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Stability indicating methods for the determination of aceclofenac

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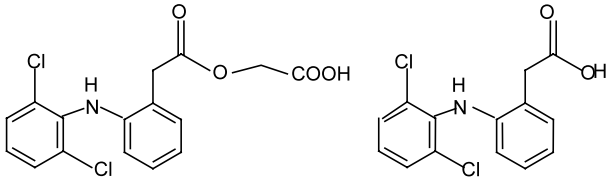
Abstract

Five new selective, precise and accurate methods for the determination of aceclofenac in the presence of its degradation product; diclofenac are described. Method A utilizes third derivative spectrophotometry at 242 nm. Method B is RSD_1 spectrophotometric method based on the simultaneous use of the first derivative of ratio spectra and measurement at 245 nm. Method C is a pH-induced difference (ΔA) spectrophotometry using UV measurement at 273 nm. Method D is a spectrodensitometric one, which depends on the quantitative densitometric evaluation of thin layer chromatogram of aceclofenac at 275 nm. Method E is RP-HPLC that depends on using methanol: water (60:40 v/v) as mobile phase at a flow rate of 1 ml/min and UV detection at 275 nm. Regression analysis of a beer's plot showed good correlation in the concentration ranges 5–40, 10–40, 15–50, 50–200, 1–50 μg/ml for methods A, B, C, D and E, respectively. These methods are suitable as stability indicating methods for the determination of aceclofenac in presence of its main degradation product, diclofenac. The proposed methods were applied for the analysis of the drug in its pharmaceutical formulation and the results obtained were compared with those obtained with the official B.P. method.

Keywords: Aceclofenac; Derivative spectrophotometry; RSD_1 spectrophotometry; ΔA spectrophotometry; TLC-densitometry; RP-HPLC

1. Introduction

Aceclofenac is 2-[(2,6-Dichlorophenyl) amino] benzene acetic acid carboxymethyl ester and is used as anti-inflammatory drug [1]. The structural formulae of aceclofenac(I) and its main degradation product, diclofenac(II), are as follows:



(I) (II)

The European pharmacopoeia supplement 2000 and the British pharmacopoeia reported HPLC methods for the determination of aceclofenac in presence of diclofenac [1,2]. Other methods include titrimetric [1], electrochemical [2,3], spectrophotometric [4], spectrofluorometric [4] and chromatographic [5] methods. None of these reported methods were used for the determination of aceclofenac in presence of its degradation product.

The main task of this work is to establish simple and accurate third derivative (D_3), ratio-spectra first derivative (RSD_1) and difference (ΔA) spectrophotometric, densitometric and high-performance liquid chromatographic (HPLC) methods which could be used as stability indicating methods for the determination of aceclofenac in presence of its main degradation product, diclofenac. These methods can be used also for the routine and quality control analysis of aceclofenac in raw material and pharmaceutical formulations.

2. Experimental

2.1. Apparatus

1. Shimadzu UV–VIS1601 PC double beam spectrophotometer with 1 cm quartz cuvets ($\Delta\lambda = 8$).
2. UV lamp with short wavelength 254 nm.

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3. TLC plates (20 × 20 cm) precoated with silica gel 60 F_{254} (E.MERCK).
4. Shimadzu-dual wavelength flying spot CS-9301 densitometer.
5. Shimadzu Class-LC 10 liquid chromatographic system equipped with Shimadzu SPD-10 A diode array UV-detector, ZORBAX® C_{18} (15 cm × 4.6 mm i.d., 5 μm particle size) column was used as stationary phase.

2.2. Samples

2.2.1. Pure samples

Aceclofenac pure sample was kindly supplied by Bristol-Myers squibb Egypt. The purity of the sample was found to be 99.9% according to the B.P. method (1998) [1].

2.2.2. Market samples

Bristaflam® tablets (Bristol-Myers Squibb, Egypt) each tablet was claimed to contain 100 mg of aceclofenac. Batch Number C005537 and H82063.

2.2.3. Preparation of the degradation product

0.3 g of pure aceclofenac were heated at reflux with 20 ml 1 N sodium hydroxide for 3 h. The solution was allowed to cool then 10 ml of 2.0 N sulphuric acid were added and the solution was heated to 90 °C. The obtained precipitate was filtered, washed and recrystalized from ether. The obtained powder (melting point (m.p.) = 157 °C) was identified and ensured using IR-spectrophotometry and TLC technique, then it was used for the preparation of the stock solution of the degradate.

2.3. Reagents and solutions

All chemicals and reagents are of pure analytical grade; in particular: absolute ethanol and methanol HPLC grade were from B.D.H. and tetrahydrofuran AR was from E. Merck.

2.3.1. Aceclofenac stock standard solution (1 mg/ml)

Weigh accurately 100 mg of aceclofenac powder, transfer to a 100 ml volumetric flask, add 40 ml absolute ethanol, shake for 10 min and complete to volume with absolute ethanol.

2.3.2. Aceclofenac working standard solutions

(i) D_3, RSD1 and ΔA spectrophotometric methods (100 μg/ml): Transfer 10 ml of aceclofenac stock standard solution to a 100 volumetric flask and complete to volume with absolute ethanol.
(ii) Densitometric method (0.5 mg/ml): Transfer 50 ml of aceclofenac stock standard solution to a 100 ml volumetric flask and complete to volume with absolute ethanol.
(iii) HPLC method (100 μg/ml): Transfer 10 ml of aceclofenac stock standard solution to a 100 volumetric flask and complete to volume with methanol:water (60:40 v/v).

2.3.3. Degradate stock solution (1 mg/ml)

Weigh accurately 100 mg of the degradate, transfer to a 100 ml volumetric flask, add 40 ml absolute ethanol, shake for 10 min and complete to volume with absolute ethanol.

2.3.4. Degradate working standard solutions

(i) D_3, RSD1 and ΔA spectrophotometric methods (100 μg/ml): Transfer 10 ml of degradate stock solution to a 100 volumetric flask and complete to volume with absolute ethanol.
(ii) Densitometric method (0.5 mg/ml): Transfer 50 ml of degradate stock solution to a 100 ml volumetric flask and complete to volume with absolute ethanol.
(iii) HPLC method (100 μg/ml): Transfer 10 ml of degradate stock solution to a 100 volumetric flask and complete to volume with methanol:water (60:40 v/v).

2.4. Laboratory prepared mixtures

2.4.1. Third derivative (D_3) spectrophotometric method

Transfer accurately aliquots from aceclofenac working standard solution equivalent to (50–400 μg) into a series of 10 ml volumetric flasks, add portions equivalent to 10–50% of the degradate from its working standard solution to the same flasks, complete to the mark with absolute ethanol.

2.4.2. RSD_1 spectrophotometric method

Transfer accurately aliquots from aceclofenac working standard solution equivalent to (100–400 μg) into a series of 10 ml volumetric flasks, add portions equivalent to 10–50% of the degradate from its working standard solution to the same flasks, complete to the mark with absolute ethanol.

2.4.3. Difference (ΔA) spectrophotometric method

Transfer accurately aliquots from aceclofenac working standard solution equivalent to (150–500 μg/ml) into two sets of 10 ml volumetric flasks, add portions equivalent to 10–40% of the degradate from its working standard solution to the same flasks, complete to the mark in one set with 0.1 N sodium hydroxide and in the other set with 0.1 N hydrochloric acid.

2.4.4. Densitometric method

Transfer accurately aliquots from aceclofenac working standard solution equivalent to (0.5–2 mg) into a series of 10 ml volumetric flasks, add portions equivalent to 10–95% of the degradate from its working standard solution to the same flasks, complete to the mark with absolute ethanol.

2.4.5. HPLC method

Transfer accurately aliquots from aceclofenac working standard solution equivalent to (10–500 μg) into a series of 10 ml volumetric flasks, add portions equivalent to 10–99% of the degradate from its working standard solution (100 μg/ml) to the same flasks, complete to the mark with methanol: water (60:40 v/v).

2.5. Procedures

2.5.1. Method A, third derivative spectrophotometric method

2.5.1.1. Linearity. Accurate aliquots equivalent to (50–400 μg) of aceclofenac were transferred from its working standard solution into a series of 10 ml volumetric flasks then made up to volume using absolute ethanol. The third derivative UV spectra of the UV-spectrum of each solution against absolute ethanol as a blank were recorded. The peak height using 242 nm as maxima and zero- crossing line as minima was measured. The calibration curve representing the relationship between the measured peak height and the corresponding concentration was constructed.

2.5.1.2. Assay of prepared mixtures. The D_3 spectra of the laboratory-prepared mixtures containing different ratios of aceclofenac and its degradate were recorded. The peak heights at 242 nm were measured. The concentration of aceclofenac in the prepared mixtures was calculated from the regression equation. Results obtained are given in Table 1.

2.5.2. Method B, RSD_1 spectrophotometric method

2.5.2.1. Linearity. Accurate aliquots equivalent to (100–400 μg) of aceclofenac were transferred from its working standard solution into a series of 10 ml volumetric flasks then made up to volume using absolute ethanol.The absorption spectra of the these solutions were divided by the 'the divisor' (the absorption spectrum of 5 μg/ml of the degradate) and the ratio spectra thus obtained were smoothed and the first derivatives of the ratio spectra were recorded. The peak amplitude at 245 nm was measured. The calibration curve representing the relationship between the measured amplitude and the corresponding concentration was constructed.

2.5.2.2. Assay of prepared mixtures. The ratio spectra first derivative curves of the laboratory-prepared mixtures containing different ratios of aceclofenac and its degradate were measured. The peak amplitude at 245 nm was measured, then the concentration of AC in the prepared mixtures was calculated from the regression equation. Results obtained are given in Table 1.

2.5.3. Method C, difference (ΔA) spectrophotometric method

2.5.3.1. Linearity. Accurate aliquots equivalent to (150–500 μg) of aceclofenac were transferred from its working standard solution (100 μg/ml) into two sets of 10 ml volumetric flasks. The volume was diluted in one set with 0.1 N sodium hydroxide and in the other set with 0.1 N hydrochloric acid. The ΔA spectrum for each concentration was recorded by placing the alkaline solution in the reference beam and the acid solution in

Table 1
Comparison between the proposed methods and the reported one for the determination of aceclofenac in the presence of its degradate

Sample number [a]	Percentage of degradate	Found (%) [b]					
		D_3 method	RSD_1 method	ΔA method	Densitometric method	RP-HPLC method	B.P. (1998) method
1	10	100.60	99.60	100.30	100.01	98.99	100.20
2	20	99.80	99.10	99.00	100.24	98.96	106.96
3	30	99.86	98.40	98.80	99.79	98.82	113.20
4	40	100.90	98.90	100.41	99.95	99.02	116.56
5	50	99.66	98.40		99.80	99.90	125.12
6	60				99.79	98.94	150.35
7	95				100.30	99.03	176.58
8	98					99.20	188.56
Mean ± SD		100.164 ± 0.55	98.88 ± 0.51	99.62 ± 0.84	99.98 ± 0.21	99.11 ± 0.33	

[a] Average of four experiments.
[b] Found (%)—Recovery percentage of aceclofenac.

the sample beam. The calibration curve relating the ΔA at 273 nm to AC concentration was constructed.

2.5.3.2. Assay of prepared mixtures. The ΔA spectra of the laboratory-prepared mixtures containing different ratios of AC and its degradate were recorded. The peak amplitude at 273 nm was measured, and then the concentration of aceclofenac in the prepared mixtures was calculated from the regression equation. Results obtained are given in Table 1.

2.5.4. Method D, spectrodensitometric method

2.5.4.1. Linearity. Accurate aliquots equivalent to (0.5–2 mg) of aceclofenac were transferred from its working standard solution (0.5 mg/ml) to a series of 10 ml volumetric flasks then the volume was completed with ethanol. 10 μl of each solution was applied to a thin layer chromatographic plate (20 × 20 cm) using 10 μl micro syringe. Spots were spaced 2 cm apart from each other, 1.5 cm from the bottom edge of the plate, the plate was placed in chromatographic tank previously saturated for 1 h with the developing mobile phase Tetrahydrofuran: methanol (90:10 v/v). The plate was developed by ascending chromatography through a distance of 16 cm, dried at room temperature (r.t.); the spots were detected under UV lamp, and scanned at 275 nm. (Photomode: reflection and scan mode: zigzag). The calibration curve representing the relationship between the recorded area under the peak and the corresponding concentration was constructed.

2.5.4.2. Assay of prepared mixtures. About 10 μl of different samples of the laboratory prepared mixtures were applied to a thin layer chromatographic plate; proceed as mentioned under linearity starting from 'Spots were spaced...'. The area under the peak was recorded and the concentration of AC was calculated from the regression equation. Results obtained are given in Table 1.

2.5.5. Method E, RP-HPLC method

2.5.5.1. Linearity. Accurate aliquots equivalent to (10–500 μg/ml) of aceclofenac working standard solution (100 μg/ml) were transferred into a series of 10 ml volumetric flasks. Methanol: water (60:40 v/v) was added to volume to give a final concentration range from 1 to 50 μg/ml. Twenty μl of the solution from each of the above was injected and the chromatograms were recorded maintaining the flow rate at 1 ml/min and monitoring the effluent at 230 nm. Peak area values were then plotted as a function of aceclofenac concentration to obtain the calibration curve.

2.5.5.2. Assay of prepared mixtures. The specified HPLC method was followed for the analysis of laboratory prepared mixtures containing different ratios of aceclofenac and its degradate. The peak area values for aceclofenac were measured then the concentration of aceclofenac in the prepared mixtures was calculated from the regression equation.

2.5.6. Assay of pharmaceutical formulation

The contents of ten tablets of Bristaflam® were thoroughly powdered and mixed, an amount of the powder equivalent to 100 mg of AC was accurately weighed in 250 ml beaker, 70 ml of absolute ethanol was added, stirred magnetically for about 30 min then filtered through a filter paper into a 100 ml volumetric flask, the beaker and the funnel were washed and the volume was completed with absolute ethanol. The solutions were diluted to the same concentrations of working standard solutions and treated according to linearity for each method.

3. Results and discussion

Aceclofenac is liable to alkaline hydrolysis. The main degradation product of AC; 'diclofenac' [1]; was prepared in the laboratory by complete alkaline hydrolysis of aceclofenac. This was achieved by reflux with 1 N sodium hydroxide for 3 h. Heating with sulphuric acid at 90 °C leads to decomposition of glycolic acid into formaldehyde, carbon monoxide and water [9].

3.1. Method A, third derivative UV-spectrophotometric method

Zero order absorption spectra of aceclofenac and its degradate in absolute ethanol show severe overlapping which interferes with the direct determination of pure aceclofenac (Fig. 1).

Derivative UV spectrophotometry has been first suggested during the last decade and soon became a well-established technique for the analysis of drugs in mixtures and in formulations [6]. The principle advantage of derivative spectrophotometry is the improvement of resolution of overlapping absorption bands, the accuracy and precision of UV absorption methods are considerably improved, and therefore derivative spectroscopy has been used in quantitative analysis when the analyte to be determined is present in admixture with other components [7].

The first (D_1) and second (D_2) derivative spectrophotometric techniques were not able to overcome this overlapping.

As shown in Fig. 2, it is clear that the overlapping observed in the zero order absorption spectra was eliminated and sharply defined, well separated peak at

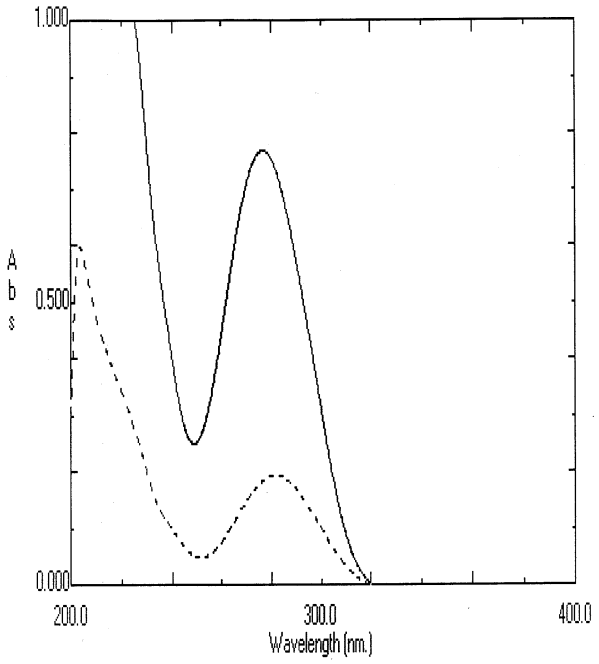

Fig. 1. Zero-order spectra of the ethanolic solutions of intact aceclofenac (30 μg/ml), [___] and degradation product (5 μg/ml), [---].

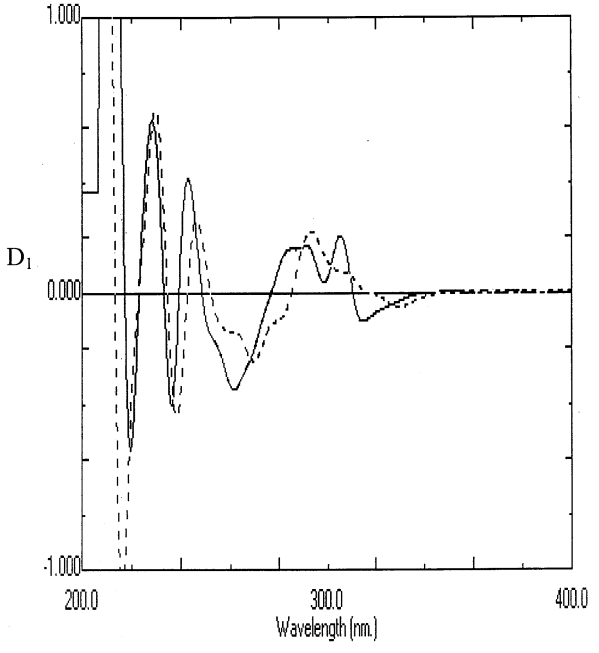

Fig. 2. Third derivative spectra of the ethanolic solutions of intact aceclofenac (30 μg/ml), [___] and degradation product (5 μg/ml), [---].

242 nm for the intact molecule which lies at the zero crossing of its degradate was obtained and used for the D_3 spectrophotometric determination of intact aceclofenac in presence of its degradate.

By applying the D_3 spectrophotometric method, a linear correlation was obtained between the peak height and the concentration over the range 5–40 μg/ml for pure aceclofenac and the following regression equation was obtained:

$$H = 0.047C + 0.0137, \quad r = 0.9997$$

where H is the peak height in millimeter at 242 nm, C is the concentration in μg/ml and r is the correlation coefficient.

3.2. Method B, RSD_1 spectrophotometric method

This method is based on the measurement of the UV absorption spectra of sample solution and storing them in the computer; then, the stored data were divided by a standard spectrum of the interfering component. The ratio spectra thus obtained were smoothed and the first derivatives were recorded [8].

Fig. 3 shows the ratio spectrum of aceclofenac and its degradate (spectrum of AC divided by the spectrum of 5 μg/ml of the degradate) and its first derivative. As can be seen, the peak at 245 nm for intact aceclofenac which lies at the zero crossing point of its degradate can be adopted for the determination of aceclofenac in presence of its degradate and in pharmaceutical formulation.

The calibration curve was obtained by plotting the peak amplitude at 245 nm of the first derivatives of the ratio spectra of aceclofenac and it shows linear relationship in the range of 10–40 μg/ml and the following regression equation was calculated:

$$A = 0.035C - 0.075, \quad r = 0.9998$$

where A stands for the peak amplitude at 245 nm, C for the concentration in μg/ml and r is the correlation coefficient.

3.3. Method C, ΔA spectrophotometric method

The ΔA spectra between 0.1 N sodium hydroxide and 0.1 N hydrochloric acid for intact aceclofenac and its degradate were recorded and from these spectral characteristics it is clear that the ΔA peak at 273 nm for the intact aceclofenac between 0.1 N hydrochloric acid and 0.1 N sodium hydroxide could be considered as the λ_{max} most suitable for adopting the ΔA technique for the selective determination of intact aceclofenac in presence of its degradate as at this maxima, ΔA for the latter reads zero (Fig. 4).

A calibration curve was constructed relating the ΔA values at 273 nm to drug concentrations showing perfect linearity in the range of 15–50 μg/ml from which the following regression equation was calculated:

$$A = 0.0098C + 0.144, \quad r = 0.9995$$

where A stands for the peak amplitude at 273 nm, C for the drug concentration in μg/ml and r is the correlation coefficient.

3.4. Method D, densitometric method

This method was applied for the determination of aceclofenac. Complete separation of aceclofenac was obtained using Tetrahydrofuran: methanol (90:10 v/v) as developing mobile phase. Quantitatively the chromatogram was scanned densitometrically at 275 nm. By applying this technique a linear correlation was obtained between the area under the peak and the concentration of aceclofenac in the range of 50–200 μg/ml. The following regression equation was calculated for aceclofenac:

$A = 0.005C + 0.063, \quad r = 0.9996$

where A is the area under the peak, C is the corresponding concentration in μg/ml and r is the correlation coefficient.

3.5. Method E, RP-HPLC method

A simple and stability indicating isocratic HPLC method was adopted for the analysis of aceclofenac in presence of its degradate and in pharmaceutical formulation. The initial study involved the use of different percentages of methanol in the mobile phase. The best peak shape was obtained with methanol: water 60:40 v/v with retention time of 1.9 min. The final dilution of

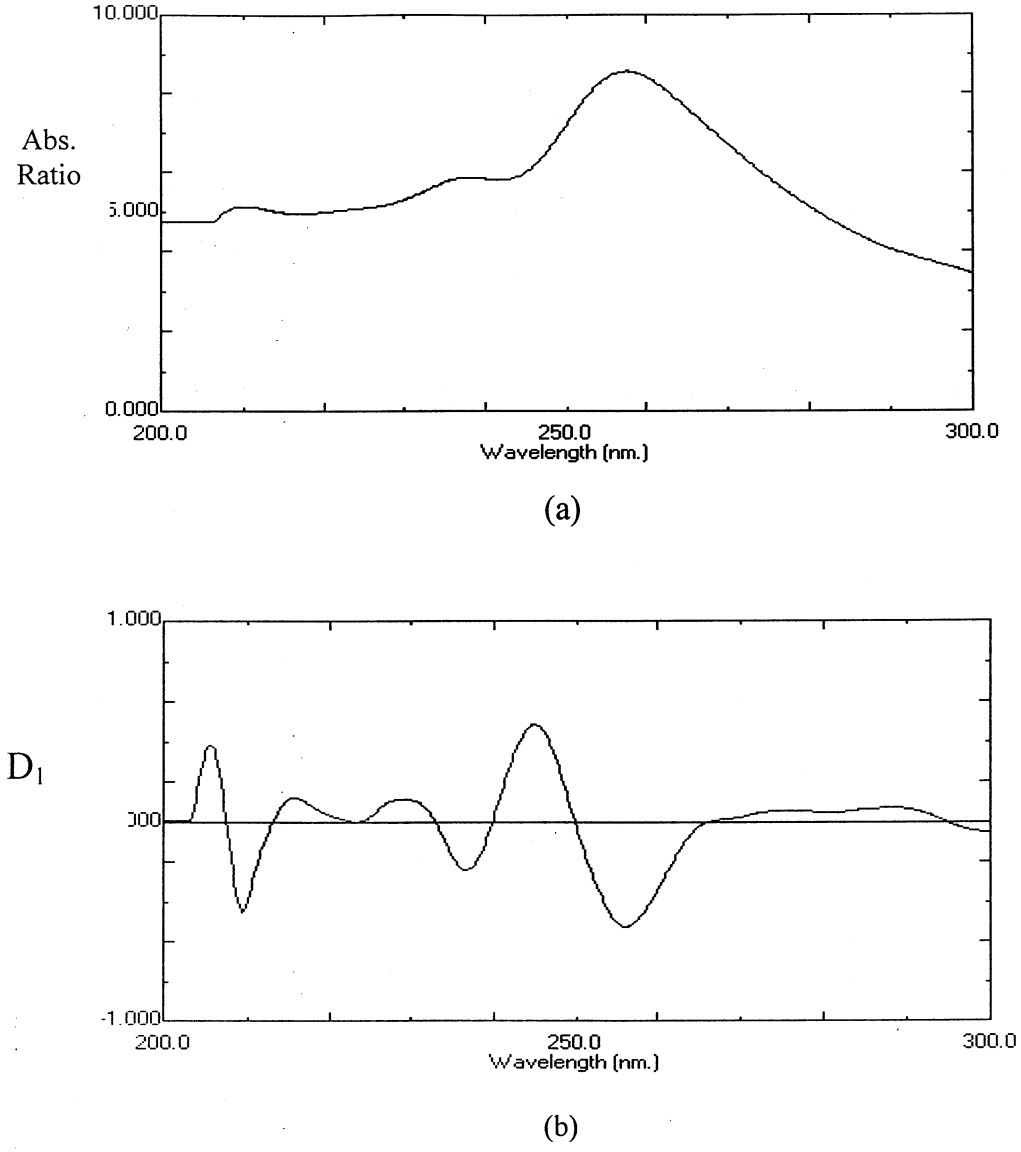

Fig. 3. Ratio-spectra and first derivative curves of the ethanolic solutions of intact aceclofenac (20 μg/ml) using 5 μg/ml of degradation product as the divisor, [___].

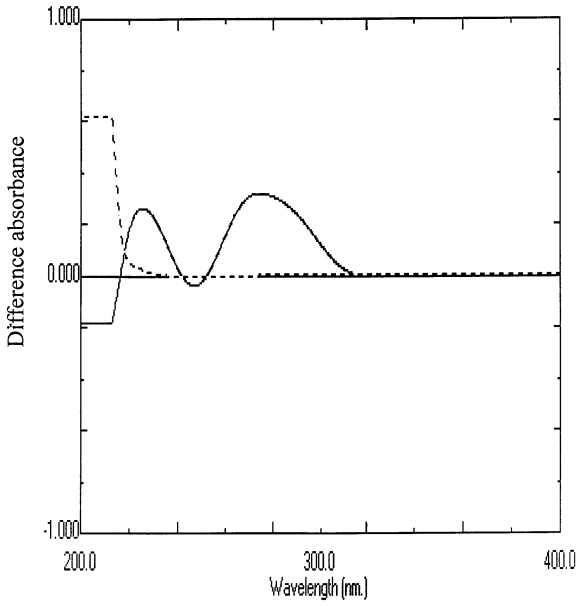

Fig. 4. Difference spectra of intact aceclofenac (15 μg/ml), [_ _ _] and degradation product (5 μg/ml), [---].

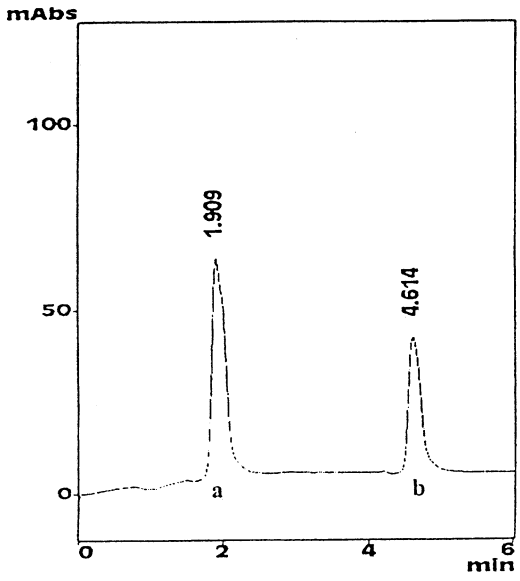

Fig. 5. HPLC Chromatogram of (a) pure aceclofenac, 20 μg/ml; (b) degradation product "diclofenac", 10 μg/ml.

samples has been done using methanol: water (60:40 v/v).

A typical chromatogram of pure aceclofenac is shown in Fig. 5. The chromatograms as shown in Fig. 5 showed no peak interferences between the drug and its degradate.

The calibration curve for aceclofenac was constructed by plotting peak area versus concentration and it showed good linearity in the range of 1–50 μg/ml. The regression equation was calculated and found to be:

$$A = 0.009C + 0.025, \quad r = 0.9996$$

where A is the peak area, C is the corresponding concentration and r is the correlation coefficient.

To assess the stability indicating selectivity of the proposed methods for the analysis of aceclofenac without interference from its main degradation product, diclofenac, separate aliquots of the degradation product of aceclofenac were mixed with the intact drug in different ratios and analyzed by the proposed methods. The results obtained are shown in Table 1. It is clear that the accuracy of the proposed methods are not affected by the presence of up to 50, 50, 40, 95, and 99% of the degradation product in the third, RSD_1 and ΔA spectrophotometric, TLC- densitometric and RP-HPLC methods respectively.

The proposed methods were applied successfully for the analysis of aceclofenac in its dosage form. Results obtained are given in Table 2.

The validity of the proposed methods was further assessed by applying the standard addition technique. Results obtained are given in Table 3.

The results obtained by applying the proposed methods were statistically compared with those obtained by applying the reference method. Table 4 shows that the values of calculated t and F are less than the tabulated ones indicating that there is no significant difference between the methods. Thus, the proposed methods could be applied as stability indicating methods for the routine and quality control analysis of aceclofenac in raw material and pharmaceutical formulations.

Table 2
Comparison between the proposed methods and the reported one for the determination of aceclofenac in pure form and in its pharmaceutical formulation

Preparation	Found (%) ± SD					
	D_3 method	RSD_1 method	ΔA method	Densitometric method	RP-HPLC method	B.P. method
Pure sample	100.164 ± 0.55	98.88 ± 0.51	99.62 ± 0.84	99.98 ± 0.21	99.11 ± 0.33	99.36 ± 0.32
Bristaflam tablets B.N. C005537	100.42 ± 0.821	100.01 ± 0.121	100.42 ± 0.252	99.68 ± 0.392	98.90 ± 0.183	98.81 ± 0.35
Bristaflam tablets B.N. H82063	99.65 ± 0.522	99.91 ± 0.143	100.12 ± 0.521	99.52 ± 0.313	99.30 ± 0.742	99.94 ± 0.62

Table 3
Application of standard addition technique to the analysis of pharmaceutical preparation of aceclofenac by the proposed methods

Method	Preparation	Claimed taken (μg/ml)	Pure added (μg/ml)	Pure found (μg/ml)	Recovery of added (μg/ml)
D_3 method	Bristaflam tablets B.N. C005537	20.00	5.00	5.05	101.00
			10.00	10.07	100.70
			15.00	14.94	99.60
			20.00	20.41	102.05
Mean ± SD					100.84 ± 1.007
RSD_1 method	Bristaflam tablets B.N. C005537	20.00	5.00	4.99	99.80
			10.00	10.02	100.20
			15.00	14.99	99.93
			20.00	19.88	99.40
Mean ± SD					99.83 ± 0.333
ΔA method	Bristaflam tablets B.N. C005537	20.00	5.00	4.99	99.80
			10.00	9.98	99.80
			15.00	14.99	99.93
			25.00	24.99	99.96
Mean ± SD					99.87 ± 0.085
Densitometric method	Bristaflam tablets B.N. C005537	1.00	0.70	0.6974	99.63
			0.80	0.7991	99.89
			0.95	0.9495	99.95
			1.00	0.9969	99.69
Mean ± SD					99.79 ± 0.154
RP-HPLC method	Bristaflam tablets B.N. C005537	20.00	10.00	9.98	99.80
			15.00	14.88	99.20
			25.00	24.85	99.40
			30.00	29.52	98.40
Mean ± SD					99.20 ± 0.588

Table 4
Statistical analysis of the results obtained by the five proposed and B.P. (1998) methods for the determination of aceclofenac

	B.P. (1998) method	D_3 spectrophotometric method	RSD_1 spectrophotometric method	ΔA spectrophotometric method	Densitometric method	HPLC method
Concentration range	300 mg	5–40 (ug/ml)	10–40 (ug/ml)	15–50 (ug/ml)	50–200 (ug/ml)	5–50 (ug/ml)
Mean (%)	99.44	100.12	100.047	99.36	98.76	99.13
SD	0.86	0.60	0.13	0.39	0.48	0.67
N	8	8	7	8	8	8
Variance	0.740	0.376	0.0164	0.154	0.259	0.451
Student's t-test		0.215 (1.761)	0.698 (1.771)	0.604 (1.761)	0.563 (1.761)	0.747 (1.761)
F test		1.09 (3.575)	1.01 (4.445)	1.03 (3.575)	1.21 (3.575)	1.08 (3.575)

*, values in parenthesis are the theoretical values of t and F (at $P = 0.05$).

4. Conclusion

The suggested methods are simple, accurate, selective and sensitive with no significant difference of the precision. Application of the proposed methods to the analysis of aceclofenac in laboratory prepared mixtures and pharmaceutical formulation shows that neither the degradation products nor the excipients interfere with the determination, indicating that the proposed methods could be applied as stability indicating methods for the determination of pure aceclofenac and in presence of its main degradation product, diclofenac, either in bulk powder or in pharmaceutical formulations [10]. Statistical analysis of the results obtained by the five proposed methods and by the reference method of B.P. (1998), revealed no significant difference within a probability of 95%. method.

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