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Simultaneous determination of desloratadine and pseudoephedrine sulfate in tablets by high performance liquid chromatography and derivative spectrophotometry

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Abstract

Simple and accurate reversed phase liquid chromatographic and first derivative spectrophotometric methods have been developed for simultaneous determination of desloratadine and pseudoephedrine in combined dosage forms. The first method is based on the separation of both drugs by high performance liquid chromatography using a C18 column and 10 mM orthophosphoric acid: acetonitrile (77:23). The drugs are eluted at 1.0 ml/min flow rate and detected at 262 nm. Ondansetron was used as internal standard. The calibration graphs of desloratadine and pseudoephedrine were linear in the range of 1.0–10.0 μg/ml and 48–480 μg/ml, respectively. The detection limits of the method were found to be 0.14 μg/ml and 3.80 μg/ml for desloratadine and pseudoephedrine, respectively. The derivative spectrophotometric method depends on measuring the first derivative amplitudes at 280 and 244 nm for desloratadine and pseudoephedrine, respectively. The calibration graphs were linear in the range of 2.5–15.0 μg/ml for desloratadine and 120–720 μg/ml for pseudoephedrine. The detection limits were found at 0.38 μg/ml and 21.45 μg/ml for desloratadine and pseudoephedrine, respectively. The proposed methods were successfully applied to the determination of these drugs in commercially available tablets.

Keywords: derivative spectrophotometry; desloratadine; HPLC; pseudoephedrine; simultaneous determination.

Introduction

Desloratadine (DE), 8-Chloro-6, 11-dihydro-11-(4-piperidinylidene)-5H-benzo (Patel et al. 2004, Qi et al. 2005) cyclo hepta [1, 2-b] pyridine; decarboethoxyloratadine (Figure 1), a major metabolite of loratadine, is a selective, potent, orally active, peripheral H1 receptor antagonist devoid of any substantial effects on the central and autonomic nervous system (McClellan and Jarvis 2001). Pseudoephedrine sulphate (PSE) (Figure 2) is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa (Benezra and McRae 1979). DE and PSE are present together in dosage form prescribed to relieve symptoms of allergic rhinitis (Shen et al. 2007).

Different analytical methods have been reported for the determination of DE or PSE alone. For determination of DE in tablets a few spectrophotometric methods are reported (Patel et al. 2004, Çaglar and Oztunc 2007). To analyze this drug in tablets, a reversed-phase liquid chromatographic (LC) method based on ion-pair formation (Qi et al. 2005) has also been described in the literature. United States Pharmacopea (USP) 24 describes a non-aqueous titration method for determination of pseudoephedrine sulfate. Various analytical methods for determination of PSE have been reviewed in the analytical profile of drug substances (Benezra et al. 1979). Other numerous methods for determination of PSE alone or in combined tablets and other pharmaceutical formulations have been reported. These include titrimetric (Jones and Marnham 1980), potantiometric (Ganjali et al. 2009, Giahi et al. 2009), spectrophotometric (Palabiyik and Onur 2004, Donmez et al. 2007, Palabiyik et al. 2008) near infrared spectroscopic (Dijiba and Niemczyk 2005), gas chromatographic (Harsono et al. 2005), high performance liquid chromatographic (Qi et al. 2003, Qui et al. 2003, Mabrouk et al. 2003, Dinc et al. 2006, Ali et al. 2007, Karakus et al. 2008, Hadad et al. 2009, Langlois et al. 2009, Asci et al. 2010, Manassra et al. 2010), capillar electrophoretic (Liu et al. 2007) and flow injection analysis (Zayed et al. 2006).

So far, no method has been described for the simultaneous determination of DE and PSE in pharmaceutical formulations. Required are simple, precise, accurate and reliable methods that can be applied in quality control laboratories for DE determination in the presence of PSE. For this purpose, LC and UV-derivative spectrophotometric assay methods have been developed in this study. These methods were especially chosen because of their usage in the determination of drugs in pharmaceutical preparations in pharmacopoeias.

Materials and methods

Chemicals

DE was kindly supplied by Schering Plough (Wicklow, Ireland). PSE and internal standard (IS), ondansetron were obtained from Deva Pharm. Ind. (Istanbul, Turkey) and Glaxo Smith Kline (Istanbul, Turkey), respectively. Commercially available ClarinexD® tablets were purchased from Schering Plough (USA); each tablet was labeled to contain 5 mg of DE and 240 mg of PSE.

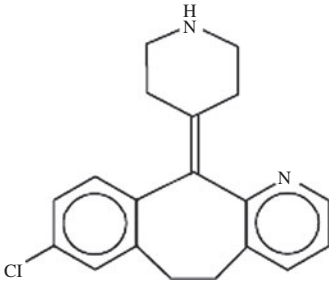

Figure 1 Desloratadine.

Analytical grade ortho-phosphoric acid, high performance liquid chromatography (HPLC) grade acetonitril and all other chemicals and solvents were purchased from Merck (Darmstadt, Germany). Water was purified by aquaMAX™–ultra (Young Lin Instrument, Korea) ultra purification water system.

Apparatus

The HPLC system (Shimadzu LC-10A, Japan) consisted of a solvent-delivery system equipped with a Reodyne injection valve with a 20 µl loop and SPD-10A detector (Shimadzu) set at 262 nm. Integrations and system parameters were controlled by the LC Solution automation system software (Shimadzu). Chromatographic separation was achieved isocratically on a Luna C18 column (250×4.6 mm I.D., 5 µm, Phenomenex) fitted with a guard column (4×3 mm I.D., Phenomenex California, USA) packed with the same material and maintained at ambient temperature. The mobile phase was 10 mM ortho-phosphoric acid (pH 2.5)-acetonitrile (77:23, v/v) with a flow rate of 1.0 ml/min.

A Shimadzu UV-160 A UV-visible spectrophotometer was used under the following operating conditions: derivative mode 1*D* (*dA/dl*), scan speed 1500 nm/min, scan range 200–350 nm, slit width 2 nm and derivation interval (Δλ) 2.8 nm. Derivative spectra were automatically obtained using 1 cm quartz cell by Shimadzu UV-160 A system software.

Solutions

Stock solutions were prepared by dissolving DE and PSE in acetonitril and water, respectively to give a concentration of 1 mg/ml for DE and 10 mg/ml for PSE. Two series of standard solutions were obtained by diluting the stock solutions with acetonitrile. A stock IS solution (1.0 mg/ml) was prepared in water and appropriate dilution was made to obtain the working solution (0.1 mg/ml). The stock solutions were stored at 4°C for 1 month.

Preparation of calibration curves for HPLC method

Standard solutions of DE and PSE were prepared by diluting the stock solutions with the mobile phase. The final concentrations were 1.0–10.0 µg/ml for DE and 48–480 µg/ml for PSE. These solution also contained IS at 10 µg/ml. HPLC analysis was carried out with 20 µl aliquots of the standard solutions under the conditions described above. The chromatograms were evaluated on the basis of DE/IS or PSE/IS ratios of the peak areas.

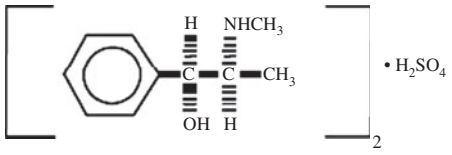

Figure 2 Pseudoephedrine sulfate.

Preparation of calibration curves for derivative spectrophotometric method

Appropriate volumes of the stock solutions were transferred into two sets of 10 ml calibrated flasks and the volumes were adjusted with acetonitrile. The first series contained varying concentrations of DE (2.5, 5.0, 7.5, 10.0, 12.5, 15.0 µg/ml) and a constant concentration of PSE (240 µg/ml). The second series contained varying concentrations of PSE (120, 240, 360, 480, 600, 720 µg/ml) and a constant concentration of DE (5 µg/ml). The first derivative spectra (1*D*) of these standard solutions were scanned against an acetonitrile blank between 200 and 320 nm. The values of the derivative amplitudes at 244 nm (1*D*244, zero-crossing point of PSE) and 280 nm (1*D*280, zero-crossing point of DE) were measured for the determination of DE and PSE, respectively. The concentrations of each compound vs. their derivative amplitudes were plotted in order to obtain the calibration graphs.

Validation of the methods

Under the experimental conditions described above, linear regression equations (intercepts and slopes) for mixtures of DE and PSE were established. The high values of the correlation coefficients and the values of *Y*-intercepts close to zero indicate the good linearity of the calibrations.

The system suitability was evaluated by six replicate analyses of the drugs reference standard at a concentration of 5 µg/ml of DE, 240 µg/ml of PSE and 10 µg/ml of IS.

Selectivity of the method was separately determined in mixtures of them with possible interfering materials, such as starch, magnesium stearate, and lactose.

Precision of the analytical method was tested by analyzing six replicate determinations of three different concentrations (high, medium and low) of DE and PSE both within-day and day-to-day.

Accuracy of the method was tested by recovery studies. The recovery tests were performed using synthetic mixtures containing various amounts of DE and PSE.

Sensitivity of the method was decided by limit of detection (LOD) and limit of quantification (LOQ). LOD and LOQ

were calculated by the equations given in ICH guidelines ICH 2003 (LOD=3.3σ/*S*; LOQ=10σ/*S*).

Assay of pharmaceutical preparations

Ten tablets were separately weighed and finely powdered. About 5 ml of water and 50 ml acetonitrile was added to the accurately weighed amount of the powder equivalent to the median mass of one tablet in a 100 ml calibrated flask. The mixture was shaken mechanically and sonicated in ultrasonic bath totally for 30 min and diluted to volume with acetonitrile and then filtered.

For the HPLC measurements the filtrate was diluted with the mobile phase to give a final concentration of 5.0 µg/ml of DE and 240 µg/ml of PSE. This solution also contained 10 µg/ml of IS.

For the derivative spectrophotometric measurements appropriate dilutions were made with acetonitrile so that the final concentrations of DE and PSE were 5.0 and 240 µg/ml, respectively.

The sample solutions were assayed using the procedures described above and the quantity of DE and PSE was calculated from the regression equations constructed for both the methods.

Results and discussion

HPLC method

The optimum chromatographic conditions were examined to get a good separation of the drugs. Successful attempts were performed isocratically on a reversed-phase column. The best chromatographic separation was obtained with acetonitrile-10 mM o-phosphoric acid (pH 2.5) (23:77, v/v) mobile phase system. A UV-detector was set at 262 nm where the two drugs have the same molar absorptivity. Retention times were 3.17 and 4.2 min for PSE and DE, respectively, and 6.1 min for IS (Figure 3).

The equations of the calibration curves were obtained from linear regression analysis of the peak area ratios of DE or PSE to IS vs. the concentration. The linearity was observed in the concentration range of 1–10 µg/ml for DE and 48–480 µg/ml for PSE.

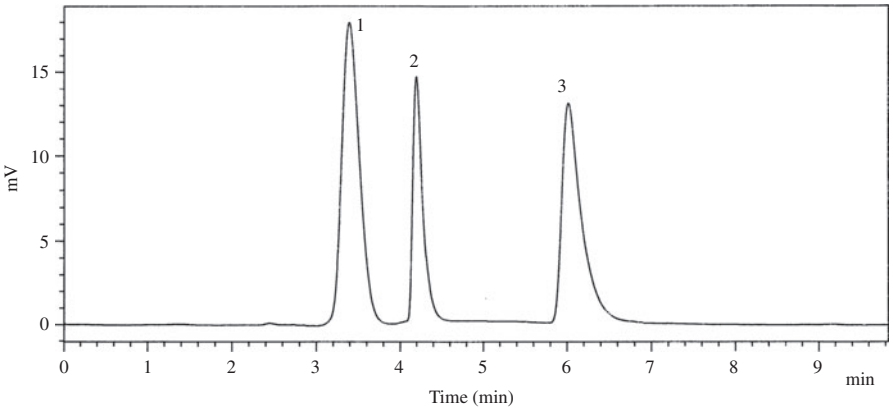

Figure 3 Chromatogram obtained with the mixture of PSE (1), DE (2) and IS (3) (5 µg/ml of DE, 240 µg/ml of PSE and 10 µg/ml of IS).

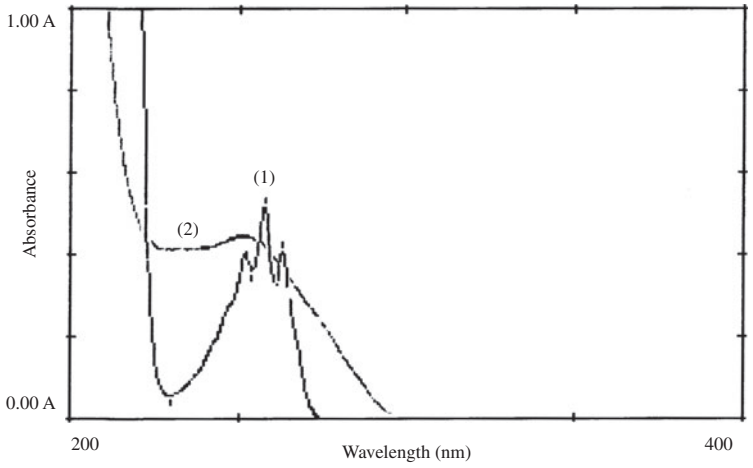

Figure 4 Zero-order absorption spectra DE (1) and PSE (2) (10 µg/ml of DE and 480 µg/ml of PSE in acetonitrile).

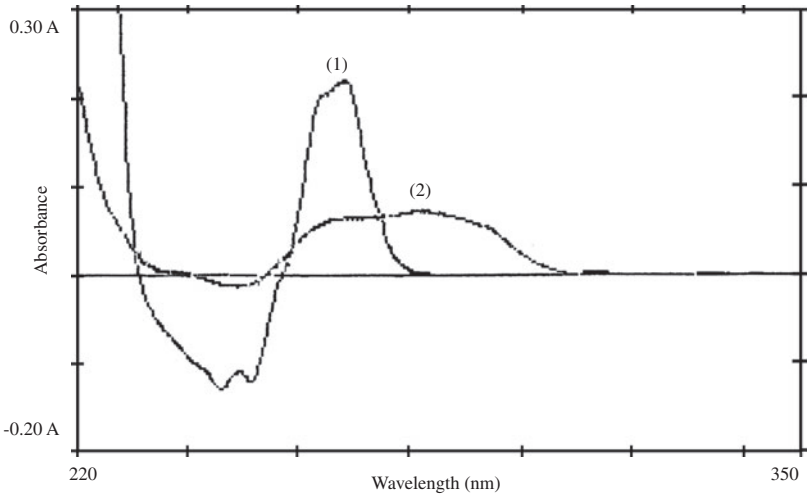

Figure 5 First-derivative spectra of DE (1) and PSE (2) (10 µg/ml of DE and 480 µg/ml of PSE in acetonitrile).

Derivative spectrophotometric method

As a second simultaneous analysis method for these drugs and to check the HPLC method results, a UV-derivative spectrophotometric method was also developed. As shown in Figure 4 the absorption spectra of DE and PSE show considerable overlapping and as a result, simultaneous determination of two drugs cannot be possible for reliable direct measurements. The study of their derivative spectra may overcome this difficulty; therefore, first, second, third and fourth derivative spectra of acetonitrile solutions of the two drugs were recorded and examined. The first derivative spectra presented spectral features which can be used for the simultaneous determination of DE and PSE (Figure 5). The zero-crossing method was used in this study with satisfactory results because it is the most common procedure for the evaluation of the overlapping spectra. DE is quantified at 280 nm where the $dA/d\lambda$ value of PSE approaches zero; similarly PSE is quantified at 244 nm where the $dA/d\lambda$ value of DE is insignificant.

Under the experimental conditions described above, linear regression equations (intercepts and slopes) for mixtures were established in the range of 2.5–15 µg/ml for DE and 120–720 µg/ml for PSE.

Validation of the methods

In order to assess the validity and applicability of the proposed methods, system suitability, linearity, selectivity, precision, accuracy and sensitivity studies were performed.

The %RDS (Relative Standard Deviation) of peak area and retention time for analytes are within 2%, indicating the suitability of the system (Table 1). The efficiency of the column as described by the number of theoretical plates for the six replicate injections was found to be 5856±64.49, 1897±35.80 (mean±SD) for DE and PSE, respectively. The USP tailing factor and resolution values were found to be 1.459±0.0180 and 3.39±0.0557 for DE; 1.045±0.0071 and 2.96±0.0446 (mean±SD) for PSE, respectively.

Quantitative parameters of the methods are summarized in Table 2. As shown, high correlation coefficient values and close to zero intercept values were obtained with the regression equations of DE and PSE. These values indicate good linearity.

The proposed methods were found to be selective for the estimation of the drug in the presence of various tablet excipients. For this purpose, a powder blend using typical tablet excipients was prepared along with the drug and then analyzed. The recoveries were not affected by the excipients and the excipient blend did not show any absorption in the range of analysis.

The precision of the methods was assessed by carrying out six replicate determinations of three different concentrations of DE and PSE both within-day and day-to-day (Table 3). RSD values were <3.567 and 3.055% for HPLC and derivative spectrophotometric methods, respectively, indicating good precision and there was no significant difference

Table 1 System suitability parameters for the determination of DE and PSE with HPLC methods (n=6).

	Retention time (min)	Area	Teoritical plate	Tailing factor	Resolution
DE					
Mean	4.2	169,614	5856	1.459	3.39
SD*	0.0126	852.313	64.4901	0.0180	0.0557
%RSD**	0.3012	0.5025	1.1013	1.2324	1.6458
PSE					
Mean	3.175	320,157	1897	1.0458	2.96
SD*	0.0105	795.8665	35.8032	0.0071	0.0446
%RSD**	0.3303	0.2486	1.8877	0.6826	1.5075
IS					
Mean	6.115	219,194	3279	1.846	5.89
SD*	0.0288	459.5805	11.8053	0.0026	0.0248
%RSD**	0.4711	0.2097	0.3600	0.1402	0.4222

*Standard deviation; **Relative standard deviation.

Table 2 Quantitative parameters for the determination of DE and PSE with HPLC and derivative spectrophotometric methods (n=6).

Methods	Parameters	DE	PSE
HPLC	Linearity range (μg/ml)	1–10	48–480
Method	Intersept (mean±SD*)	0.0361±0.0054	0.0237±0.0053
	Slope (mean±SD*)	0.1259±0.0030	$0.0046\pm8.6\times10^{5}$
	Correlation coefficient (mean±SD*)	$0.9987\pm7.6\times10^{4}$	$0.9992\pm3.2\times10^{4}$
	LOD** (μg/ml)	0.14	3.80
	LOQ*** (μg/ml)	0.43	11.52
Derivative	Linearity range (μg/ml)	2.5–15	120–720
Spectrophotometric	Intersept (mean±SD*)	$0.0022\pm9.4\times10^{4}$	0.0041±0.0013
Method	Slope (mean±SD*)	$0.0079\pm5.3\text{x}10^{4}$	$0.0002\pm4.1\times10^{5}$
	Correlation coefficient (mean±SD*)	$0.9997\pm1.7\times10^{4}$	$9.9992\pm5.2\times10^{4}$
	LOD** (μg/ml)	0.38	21.45
	LOQ*** (μg/ml)	1.14	65.00

*Standard deviation; **Limit of detection; ***Limit of quantification.

Table 3 Within-day and day-to-day precision and accuracy of the HPLC and derivative spectrophotometric methods (n=6).

	HPLC method				Derivative spectrophotometric method			
Drugs	Added (μg/ml)	Found (μg/ml)	RSD* (%)	RME** (%)	Added (μg/ml)	Found (μg/ml)	RSD* (%)	RME** (%)
DE	Within-day				Within-day			
	2.0	2.005	2.202	-0.250	3.0	2.985	1.096	-0.500
	6.0	6.022	1.635	0.361	7.5	7.583	0.490	1.111
	10.0	9.994	1.955	-0.056	10.0	9.93	1.028	-0.758
	Day-to-day				Day-to-day			
	2.0	1.985	3.501	-0.750	3.0	2.980	1.776	-0.667
	6.0	6.052	1.928	0.861	7.5	7.590	1.152	1.200
	10.0	9.970	2.375	-0.292	10.0	9.935	1.036	-0.652
PSE	Within-day				Within-day			
	50.0	48.66	3.003	-2.611	240	242.72	3.055	1.111
	150.0	150.825	3.567	0.554	360	362.16	0.974	0.600
	250.0	250.666	0.467	0.268	480	484.90	0.845	1.019
	Day-to-day				Day-to-day			
	50.0	48.80	2.718	-2.389	240	244	1.776	1.667
	150.0	150.15	3.329	0.102	360	362.30	1.152	0.633
	250.0	249.895	1.350	-0.042	480	484.96	1.036	1.037

*Relative standard deviation; **Relative mean error.

between the assays which were tested using both methods on the same day or different days. The relative mean errors were <1.667% and +2.611% for derivative spectrophotometric and HPLC methods, respectively.

Accuracy was determined by analyzing synthetic mixtures of each drug in different ratios. The mean percentage recoveries (±RSD) were found to be 99.59±1.85 for DE and 99.69±2.32 for PSE in HPLC (Table 4), 99.86±1.06 for DE and 100.69±0.72 for PSE in derivative spectrophotometric (Table 5) methods.

LOD and LOQ were calculated by the equations given in ICH guidelines (ICH 2003). LOD and LOQ for DE were found to be 0.14 μg/ml and 0.43 μg/ml for HPLC method; 0.38 μg/ml and 1.14 μg/ml for derivative spectrophotometric method, respectively, while for PSE the corresponding values were 3.80 μg/ml and 11.52 μg/ml for HPLC method, 21.45 μg/ml and 65.00 μg/ml for derivative spectrophotometric method, respectively.

The proposed methods were applied to the determination of DE and PSE in tablets and the results were statistically

Table 4 Recovery data obtained different mixtures by using HPLC method.

	DE				PSE			
Mix. no	Added (µg/ml)	Found (µg/ml)	Recovery (%)	RME* (%)	Added (µg/ml)	Found (µg/ml)	Recovery (%)	RME (%)
1	1.0	0.95	95.00	-5.00	80.0	78.06	97.58	-2.425
2	2.0	1.99	99.50	-0.50	150.0	150.63	100.42	0.42
3	3.0	2.96	98.67	-1.33	200.0	193.2	96.60	-3.40
4	4.0	4.07	101.75	1.75	225.0	225.85	100.38	0.38
5	5.0	5.05	101.00	1.00	280.0	283.19	101.14	1.14
6	6.0	6.03	100.5	0.5	330.0	332.97	100.90	0.90
7	7.0	7.03	100.43	0.43	400.0	400.36	100.09	0.09
8	8.0	7.99	99.88	-0.125	450.0	447.75	99.50	-0.50
9	9.0	9.01	100.11	0.111	500.0	481.65	96.33	-3.67
10	10.0	9.90	99.08	-1.00	350.0	364.0	104.00	4.00
Mean Recovery %±SD**			99.59±1.85[a]				99.69±2.32[b]	

*Relative mean error; **Standard deviation; [a]Relative standard deviation for DE=1.86; [b]for PSE=2.33.

Table 5 Recovery data obtained different mixtures by using derivative spectrophotometric method.

	DE				PSE			
Mix. no	Added (µg/ml)	Found (µg/ml)	Recovery (%)	RME* (%)	Added (µg/ml)	Found (µg/ml)	Recovery (%)	RME (%)
1	3.5	3.43	98.00	-2.00	240.0	242.20	100.91	0.91
2	3.0	2.98	99.33	-0.66	600.0	606.00	101.00	1.00
3	4.5	4.50	100.00	-0.00	500.0	499.85	99.97	-0.03
4	9.0	9.07	100.78	0.78	720.0	715.17	99.33	-0.67
5	8.0	8.01	100.13	0.13	650.0	653.25	100.50	0.50
6	4.0	4.04	101.00	1.00	400.0	403.00	100.75	0.75
7	10.0	9.93	99.30	-0.70	480.0	489.60	102.00	2.00
8	11.0	10.83	98.45	-1.545	160.0	161.07	100.67	0.67
9	6.0	6.03	100.50	0.50	120.0	120.51	100.43	0.43
10	7.5	7.58	101.07	-1.07	360.0	364.78	101.33	1.33
Mean Recovery %±SD**			99.86±1.06[a]				100.69±0.72[b]	

*Relative mean error; **Standard deviation; [a]Relative standard deviation for DE=1.06; [b]for PSE=0.72.

Table 6 Assay results of tablets containing 5 mg DE and 240 mg PSE (n=6).

Drugs	Statistical value	Derivative spectrophotometric method		HPLC method
DE	Mean	4.95		4.96
	SD	0.1049		0.061
	RSD	1.41		0.82
	T		0.20	
	F		2.96	
PSE	Mean	242.30		243.84
	SD	0.071		0.068
	RSD	0.56		0.53
	T		2.08	
	F		1.09	

P=0.05; t=2.23; F=5.05.

compared with each other using Student's t- and F-ratio tests (Table 6). At 95% confidence level there was no significant difference between the two methods with respect to mean values and standard deviations.

Concluding remarks

This is the first time that liquid chromatographic and UV-derivative spectrophotometric methods are being reported for the determination of DE together with PSE in pharmaceutical formulations. There is no significant difference in terms of precision between the two methods. Only a few minutes (<4.5 min) are required for the analysis in the UV-derivative spectrophotometric method and 7 min for HPLC method. Being simple, specific, of good accuracy and high precision, the proposed methods are suitable for the routine analysis and quality control of these drugs in tablets.

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