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Derivative ratio spectra–zero crossing spectrophotometry and LC method applied to the quantitative determination of paracetamol, propyphenazone and caffeine in ternary mixtures

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Abstract

Two methods were used to determine paracetamol, caffeine and propyphenazon in ternary mixtures and tablets. Derivative ratio spectra–zero crossing procedure was based on the simultaneous use of the first derivative of ratio spectra and measurements of derivative ratio analytical signals corresponding to the zero crossing points of wavelengths. By using propyphenazon as a divisor, the amounts of paracetamol and caffeine in the ternary mixture were determined by measuring the first derivative ratio amplitudes at 242.8 nm (zero-crossing point for caffeine) and 251.2 and 273.8 nm (zero-crossing point for paracetamol) respectively. Also by using paracetamol as a divisor, the contents of propyhenazon and caffeine in the same ternary mixture were determined by measuring the first derivative ratio amplitudes at 244.8 and 276.9 nm (zero-crossing point for caffeine) and 250.6 and 274.0 nm (zero-crossing point for propyphenazon), respectively. For the HPLC procedure, a Nucleosil C_{18} column and a mobile phase consisted of water and methanol (20:80) were used to separate three compounds with cetrimide as an internal standard. The flow rate was 1.0-ml/min with an ultraviolet (UV) detection at 254 nm. Both methods were also applied to the determination of these three compounds in ternary mixtures and tablet formulation. The analytical results were quite good in all cases.

Keywords: Derivative ratio spectra–zero crossing spectrophotometry; HPLC method; Quantitative determination; Caffeine; Paracetamol; Propyphenazon

1. Introduction

The mixture of paracetamol, propyphenazon and caffeine is used in analgesic pharmaceutical preparations. The quantitative determination of drugs in pharmaceutical formulations containing

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paracetamol, propyphenazon and caffeine, and their mixtures with different active compounds using various methods including spectrophotometry [1–13], gas chromatography [14,15] and HPLC [16–21], have been demonstrated for several mixtures and pharmaceutical preparations.

Salinas et al. have proposed [20] a new spectrophotometric method for the simultaneous determination of two compounds in binary mixtures. A new method was developed from this theory for resolving ternary mixtures, as explained below.

Berzas Nevado et al. [21] have developed a new method for the resolution of ternary mixtures of compounds by the derivative ratio spectra–zero crossing method. This method is based on the simultaneous use of the derivative ratio spectra and the measurements of the amplitude at the zero-crossing points in the derivative spectrum of the ratio spectra. The other authors for the drug analysis [1,2] also applied this same method.

In the literature, one or two of these compounds has been determined in their mixtures with different compounds by different spectrophotometric methods or others. For example, caffeine has been analyzed only in the binary and ternary mixture by using a numerical method spectrophotometrically [5]. Moreover, this method is necessary to the use of complex calculation procedure. Therefore, in this paper the derivative ratio spectra–zero crossing spectrophotometry and HPLC method have been applied successfully to the analysis of the synthetic ternary mixtures and tablets containing paracetamol, propyphenazon and caffeine, which have closely overlapped spectra. The spectrophotometric method was compared with the HPLC method developed by us (as a comparison method).

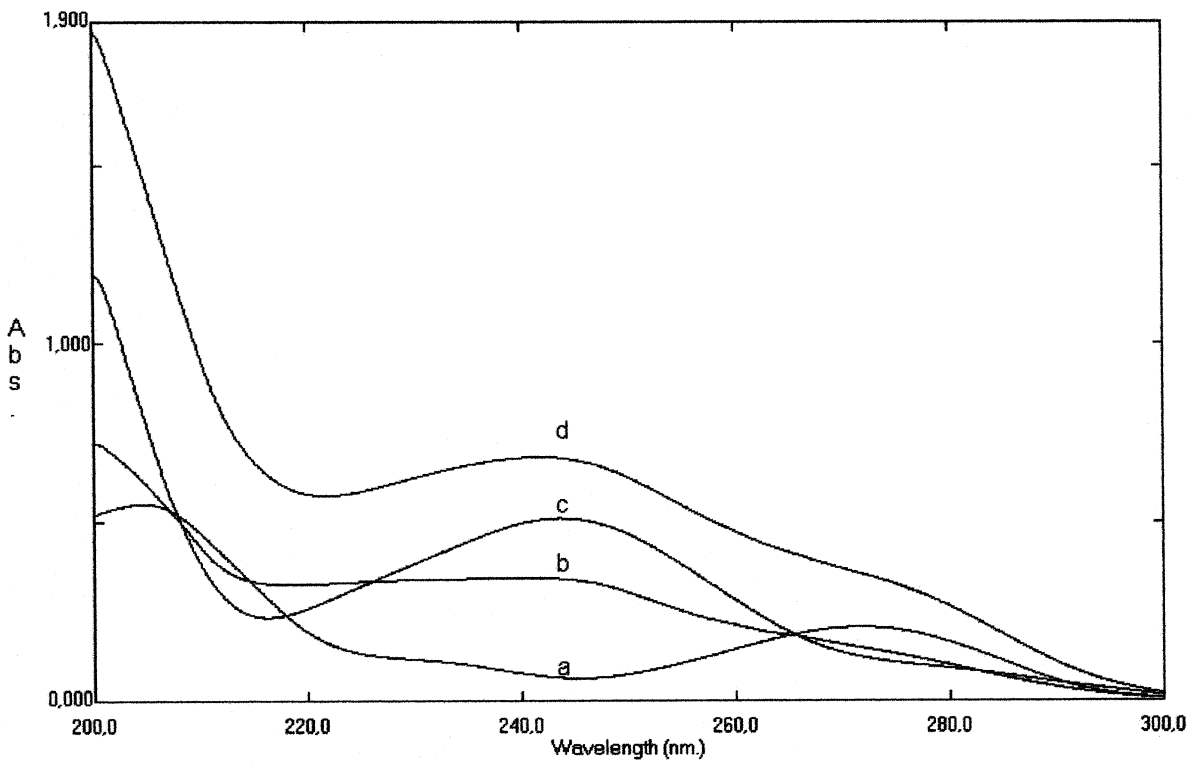

Fig. 1. Absorption spectra of (a) 3 μg/ml CAF, (b) 8 μg/ml PRO, (c) 6 μg/ml PAR, (d) their mixture.

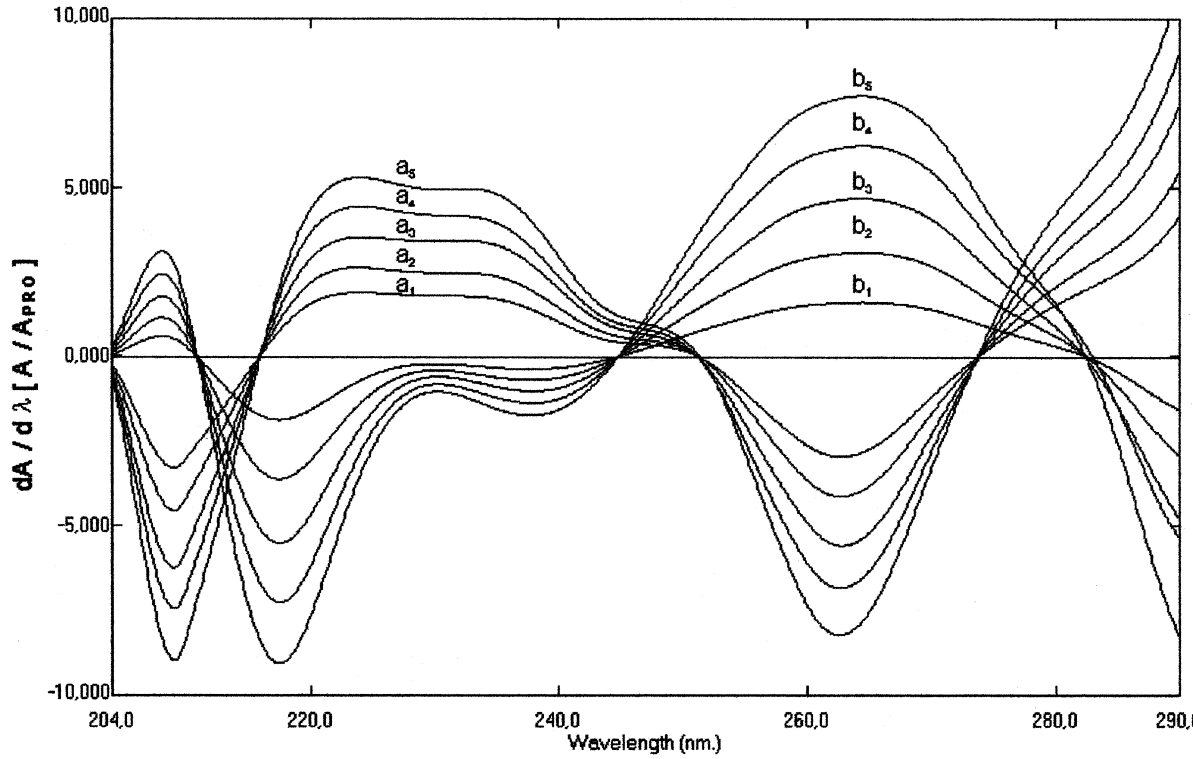

Fig. 2. First derivative of the ratio spectra of PAR (a_1) 4 μg/ml, (a_2) 6 μg/ml, (a_3) 8 μg/ml, (a_4) 10 μg/ml, (a_5) 12 μg/ml, and of CAF; (b_1) 1 μg/ml, (b_2) 2 μg/ml, (b_3) 3 μg/ml, (b_4) 4 μg/ml, (b_5) 5 μg/ml (when PRO was used as divisor) in 0.1 M HCl ($\Delta\lambda = 4$ nm).

2. Experimental

2.1. Apparatus

A Shimadzu 1601 double beam spectrophotometer (the fixed slit width (2 nm)) connected to an IBM-PC computer loaded with Shimadzu UVPC Software and an HP 600 printer were used for all the absorbance measurements and treatment of data.

The HPLC equipment consisting of a Jasco PU–980 model pump, with a Jasco UV-975 model detector connected to a computer loaded with Borwin Software and an HP 600 printer were used.

2.2. Pharmaceutical preparation

A commercial pharmaceutical product (Minoset® tablet, Roche Pharm. Ind., Turkey, Batch no. 41), containing 250 mg paracetamol (PAR), 150 mg propyphenazon (PRO), and 50 mg caffeine (CAF) per tablet, was studied. PAR, PRO and CAF were kindly donated by Roche Pharm. Ind., Turkey.

2.3. Stock solutions

Stock solutions of 50 mg/100 ml of PAR, PRO and CAF were prepared in 0.1 M HCI for spectrophotometric procedures and in methanol for HPLC procedure.

2.4. Reagents

All the solvents were of analytical reagent grade. In HPLC method, HPLC grade methanol and double distilled water were used.

2.5. Standard solutions

For spectrophotometry: Working standard solutions and their synthetic mixtures were prepared in 25-ml volumetric flasks containing 4–12 μg/ml of PAR and PRO and 1–5 μg/ml of CAF by using their stock solutions. The zero-order spectra were recorded with a sampling interval of $\Delta\lambda = 0.1$ nm and a scan speed about 1500 nm/min against a reagent blank (0.1 M HCI) and stored in the computer.

For HPLC: Working standard solutions and synthetic mixtures were prepared containing 4–32 μg/ml of PAR, 4–36 μg/ml of PRO, and 1–28 μg/ml of CAF with cetrimide (0.6 mg/ml) as internal standard (IS) in methanol. These solutions were filtered through 0.45 μm membrane filter before injection.

2.6. Sample solutions

In spectrophotometric method, 20 tablet were accurately weighed and powdered in a mortar. An amount of the powder equivalent to a tablet was dissolved in 0.1 M HCI in 100 ml-calibrated flasks. After 30 min of shaking, the solution was filtrated and the residue was washed three times with 10 ml solvent then the volume was completed to 100 ml with 0.1 M HCI (solution 1). The solution 1 was diluted 1:250 with the same solvent.

In HPLC method, the same procedure was realized by using methanol as solvent (solution 2). The solution 2 was diluted 1:125 with methanol.

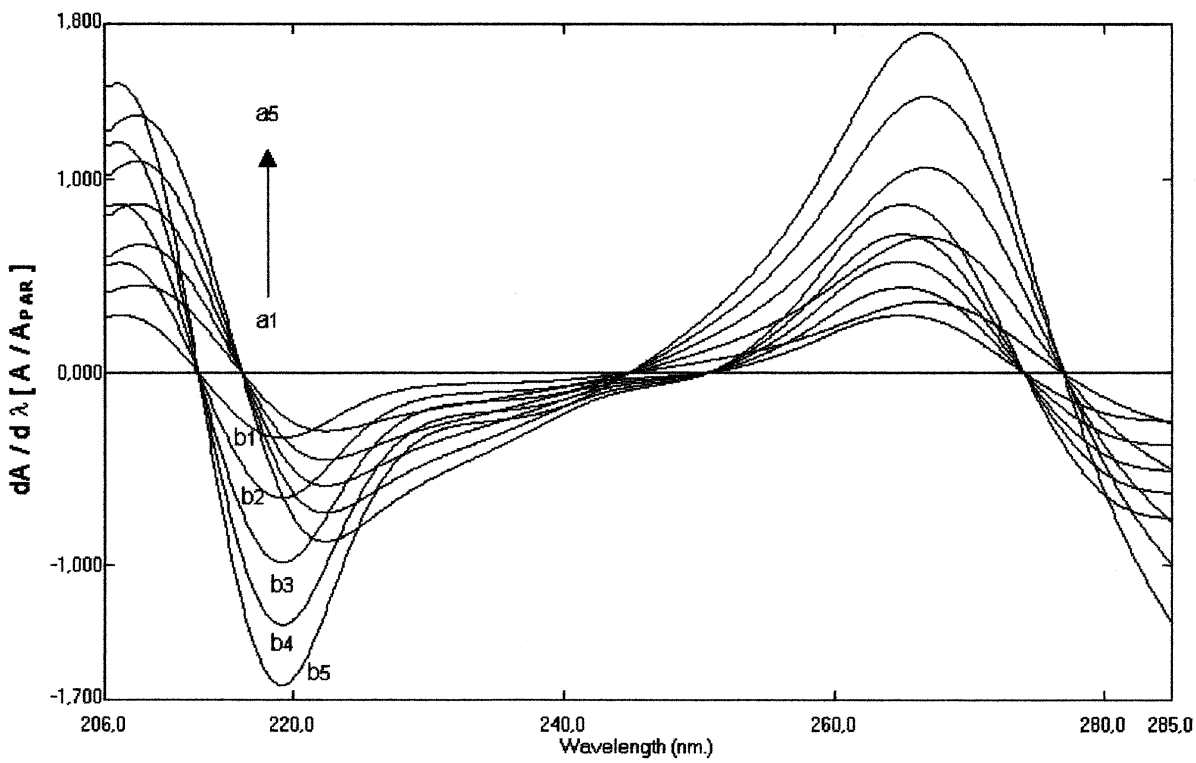

Fig. 3. First derivative of the ratio spectra of PRO (a_1) 4 μg/ml, (a_2) 6 μg/ml, (a_3) 8 μg/ml, (a_4) 10 μg/ml, (a_5) 12 μg/ml, and of CAF; (b_1) 1 μg/ml, (b_2) 2 μg/ml, (b_3) 3 μg/ml, (b_4) 4 μg/ml, (b_5) 5 μg/ml (when PAR was used as divisor) in 0.1 M HCl ($\Delta\lambda = 4$ nm).

Table 1
Results obtained for different synthetic mixtures using the proposed derivative ratio–zero crossing spectrophotometry

Synthetic ternary mixtures			8 μg/ml PRO as divisor			
PAR[a]	PRO[a]	CAF[a]	PAR		CAF	
			Found (μg)	Recovery (%)	Found (μg)	Recovery (%)
4.00	6.00	2.00	4.01	100.3	1.98	98.0
6.00	6.00	2.00	6.04	100.7	2.01	100.5
8.00	6.00	2.00	7.95	99.4	1.98	99.0
10.00	6.00	2.00	10.10	101.0	2.02	100.5
12.00	6.00	2.00	12.08	100.7	1.98	99.0
10.00	4.00	2.00	10.05	100.5	2.00	100.0
10.00	6.00	2.00	10.10	101.0	1.96	98.0
10.00	8.00	2.00	9.95	99.5	1.99	99.5
10.00	10.00	2.00	9.89	98.9	2.02	100.5
10.00	12.00	2.00	9.95	99.5	1.99	99.5
10.00	6.00	1.00	10.01	100.1	1.01	101.0
10.00	6.00	2.00	10.05	100.5	1.98	99.0
10.00	6.00	3.00	9.98	99.8	3.01	100.3
10.00	6.00	4.00	10.02	100.2	4.02	100.5
10.00	6.00	5.00	10.08	100.8	4.97	99.4
				$\overline{X} = 100.2$ RSD[b] = 0.64		$\overline{X} = 99.6$ RSD[b] = 0.93

[a] Added (μg).
[b] RSD, relative standard deviation.

3. Methods

3.1. Derivative ratio spectrum–zero crossing method

The absorption spectra of PAR, CAF and their ternary mixture with PRO, were divided by a standard spectrum of PRO and the first derivative of the ratio spectra was plotted. In the ternary mixture, the concentrations of PAR and CAF were proportional to the first derivative ratio signals at 242.8 nm (zero-crossing point for CAF) and 251.2 and 273.8 nm (zero-crossing point for PAR), respectively, in the first derivative of the ratio spectra. Calibration graphs were obtained by measuring the derivative ratio amplitudes against the increasing concentrations of pure PAR and pure CAF and by using pure PRO as a divisor. The contents of PAR and CAF can be determined by use of the above mentioned calibration graphs.

By using the similar procedure, the stored spectra of PRO, CAF and their ternary mixture with PAR were divided by a standard spectrum of PAR and the first derivative of result was traced. PRO and CAF were proportional to derivative ratio signals at 244.8 and 276.9 nm (zero-crossing point for CAF) and 250.6 and 274.0 nm (zero-crossing point for PRO), respectively, in the first derivative of the ratio spectra. For the determination of PRO and CAF, the calibration graphs were obtained by measuring the first derivative ratio values, in versus to the increasing concentrations of pure PRO and pure CAF, and by using pure PAR as a divisor. With this procedure, PRO and CAF can be determined. In this case, the amount of CAF in ternary mixture has been determined by both spectrophotometric procedures.

3.2. HPLC method

The chromatograms of three compounds were plotted and stored in the computer. The detector responses were measured in terms of peak area.

Table 2
Results obtained for different synthetic mixtures using the proposed derivative ratio–zero crossing spectrophotometry

Synthetic ternary mixtures			6 μg/ml PAR as divisor			
PAR[a]	PRO[a]	CAF[a]	PRO		CAF	
			Found (μg)	Recovery (%)	Found (μg)	Recovery (%)
4.00	6.00	2.00	5.95	99.2	2.01	100.5
6.00	6.00	2.00	5.83	97.2	1.98	99.0
8.00	6.00	2.00	5.83	97.2	1.95	97.5
10.00	6.00	2.00	6.10	101.7	1.98	99.0
12.00	6.00	2.00	5.91	98.5	2.01	100.5
10.00	4.00	2.00	3.92	98.0	1.97	98.5
10.00	6.00	2.00	5.90	98.3	2.00	100.0
10.00	8.00	2.00	8.10	101.3	2.02	101.0
10.00	10.00	2.00	9.85	98.5	1.98	99.0
10.00	12.00	2.00	12.03	100.3	1.99	99.5
10.00	6.00	1.00	5.85	97.5	0.98	98.0
10.00	6.00	2.00	6.08	101.3	2.01	100.5
10.00	6.00	3.00	6.02	100.3	2.98	99.3
10.00	6.00	4.00	5.94	99.0	4.01	100.3
10.00	6.00	5.00	6.01	100.2	5.03	100.6
				$\overline{X} = 99.2$ RSD = 1.54		$\overline{X} = 99.5$ RSD = 1.05

[a] Added (μg).

The data was processed using Borwin software. Separation was carried out at ambient temperature on Nucleosil 100-5 C_{18} (5 μm, 250 × 4.6 mm^2 i.d.) column (Macherey–Nagel, Germany) and the mobile phase consisted of water and methanol (20:80). The Flow rate was set at 1.0 ml/min with 10 μl as injection volume. The photometric detection was performed at 254 nm.

4. Results and discussion

The absorption spectra of the three compounds, PAR, PRO and CAF overlapped closely in the region 200.0–300.0 nm in Fig. 1. For this reason, the determination of the above compounds was not possible from direct measurements of absorbances in the zero-order spectra. On the other hand, also the classical derivative spectrophotometric method was tested (from first to fourth) for simultaneous determination of these three compounds in the same mixture. By these methods, in the same order of derivative spectra and method of direct derivative absorbance measurement could not been realized for the PAR, PRO and CAF determinations within same mixture.

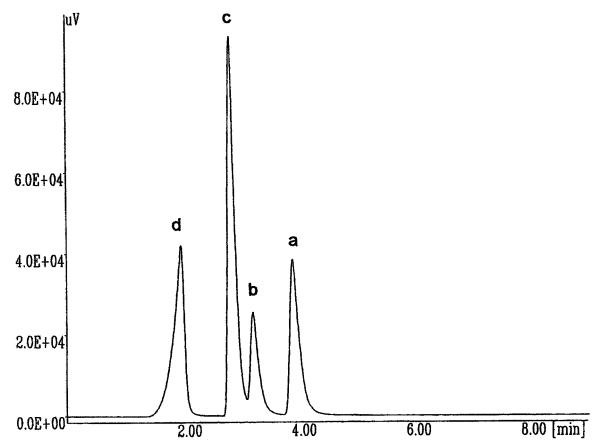

Fig. 4. Typical chromatograms of (a) 6 μg/ml PRO, (b) 2 μg/ml CAF, (c) 10 μg/ml PAR, (d) 0.6 mg/ml cetrimide as internal standard (IS).

Table 3
Results obtained for different synthetic mixtures using the developed HPLC method

Synthetic mixtures			PAR		PRO		CAF	
PAR[a]	PRO[a]	CAF[a]	Found (μg)	Recovery (%)	Found (μg)	Recovery (%)	Found (μg)	Recovery (%)
4.00	12.00	4.00	8.01	100.1	11.90	99.2	3.98	99.5
8.00	12.00	4.00	15.85	99.1	12.01	100.1	4.05	101.3
16.00	12.00	4.00	23.90	99.6	11.96	99.7	4.02	100.5
24.00	12.00	4.00	32.10	100.3	12.05	100.4	4.00	100.0
32.00	12.00	4.00	39.85	99.6	12.01	100.1	4.05	100.3
20.00	4.00	4.00	19.85	99.3	4.08	102.0	4.02	100.5
20.00	12.00	4.00	19.94	99.7	11.79	98.3	3.98	99.5
20.00	20.00	4.00	20.04	100.2	19.65	98.3	4.02	100.5
20.00	28.00	4.00	19.94	99.7	28.02	100.1	3.98	99.5
20.00	36.00	4.00	20.08	100.4	36.05	100.1	4.01	100.3
20.00	12.00	1.00	19.85	99.3	12.05	100.4	0.99	99.0
20.00	12.00	4.00	20.40	100.2	11.90	99.2	3.95	98.8
20.00	12.00	12.00	20.02	100.1	11.95	99.6	11.99	99.9
20.00	12.00	20.00	19.90	99.5	12.06	100.5	19.58	97.9
20.00	12.00	28.00	19.95	99.8	12.00	100.0	28.20	100.7
				$\overline{X} = 99.8$ RSD = 0.40		$\overline{X} = 99.9$ RSD = 0.91		$\overline{X} = 99.9$ RSD = 0.87

[a] Added (μg).

4.1. Ratio spectra derivative–zero crossing method

In this method, the absorption spectra of the solutions of PAR and CAF in 0.1 M HCl recorded between 204.0–290.0 nm and were divided by the spectrum of the standard solution of 8 μg/ml PRO. The resulting ratio spectra were smoothed at $\Delta\lambda = 8$ nm and their first derivative were plotted with intervals of $\Delta\lambda = 4$ nm and scaling factor of 100 as could be seen in Fig. 2. The concentrations of PAR and CAF in the ternary mixture were determined by measuring the derivative ratio analytical signals at 242.8 nm for PAR and 251.3 and 273.8 nm for CAF in the first derivative spectra of the ratio spectra.

In the same way, the absorption spectra of the solutions of PRO and CAF in 0.1 M HCl were divided by the spectrum of the standard solution of 6 μg/ml PAR and their ratio spectra were obtained in the spectral region 206.0–285.0 nm. The ratio spectra were smoothed at $\Delta\lambda = 8$ nm. First derivative of the ratio spectra was traced with intervals of $\Delta\lambda = 4$ nm and scaling factor of 100 as could be seen in Fig. 3. The concentrations of PRO and CAF in the ternary mixture were determined by measuring the signals at 244.8 and 276.9 nm for PRO and 250.6 and 274.0 nm for CAF in the first derivative spectra of the ratio spectra.

In the method, various mixtures of PAR, PRO and CAF were prepared and tested between 4–12 μg/ml for PAR and PRO and 1–5 μg/ml for CAF in the ternary mixture. Mean recoveries and the relative standard deviations were found to be 100.2 and 0.64% for PAR, 99.6 and 0.93% for CAF when PRO was used as a divisor (Table 1) and also 99.2 and 1.54% for PRO and for CAF 99.5 and 1.05% when PAR was used as a divisor (Table 2), respectively in the synthetic mixtures prepared by adding known amounts of PAR, PRO and CAF.

The main instrumental parameter conditions were optimized to obtain the most distinct curve of first derivative of the ratio spectra. For selecting a divisor of the appropriate concentration, some divisor concentrations were tested in the determination. The standard solutions of 8 μg/ml

Table 4
Parameters of regression lines for three compounds by the derivative ratio spectra–zero crossing and HPLC methods

Methods	λ (nm)	Linearity range (μg/ml)	Equation ($Y=aC+b$)	Regression coefficient (r)	a(SE)	b(SE)	LOD (μg/ml)	LOQ (μg/ml)	RSD (%)
Derivative ratio Spectra–zero crossing spectrophotometry	242.8	4–12	$Y^a=9.9\times10^{-1}C_{PAR}+3.4\times10^{-2}$	0.9988	2.23×10^{-4}	1.20×10^{-5}	0.29	0.98	0.75
	251.2	1–5	$Y^a=7.2\times10^{-1}C_{CAF}+6.4\times10^{-3}$	0.9999	3.10×10^{-5}	5.10×10^{-6}	0.10	0.34	0.23
	273.8	1–5	$Y^a=9.4\times10^{-1}C_{CAF}+1.8\times10^{-2}$	0.9998	2.42×10^{-3}	2.15×10^{-4}	0.21	0.71	0.09
	244.8	4–12	$Y^b=7.4\times10^{-2}C_{PRO}+1.0\times10^{-3}$	0.9988	1.29×10^{-4}	4.20×10^{-5}	0.35	1.20	1.40
	276.9	4–12	$Y^b=3.0\times10^{-2}C_{PRO}+1.4\times10^{-3}$	0.9996	2.52×10^{-3}	1.35×10^{-5}	0.19	0.65	1.08
	250.6	1–5	$Y^b=7.2\times10^{-1}C_{CAF}+9.0\times10^{-4}$	0.9998	2.70×10^{-5}	4.50×10^{-6}	0.17	0.64	0.92
	274.0	1–5	$Y^b=1.4\times10^{-1}C_{CAF}+1.8\times10^{-2}$	0.9995	2.26×10^{-3}	2.33×10^{-4}	0.13	0.50	0.47
HPLC method	254.0	4–32	$Y=2.0\times10^{-1}C_{PAR}-9.0\times10^{-2}$	0.9989	2.10×10^{-4}	2.10×10^{-3}	0.30	0.88	1.21
	254.0	4–36	$Y=1.9\times10^{-2}C_{PRO}-4.2\times10^{-2}$	0.9987	2.35×10^{-4}	1.45×10^{-3}	0.25	0.41	0.89
	254.0	1–28	$Y=5.4\times10^{-3}C_{CAF}+5.3\times10^{-4}$	0.9995	1.30×10^{-5}	8.10×10^{-6}	0.36	0.66	0.99

C_{PAR}, μg/ml of paracetamol; C_{PRO}, μg/ml of propyphenazon; C_{PAR}, μg/ml of caffeine; Y^a, absorbance values when PRO used as divisor; Y^b, absorbance values when PAR used as divisor; a, slop; b, intercept; SE, standatd error; RSD, relative standard devition.

of PRO for determining PAR and CAF and of 6 μg/ml of PAR for the determination of PRO and CAF in their ternary mixtures were found suitable. The smoothing function for the ratio spectra and the influence of the $\Delta\lambda$ for the first derivative of the ratio spectra were tested and found very appropriate to use the values of $\Delta\lambda = 8$ and of $\Delta\lambda = 4$, respectively, in the determination of the compounds. Furthermore, the scaling factor = 100 for the first derivative of the ratio spectra was tested and found suitable as for all the determinations.

4.2. HPLC method

HPLC method was developed to provide a specific procedure suitable for the rapid quality control analysis of PAR, CAF and PRO, as referee method for the proposed spectrophotometric method. Several mobile phase systems and different IS were tested for separation and determination of the compounds and were found suitable mobile phase water–methanol (20:80 v/v) and cetrimide as IS. At a flow of 1.0 ml/min, retention times for IS, PAR, CAF and PRO were 1.96, 2.84, 3.22 and 3.97 min, respectively (Fig. 4). The ratio of the peak area analyte to IS were plotted against the concentration of PAR, CAF and PRO. In this case, a straight line was obtained. By using these calibration graphs, the content of PAR, CAF and PRO was determined in the samples containing these compounds.

As could be seen in Table 3, in order to demonstrate the validity and applicability of HPLC method, recovery studies were performed by analysing synthetic mixtures of PAR, PRO and CAF which prepared different composition ratios. The mean recoveries and relative standard deviations of PAR, PRO and CAF were found as 99.8 and 0.04%, 99.9 and 0.91%, and also 99.9 and 0.87%, respectively (Table 3).

For application of these methods, the regression equation, correlation coefficients and linearity ranges were illustrated in Table 3 for the determinations of PAR, PRO and CAF in their ternary mixture.

To check the precision of both methods, the detection of limit (LOD) and limit of quantification (LOQ) were calculated by using the data obtained from ten replicate measurements or standard solutions of PAR (10 μg/ml) and of PRO (6 μg/ml) and CAF (2 μg/ml) individually (Table 4).

A good coincidence was observed for the assay results of the tablet dosage form by the application of these methods proposed in this paper (Table 5). Statistical data obtained by using Student's t-test and F-tests found no significant difference between performance of both methods as regards to accuracy and precision (Table 5).

Table 5
Determination of paracetamol, propyphenazon, and caffeine in tablets using the derivative ratio spectra–zero crossing and HPLC methods

Compounds	Derivative ratio spectra–zero crossing spectrophotometry	HPLC method
Paracetamol mean ± SD	249.5 ± 0.8	250.0 ± 0.9
	$t_{calculated} = 0.557$	$t_{theoretical} = 2.26(P = 0.05)$
	$F_{calculated} = 0.184$	$F_{theoretical} = 3.18$
Propyphenazon mean ± SD	150.1 ± 0.8	150.0 ± 0.9
	$t_{calculated} = 0.7108$	$t_{theoretical} = 2.26(P = 0{,}05)$
	$F_{calculated} = 0.0371$	$F_{theoretical} = 3.18$
Caffeine mean ± SD	49.5 ± 0.8	50.0 ± 0.9
	$t_{calculated} = 0.856$	$t_{theoretical} = 2.26(P = 0{,}05)$
	$F_{calculated} = 0.547$	$F_{theoretical} = 3.18$

Results obtained are average of ten experiments for each; SD, standard deviation.

5. Conclusion

In conclusion, a spectrophotometric method was proposed for simultaneous determination of PAR, PRO and CAF in synthetic ternary mixtures and tablets. The validation of the results obtained in this spectral method was realized by using the developed HPLC method. In spite of the

three compounds which produce a perfect overlapping spectrum in the zero-order spectra, the first derivative ratio–zero crossing spectrophotometry in this paper has given the good results for the simultaneous determination of three compounds in the ternary mixture, without requiring a separation procedure. This can be considered as a superiority of the spectrophotometric determination method over HPLC method for the resolution of ternary mixtures. The HPLC method may be considered more specific than the derivative ratio–zero crossing procedure, but it is a more costly method and it is necessary that a separation procedure is used.

These methods can be used in the routine analysis of compounds for the multi-mixtures and for the pharmaceutical preparations containing these mixtures.

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