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Analysis of diflunisal by electrochemical methods

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Abstract

A new differential pulse polarographic (DPP) and differential pulse adsorptive stripping voltammetric (DPAdSV) methods for the electrochemical behavior and quantitative determination of diflunisal were described. In these voltammetric methods, the peak potential of diflunisal was found as −0.31 V (vs. Ag/AgCI) with selected Britton–Robinson buffer (BR, pH 7.8) as a supporting electrolyte. The variation of the peak current with the concentration of diflunisal were linear in the 9.0–40.0 and 4.0–30.0 μg ml^{-1} concentration ranges for DPP and DPAdSV methods, respectively. The limits of detection (LOD) were found as 5.0 and 0.1 μg ml^{-1} for DPP and DPAdSV methods, respectively. The developed methods were validated by evaluation of the validation parameters. The characteristics of the peak current of diflunisal were examined in detail and the results proved that the peak current has an adsorption characteristic. The developed methods were proposed for rapid determination of diflunisal in commercial tablets. The recovery studies showed that developed assays had a good accuracy and precision with mean recoveries 99.92 and 100.02% and mean variation coefficients 0.29 and 0.24% in DPP and DPAdSV methods, respectively.

Keywords: Diflunisal; Differential pulse polarography; Differential pulse adsorptive stripping voltammetry; Tablet analysis

1. Introduction

Diflunisal (5-(2′,4′-difluorophenyl) salicylic acid) is a synthetic analog of salicylic acid (Fig. 1) and has analgesic and anti-inflammatory activity [1,2]. A comparison of the pharmacological profile of diflunisal with those of some well known anti-inflammatory agents such as aspirin, ibuprofen and indomethacin showed that diflunisal is more potent and less toxic than these drugs [3]. Diflunisal can be determined by spectrophotometry [4,5], chromatography [6–10], immunoassay [11] and luminescence methods [12]. No electrochemical study has been found in the literature for diflunisal. There is only one study that used an electrochemical detector in high-performance liquid chromatography and diflunisal was detected at oxidation potential +0.9 V with amperometric assay [13].

The aim of this study was to develop simple, sensitive and validated electrochemical methods for the determination of diflunisal by differential pulse polarographic (DPP) and differential pulse adsorptive stripping voltammetric (DPAdSV) and to apply these methods to the pharmaceutical

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preparation. The results obtained by the developed methods were compared with the spectrofluorimetric method in the literature [4].

2. Experimental

2.1. Instrument

A PAR Model 174A polarograph with a PAR Model 303A static mercury drop electrode in the DPP and DPAdSV modes was used [14]. The reference electrode was an Ag/AgCl electrode and a platinum wire was used as the auxiliary electrode. Modified PAR glass polarographic cells were used in the study [15]. Data were recorded on a Houston Omnigraphic Model 2000 X-Y recorder. All measurements were done at 23°C ± 0.5. Nitrogen gas was used for deoxygenation. Controlled-potential electrolysis with a mercury pool electrode was carried out with the Heath Model EUA-19 2 instrument. Spectrofluoriphotometer (Shimadzu, RF-5301PC) was used for the comparison with developed methods. Orion Model pH meter was used for pH measurements.

2.2. Reagents and solutions

The diflunisal standard was obtained from Adilna-Sanovel Drug Industry. The purity of standard checked with its melting point, UV and IR spectra.

Stock solution of diflunisal was prepared in methanol (1000 μg ml^{-1}). Standard solutions were diluted from stock solution to a suitable concentrations daily. All solutions were prepared using double-distilled deionized water and analytical reagent grade chemicals. Triple distilled mercury was used throughout the experiments. The supporting electrolyte was prepared by mixing the solutions of boric, phosphoric and acetic acids (Britton–Robinson buffer (BR)), adjusted to pH 7.8 with 0.1 N sodium hydroxide. DOLPHIN® 500 tablets as pharmaceuticals were used for analysis.

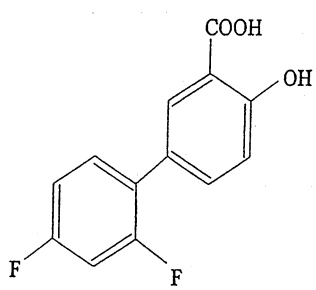

Fig. 1. Chemical structure of diflunisal.

2.3. Preparation of synthetic tablet samples

Synthetic tablet sample was prepared into a test tube by spiking a placebo (mixture of tablet excipients) with accurately weighed amounts of diflunisal at a concentration of the commercial tablets (500.0 mg). Fifteen ml of water was added, the mixture was shaken on a vortex for 10 min, then the test tube was mechanically shaken for 20 min and centrifuged at 2000 rpm. Aqueous phase was taken by decantation, residue was dissolved in methanol and transferred to a 100 ml calibrated flask. It was sonicated for 15 min in an ultrasonic cleaner and diluted to the volume with methanol. An aliquot of this suspension was transferred to the test tube and centrifuged, then suitable volume of the solution was added to the polarographic cell which contained 5 ml of supporting electrolytes.

2.4. Preparation of tablet samples

Ten tablets were weighed, powdered and an amount of one tablet corresponded to 500 mg of the diflunisal was weighed into the test tube. Preparation of tablet samples was done as synthetic samples.

2.5. Procedures

For DPP method: a 5 ml supporting electrolyte (BR buffer, pH 7.8) was deoxygenated with prepurified nitrogen for 12 min and all scans were performed under nitrogen stream. The polarogram of the supporting electrolyte was recorded. Then, diflunisal standard solution was added by an Eppendorf micropipet and solution was deoxygenated with nitrogen for 5 min. The potential

was scanned over the range of −0.15 to −0.5 V versus Ag/AgCl. A well-defined DPP peak was observed at about −0.31 V versus Ag/AgCl. Pulse amplitude 100 mV, potential scan rate 5 mV s^{-1}, drop time 1 s, drop size medium, current range 5 μA, temperature 23°C were selected as optimum operating conditions.

For DPAdSV method: a 5 ml supporting electrolyte (BR buffer, pH 7.8) was deoxygenated with prepurified nitrogen for 12 min in the initial cycle. An accumulation potential (−0.15 V) was applied to the working electrode while the solution was stirred continuously. After a rest time (15 s), a cathodic differential pulse scan was initiated. The voltammograms were recorded under the operational parameters as follows; pulse amplitude 100 mV, scan rate 5 mV s^{-1}, drop size medium, accumulation time 2 min, rest time 15 s. The peak potential was seen −0.31 V as DPP method.

3. Results and discussion

3.1. Method development

Standard diflunisal solution was prepared in various solvents, then methanol was chosen as a suitable solvent.

As shown in Fig. 2, direct-current (DC), tast, pulse and differential pulse (DPP) polarographic techniques were applied for assay of diflunisal.

The DPP technique was the most sensitive and its peak current was higher then the other polarographic techniques. The defined peaks were observed at −0.31 V versus Ag/AgCl.

The maximum signal was obtained in the BR buffer. The peak currents were high and linear between pH 7.4 and 8.4 in the neutral medium in the BR buffer (Fig. 3). In this range of the pH, diflunisal molecule was electroactive and adsorbed on the static mercury drop electrode and simply desorbed from the surface. Diflunisal molecule has two fluor atoms therefore it is lypophilic [3] and this lypophilic character explains the basis of adsorption of the compound on the mercury drops.

There was no linear relation between the peak currents and pH values (pH < 7.4), but the peak currents decreased with dissociation of phenol from diflunisal molecules at basic pH values (pH > 8.4). Therefore, the BR buffer was found to be the best buffer in the range of pH from 7.4 to 8.4 and the BR buffer at pH 7.8 was selected as the supporting electrolyte in subsequent experiments. The influence of pulse amplitude, scan rate, drop size, drop time on the peak current was examined and optimum parameters for diflunisal in DPP assay was determined (Table 1).

In this work; another electrochemical method, DPAdSV method was also developed in order to study for lower concentrations. Pulse amplitude, scan rate, and drop size were examined for the optimization study of the DPAdSV method and these parameters were similar to the selected conditions of the DPP method. In addition to this study, accumulation time and rest time were also examined and optimum parameters for DPAdSV method were given in Table 2.

At the analysis, variation of the peak current with the temperature was an important parameter to explain the character of the current. Therefore, influence of the temperature on the peak current was investigated in the range of 19–25°C (Table 3) and the decrease in the peak current was observed with increasing temperature. Temperature coefficient of the diflunisal was found to be 5.52% deg. $°C^{-1}$ with standard deviation (S.D.) of 0.28. These results clearly indicate that the current was adsorption-controlled and this outcome was also confirmed by means of the temperature coefficient of 5–10% for 1°C temperature difference taken from the adsorption current. In addition, the controlled potential electrolysis was carried out for explanation of the electrode process. Controlled-potential electrolysis was performed using 30.0 μg ml^{-1} diflunisal in 50.0 ml BR buffer at pH 7.8 and the potential of electrolysis was −0.7 V. Controlled-potential electrolysis was carried out during 12 h at this potential at a mercury pool electrode. The solution samples which were taken from the cell before and after electrolysis were lyophilized and prepared as discs with KBr. There was no difference at the IR spectrum of these solutions. This result showed that there was no electron transfer and the current was controlled by adsorption.

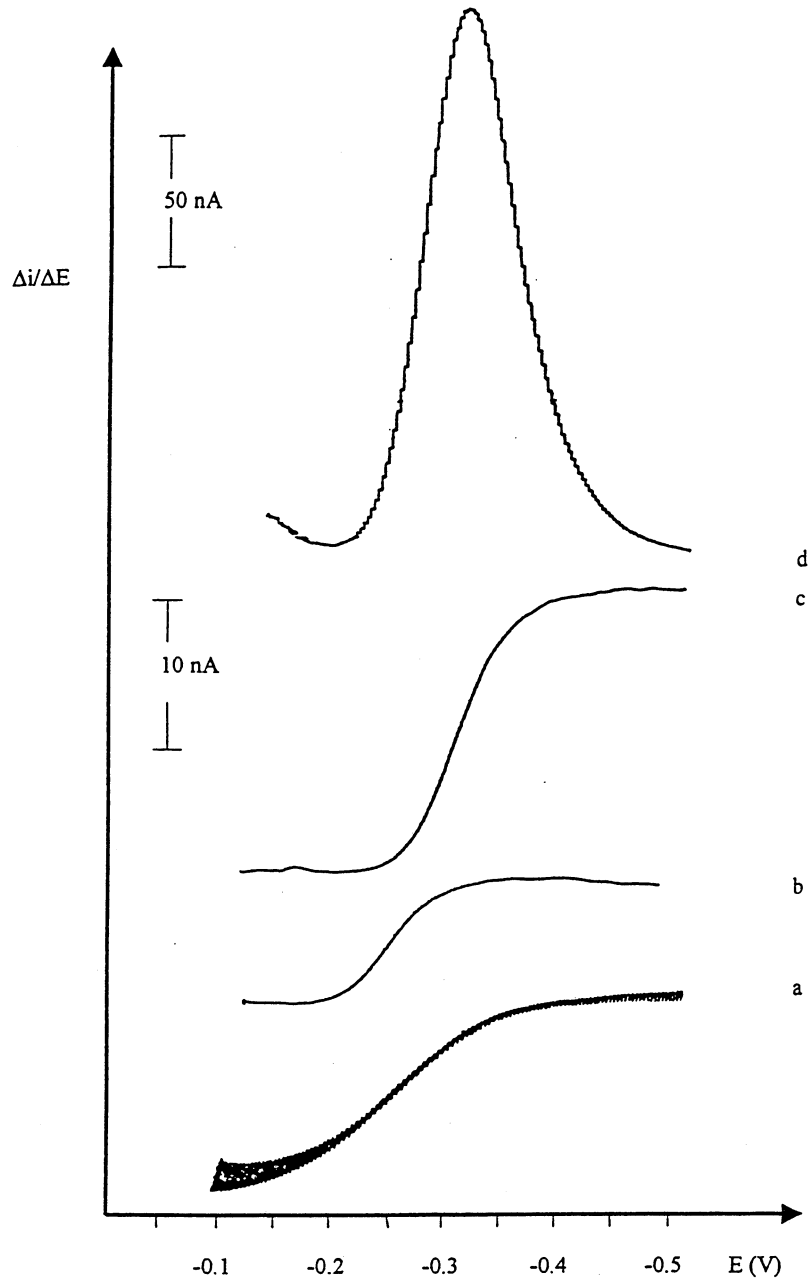

Fig. 2. Different polarographic techniques for determination of diflunisal (diflunisal concentration; 75.0 μg ml^{-1}): (a) direct-current polarography; (b) tast polarography; (c) pulse polarography; (d) differential pulse polarography.

The adsorption phenomenon and formation of the adsorption layer were confirmed from the curves of the peak current versus accumulation time in Fig. 4. The variation of the peak currents with the different accumulation times (0.25, 0.5, 1, 2, 3, 4, 5, and 6 min) was examined with three different concentrations (5.0, 10.0, and 15.0 μg ml^{-1}) at constant scan rate (5 mV s^{-1}). The short

accumulation time (2 min) was explained by the fast saturation of the electrode surface. Increase of adsorption layer on the surface with increase of concentration at the selection appropriate accumulation time (which was 2 min) was observed at each of three diflunisal concentrations. The peak current–time curves in this study were also supported by reports in the literature [16]. The different scan rates (1, 2, 5, 10, and 20 mV s^{-1}) at three different concentrations, the variation of the peak currents against scan rate was drawn at constant accumulation time. These results showed that the optimum desorption of the molecule from the electrode surface at each of three different concentrations at a scan rate of 5 mV s^{-1} and the current was only adsorption controlled and the electrode process was run with adsorption and desorption phenomenons.

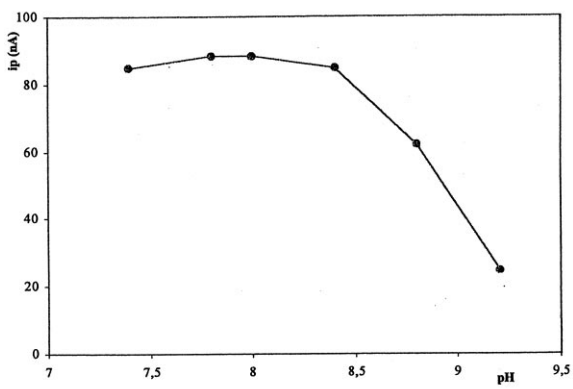

Fig. 3. The effect of pH on the peak current of diflunisal.

Table 1
Influence of pulse amplitude (ΔE), scan rate (v), drop size (A) and drop time (t) on the peak current (i_p) (diflunisal concentration: 30.0 μg ml^{-1})

ΔE (mV)	v (mV s^{-1})	A [b]	t (s)	i_p (nA)
5	5	S	1	1.97
10	5	S	1	5.91
25	5	S	1	12.80
50	5	S	1	25.59
100[a]	5	S	1	55.12
100	1	S	1	59.06
100	2	S	1	58.07
100	5[a]	S	1	55.12
100	10	S	1	43.31
100	5	S	1	55.12
100	5	M[a]	1	76.77
100	5	L	1	118.11
100	5	M	0.5	74.80
100	5	M	1[a]	76.77
100	5	M	2	60.04
100	5	M	5	43.31

[a] Selected parameters.
[b] Area ratio of mercury drop: small (S), medium (M), large (L) (1:1.6:2.5).

3.2. Method validation

3.2.1. Linearity range

The calibration graph of the peak current versus concentration was found to be linear over the range of 9.0–40.0 μg ml^{-1} for diflunisal in the DPP method. The linearity was checked by preparing standard solutions at 13 different concentrations. The peak current was deviated from linearity and then remained constant when diflunisal concentrations were higher than 40.0 μg ml^{-1}. This result showed that diflunisal was strongly adsorbed on the electrode surface and the amount of diflunisal on the electrode surface limited due to surface saturation. The linear equation was obtained; $y(i) = -4.792 + 2.138 \times C$, $r = 0.9990$, where $y(i)$ is the peak current in nA, $\times C$ is the concentration in μg ml^{-1} and r is the correlation coefficient.

Voltammetric curve was obtained from the peak current versus increase of diflunisal concentrations ($n = 14$). The linearity of DPAdSV method was found over the range of 4.0–30.0 μg ml^{-1} for diflunisal. The linear response of the peak current versus concentration was obtained; $y(i) = 124.781 + 3.130 \times C$, $r = 0.9993$.

In the spectrofluorimetric method, fluorescence intensity (F) was linearly related to the concentration over the range 0.05–2.0 μg ml^{-1}, $r = 0.9991$ ($n = 14$).The results of calibration curves for three methods were given in Table 4.

3.2.2. Sensitivity

The limits of detection (LOD) for DPP and DPAdSV were found as 5.0 and 0.1 μg ml^{-1}, respectively. The peak is not resolved from the noise at concentrations lower than 5.0μg ml^{-1} (for DPP) and 0.1 μg ml^{-1} (for DPAdSV). The

Table 2
Influence of pulse amplitude (ΔE), scan rate (v), drop size (A), accumulation time (t_{acc}) and rest time (t) on the peak current (i_p) (diflunisal concentration: 12.0 μg ml^{-1})

ΔE (mV)	v (mV/s)	A[b]	t_{acc} (min)	t (s)	i_p (nA)
5	5	S	1	15	5.91
10	5	S	1	15	9.84
25	5	S	1	15	23.62
50	5	S	1	15	55.12
100[a]	5	S	1	15	156.50
100	1	S	1	15	161.42
100	2	S	1	15	157.48
100	5[a]	S	1	15	156.50
100	10	S	1	15	139.76
100	5	S	1	15	156.50
100	5	M[a]	1	15	158.30
100	5	L	1	15	180.40
100	5	M	0.5	15	137.80
100	5	M	1	15	158.30
100	5	M	2[a]	15	161.42
100	5	M	5	15	133.86
100	5	M	2	10	162.40
100	5	M	2	15[a]	161.42
100	5	M	2	30	160.43
100	5	M	2	45	162.40

[a] Selected parameters.
[b] Area ratio of mercury drop: small (S), medium (M), large (L) (1:1.6:2.5).

values of LOD were obtained at a signal to noise ratio greater than 3.0. The limits of quantitation (LOQ) were found as 9.0 and 4.0 μg ml^{-1} for DPP and DPAdSV, respectively.

3.2.3. Specificity/selectivity

Specificity is the ability of the method to measure the analyte response in the presence of all the potential impurities. For the specificity test, polarograms of the standard solutions of tablet excipients as the sunset yellow (E110) and titanedioxyde (TiO_2) were recorded at selected conditions. Only E110 interfered with the analysis of diflunisal. Therefore, extraction was carried out before polarographic analysis in synthetic tablet samples. E110 dissolves in water but diflunisal does not, hence, in synthetic tablet samples, E110 was extracted with water then solid residue was dissolved in methanol. Thus, E110 was taken to the aqueous solution and was eliminated from synthetic tablet samples. The response of the analyte in this mixture was compared with the response of pure diflunisal. It was found that assay results were not changed. Therefore, impurities as E110 did not interfere with the quantitation of diflunisal in synthetic tablet samples. The assay results were given in Table 5.

3.2.4. Application of method to the pharmaceutical preparation

The quantity of diflunisal in tablet samples was analyzed as synthetic tablet samples by DPP and

Table 3
The temperature coefficient for the peak currents obtained of diflunisal by differential pulse adsorptive stripping voltammetric (DPAdSV) method

Temperature, T (°C)	Peak current, i_p (nA)	Temperature coefficient, $-(\%\Delta i_p/°C)$
19	360.24	4.97
22	194.88	5.68
23	159.45	5.92
25	128.94[a]	

[a] Reference peak current.

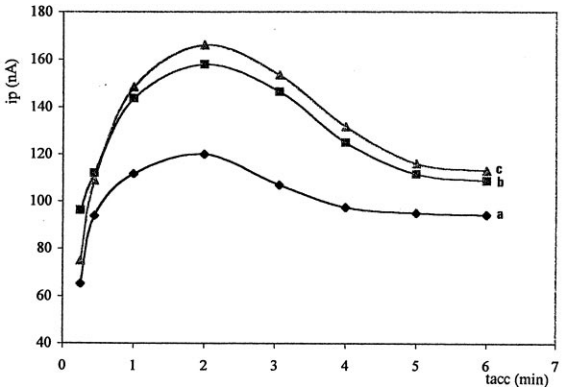

Fig. 4. The effect of the accumulation time on the stripping voltammograms: (a) 5.0; (b) 10.0 and (c) 15.5 μg ml^{-1} (scan rate; 5 mV s^{-1}).

DPAdSV methods. For these studies, a different series of the 15 tablets containing 500.0 mg diflunisal was selected. The mean values of 500.61 mg $\pm$ 0.67 and 501.37 mg $\pm$ 0.36 (with variation coefficients of 0.52 and 0.28%) were found for DPP and DPAdSV methods, respectively.

The standard addition technique was used for the quantitative analysis of diflunisal in tablets by DPP and DPAdSV (Fig. 5) methods.

3.2.5. Accuracy

The accuracy of a method is the degree of the nearness to the real value of the observed analysis results [17]. The accuracy of developed methods was carried out by spiking a placebo with accurately weighed amounts of diflunisal at concentration of the commercial tablets (500.0 mg). The results of the analyses of synthetic tablet samples are given in Table 6. The mean recoveries were found to be 99.92 and 100.02% for DPP and DPAdSV methods, respectively. As can be seen, the best accuracy given as recovery values was obtained by using DPP and DPAdSV methods.

3.2.6. Precision

The precision and reproducibility of these developed methods (DPP, DPAdSV) for diflunisal were determined in five replicative analysis at six synthetic tablet samples (Table 6). The mean variation coefficients were found to be 0.29 and 0.24% for DPP and DPAdSV methods, respectively. The variation coefficients were found less than 2%, indicating that two methods were precise and confidence.

3.2.7. Robustness and ruggedness

The ruggedness test of the analytical assay method is defined as degree of reproducibility of assay results obtained by the successful applications of the assay over time and multiple laboratories and analyst [18].

The same standard was analyzed with DPP and DPAdSV methods using the same instrument by two analysts. The methods were found to be rugged with the results of variation coefficients were 0.25 and 0.26% for DPP, 0.21 and 0.23% for DPAdSV methods for first and second analysts, respectively.

The robustness of presented methods in this study was tested changing parameters, such as solvent type and optimize parameters involved in pulse amplitude (ΔE), scan rate (v), drop size (A), drop time (t), accumulation time (t_{acc}), rest time (t) were chosen for this study.

The results showed no statistical differences between different analysts.

3.2.8. Stability

In this study, diflunisal stock solutions for controlling the stability were kept in the dark at + 4°C during 1 month and were analyzed at different times (like every day). It has been seen that repeatable peak currents of diflunisal solutions occurred and were stable during 1 month.

The stability indicating assay for diflunisal was established by heating and by adding 0.1 N HCl solution for acidic conditions and 0.1 N NaOH solution for alkaline conditions.

The results pointed out that diflunisal maintained an unchanged structure, despite the temperature variations (19, 22, 23, 25°C for 1 h).

In the 0.1 N HCl and 0.1 N NaOH solutions a suspension occurred, however, peak of diflunisal could not be seen in the 0.1 N HCl and 0.1 N NaOH solutions.

4. Conclusion

The developed methods were validated by evaluation of the validation parameters. The LOD, the linearity ranges, equation of calibration curves, standard errors of slope and intercept, correlation coefficient, standard errors of correlation coefficient and determination coefficient for three methods were obtained as given in Table 4.

Analysis results of developed methods presented here for the determination of diflunisal were compared with the spectrofluorimetric

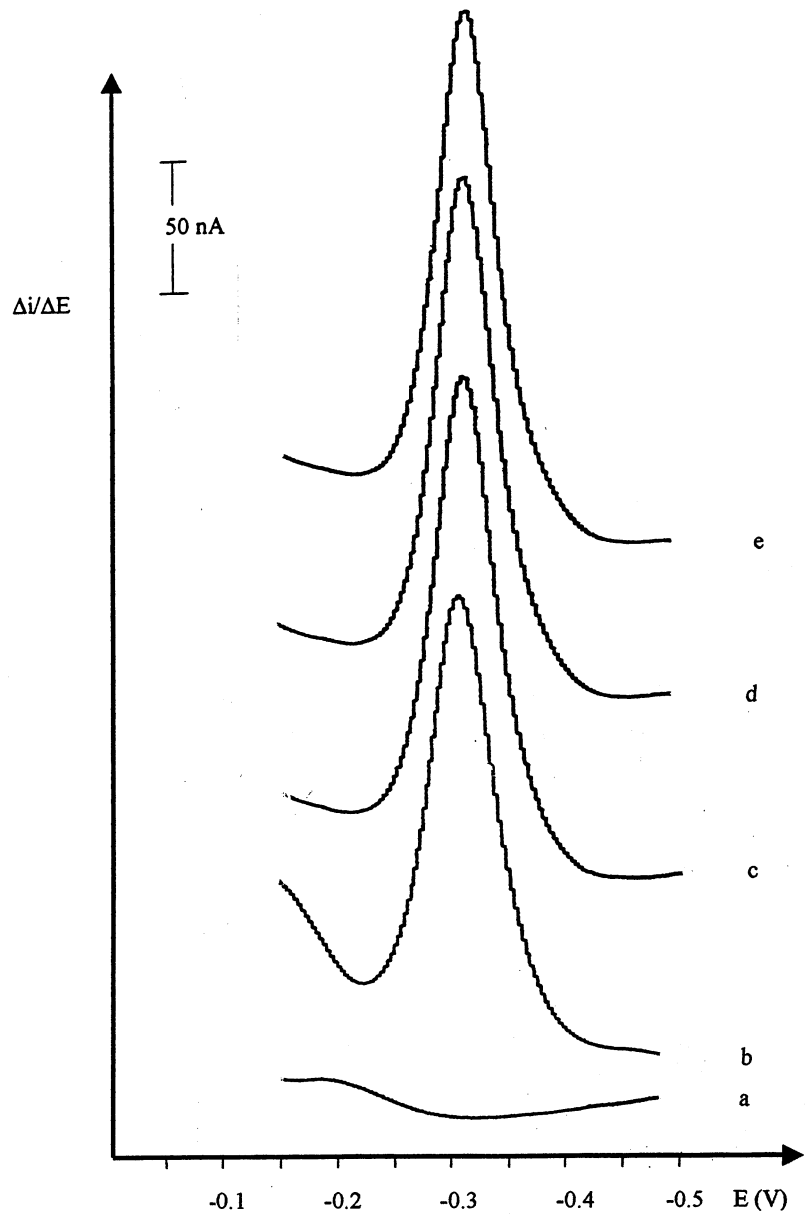

Fig. 5. Differential pulse adsorptive stripping voltammetric (DPAdSV) polarograms of diflunisal in tablet sample: (a) supporting electrolyte (5 ml); (b) 5.0 μl tablet sample; (c–e) successive additions of 10.0 μl of 1000 μg ml^{-1} standard diflunisal solution.

Table 4
The determined parameters for calibration curves of diflunisal obtained from developed methods and comparison method[a]

Methods	DPP ($n=13$)	DPAdSV ($n=14$)	Fluorimetry ($n=14$)
LOD (μg ml^{-1})	5.0	0.10	0.05
Linearity range (μg ml^{-1})	9.0–40.0	4.0–30.0	0.05–2.0
Regression equation ($y=a+bx$)	$y(i)=-4.792+2.138\times(C)$	$y(i)=124.781+3.130\times(C)$	$y(F)=21.529+301.990\times(C)$
Standard error of intercept	2.49×10^{-3}	3.85×10^{-3}	2.24×10^{-4}
Standard error of slope	2.24×10^{-4}	2.11×10^{-4}	8.16×10^{-4}
r	0.9990	0.9993	0.9991
Sr	0.01	0.01	0.01
r^2	0.9980	0.9986	0.9982

[a] LOD, the limit of detection; $y(i)$, peak current; $x(C)$, concentration of diflunisal; $y(F)$, fluorescence intensity; r, correlation coefficient; Sr, standard error of correlation coefficient; r^2, determination coefficient.

Table 5
Specificity results of the differential pulse polarographic (DPP) and differential pulse adsorptive stripping voltammetric (DPAdSV) methods[a]

Sample no.	DPP method		DPAdSV method	
	Pure sample 500.0 (mg)	Synthetic tablet samples ($n=5$) $\bar{x}$ (mg)	Pure sample 500.0 (mg)	Synthetic tablet samples ($n=5$) $\bar{x}$ (mg)
1	500.12	500.10	500.17	500.15
2	498.57	498.50	499.85	499.90
3	500.15	500.20	500.13	500.15
4	499.29	499.25	500.15	500.20
5	500.21	500.20	499.95	499.90
6	499.30	499.25	500.10	500.15
$\bar{x}$	499.61 ± 0.27	499.58 ± 0.29	500.06 ± 0.053	500.08 ± 0.057
S	0.66	0.70	0.13	0.14
CV (%)	0.13	0.14	0.026	0.028

[a] $\bar{x}$ (mg), mean ± S.E., standard error; S, standard deviation; CV, variation coefficient.

method [4] by using the variance analysis. And, no statistically significant difference was found between three methods (Table 7). DPP and DPAdSV methods were found to be suitable and reliable methods as spectrofluorimetric method in the literature.

The LOD was low and the linearity range was wider than proposed GC [8] and HPLC [4,13] methods for chromatographic analysis of diflunisal in the literature. The proposed methods are cheaper (like chemicals and instrument) and simpler than chromatographic methods. It might be an alternative to the methods in the literature.

The results obtained from this study showed that the proposed methods can be recommended for the determination of diflunisal in tablets. The developed methods could be easily used in quality control laboratory for the analysis of diflunisal in pharmaceutical preparation.

Table 6
Precision, reproducibility and accuracy studies of differential pulse polarographic (DPP) and differential pulse adsorptive stripping voltammetric (DPAdSV) methods for the determination of diflunisal from synthetic tablet samples[a]

Sample no.	Nominal value of diflunisal (mg)	DPP method			DPAdSV method		
		Found value of diflunisal ($n = 5$) ($\bar{x}$ (mg) $\pm$ S)	CV (%)	R (%)	Found value of diflunisal ($n = 5$) ($\bar{x}$ (mg) $\pm$ S)	CV (%)	R (%)
1	500.0	500.10 ± 1.24	0.25	100.02	500.15 ± 1.32	0.26	100.03
2	500.0	498.50 ± 1.15	0.23	99.70	499.90 ± 1.23	0.25	99.98
3	500.0	500.20 ± 1.77	0.35	100.04	500.15 ± 1.07	0.21	100.03
4	500.0	499.25 ± 1.71	0.34	99.85	500.20 ± 1.44	0.29	100.04
5	500.0	500.20 ± 1.44	0.29	100.04	499.90 ± 1.05	0.21	99.98
6	500.0	499.25 ± 1.30	0.26	99.85	500.15 ± 1.02	0.20	100.03
			$\bar{x}$: 0.29	$\bar{x}$: 99.92		$\bar{x}$: 0.24	$\bar{x}$: 100.02

[a] ($\bar{x}$ (mg) $\pm$ S): mean $\pm$ S, standard deviation for five deteminations. CV, variation coefficient; R, recovery.

Table 7
Statistical evaluation of obtained data from three methods (500 mg diflunisal in one tablet of DOLPHIN® 500)[a]

Statistical values	DPP method	DPAdSV method	Spectrofluorimetric method	F values
n	15	15	15	
$\bar{x}$	500.61 ± 0.67	501.37 ± 0.36	501.49 ± 0.37	$F_H = 5.62 \times 10^{-4}$
S	2.61	1.41	1.42	$F_T = 3.34$
CV (%)	0.52	0.28	0.28	
CI	499.18–502.04	500.60–502.14	500.70–502.28	

[a] n, number of sample; $\bar{x}$, mean; S, standard deviation; CV, variation coefficient; CI, confidence intervals ($\alpha = 0.05$); F_H, calculated F value; F_T, theoretical F value ($\alpha = 0.05$).

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