derivative method, analytical signals were measured at the wavelengths corresponding to either maximums or minimums for both drugs in the first derivative spectra of the ratio spectra obtained by dividing the standard spectrum of one of two drugs in 0.1 M NaOH:methanol (1:9). In the chemometric techniques, classical least-squares, inverse least-squares and principal component regression (PCR), the training was randomly prepared by using the different mixture compositions containing two drugs in 0.1 M NaOH:methanol (1:9). The absorbance data was obtained by the measurements at 13 points in the wavelength range 235–355 nm in the absorption spectra. Chemometric calibrations were constructed by the absorbance data and training set for the prediction of the amount of MEF and PAR in samples. In the third chemometric method, PCR, the covariance matrix corresponding to the absorbance data was calculated for the basis vectors and matrix containing the new coordinates. The obtained calibration was used to determine the title drugs in their mixture. Linearity range in all the methods was found to be 2–10 μg/ml of MEF and 4–20 μg/ml of PAR. Mean recoveries were found satisfactory (> 99%). The procedures do not require any separation step. These methods were successfully applied to a pharmaceutical formulation, tablet, and the results were compared with each other.

Keywords: Mefenamic acid; Paracetamol; Ratio spectra derivative method; Chemometric methods; Pharmaceutical preparation

1. Introduction

Combination of mefenamic acid (MEF) with paracetamol (PAR) is frequently prescribed as an analgesic and anti-inflammatory agent in rheumatoid arthritis. Various methods including spec-

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0731-7085/02/$ - see front matter
PII: S0731-7085(02)00031-6

trophotometry [1–5], and HPLC [6] have been used for the determination of MEF and PAR in pharmaceutical preparations containing MEF + PAR mixture.

Salinas et al. [7], developed a new method for analysis of mixtures with overlapped spectra. Salinas's method is based on the use of the first derivative of the ratio spectra. In this method, the concentrations of active compounds were determined by measuring the amplitudes of the minimum or maximum at points corresponding to the selected wavelengths. Berzas Nevado et al. [8–11] and Dinç and Onur [12–17] applied the same method to determine the active compounds in different mixtures.

Chemometric calibration techniques can be summarized as classical least-squares (CLS), inverse least-squares calibrations (ILS), principal component regression (PCR) and partial least squares regression (PLSR) techniques [18–23]. Chemometric calibration techniques in spectral analysis is gaining importance in the quality control of drugs in mixtures and pharmaceutical formulations containing two or more drugs with overlapping spectra due to not need any separation procedure before determination step. In the chemometric techniques, a calibration is constructed by the training set containing all the compounds and their absorbance values. The built calibration is used to predict the concentration of the compounds in samples. The chemometric calibrations do not require any pretreatment as separation in HPLC and derivation in derivative spectrophotometry. In addition, these techniques can be successfully applied to all the analysis methods. Dinç and Onur used these techniques for the simultaneous analysis of a binary and a ternary mixture [24,25].

In this study, ratio spectra derivative spectrophotometry and three chemometric methods are proposed for the simultaneous determination of MEF and PAR in their mixtures and pharmaceutical preparation, tablet. We observed that the proposed methods gave the best resolution of the title drugs in samples. The results obtained in the ratio derivative spectra and chemometric techniques were compared with the results of the difference spectrophotometry [5] and the HPLC methods [6].

2. Experimental

2.1. Apparatus

Shimadzu 1601 PC double beam spectrophotometer with a fixed slit width (2 nm) connected to a computer loaded with Shimadzu UVPC software was used for all the spectrophotometric measurements.

In ratio spectra derivative spectrophotometry, range was selected as 220.0–375.0 nm ($\Delta\lambda = 8$ nm, scaling factor = 10) for reading the analytical signals. The ordinate maximum and minimum settings were $(+1.8)$–(-1.3) for MEF in 285.0–375.0 nm range and $(+3.0)$–(-2.3) in 220.0–330.0 nm range for PAR in their mixture.

2.2. Materials

MEF and PAR were kindly donated by Ibrahim Ethem Pharm. Ind., Turkey and used without further purification.

All the solvents used in spectrophotometric analysis were of analytical reagent grade.

2.3. Standard solutions

Solutions of 100 mg/100 ml of MEF and 100 mg/100 ml PAR were prepared respectively, in 0.1 M NaOH:methanol (1:9).

2.4. Sample preparation

Twenty tablets were accurately weighed and powdered in a mortar. An amount of the tablet mass equivalent to one tablet content was dissolved in 60 ml of 0.1 M NaOH:methanol (1:9). After 30 min of mechanically shaking the solution was filtered in a 100 ml volumetric flask through Sartorius Minisart® 20 mμ single use filter. The residue was washed three times with 10 ml solvent then the volume was completed to 100 ml with the same solvent. This solution was diluted 1:500 with 0.1 M NaOH:methanol (1:9). All the spectrophotometric methods were applied to the latest diluted solution.

2.5. Commercial pharmaceutical preparation

Lanagesic® (500 mg PAR, 250 mg MEF and excipients (lactose, starch, avicel, povidon, sodium dodecylsulfate, aerosil and magnesium stearate)/tablet) Tata Pharma, Bombay, India (batch no: L.T.103) was assayed.

3. Results and discussion

3.1. Ratio spectra first derivative spectrophotometry

The ratio spectra of different MEF standards at increasing concentrations in 0.1 M NaOH: methanol (1:9) obtained by dividing each with the stored spectrum of the standard solution of PAR by computer aid are shown in Fig. 2a and the first derivative of these spectra (^{1}DD) traced with the interval of $\Delta\lambda = 8$ nm (scaling factor = 10) are illustrated in Fig. 2b. As seen in Fig. 2b, there exist one maxima (327.5 nm) and one minima (363.5 nm) and we found that two of them are suitable for the determination of MEF in MEF + PAR mixture. We selected 327.5 nm for the determination of this compound in the assay of synthetically prepared pharmaceutical preparation, tablet, due to its more suitable mean recovery among the wavelengths mentioned (Table 1). The ratio and ratio derivative spectra of the solutions of PAR at different concentrations in 0.1 M NaOH:methanol (1:9) traced with the interval of $\Delta\lambda = 8$ nm (scaling factor = 10) by using the standard spectrum of MEF as divisor by computer aid was demonstrated in Fig. 3a and b, respectively. In these spectra, one maxima (245.3 nm) and one minima (271.2 nm) were found suitable for the quantification of PAR in MEF + PAR. Measured analytical signals at these wavelengths are proportional to the concentrations of the drugs. We selected 245.3 nm for the determination

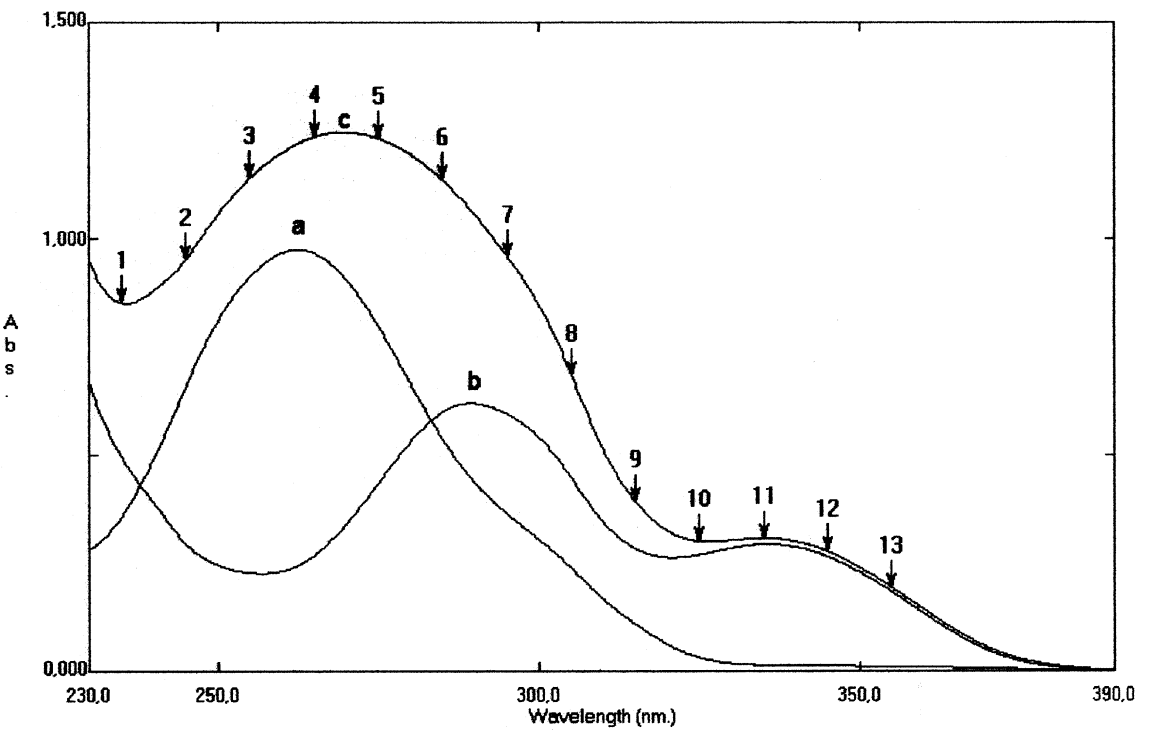

Fig. 1. Zero-order absorption spectra of (a) 12 μg/ml solution of MEF, (b) 12 μg/ml solution of PAR in 0.1 M NaOH:methanol (1:9), (c) their mixture.

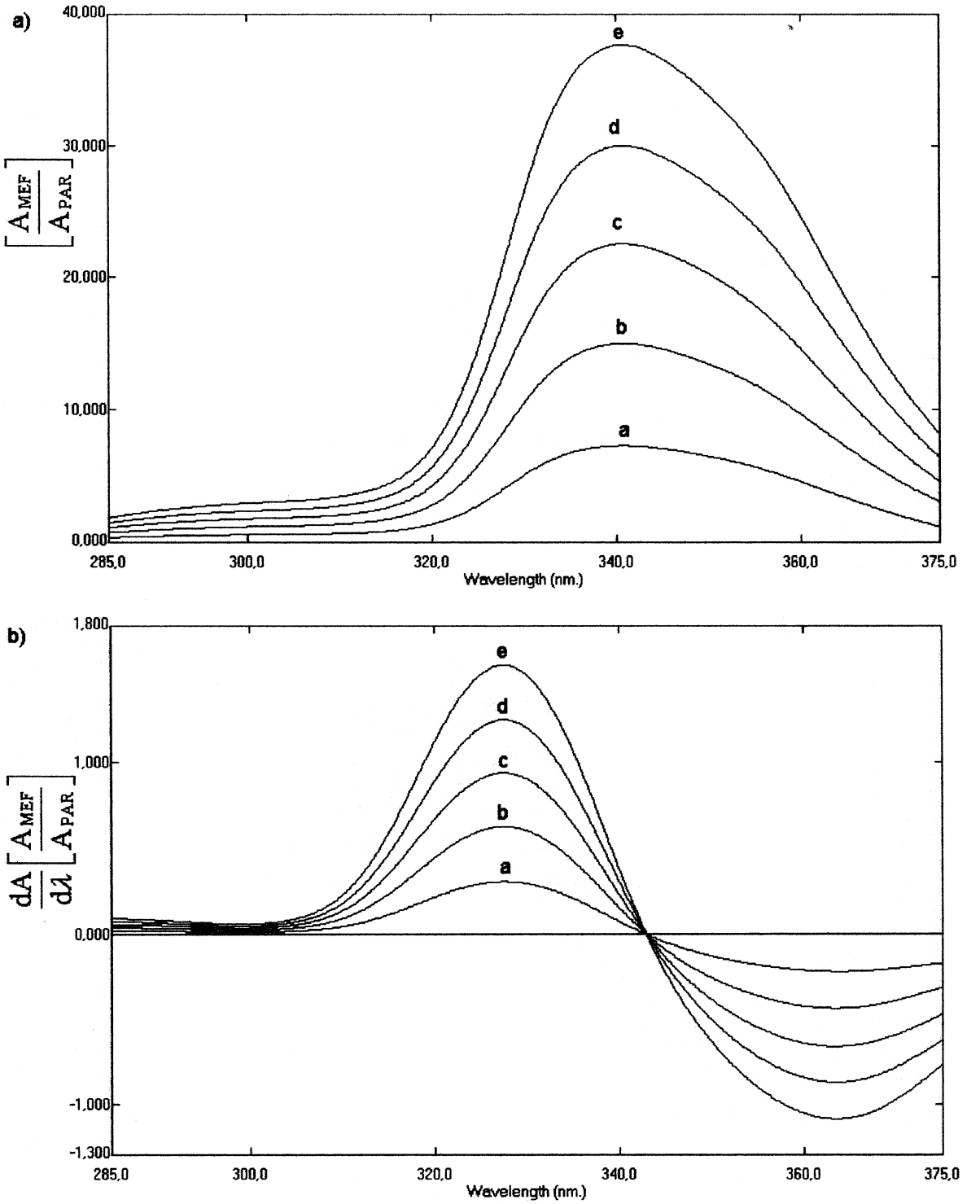

Fig. 2. Ratio spectra (a) and first derivative of the ratio spectra (b) of (a) 2 μg/ml, (b) 4 μg/ml, (c) 6 μg/ml, (d) 8 μg/ml, (e) 10 μg/ml solution of MEF in 0.1 M NaOH:methanol (1:9) when 12 μg/ml solution of PAR in 0.1 M NaOH:methanol (1:9) used as divisor ($\Delta\lambda = 8$ nm, scaling factor = 10).

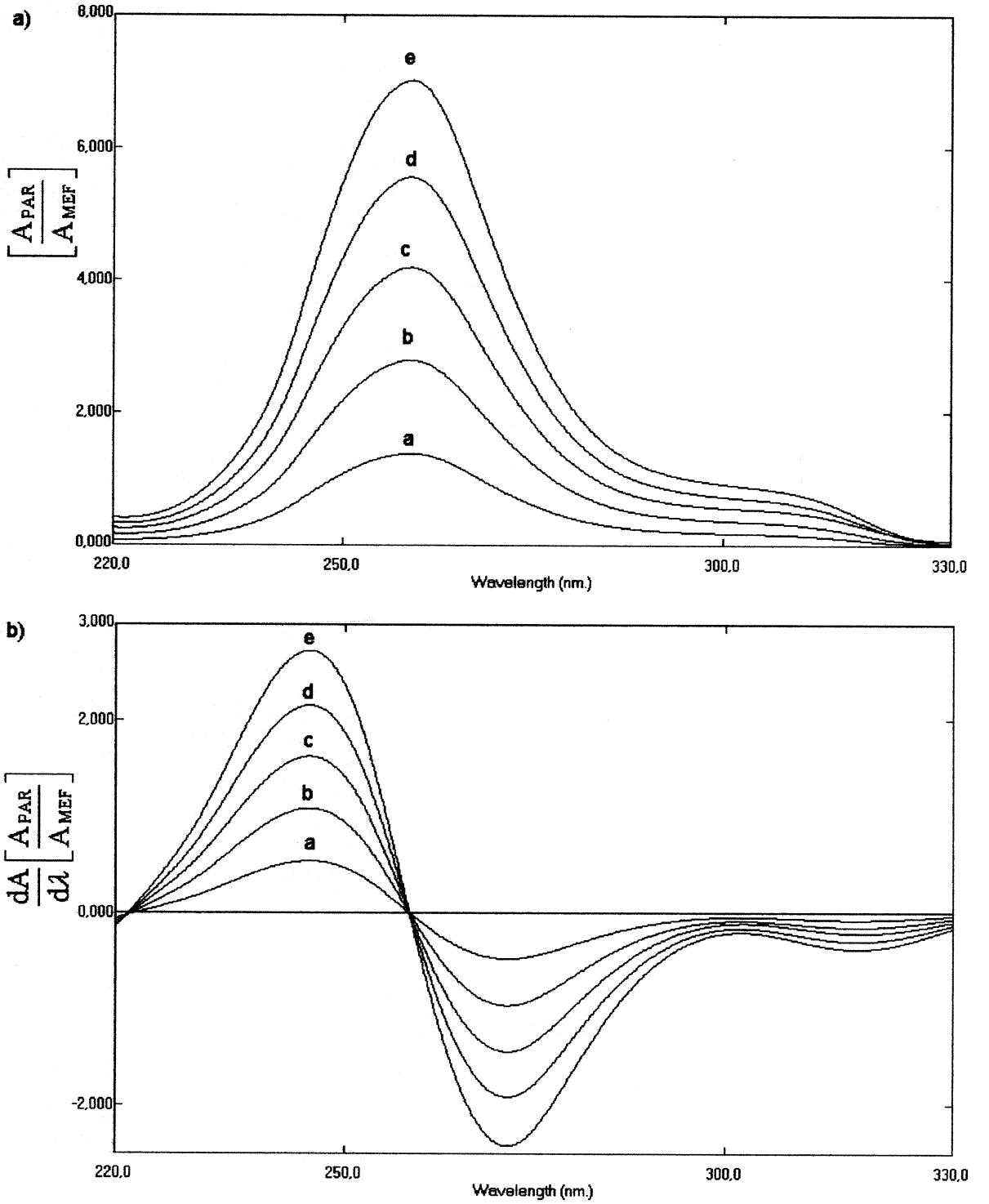

Fig. 3. Ratio spectra (a) and first derivative of the ratio spectra (b) of (a) 4 μg/ml, (b) 8 μg/ml, (c) 12 μg/ml, (d) 16 μg/ml, (e) 20 μg/ml solution of PAR in 0.1 M NaOH:methanol (1:9) when 6 μg/ml solution of MEF in 0.1 M NaOH:methanol (1:9) used as divisor ($\Delta\lambda = 8$ nm, scaling factor = 10).

Table 1
Recovery results for MEF and PAR in synthetic mixtures by ratio spectra first derivative spectrophotometry

Mixture no.	Added (μg)	MEF recovery (%)		Added μg	PAR recovery (%)	
		327.5 nm	363.5 nm		245.3 nm	271.2 nm
1	2	104.9	103.6	12	100.1	100.5
2	4	97.7	99.6	12	100.7	100.3
3	6	101.9	104.9	12	100.1	100.6
4	8	101.2	103.6	12	100.8	101.6
5	10	98.4	99.6	12	100.9	102.0
6	6	99.6	101.3	4	101.7	103.3
7	6	101.9	102.9	8	100.6	101.4
8	6	100.7	104	12	100.2	100.8
9	6	102.6	104.5	16	99.9	100.4
10	6	98.9	99.7	20	101.7	102.1
$n = 10$	$\bar{x}$	100.8	102.4		100.7	101.3
	RSD	2.17	2.07		0.64	0.97

RSD, relative standard deviation.

of this compound in the assay of synthetically prepared pharmaceutical preparation, tablet, due to its lower RSD value and suitable mean recovery among the wavelengths mentioned (Table 1).

Calibration graphs were established from analytical signals measured at 327.5 and 363.5 nm for standards containing 2–10 μg/ml of MEF and at 245.3 and 271.2 nm for standards containing 4–20 μg/ml of PAR corresponding to maxima and minima in the absence of each other.

In this method, the detection limit for 10 replicate measurements was calculated as 1.15 μg/ml at 327.5 nm and 1.10 μg/ml at 363.5 nm for MEF and 1.17 μg/ml at 245.3 nm and 2.50 μg/ml at 271.2 nm for PAR, whereas the limit of quantification was linear in the range of 2–10 μg/ml for MEF (6 μg/ml) and 4–20 μg/ml for PAR (12 μg/ml), respectively.

In the method, the mean recoveries and relative standard deviations calculated for synthetic mixtures prepared in our laboratory were illustrated in Table 1. Also, Beer's law compliance for both compounds, the regression equations and correlation coefficients were summarized in Table 2. Mean recoveries and relative standard deviations of the method were found satisfactory.

Divisor concentration is main instrumental parameter. The standard spectra of 6.0 μg/ml of MEF and 12.0 μg/ml of PAR was considered as suitable for the determination of MEF and PAR, respectively, as divisor. The $\Delta\lambda$ found as optimum for the first derivative of their ratio spectra was 8 nm.

A critical evaluation of all the proposed methods was performed by statistical analysis of the data, where slopes, intercepts and correlation coefficients were shown in Table 2.

Summary of the assay results for commercial preparation was shown in Table 7. The results of three chemometric methods and ratio spectra derivative spectrophotometry developed by us for the same commercial formulation were compared by one-way ANOVA test.

3.2. Chemometric techniques

Fig. 1 shows the zero-order absorption spectra for MEF and PAR and their binary mixture in 0.1 M NaOH:methanol (1:9). For the chemometric techniques, the absorbance data matrix for the training set concentration matrix were obtained by the measurements of absorbances between 235.0 and 355.0 nm in the intervals with $\Delta\lambda = 10$ nm at 13 wavelengths in the zero-order absorption spectra. In these techniques, calibration or regression was obtained by using the absorbance data matrix and concentration data matrix for prediction of the unknown concentrations of

Table 2
Calibration graphs of MEF and PAR by ratio spectra derivative spectrophotometric procedures

Drug	λ (nm)	Regression equations		r	Concentration range (μg/ml)
		a (SE)	b (SE)		
MEF	327.5	1.58×10^{-1} (5.12×10^{-3})	9.60×10^{-3} (2.50×10^{-4})	0.9999	2.0–10.0
MEF	363.5	-1.08×10^{-3} (6.90×10^{-4})	7.90×10^{-3} (5.33×10^{-5})	0.9999	2.0–10.0
PAR	245.3	1.36×10^{-1} (2.28×10^{-3})	-3.80×10^{-3} (6.30×10^{-4})	0.9999	4.0–20.0
PAR	271.2	-1.21×10^{-1} (2.71×10^{-3})	8.20×10^{-3} (3.96×10^{-4})	0.9999	4.0–20.0

a = slope; b = intercept; r = correlation coefficient; SE = standard error.

MEF and PAR in their binary mixtures and pharmaceutical formulations. In the PCR, the covariance matrix corresponding to the absorbance matrix were calculated for the basis vectors and matrix containing the new coordinates. The obtained calibrations were used for the determination of title drugs in their mixture. The numerical values were calculated by using '*Maple V*' software in all the chemometric methods.

The predictive ability of a model can be defined in various ways. The most general expression is the standard error of prediction (SEP) which is given in the following equation:

$$\mathrm{SEP}=\sqrt{\frac{\sum_{i=1}^{N}(C_i^{\mathrm{Added}}-C_i^{\mathrm{Found}})^2}{n}}$$

where C_i^{Added} is the added concentration of drug, C_i^{Found} is the predicted concentration of drug and n is the total number of synthetic mixtures.

In order to test the proposed techniques, the sets of synthetic mixtures containing the two drugs in variable composition were prepared. The results obtained in the application of CLS, ILS and PCR methods to the same binary mixture are indicated in Tables 3–5. The SEP were completely acceptable (0.0312, 0.0297 and 0.0286 for MEF and 0.1058, 0.1030 and 0.1124 for PAR, respectively for CLS, ILS and PCR methods) (Table 6).

In Table 5, r is defined as the correlation between constituent concentrations and shows the absorbance effects relating to the constituent of interest. r values obtained in the methods close to 1 mean no interference was coming from the other constituents in this set of synthetic mixtures.

Another statistical value is the standard error of calibration (SEC) and the calculation of this value was realized by using following equation:

$$\mathrm{SEC}=\sqrt{\frac{\sum_{i=1}^{N}(C_i^{\mathrm{Added}}-C_i^{\mathrm{Found}})^2}{n-p-1}}$$

where C_i^{Added} is the added concentration of drug, C_i^{Found} is the predicted concentration of drug and n is the total number of synthetic mixtures, p is the number of components in the mixtures.

The errors of prediction (SEC) were found acceptable in CLS and ILS methods (0.0373, 0.0355 and 0.0341 for MEF and 0.1264, 0.1231 and 0.1343 for PAR), respectively (Table 6) in the synthetic mixtures containing these two drugs in variable compositions prepared as indicated in Tables 3–5.

Table 3
Recovery results for MEF and PAR in synthetic mixtures by CLS technique

Added (μg)		Found (μg)		Recovery (%)	
PAR	MEF	PAR	MEF	PAR	MEF
4.0	6.0	4.00	5.99	100.0	99.8
8.0	6.0	7.98	5.98	99.8	99.7
12.0	6.0	11.98	6.01	99.8	100.1
16.0	6.0	15.92	6.05	99.5	100.8
20.0	6.0	20.31	6.00	101.6	100.0
12.0	2.0	11.97	2.04	99.7	102.1
12.0	4.0	12.02	4.05	100.1	101.3
12.0	6.0	11.96	5.99	99.7	99.8
12.0	8.0	12.04	8.03	100.4	100.4
12.0	10.0	12.06	10.04	100.5	100.4
$\bar{x}$				100.1	100.4
RSD				0.61	0.77

Table 4
Recovery results for MEF and PAR in synthetic mixtures by ILS technique

Added (μg)		Found (μg)		Recovery (%)	
PAR	MEF	PAR	MEF	PAR	MEF
4.0	6.0	4.00	6.00	100.0	100.0
8.0	6.0	7.98	5.92	99.8	98.7
12.0	6.0	11.94	6.01	99.5	100.1
16.0	6.0	15.90	6.05	99.4	100.8
20.0	6.0	20.28	6.10	101.4	101.7
12.0	2.0	11.97	2.08	99.7	102.1
12.0	4.0	12.02	4.00	100.1	100.0
12.0	6.0	11.86	5.99	98.8	99.8
12.0	8.0	12.08	8.08	100.4	101.0
12.0	10.0	12.06	10.04	100.5	100.4
$\bar{x}$				100.0	100.5
RSD				0.71	0.98

Mean recoveries and relative standard deviations for the CLS, ILS and PCR techniques were found as 100.1 and 0.71%, 100.5 and 0.98%, 100.3 and 0.60% for MEF and 100.4 and 0.77%, 100.0 and 0.71%, 100.1 and 0.68% for PAR, respectively in the synthetic mixtures of both drugs (Tables 3–5).

Linearity range was 2–10 μg/ml for MEF and 4–20 μg/ml for PAR in all chemometric methods.

Table 5
Recovery results for MEF and PAR in synthetic mixtures by PCR technique

Added (μg)		Found (μg)		Recovery (%)	
PAR	MEF	PAR	MEF	PAR	MEF
4.0	6.0	3.99	5.99	99.7	99.9
8.0	6.0	7.98	5.99	99.7	99.9
12.0	6.0	11.98	6.00	99.8	100.0
16.0	6.0	15.93	5.98	99.6	99.8
20.0	6.0	20.32	6.04	101.6	100.6
12.0	2.0	11.94	2.03	99.5	101.4
12.0	4.0	12.00	4.05	100.0	101.3
12.0	6.0	11.96	5.98	99.7	99.8
12.0	8.0	12.06	8.02	100.5	100.3
12.0	10.0	12.09	10.05	100.8	100.5
$\bar{x}$				100.1	100.3
RSD				0.68	0.60

Table 6
Summary of statistics in CLS, ILS and PCR techniques for MEF and PAR in the mixture

Parameters	Methods	PAR	MEF
SEP	CLS	0.1058	0.0312
	ILS	0.1030	0.0297
	PCR	0.1124	0.0286
SEC	CLS	0.1264	0.0373
	ILS	0.1231	0.0355
	PCR	0.1343	0.0341
r	CLS	0.9998	0.9999
	ILS	0.9997	0.9999
	PCR	0.9997	0.9999
Intercept	CLS	−0.1540	0.0080
	ILS	−0.1550	0.0020
	PCR	−0.1606	0.0071
Slope	CLS	1.0145	1.0005
	ILS	1.0145	1.0004
	PCR	1.0153	1.0001

3.3. Applications

Comparison of the spectra of MEF and PAR in standard and drug formulation solutions showed that the wavelength of maximum absorbances in the zero-order spectra did not changed. It has been decided that excipients placed in the commercial preparations selected (lactose, starch, avicel, povidon, sodium dodecylsulfate, aerosil and magnesium stearate) did not interfere the quantitation of MEF and PAR in these methods. All the results obtained by using the methods described above, ratio spectra derivative spectrophotometry and three chemometric methods (CLS, ILS and PCR), were compared with each other using one-way ANOVA test including 10 replicates for synthetic mixtures. Snedecor F values below the tabulated level ($F = 2.86$, $n_1 = 3$, $n_2 = 36$) were obtained in all cases indicating that there was no significant difference between the methods compared.

It is important that all the analyses by proposed methods must be performed in 8 h after the solutions were prepared due to the decomposition of MEF in 0.1 M NaOH:methanol (1:9).

Table 7
Assay results of commercial preparation (mg/tablet)

Methods	MEF		PAR	
	[a](250 mg/tablet)[b]mean ± [c]SD	*F-value	[a](500 mg/tablet) [b]mean ± [c]SD	*F-value
CLS	245.6 ± 1.0	1.14	492.8 ± 4.8	1.64
ILS	245.5 ± 1.0	1.14	493.1 ± 4.7	1.64
PCR	244.8 ± 0.4	1.14	490.6 ± 3.1	1.64
Ratio spectra derivative (^{1}DD)	245.4 ± 1.2	1.14	490.9 ± 2.0	1.64
Difference spectrophotometry [5]	248.3 ± 3.0		494.7 ± 3.9	
HPLC [6]	247.9 ± 10.2		508 ± 13.5	

[a] Label claim.
[b] Obtained results are average of ten tablets for four techniques.
[c] SD, standard deviation.
* Theoretical value for F at P: 0.05 level = 2.86 ($n_1 = 3$, $n_2 = 36$).

4. Conclusion

The proposed methods, ratio spectra derivative spectrophotometry and three chemometric methods could be applied with great success for the simultaneous determination of MEF and PAR in mixtures and the pharmaceutical formulation selected containing its binary mixture without interference of each other. Easy measurements on the separate peaks, higher values of analytical signals and no need to work only at zero-crossing points (sometimes co-existing compounds have no maximum or minimum at these wavelengths) is an advantage for ratio spectra derivative spectrophotometry in comparison with the derivative spectrophotometry [1]. For the same pharmaceutical preparation, it was observed that the experimental results obtained by three numerical and graphical methods are very close to each other. When our proposed methods are compared with other literature methods, we observed that our results were more reliable and reproducible than difference spectrophotometry [5] and HPLC [6] mentioned in the introduction. Satisfactory results were obtained by using chemometric methods but they need software for the mathematical calculations. Using only zero-order spectra in the procedures and not need any other mode, such as derivative mode, in the instruments are an advantages for the chemometric methods. Very similar results were obtained in CLS and ILS techniques. Relative standard deviation in ratio spectra derivative spectrophotometry was found higher for MEF than those obtained in chemometric techniques. These four methods were found suitable for simple, accurate and precise routine analysis of the pharmaceutical preparation selected. Good agreement was seen in the assay results of pharmaceutical preparation, tablet, for all the methods proposed.

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