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Simultaneous spectrophotometric determination of pseudoephedrine hydrochloride and ibuprofen in a pharmaceutical preparation using ratio spectra derivative spectrophotometry and multivariate calibration techniques

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Abstract

Spectrophotometric methods are described for the simultaneous determination of pseudoephedrine hydrochloride and ibuprofen in their combination. The obtained data were evaluated by using five different methods. In the first method, ratio spectra derivative spectrophotometry, analytical signals were measured at the wavelengths corresponding to either maximums and minimums for both drugs in the first derivative spectra of the ratio spectra obtained by using each other spectra as divisor in their solution in 0.1 M HCl. In the other four spectrophotometric methods using chemometric techniques, classical least-squares, inverse least-squares, principal component regression and partial least-squares (PLS), the concentration data matrix were prepared by using the synthetic mixtures containing these drugs in methanol:0.1 M HCl (3:1). The absorbance data matrix corresponding to the concentration data matrix was obtained by the measurements of absorbances in the range 240–285 nm in the intervals with $\Delta\lambda = 2.5$ nm at 18 wavelengths in their zero-order spectra, then, calibration or regression was obtained by using the absorbance data matrix and concentration data matrix for the prediction of the unknown concentrations of pseudoephedrine hydrochloride and ibuprofen in their mixture. The procedures did not require any separation step. The linear range was found to be 300–1300 μg/ml for ibuprofen and 100–1300 μg/ml for pseudoephedrine hydrochloride in all five methods. The accuracy and the precision of the methods have been determined and they have been validated by analyzing synthetic mixtures. The five methods were successfully applied to tablets and the results were compared with each other.

Keywords: Pseudoephedrine hydrochloride; Ibuprofen; Ratio spectra derivative spectrophotometry; Chemometric methods; Pharmaceutical preparation

1. Introduction

The combination of pseudoephedrine hydrochloride (PSE) with ibuprofen (IB) is frequently prescribed as an anthistaminic drug. Various methods including spectrophotometry [1–8], HPLC [9–16], gas

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chromatography [17], NMR [18] and MEKC [19] have been used for the determination of PSE and spectrophotometry [20,21] and HPLC [22–31] have been used for the determination of IB in pharmaceutical preparations.

Ivanoviç et al. [3] used second derivative spectrophotometry, Kale et al. [7] used classical spectrophotometric measurement at two wavelengths for the simultaneous analysis of PSE + IB mixture in pharmaceutical formulations.

Chemometric calibration techniques in spectral analysis are widely used in the quality control of drugs in mixtures and pharmaceutical formulations containing two or more drugs with overlapping spectra as separation procedures in the drug determinations are not required [32–36]. We have also used these techniques for the simultaneous analysis of binary and a ternary mixtures [37–40].

In this study; ratio spectra derivative spectrophotometry and four chemometric methods for processing the spectral data are proposed for the simultaneous determination of PSE and IB in their binary mixtures and in a tablet.

2. Experimental

2.1. Apparatus

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

In ratio spectra derivative spectrophotometry, the range was selected as 240.0–285.0 nm ($\Delta\lambda = 2.5$ nm) for reading the analytical signals. The ordinate maximum and minimum settings were (+1)–(−1) in 240.0–265.0 nm range for IB and PSE in their mixture (scaling factor = 10).

In the chemometric methods, original spectra of IB and PSE in methanol:0.1 M HCl (3:1) in 240–285 nm range were used.

2.2. Computer hardware and software

In the chemometric procedures *Matlab 6.2*, *Maple V* and *Minitab 12.2* software were used and run on PC Pentium III, 1500 MHz computer.

2.3. Materials

Pseudoephedrine hydrochloride and ibuprofen were kindly donated by DİNÇTAŞ Pharm. Ind., Turkey and used without further purification.

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

2.4. Standard solutions

Solutions of 1 mg/ml of pseudoephedrine hydrochloride and 1 mg/ml ibuprofen were prepared respectively, in methanol:0.1 M HCl (3:1).

2.5. Sample preparation

Twenty tablets were accurately weighed and powdered in a mortar. An amount of the tablet mass equivalent to one tablet was dissolved in 60 ml of methanol:0.1 M HCl (3:1). After 30 min of mechanical shaking, the solution was filtered in a 100 ml volumetric flask. The residue was washed three times with 10 ml of solvent and the volume was made up to 100 ml with the same solvent. 27.5 ml of this solution was made up to 50 ml with methanol:0.1 M HCl (3:1). All the spectrophotometric methods were applied to the final solution.

2.6. Commercial pharmaceutical preparation

Dolorin Cold® (200 mg ibuprofen and 30 mg pseudoephedrine hydrochloride per tablet) DİNÇTAŞ Pharm. Ind., Turkey (batch no: 6L 7198) was assayed.

2.7. Chemometric methods

2.7.1. Classical least-squares (CLS)

Calibration is based on a set of *n* samples of known concentrations for which the spectra are measured. By means of the calibration sample set, estimation of coefficients is possible by solving for the matrix K according to the general least-squares solution:

$$K = (C^{\mathrm{T}}C)^{-1}C^{\mathrm{T}}A$$

where C is calibration matrix, and A is absorbance matrix.

The analysis is then based on the spectrum a_0 of the unknown sample by use of:

$$C_0 = a_0 K^{\mathrm{T}}(KK^{\mathrm{T}})^{-1}$$

2.7.2. Inverse least-squares (ILS)

The calibration coefficients are now the elements of the *P*-matrix that are estimated by the generalized least-squares solution according to:

$$P = (A^{\mathrm{T}}A)^{-1}A^{\mathrm{T}}C$$

where C is calibration matrix, and A is absorbance matrix.

Analysis is carried out by direct multiplication of the measured sample spectrum a_0 by the *P*-matrix:

$$C_0 = a_0 P$$

2.7.3. Principal component regression (PCR)

In the spectral work, the following steps can explain the fundamental concept of PCR.

The original data obtained in absorbances (A) and concentrations (C) of analytes were reprocessed by mean-centring as A_0 and $\boldsymbol{C}_0$, respectively. Using the ordinary linear regression

$$C = a + b \times A$$

the coefficients a and b: $b = P \times q$, where P is the matrix of eigenvectors and q is the C-loadings given by $q = D \times T^{\mathrm{T}} \times A_0$. Here T^{T} is the transpose of the score matrix T. D is a diagonal matrix having on the components the inverse of the selected eigenvalues. Knowing b one can easily find a by using the formula $a = C_{\mathrm{mean}} - A^{\mathrm{T}}_{\mathrm{mean}} \times b$, where $A^{\mathrm{T}}_{\mathrm{mean}}$ represents the transpose of the matrix having the entries of the mean absorbance values and C_{mean} is the mean concentration of the calibration set.

2.7.4. Partial least-squares (PLS)

In the UV-Vis spectra, the absorbance data (A) and concentration data (C) are mean centered to give data matrix A_0 and vector $\boldsymbol{C}_0$. The orthogonalized PLS algorithm has the following steps.

The loading weight vector W has the following expression:

$$W = \frac{A_0^{\mathrm{T}}C_0}{C_0^{\mathrm{T}}C_0}.$$

The scores and loadings are given by:

$$t_1 = A_0 W,$$

$$P_1 = \frac{A_0^{\mathrm{T}}t_1}{t_1^{\mathrm{T}}t_1},$$

$$q_1 = \frac{C_0^{\mathrm{T}}t_1}{t_t^{\mathrm{T}}t_1}.$$

The matrix and vector of the residuals in A_0 and C_0 are:

$$A_1 = A_0 - t_1 p_1^{\mathrm{T}},$$

$$C_1 = C_0 - t_1 q_1^{\mathrm{T}}.$$

From the general linear equation, the regression coefficients were calculated by:

$$b = W(P^{\mathrm{T}}W)^{-1}q,$$

$$a = C_{\mathrm{mean}} - A^{T}_{\mathrm{mean}}b.$$

The builded calibration equations is used for the estimation of the compounds in the samples.

3. Results and discussion

3.1. Ratio spectra first derivative spectrophotometry

The ratio spectra of different PSE standards at increasing concentrations in methanol:0.1 M HCl (3:1) obtained by dividing each with the stored spectrum of the standard solution of IB (700 μg/ml in methanol:0.1 M HCl (3:1)) are shown in Fig. 1a and the second derivative of these spectra (^{2}DD) traced with the interval of $\Delta\lambda = 2$ nm (scaling factor = 10) are illustrated in Fig. 1b. As seen in Fig. 1b, there exist one maximum (254.4 nm) and two minima (252.2 and 257.3 nm) and we found that all three were suitable for the determination of PSE in PSE + IB mixture. We selected 252.2 for the determination of this compound in the assay of synthetically prepared pharmaceutical preparation, tablet, due to its lower R.S.D. value and more suitable mean recovery compared to the other wavelength (Table 1). The ratio and ratio derivative spectra of the solutions of IB in different concentrations in methanol:0.1 M HCl (3:1) traced

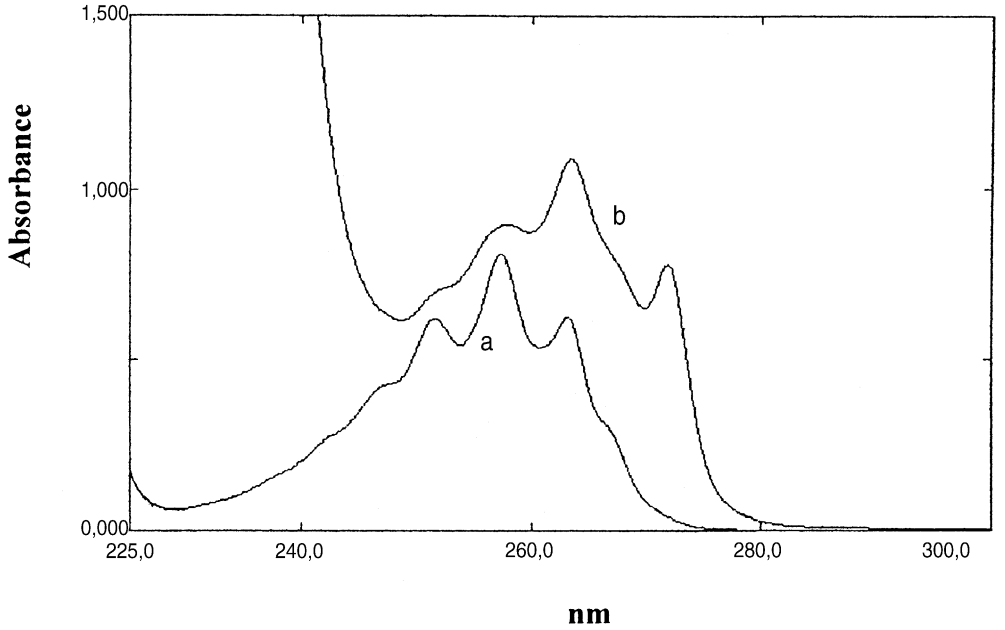

Fig. 1. Ratio spectra (a) and second derivative of the ratio spectra (b) of (a) 300 μg/ml, (b) 700 μg/ml, (c) 1100 μg/ml pseudoephedrine hydrochloride in methanol:0.1 M HCl (3:1) when in the presence of 700 μg/ml of ibuprofen in methanol:0.1 M HCl (3:1) used as divisor ($\Delta\lambda = 2$ nm, scaling factor = 10).

with the interval of $\Delta\lambda = 2$ nm (scaling factor = 10) by using the standard spectrum of PSE (900 μg/ml in methanol:0.1 M HCl (3:1)) as divisor by computer aid was demonstrated in Fig. 2a and b, respectively. In these spectra, two maxima (251.2 and 257.4 nm) and one minimum (254.2 nm) were found suitable for the quantification of IB in PSE + IB.

Measured analytical signals at these wavelengths are proportional to the concentrations of the drugs. We selected 254.2 nm for the determination of this compound (IB) in the assay of the tablet, due to its lower R.S.D. value and suitable mean recovery among the wavelengths mentioned (Table 1).

Calibration graphs were established from analytical signals measured at 252.2, 254.4 and 257.3 nm for standards containing 100–1300 μg/ml of PSE and at 251.2, 254.2 and 257.4 nm for standards containing 300–1300 μg/ml IB corresponding to maxima and minima in the absence of each other.

In the method, the mean recoveries (±confidence interval calculated as $x \pm (t \times \text{S.D.}/\sqrt{n})$, where x is the mean value, S.D. the standard deviation, n the number of experiment and t the tabulated value for $n - 1$ degree of freedom) and relative standard deviations calculated for synthetic mixtures prepared in our laboratory are illustrated in Table 1. Also, Beer's law

Table 1
Recovery results for PSE and IB in synthetic mixtures by ratio spectra second derivative spectrophotometry

No. repetition of unit (nm)	PSE			IB		
	252.2 nm	254.2 nm	257.4 nm	251.2 nm	254.2 nm	257.4 nm
Mean recovery (%)[a]	99.6 (±0.95)	98.2 (±2.45)	109.3 (±4.20)	98.5 (±0.34)	99.0 (±0.51)	98.9 (±1.64)
R.S.D. (%)	1.66	4.33	6.65	0.60	0.89	2.87

$n = 14$; R.S.D.: relative standard deviation; CI: confidence interval.
[a] The values in parenthesis are ±CI for $P = 0.05$.

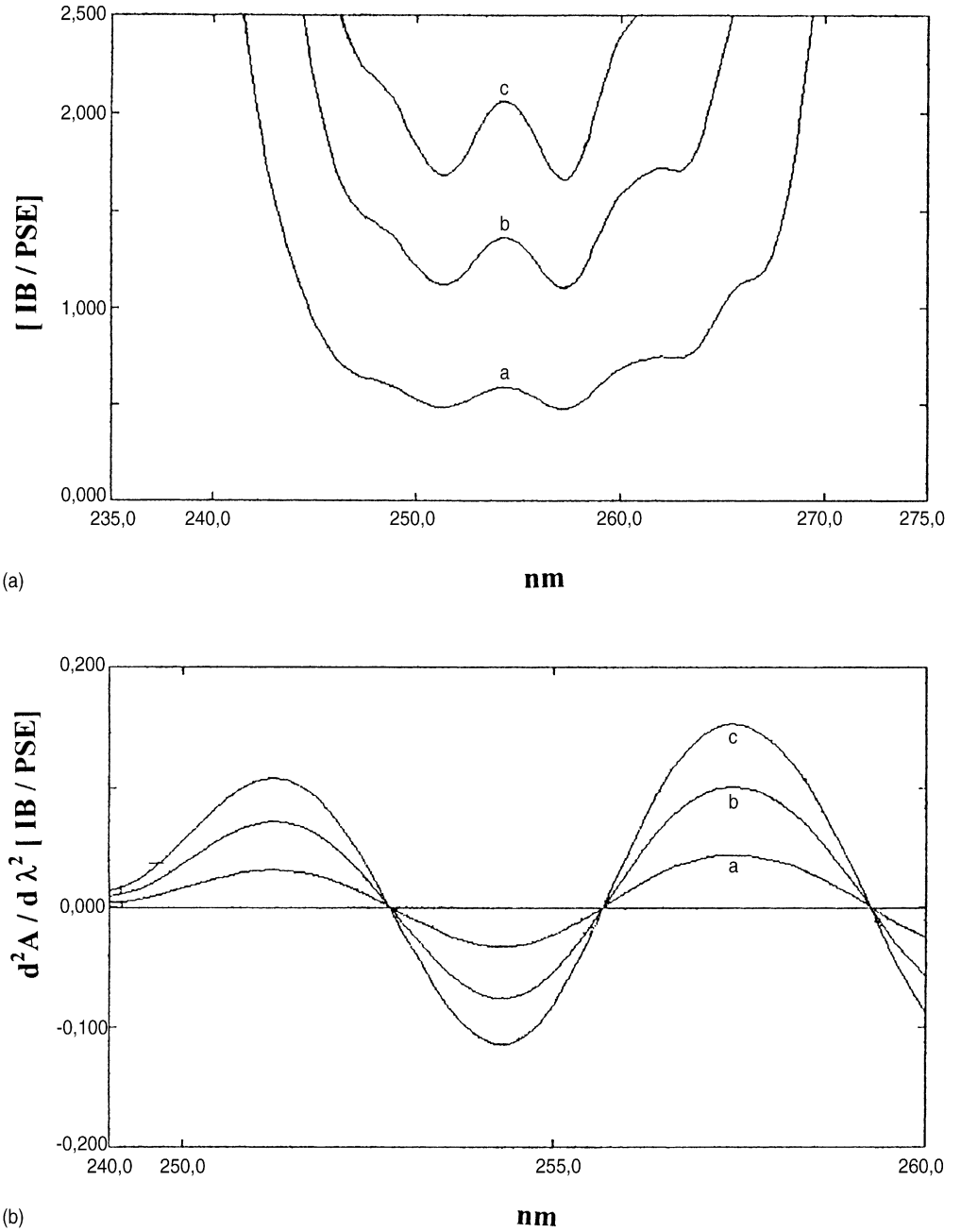

Fig. 2. Ratio spectra (a) and second derivative of the ratio spectra (b) of (a) 300 μg/ml, (b) 700 μg/ml, (c) 1100 μg/ml ibuprofen in methanol:0.1 M HCl (3:1) when in the presence of 900 μg/ml of pseudoephedrine hydrochloride in methanol:0.1 M HCl (3:1) used as divisor ($\Delta\lambda = 2$ nm, scaling factor = 10).

Table 2
Beer's Law data and statistical analysis for the calibration graphs of PSE and IB using ratio spectra derivative spectrophotometric procedures

Compounds	λ (nm)	Regression equations		r	Concentration range (μg/ml)
		a (S.E.)	b (S.E.)		
PSE	252.2	-8.4×10^{-5} (1.5×10^{-6})	3.2×10^{-4} (1.2×10^{-3})	0.9985	100–1300
PSE	254.4	6.4×10^{-5} (9.0×10^{-7})	1.8×10^{-5} (7.2×10^{-4})	0.9996	100–1300
PSE	257.3	-1.1×10^{-4} (1.9×10^{-6})	3.2×10^{-4} (1.6×10^{-4})	0.9980	100–1300
IB	254.2	-1.0×10^{-4} (1.6×10^{-6})	-4.1×10^{-3} (1.4×10^{-3})	0.9990	300–1300
IB	251.2	9.5×10^{-5} (1.4×10^{-6})	3.7×10^{-3} (1.2×10^{-3})	0.9992	300–1300
IB	257.4	1.4×10^{-4} (2.2×10^{-6})	5.4×10^{-3} (1.9×10^{-3})	0.9990	300–1300

a = slope, b = intercept, r = correlation coefficient, S.E. = standard error; $n = 10$.

compliance for both compounds, the regression equations and correlation coefficients are summarized in Table 2. Mean recoveries and relative standard deviations of the method were found satisfactory.

Divisor concentration is the main instrumental parameter. The standard spectra of 700 μg/ml of IB and 900 μg/ml of PSE were considered as suitable for the determination of PSE and IB, respectively as divisor. The Δλ found as optimum for the first derivative of their ratio spectra was 2 nm.

LOD was found to be 60 μg/ml for IB and 20 μg/ml for PSE (determined as blank + 3S.D.), LOQ was found 300 μg/ml for IB and 100 μg/ml for PSE (determined as blank + 10S.D.) in the method.

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

A summary of the assay results for the commercial preparation are shown in Table 8. The results of four chemometric methods and ratio spectra derivative spectrophotometry developed by us for the same commercial formulation were compared by Student's *t*-test. The calculated (experimental) *t*-values did not exceed the tabulated (theoretical) values in the test, indicating that there was no significant difference between the methods compared.

3.2. Chemometric techniques

The numerical values were calculated by using '*Matlab 6.2*, *Maple V* and *Minitab 12.2*' software in chemometric methods. Fig. 3 shows the zero-order absorption spectra for PSE and IB and their binary mixture in 0.1 M HCl. For three techniques, the absorbance data matrix for the training set concentration matrix (Table 3) were obtained by the measurement of absorbances between 245.0 and 285.0 nm in the intervals with $\Delta\lambda = 2.5$ nm at 17 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 PSE and IB in their binary mixtures and pharmaceutical formulations.

Regression coefficients for PCR and PLS technique and their standard errors were illustrated in Table 4.

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 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} the predicted concentration of drug and n 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, PCR, ILS and PLS methods to the same binary mixture are indicated in Table 4. The errors of prediction were acceptable (5.97, 7.18, 7.01 and 13.1 for PSE and 7.60, 5.98, 5.97 and 9.70 for IB, respectively for CLS, PCR, ILS and PLS methods) (Table 5).

In Table 5, r is defined as the correlation between constituent concentrations and shows the absorbance effects relating to the constituent of interest. The r

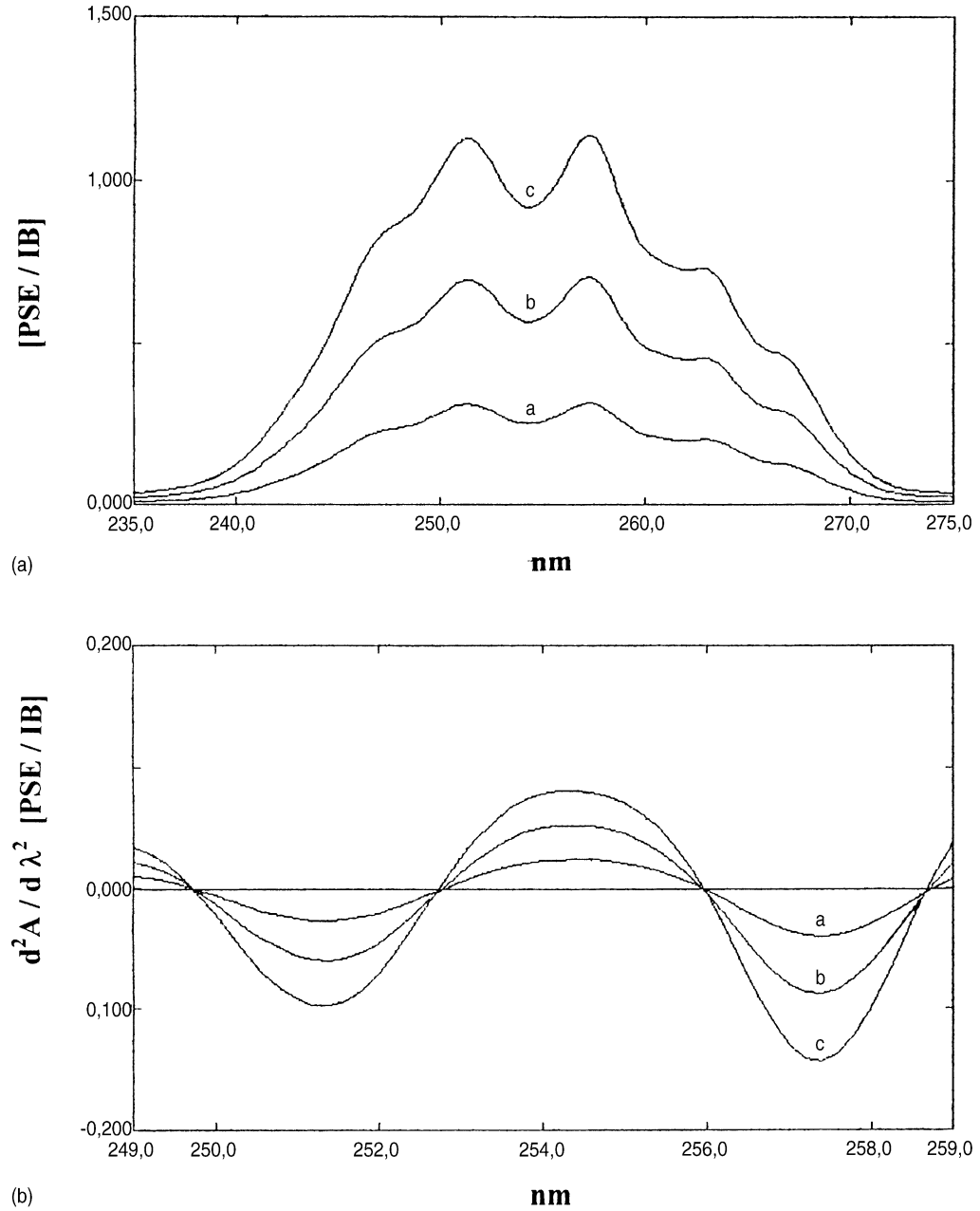

Fig. 3. Zero-order absorption spectra of (a) 900 μg/ml solution of pseudoephedrine hydrochloride, (b) 700 μg/ml solution of ibuprofen in methanol:0.1 M HCl (3:1).

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

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

Table 3
Training set used in PCR and PLS techniques

Mixture no.	IB (μg/ml)	PSE (μg/ml)
1	100	1300
2	500	1000
3	0	600
4	900	800
5	1300	900
6	160	100
7	160	500
8	160	800
9	200	0
10	160	760

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

The errors of prediction (SEC) were found to be acceptable in CLS, PCR, ILS and PLS methods (6.45, 7.76, 7.57 and 14.17 for PSE and 8.21, 6.46, 6.45 and 10.5 for IB) respectively (Table 5) in the synthetic mixtures containing these two drugs in variable compositions prepared as indicated in Table 6.

Mean recoveries and relative standard deviations for the CLS, PCR, ILS and PLS techniques were found to be 99.5 and 1.65%, 100.5 and 1.29%, 99.4 and 1.83%, 100.4 and 2.43% for PSE and 99.8 and 0.85%, 99.8 and 0.99%, 99.9 and 0.90%, 100.1 and 1.49% for IB, respectively in the synthetic mixtures of both drugs (Table 6).

Table 5
Summary of statistics in CLS, PCR, ILS and PLS methods for PSE and IB in the mixture

	CLS	PCR	ILS	PLS
SEP				
PSE	5.97	7.18	7.01	13.1
IB	7.60	5.98	5.97	9.7
SEC				
PSE	6.45	7.76	7.57	14.1
IB	8.21	6.46	6.45	10.5
r				
PSE	0.9999	0.9998	0.9998	0.9995
IB	0.9998	0.9998	0.9999	0.9995
Intercept				
PSE	0.99	0.99	0.99	0.99
IB	0.99	0.99	0.99	0.99
Slope				
PSE	0.13	4.45	1.04	3.98
IB	7.86	2.13	0.13	6.77

Table 4
Regression coefficients in PCR and PLS techniques

	PCR				PLS			
	PSE		IB		PSE		IB	
	Regression coefficients	Standard error	Regression coefficients	Standard error	Regression coefficients	Standard error	Regression coefficients	Standard error
a_0	99.62		134501		–	–	–	–
a_1	4267.42	0.000141657	22885.76	0.000615705	10235	0.00048458	−4847	0.00035209
a_2	−13837.35	0.000156882	−40621.09	0.000682078	4367	0.00026030	−2046	0.00018913
a_3	−64298.89	0.000338089	−169752.90	0.000146981	−131	0.00015959	117	0.00011596
a_4	17129.88	0.000278586	151766.40	0.000121114	−3033	0.00013881	1522	0.00010086
a_5	−16775.20	0.000104104	−127259.50	0.000452622	−5214	0.00015132	2584	0.00010995
a_6	17234.61	0.000488079	173672.40	0.000212170	−5798	0.00017040	2874	0.00012381
a_7	31358.94	0.000347655	51327.93	0.000151143	−5201	0.00017888	2588	0.00012997
a_8	28526.54	0.000304321	148127.80	0.000132301	−8756	0.00022208	4327	0.00016136
a_9	−13992.28	0.000512483	−35441.97	0.000222802	−3288	0.00018795	1663	0.00013656
a_{10}	−24076.02	0.000294267	−203628.20	0.000127935	−3322	0.00021351	1688	0.00015513
a_{11}	1965.98	0.000209331	−47036.75	0.000910099	−492	0.00019889	306	0.00014451
a_{12}	−27747.35	0.000490039	−194502.40	0.000213047	1832	0.00016819	−837	0.00012200
a_{13}	37338.98	0.000714439	270328.40	0.000310611	4665	0.0001554	−2226	0.00011302
a_{14}	−17403.59	0.000603786	−177138.50	0.000262508	6311	0.00018413	−3023	0.00013379
a_{15}	226023.60	0.0000803368	1114195	0.000049273	2106	0.000055776	−1010	0.000040527
a_{16}	−213082.30	0.0000724276	−750023.40	0.0000314887	1361	0.000022719	−658	0.000016507
a_{17}	164012.10	0.00000575519	502251.40	0.0000025021	458	0.0000076145	−221	0.0000055326

Table 6
Recovery results for PSE and IB in synthetic mixtures by chemometric techniques

	CLS		ILS		PCR		PLS	
	PSE	IB	PSE	IB	PSE	IB	PSE	IB
Mean recovery (%, ±CI for $P = 0.05$)	99.5 (±0.95)	99.8 (±0.48)	99.4 (±1.06)	99.9 (±0.52)	100.5 (±0.74)	99.8 (±0.55)	100.4 (±1.35)	100.1 (±0.83)
R.S.D. (%)	1.65	0.85	1.83	0.90	1.29	0.99	2.43	1.49

$n = 14$.

Cross-validation was performed for the PCR and PLS methods and RMS errors were found as 1.89 and 2.86 for PSE and IB in the PCR method, respectively and 1.92 and 2.87 for PSE and IB in the PLS method, respectively.

The linear range was 100–1300 μg/ml for PSE and 300–1300 μg/ml for IB in all chemometric methods.

The LOD was found to be 62 μg/ml for IB and 23 μg/ml for PSE (determined as blank + 3S.D.), the LOQ was found to be 300 μg/ml for IB and 100 μg/ml for PSE (determined as blank + 10S.D.) in all the methods.

Elements of *K*-matrix represent absorptivities with reference to the spectra of the individual constituents if the concentrations were taken as molar absorptivities.

3.3. Precision

The precision was determined by means of a one-way ANOVA including 10 replicates carried out on three successive days using ratio spectra derivative spectrophotometry and the four chemometric methods (CLS, PCR, ILS and PLS) for synthetic mixtures. Snedecor *F* values below the tabulated levels were obtained in all cases ($F = 4.21$, $n_1 = 2$, $n_2 = 27$; Table 7) so there were no significant differences between the result obtained in the determination of each drug in the presence of the other on different days. The highest R.S.D. (%) values were obtain for the ILS method for the between days and within days results for both IB and PSE (2.11 and 3.21% for IB and 3.91 and 3.95% PSE; Table 7).

3.4. Applications

Comparison of the spectra of PSE and IB in standard and drug formulation solutions showed that the wavelength of maximum absorbances in the zero-order spectra did not change. Further, after the addition of known amounts of PSE and IB to the commercial formulation we found that the amount of these drugs did not change. This shows that the excipients present in the commercial preparation selected (lactose, starch, avicel, povidon, sodium dodecylsulfate, aerosil and magnesium stearate) did not interfere in the quantitation of PSE and IB in these methods. All the results obtained by using the methods described above were compared with each other and no significant

Table 7
Analysis of variance (ANOVA) for the proposed methods

Parameters	Classical least-squares		Inverse least-squares		Principle component regression		Partial least-squares		Ratio spectra derivative spectrophotometry	
	IB	PSE	IB	PSE	IB	PSE	IB	PSE	IB	PSE
Between-days variance	10.10	15.64	15.80	19.80	14.42	12.53	16.34	12.88	10.93	10.77
Within-days variance	10.10	9.69	10.40	19.60	11.40	11.23	13.64	11.90	8.76	4.27
F ratio	1.00	1.61	1.52	1.01	0.13	0.83	1.20	1.08	1.25	2.52
Mean value	522.2	487.4	490.7	500.7	518.4	488.4	514.8	491.8	493.9	491.7
Between-days R.S.D. (%)	1.83	3.12	3.21	3.95	2.78	2.56	3.17	2.61	1.54	3.61
Within-days R.S.D. (%)	1.83	1.99	2.11	3.91	2.20	2.29	2.65	2.42	2.87	3.13

Between-day and within-day degrees of freedom 2 and 27, respectively. The critical *F* ratio value for 2 and 27 degrees of freedom and a confidence level of 95% is 4.21.

Table 8
Assay results of commercial preparation marketed in Turkey (mg per tablet)

Methods	PSE (label claim = 30 mg per tablet)		IB (label claim = 200 mg per tablet)	
	Mean ± S.D.[a]	*t* values	Mean ± S.D.	*t* values
Classical least-squares (CLS)	30.1 ± 2.17	CLS − ILS = 0.12; CLS − PCR = 0.07; CLS − ^{2}DD = 1.16; CLS − PLS = 0.08; ILS − ^{2}DD = 0.99; ILS − PCR = 0.14; ILS − PLS = 0.04; PCR − ^{2}DD = 0.24; PLS − ^{2}DD = 0.52; PCR − PLS = 0.05	202.5 ± 4.31	CLS − ILS = 0.25; CLS − PCR = 0.02; ^{2}DD − CLS = 1.16; CLS − PLS = 2.00; PCR − ^{2}DD = 0.65; ILS − ^{2}DD = 0.92; ILS − PCR = 0.15; ILS − PLS = 2.10; PLS − ^{2}DD = 2.00; PCR − PLS = 1.23
Inverse least-squares (ILS)	30.2 ± 2.05		202.0 ± 0.15	
Principal component regression (PCR)	30.0 ± 4.55		202.4 ± 5.58	
Partial least-squares (PLS)	30.2 ± 2.30		198.6 ± 2.81	
Ratio spectra derivative spectrophotometry (^{2}DD)	30.4 ± 0.16		200.8 ± 1.56	

Obtained results are average of ten tablets for three techniques. Theoretical value for *t* at *P*: 0.05 level = 2.26.
[a] S.D.: standard deviation.

difference was observed between the amount of drugs found as theoretical values for *t* at $P = 0.05$ level for commercial formulation (Table 8). Standard deviations in the assay using chemometric techniques in spectrophotometric analysis were found to be higher than that of obtained with ratio derivative spectrophotometric method.

4. Conclusions

The proposed methods, ratio spectra derivative spectrophotometry and four chemometric methods based on processing the spectral data could be applied to the simultaneous determination of PSE and IB in mixtures and the pharmaceutical formulation selected containing its binary mixture without interference of each other. There were no significant differences between the linearity ranges of methods proposed in the text and those in the literature. However, the lowest relative standard deviations were obtained for pseudoephedrine hydrochloride and for ibuprofen in ratio spectra second derivative spectrophotometry and classical least-squares techniques, respectively, in comparison with each other and the literature methods. Based on our investigations we would recommend the use of the second derivative spectrophotometry and classical least-squares methods as providing the best balance between accuracy, precision and ease of use. Due to the absence of an official method for this binary mixture, all the methods proposed in this article were compared with each other. These five methods were found suitable for simple 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 in the text. “Based on our investigations we would recommend the used of the . . . method as providing the best balance between accuracy, precision and ease of use”.

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