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Short communication

Alternative and improved method for the simultaneous determination of fexofenadine and pseudoephedrine in their combined tablet formulation

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Abstract

An alternative method for the determination of fexofenadine (FEX) and pseudoephedrine (PSE) in their combined tablet formulation has been developed, employing the partial least squares (PLS) analysis of spectral data of the analytes in their pharmaceutical association. A full-factorially designed set of 16 synthetic samples was employed for calibration purposes. The calibration models were constructed with wavelengths selection, in the ultraviolet region, according to their predictive ability. These were validated internally by the leave-one-out procedure and externally, employing appropriate sets of validation samples. The described method was linear for both analytes, over the range 160.6–301.2 mg L^{-1} for FEX ($R^2 = 0.9993$) and between 325.6 and 610.5 mg L^{-1} for PSE ($R^2 = 0.9992$). It was accurate, exhibiting 99.8% and 99.9% drug recoveries for FEX and PSE, respectively ($N = 9$), while in the intermediate precision experiment relative standard deviations were 1.4% for FEX and 1.2% for PSE.

The contents of both analytes were assayed in commercial tablets employing this method and the results were compared with those furnished by HPLC, being in good statistical agreement. The method represents an improvement over the first derivative of spectral ratio (DSR) technique and allows high sample throughput with minimum reagent consumption and waste generation. The obtained results confirm that the method is highly suitable for its intended purpose.

Keywords: Pseudoephedrine hydrochloride; Fexofenadine hydrochloride; Tablets; Chemometric determination; Improved method

1. Introduction

The pharmacological association (1:2, w/w) between the hydrochlorides of fexofenadine (FEX) and pseudoephedrine (PSE) is the novel replacement of the less safe terfenadine–pseudoephedrine admixture. This combination has been recently approved as a once-a-day formulation [1], and is now widely used to relieve symptoms of allergic conditions, especially seasonal allergic rhinitis, due to the complementary activity of its components [2].

FEX (Fig. 1) is a non-cardiotoxic and non-sedative terfenadine metabolite, which acts as a selective second-generation histamine H_1 receptor antagonist, relieving the uncomfortable manifestations of rhinitis. On the other hand, PSE is an α-adrenoreceptor agonist, useful for relieving nasal congestion [3]. FEX and PSE, but not the FEX-PSE association, are official in the USP29 [4].

PSE is a component of various medications and has been determined by different chromatographic and spectroscopic means [5]. However, analytical methods reporting the determination of FEX alone are relatively uncommon. In pharmaceutical dosage forms, it was quantified by ion–complex reactions [6], capillary electrophoresis [7,8], anodic voltammetry [9] and HPLC with ultraviolet detection [10,11]. In biological fluids, FEX has been determined employing anodic voltammetry [9] as well as HPLC with different detections, including ultravio-

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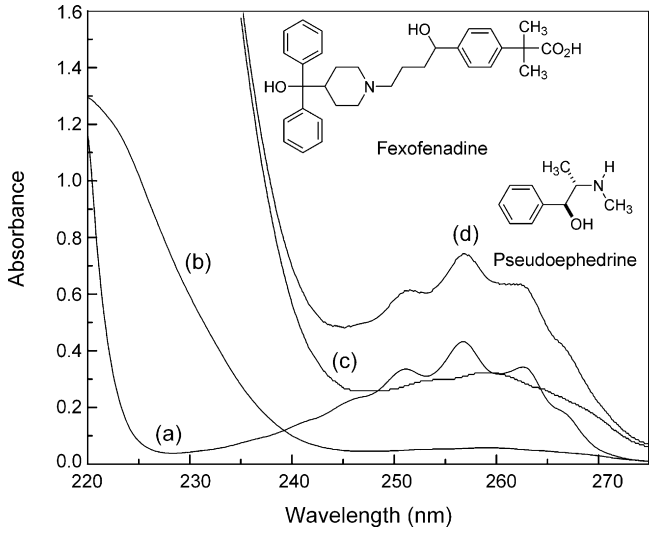

Fig. 1. Chemical structures of FEX and PSE and electronic excitation spectra of (a) PSE (460 mg L^{-1}); (b) FEX (40.2 mg L^{-1}); (c) FEX (230 mg L^{-1}) and (d) mixture of PSE (460 mg L^{-1}) and FEX (230 mg L^{-1}) in 0.01 N HCl-MeOH (80:20, v/v).

let [12], mass spectrometry [13–15] and fluorescence [16]. The combined FEX–PSE formulation has been studied in its dosage form by HPLC [17] and in plasma samples by HPLC with electrospray ionization and tandem mass spectrometry [18], as well as employing ion-interaction chromatography [19].

Recently, a first derivative of the spectral ratio (DSR) spectrophotometric method for the simultaneous analysis of FEX and PSE in pharmaceutical dosage forms, has been reported [20]. This prompted us to analyze the performance of this procedure and disclose the development of a simple and reproducible chemometric method for the simultaneous determination of FEX and PSE in tablets, as a practical and convenient alternative to the derivative methodology.

2. Experimental

2.1. Instrumentation

A Shimadzu UV-1601PC double beam spectrophotometer with a fixed slit width of 2 nm, and Shimadzu's UV-Probe software, were employed. Spectra were acquired in 1-cm quartz cells, at 1 nm intervals for PLS and at 0.1 nm for DSR, against a blank of solvent and individually saved as ASCII files. All the computing routines involving manipulation of spectral data and including the DSR method, the PLS algorithm and the variable selection strategy, were carried out in Matlab 5.3 (Mathworks, Natwick, USA) [21]. For HPLC analyses, a Varian Prostar liquid chromatograph fitted with a 5 μm analytical C_8 column (Luna, Phenomenex), a 20 μL injection loop and a variable wavelength UV-detector, was used. The determinations were performed at room temperature with the eluent pumped at 1.2 mL min^{-1}. Detection was carried out at 220 nm. FEX was chromatographed in 52:48 (v/v) MeCN–MeOH:triethylamine-phosphate (1%, pH 3.7) buffer, where its retention time was 6.0 min. PSE was eluted with 60:40 (v/v) MeCN–MeOH:phosphate (67 mM, pH 7.8) buffer, where its retention time was 6.4 min. Chromatograms were acquired and processed with Varian's Galaxie software. Statistical analyses were performed with Origin 7.5 (OriginLab Co., Northampton, MA).

2.2. Chemicals

Pharmaceutical-grade fexofenadine hydrochloride and pseudoephedrine hydrochloride drug substances were a gift from Laboratorios Lazar (Buenos Aires, Argentina). HPLC-grade methanol and acetonitrile were purchased from Fischer Scientific (Pittsburgh, PA). HPLC-grade water was obtained from a Milli-Q system (Millipore, Bedford, MA). Double-distilled water was used for preparing the samples. Commercial tablets containing the pharmaceutical association (60 mg FEX and 120 mg PSE) were acquired in a local pharmacy. All other chemicals were of analytical grade, and were used as received.

2.3. Procedures

2.3.1. Stock solutions

Stock standard solutions of FEX (1004 mg L^{-1}) and PSE (1018 mg L^{-1}) were separately prepared by dissolving accurately weighed amounts of the drugs in 0.01 N HCl–MeOH (80:20, v/v). For DSR, a solution of FEX (100.4 mg L^{-1}) was prepared by 1:10 dilution of its stock solution.

2.3.2. Preparation of calibration and external validation samples

2.3.2.1. For PLS. Samples were prepared in 10 mL volumetric flasks, by admixture of appropriate volumes of their stock solutions and dilution to the mark with 0.01 N HCl–MeOH (80:20, v/v), to obtain the FEX and PSE concentration levels shown in Table 2. The UV spectra of the samples were acquired between 235 and 275 nm within the next 2 h and processed employing the PLS algorithm. Validation samples included three sets of nine synthetic mixtures each, of FEX (210.1, 243.3, 298.6 mg L^{-1}) and PSE (417.4, 483.0 and 549.2 mg L^{-1}).

2.3.2.2. For DSR. Samples were prepared as for PLS to obtain concentration levels of 20.1, 30.1, 40.2, 50.2 and 60.2 mg L^{-1} for FEX and of 305.3, 407.0, 457.8, 508.8 and 610.5 mg L^{-1} for PSE. The UV spectra of the samples were acquired within the next 2 h, between 220 and 245 nm for FEX and between 240 and 275 nm for PSE. Spectra of pure FEX and PSE samples were divided, amplitude by amplitude, by standard spectra of PSE (407.0 mg L^{-1}) and FEX (200.8 mg L^{-1}), respectively. The calibration graph was obtained by plotting the amplitudes of the first derivatives of the resulting spectral ratios, obtained by the procedure of Savitsky-Golay ($\Delta\delta = 2$ nm), at 225.1 nm for FEX and 255.1 nm for PSE against the corresponding analyte concentrations.

2.3.2.3. For HPLC. Five standard samples of each analyte (60.2–361.4 mg L^{-1} for FEX and 244.2–732.6 mg L^{-1} for PSE) were prepared in 10 mL volumetric flasks, by dilution of appropriate volumes of their stock solutions with MeCN–MeOH (1:1,

v/v). Samples were filtered through a 0.47 μm membrane filter before injection. The calibration graphs were obtained by plotting the peak areas against the corresponding analyte concentrations.

2.3.3. Determination of FEX and PSE in the pharmaceutical formulation

Twenty tablets were accurately weighed, ground by use of a pestle and mortar, and finally homogenized. Analyses were performed on the resulting fine powder.

2.3.3.1. For PLS. An appropriate amount of the above homogeneous powder (ca. 800 mg, equivalent to a tablet) was accurately weighed, transferred to a 50 mL volumetric flask and mechanically shaken 30 min in 12.5 mL MeOH. Then the flask was completed to the mark with 0.01 N HCl, and the liquid was filtered. For the determination of the analytes, an aliquot of the solution was diluted 1:5 in a 10 mL flask with the same solvent. The UV-spectrum of the sample was acquired within the next 2 h and processed with the PLS calibration model.

2.3.3.2. For DSR. Samples were prepared as for PLS, except that for the determination of FEX, an additional 1:5 dilution was prepared in a 10 mL volumetric flask. Spectra of the samples were acquired, divided by the corresponding divisor spectra and derived as detailed in Section 2.3.2.2; the spectral amplitudes of the first derivatives, at 225.1 nm for FEX and at 255.1 nm for PSE, were interpolated in the DSR calibration graphs.

2.3.3.3. For HPLC. Samples were prepared as for PLS, except that MeCN–MeOH (1:1, v/v) was used as solvent for effecting the final 1:5 dilution. The samples were filtered through a 0.47 μm membrane filter before injection. Resulting peak areas were interpolated in the corresponding HPLC calibration graphs.

3. Results and discussion

The electronic excitation spectra of FEX (40.2 mg L^{-1}) and PSE (460.0 mg L^{-1}) between 220 and 275 nm, as well as those of FEX (230.0 mg L^{-1}) and its mixture with PSE (460.0 mg L^{-1}) are shown in Fig. 1. Spectra of the pure compounds are strongly overlapped, with the analytes displaying absorptions of approximately the same magnitude in the region between 245 and 270 nm; however, at lower wavelengths the absorbance of FEX changes from 0.6 to 30 times that of PSE. It was informed that the strong spectral overlap prevents the use of simple derivative techniques for the simultaneous quantification of the analytes [21].

3.1. First derivative of spectral ratio

Fig. 2 shows the implementation of the published DSR method for the determination of FEX and PSE, with its most significant details reported in Table 1. Calibration graphs were obtained by plotting the amplitudes (Amp) of the first derivatives of the spectral ratios at 225.1 nm for FEX and 255.1 nm for PSE against the corresponding concentrations of pure FEX and PSE. Eqs. (1) and (2), derived from the corresponding regression lines, allowed the determination of both analytes in concomitantly processed validation and tablet samples

$$[\text{FEX, mg L}^{-1}] = 0.0 + 82.9\,\text{Amp}_{225.1} \quad (1)$$

$$[\text{PSE, mg L}^{-1}] = 13 + 2.17 \times 10^4\,\text{Amp}_{255.1} \quad (2)$$

A set of five validation samples were used to test the accuracy and precision of the method, providing reasonable recoveries of FEX (98.8 ± 1.2%) and PSE (102.2 ± 1.8%), but exposing several drawbacks of the method. The quantification of the analytes requires high-resolution (0.1 nm) spectra and is not simultaneous, since it must be carried out separately, on different dilutions of the unknown samples. This limitation is due to the fact that in the pharmacological association, at concentrations where absorbance of FEX obeys Beer's law, the most abundant but poorly absorbing PSE cannot be quantified with due accuracy and precision. Conversely, more concentrated samples allow proper quantification of PSE; however, under these conditions the quality of the prediction of FEX is unacceptable. In addition, the determination of FEX, which

Table 1
Relevant statistical parameters of the calibration line for the determination of FEX and PSE by the DSR method

Parameter	FEX	PSE
Wavelength region (nm)	220–245	240–275
Number of calibration standards (*N*)	5	5
Concentration range (mg L^{-1})	20.1–60.2	305.3–610.5
Concentration levels (mg L^{-1})	20.1, 30.1, 40.2,50.2, 60.2	305.3, 407.0, 457.8,508.8, 610.5
Divisor spectrum (mg L^{-1})	407.0	200.8
Measurement wavelength (nm)	225.1	255.1
Slope (±S.D.) of the calibration plot ($\times 10^{-4}$)	120.6 ± 1.2	0.46 ± 0.02
Intercept (±S.D.) of the calibration plot ($\times 10^{-4}$)	−3.8 ± 5.1	6.0 ± 7.4
R^2	0.9999	0.9982
Number of validation samples (*N*)	5	5
Concentration range (mg L^{-1})	30.4–50.7	310.8–503.0
Concentration levels (FEX/PSE, mg L^{-1})	30.4/310.8; 40.6/402.4; 50.7/503.0; 30.4/503.0; 50.7/301.8	
Analyte recovery ± R.S.D. (%)	98.8 ± 1.2	101.1 ± 1.4

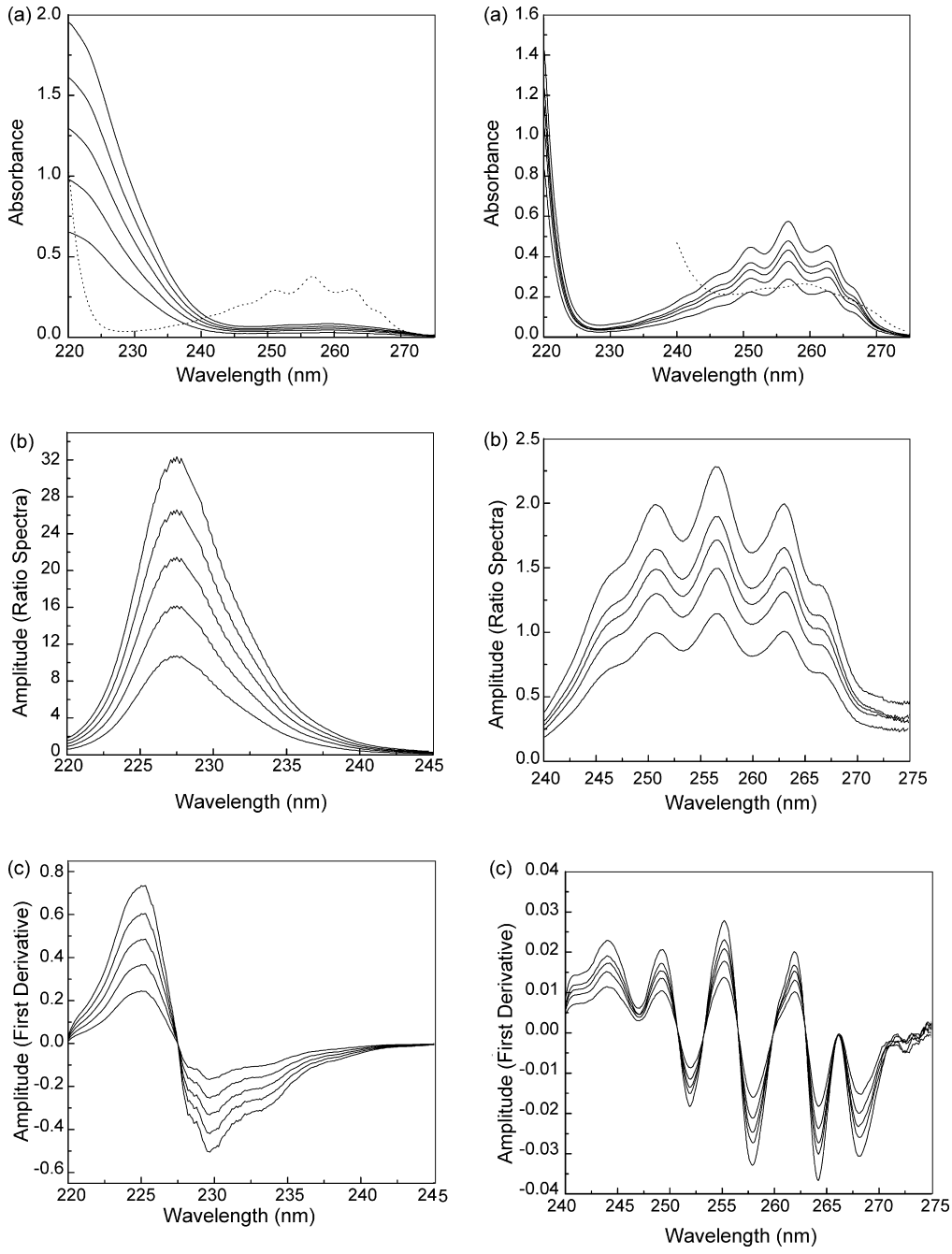

Fig. 2. Left: (a) Spectra of standards of FEX (20.1–60.2 mg L^{-1}) and divisor spectrum (dotted line) in 0.01 N HCl-MeOH (80:20, v/v); (b) spectra of FEX divided by a standard spectrum of PSE (407.0 mg L^{-1}) and (c) first derivatives of spectral ratios. The equation of the calibration curve is $\text{amplitude}_{225.1} = -3.8 \times 10^{-4} + 120 \times 10^{-4}$ [FEX]; $R^2 = 0.9998$ ($p < 0.05$). Right: (a) spectra of standards of PSE (305.3–610.5 mg L^{-1}) and divisor spectrum (dotted line) in 0.01 N HCl–MeOH (80:20, v/v); (b) Spectra of PSE divided by a standard spectrum of FEX (200.8 mg L^{-1}) and (c) first derivatives of spectral ratios. The equation of the calibration curve is $\text{amplitude}_{255.1} = 6.0 \times 10^{-4} + 0.46 \times 10^{-4}$ [PSE]; $R^2 = 0.9987$ ($p < 0.05$).

requires an additional dilution of the unknown, takes place at 225.1 nm where the PSE divisor spectrum has low absorption; moreover, the latter has important absorbance variations in the 222–228 nm region. These factors turn the resulting quotient too prone to errors due to instrumental noise and make the calibration line too sensitive to variations in the divisor spectra.

Analogously, the determination of PSE is not exempt from inconveniences, since its results are subtly influenced by the measuring wavelength, as shown in Fig. 3a. In addition, the published procedure employs a low concentration FEX divisor spectrum which displays absorbances close to spectral noise in the region of interest, as evidenced in Fig. 2a, a pitfall that can be circumvented employing a divisor spectrum of a higher concentration, such as that used in this work (Fig. 2b).

In this scenario, where conditions are adverse for both analytes, it can be anticipated that DSR suffers from several disadvantages, making clear the need of an alternative method.

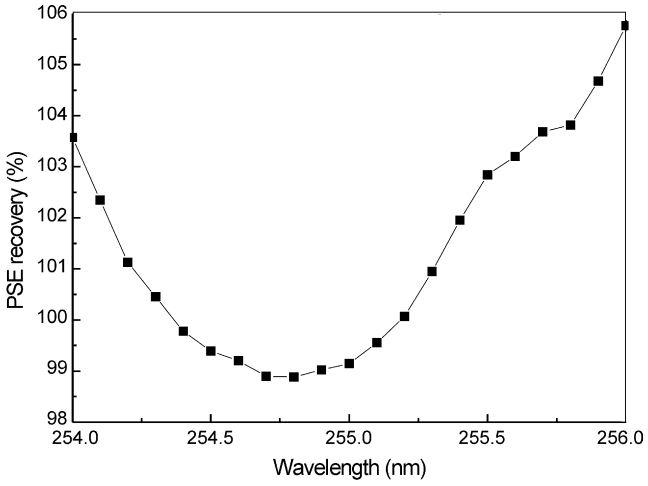

Fig. 3. Wavelength dependence of the recovery of PSE in the DRS method.

3.2. Partial least squares

In view of the pitfalls of the DSR method, we decided to develop a multivariate calibration-assisted approach for the simultaneous determination of FEX and PSE, based on the partial least squares (PLS) algorithm. The mathematical grounds of PLS, have been extensively discussed elsewhere, including its advantages over other multivariate regression methods [22–24].

To establish the calibration models, a set of 16 standards of known concentrations of FEX and PSE in their linear ranges, covering ± 30% of the expected final concentrations of the analytes, was employed. The concentrations of the samples were distributed in a 4^2 full factorial design and the mean-centered electronic spectra of the samples were used as predictor variables.

The best spectral intervals and the optimal number of latent variables for each PLS model were obtained by the joint use of a minimum prediction residual error sum of squares (PRESS) search, employing the moving window of variable size strategy with the "leave one out" cross-validation procedure, which is known to enhance the performance of the method [25]. PRESS (Eq. (3)) is the sum of squares of the differences between predicted and real values of the analytes' concentrations; thus, it is a measure of the predicting ability of the calibration model

$$\text{PRESS} = \left[\sum_{i=1}^{N}(\hat{C}_i - C_i)^2\right]^{0.5} \quad (3)$$

The "leave one out" cross-validation technique systematically generates PLS validation models by excluding one by one each sample from the dataset and then predicting the value for the omitted sample. After this is accomplished for every sample in the dataset, a prediction residual error sum of squares (PRESS) for the PLS cross-validated model is calculated. The cross-validated model with less latent variables that yields the minimum PRESS, and hence the highest cross-validated R^2, determines the optimal number of latent variables to be included in the PLS model.

The optimized models exhibited very good values of their statistical parameters, such as the root-mean-square error of prediction (RMSEP, Eq. (4)), the relative prediction error during calibration (REC (%), Eq. (5)) and the square of the correlation coefficient (R^2)

$$\text{RMSEP} = \left[\frac{1}{N}\sum_{i=1}^{N}(\hat{C}_i - C_i)^2\right]^{0.5} \quad (4)$$

$$\text{REC}\,(\%) = 100\frac{\text{RMSEP}}{C_{\text{mean}}} \quad (5)$$

RMSEP is an indication of the average error in the analysis by cross-validation for each component in the calibration matrix, where C_i is the true concentration of the analyte in the ith calibration sample, $\hat{C}_i$ represents its estimated concentration and

Table 2
Statistical data and figures of merit of the UV-PLS calibration models for FEX and PSE

Parameter[a]	FEX	PSE
Optimal wavelength interval (nm)	241–274	242–258
Concentration range (mg L^{-1})	160.6–301.2	325.6–610.5
Concentration levels (mg L^{-1})	160.6, 214.1, 267.7, 301.2	325.6, 420.6, 516.1, 610.5
Number of samples (N)	16	16
Number of latent variables	2	3
PRESS [(mg L^{-1})^2]	40	480
RMSEP (mg L^{-1})	1.52	3.44
REC (%)	0.67	0.75
R^2	0.9993	0.9992
Slope (± S.D.) of the predicted vs. real concentration plot	0.999 ± 0.007	0.999 ± 0.007
Intercept (± S.D.) of the predicted vs. real concentration plot	0.2 ± 1.6	0.4 ± 3.6
Selectivity	0.37	0.12
Sensitivity (SEN)	0.0024	0.0003
Analytical sensitivity [(γ), L mg^{-1}]	0.224	0.033
Minimum concentration difference [(γ^{-1}), mg L^{-1}]	4.47	30.7

[a] PRESS = $\Sigma(\hat{C}_i - C_i)^2$, where $\hat{C}_i$ and C_i are the predicted and real concentrations of the ith analyte, respectively. RMSEP = $[(\Sigma(\hat{C}_i - C_i)^2)/N]^{0.5}$ = $(\text{PRESS}/N)^{0.5}$, where N is the number of samples employed during the calibration. REC (%) = 100 RMSEP/C_{mean}, where C_{mean} is the mean of the calibration concentrations of the analyte. $R^2 = 1 - [\text{PRESS}/(\Sigma(\hat{C}_i - C_{\text{mean}})^2)]$. Sums are over the entire range of N samples. SEN = $1/||b_k||$, where b_k is the vector containing the final regression coefficients of analyte k. γ = SEN/σ_0, where σ_0 is the standard deviation of the blank.

Table 3
Results of the determination of accuracy and precision of the UV-PLS method[a]

Analyte	Sample number									Mean	R.S.D.
	1	2	3	4	5	6	7	8	9		
Accuracy											
FEX (mg L^{-1})	210.1	243.3	298.6	210.1	243.3	298.6	210.1	243.3	298.6		
FEX, Recovery (%)	100.2	98.3	98.9	99.5	100.3	100.0	100.1	101.5	99.3	99.8	0.9
PSE (mg L^{-1})	417.4	417.4	417.4	483.0	483.0	483.0	549.2	549.2	549.2		
PSE, Recovery (%)	99.0	98.7	100.9	100.9	98.9	100.3	99.5	99.8	100.8	99.9	0.9

	Analyte							
	Fexofenadine				Pseudoephedrine			
	Day 1	Day 2	Day 3	Mean	Day 1	Day 2	Day 3	Mean
Precision								
Recovery (%)	99.8	98.1	99.1	99.0	99.9	98.4	99.0	99.1
R.S.D. (%)[a]	0.9	1.9	1.5	1.4	0.9	1.1	1.5	1.2

Analyte	Source of error	Sum of squares	Degrees of freedom	Mean square	F, $F_{(0.95,\,2,\,24)} = 3.403$
FEX	Between means	7.94	2	3.969	1.174
	Within each group	81.16	24	3.382	
	Total	89.10	26		
PSE	Between means	1.59	2	0.796	0.396
	Within each group	48.21	24	2.009	
	Total	49.80	26		

[a] Top: accuracy of the method. Mean recovery data of FEX and PSE and their relative standard deviations, corresponding to a set of nine validation samples. Middle: precision of the method; analysis of three independent sets of nine validation samples each. Bottom: ANOVA test on the drug recovery data in the precision test.

N is the total number of samples used in the prediction set. On the other hand, REC (%) informs the prediction error as a percentage of the mean concentration (C_{mean}) and R^2 is an indication of the quality of fit of the straight line in the $\hat{C}_i$ versus C_i plot.

A summary of statistical data and figures of merit of the PLS models for each analyte is provided in Table 2. Two latent variables were required for the determination of FEX, while PSE demanded the use of three factors. The predicted versus observed results passed a joint comparison test of zero intercept and slope of unity at a 95% confidence level, which indicates that the method is not biased, providing true results [26].

Accuracy and precision of the method were assessed by analysis of three validation sets of nine samples each. Their analyte

Table 4
Determination of FEX and PSE in pharmaceutical tablets employing the UV-PLS method

Sample number	Analyte[a]					
	Amount recovered of FEX (%)			Amount recovered of PSE (%)		
	HPLC[b]	UV-PLS	DSR	HPLC[c]	UV-PLS	DSR
1	98.5	97.4	91.4	105.9	104.6	102.4
2	99.0	98.0	91.5	106.4	104.8	102.2
3	99.0	98.4	94.3	106.1	104.4	102.1
4	96.5	97.0	92.6	104.6	103.8	101.3
5	96.6	97.0	92.8	104.5	104.2	101.7
6	96.1	96.7	92.9	102.9	104.2	101.3
7	97.4	97.8	95.7	102.2	104.0	100.8
8	97.4	98.0	95.8	103.5	104.4	101.8
9	97.6	98.0	96.3	103.3	104.6	101.7
Mean (%)	97.6	97.5	93.7	104.4	104.3	101.7
R.S.D. (%)	1.1	0.6	1.9	1.5	0.3	0.6
t ($t_{crit\ (0.95,\,7)} = 2.12$)		0.19	5.33		0.20	5.01

Comparison with the first derivative of spectral ratio (DSR) and HPLC methodologies.
[a] Label claim is 60 mg FEX and 120 mg PSE.
[b] [FEX, mg L^{-1}] = $-1.1 + 2.92 \times 10^{-5}$ AUC; $R = 0.9998$; $N = 5$.
[c] [PSE, mg L^{-1}] = $39.3 + 1.8 \times 10^{-5}$ AUC; $R = 0.9970$; $N = 5$.

concentrations were determined on three separate occasions, resulting in near quantitative analyte recoveries and good inter- and intra-day precision, as shown in Table 3. An ANOVA test carried out on the data gave experimental F values of 1.17 and 0.40 for FEX and PSE, respectively, demonstrating at a 95% confidence level ($F_{0.95,\,2,\,24} = 3.40$) that the method is accurate and precise.

3.3. Application: simultaneous determination of FEX and PSE in commercial tablets

Once validated, the UV-PLS method was applied to the simultaneous determination of FEX and PSE in commercial tablets, with the results detailed in Table 4. For the sake of comparison, results from the DSR method and HPLC [10,11,15] are also informed, the latter being used as reference method. It was observed that results of the UV-PLS procedure were in good statistical agreement ($p < 0.05$) with those furnished by HPLC, while the DSR method tended to slightly underestimate both analytes, to the point of not being statistically equivalent to HPLC. While the reasons for the non-equivalence remain unknown, it is not unlikely that non-modeled compounds present in the tablet, may be acting as interferences.

4. Conclusion

Procedures for simultaneous analysis are now being increasingly used for estimation of drugs in multi-component pharmaceutical formulations due to their inherent advantages, among them reduction of time-consuming extraction and separation procedures. An alternative and improved method has been developed for the simultaneous quantification of fexofenadine and pseudoephedrine in their combined tablet formulation, by chemometric evaluation of spectral data of the analytes in selected UV regions.

The method is adequately sensitive, enabling the accurate and precise simultaneous determination of the analytes over satisfactory concentration ranges without the need of special or unattractive and laborious sample-pretreatment steps, apart from their dissolution and filtration. The method, which is advantageously time- and cost-efficient, was successfully applied to the quantification of the analytes in commercial samples of the studied association, with results being in good statistical agreement with HPLC data; therefore, it is considered useful for routine quality monitoring of pharmaceuticals.

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