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Voltammetric, spectrofluorimetric and spectrophotometric methods to determine flufenamic acid

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Abstract

Simple, rapid and sensitive voltammetric, spectrofluorimetric and spectrophotometric methods for determination of flufenamic acid (FF) in bulk powder and capsule dosage form are presented. The methods are based on the cyclisation reaction of FF with concentrated sulphuric acid to produce the corresponding acridone derivative. The voltammetric method is based on the adsorptive stripping differential pulse (DP) technique. The acridone derivative is determined over the concentration range of 8–60 ng ml^{-1} using adsorptive preconcentration at the hanging mercury drop electrode (HMDE). The lower detection limit was found to be 1.02 ng ml^{-1}. The fluorimetric and spectrophotometric methods are based on the measurement of the fluorescence intensity at 450 nm ($\lambda_{ex} = 400$ nm)and peak-to-peak measurements of the first- (D_1) and second-derivative (D_2) curves, respectively. Beer's law is obeyed over the concentration ranges of 2–20 ng ml^{-1} and 0.2–8.0 μg ml^{-1} for the fluorimetric and spectrophotometric measurements, respectively. The three methods were proved to be accurate and reproducible as indicated by a relative standard deviation of $< 2\%$.

Keywords: Voltammetry; Spectrofluorimetry; Spectrophotometry; Flufenamic acid

1. Introduction

Flufenamic acid (FF), *N*-(3-trifluoromethylphenyl) anthranilic acid, is a non-steroidal anti-inflammatory drug. It has analgesic and antipyretic properties. It is used in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis [1].

Several liquid-chromatographic studies concerned with the analysis of this compound in biological fluids [2–5] have been reported. High resolution gas chromatography determination has been proposed [6]. Simple spectrophotometric methods including colour reactions [7–10] and UV measurement [11] have been described.

The fluorescent properties of such a model of anthranilic acid derivative have been widely exploited for analytical purposes. Some of the early studies reported by Mehta and Schulman [12] affirmed that the native fluorescence exhibited by FF in organic solvents, e.g. dioxan and chloro-

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form, could be useful for its determination. Miller et al. [13] reported that FF showed no significant fluorescence at room temperature in acidic, neutral or alkaline ethanol solution. Investigations by Dell and Kutschbach [14] indicated that the fluorescence intensity of FF is strongly increased by the addition of a halogenoacetic acid with a pK_a value < 1 (e.g. trichloroacetic acid). Recently the fluorescence characteristics of FF in different aqueous organised media were investigated and a fluorimetric determination method in pharmaceutical preparation was described [15].

Other spectrofluorimetric methods employed for the determination of FF involve the use of fluorogenic agents [16,17].

Dell and Kamp [18] have studied the cyclisation reaction of FF with concentrated sulphuric acid to give a mixture of two isomeric trifluoromethyl acridones. The UV-maxima and fluorescence maxima (excitation and emission) in neutral, acidic and alkaline methanol have been identified. The authors have carried out a study of the reaction on biological samples spiked with FF and separated on TLC plate. No recovery data have been given in that article [18].

The cyclisation reaction of FF with concentrated sulphuric acid has not been used in pharmaceutical analysis. In the present work, the latter reaction is adopted for quantitative analytical methods to be favourably applied to the analysis of FF in pharmaceutical dosage forms.

The analytical review of FF indicated that no polarographic method of determination, concerning the reduction at the mercury drop electrode, has been reported. Thus one of the important aim of this work is to establish a simple voltammetric analytical method. Taking into consideration that the acridone derivative, cyclised FF product, is electrochemically reactive, its polarographic reduction behaviour at the mercury electrode was investigated. The voltammetric measurement is carried out on the cathodic peak which is most possibly attributed to the reduction of the carbonyl group. Further intention was directed to explore the properties of the adsorption process of acridone derivative at the mercury electrode to be used as a preconcentration step prior to the voltammetric measurement. A study of the factors that may influence both the accumulation process and the voltammetric response was carried out.

Depending on the results obtained, a highly sensitive cathodic stripping voltammetric procedure for determination of FF by adsorption accumulation was developed.

In this article, the study of the fluorescence characteristics of the acridone derivative indicated good sensitivity. As a consequence a fluorimetric method was developed for the estimation of FF down to nanogram levels.

Taking the advantage of the increase of the UV absorptivity of the acridone derivative in acidic and alkaline ethanol media relative to that of FF, a derivative-spectrophotometric method (first- and second-order) is presented for the analysis of FF.

The applicability of the above three proposed methods were demonstrated by the analysis of FF in commercial capsules.

2. Experimental

2.1. Apparatus

The voltammograms were obtained with a Metrohm 693 VA Processor. A Metrohm 694 VA Stand was used in the hanging mercury drop electrode (HMDE) mode. The three electrode system was completed by means of a Ag/AgCl (saturated KCl) reference electrode and a Pt auxilary electrode.

Fluorescence spectra and measurements were taken on a Perkin–Elmer 650-10S spectrofluorimeter, equipped with 1 cm quartz cell, a 150 W Xenon arc lamp, excitation and emission grating monochromators and a Perkin–Elmer recorder model 56. Slit-widths for both monochromators were set at 10 nm. The scan speed was set at 120 nm min^{-1}. The emission intensity measuring system of the instrument was calibrated daily by using the Perkin–Elmer set of fluorescent polymer blocks.

Spectrophotometric spectra were performed with a Perkin–Elmer model 550S UV–VIS spectrophotometer with 1 cm quartz cuvettes and a Hitachi model 561 recorder.

2.2. Materials and reagents

All experiments were performed with analytical-reagent grade chemicals and pure solvents. Flufenamic acid was purchased from Sigma Chemical Co. (Germany) and used as received. Pinox capsules (labelled to contain 100 mg FF per capsule) was obtained from the market (Alexandria Co., Egypt).

2.3. Standard solution

A 2 mg ml^{-1} stock standard solution of FF was prepared in ethanol. From this solution, intermediate dilution steps were made with ethanol in accordance with the concentration range used in the analytical technique followed.

2.4. Preparation of reaction solutions

Suitable separate aliquots of standard ethanolic FF solution were evaporated to dryness in a boiling water bath. Separate volumes (0.5 ml each) of concentrated sulphuric acid were added to the residues. The resultant reaction solutions were heated in a boiling water bath for 15 min.

2.5. Procedure for polarographic analysis

The reaction solution was made to 10 ml with distilled water (the final concentration range obtained is 8–60 ng ml^{-1}). Then it was placed in the voltammetric cell. The stirrer was switched on and the solution was purged with nitrogen gas for 5 min. The accumulation potential was then applied to a new mercury drop, whilst still stirring the solution. Following the accumulation period, the stirring was stopped and allowed to equilibrate for 10 s. The voltammogram was obtained by applying a negative going potential scan. Unless otherwise stated, the following parameters were used; accumulation time 60 s, accumulation potential -0.5 V, pulse amplitude -100 mV for differential pulse stripping. The maximum drop size 9 (ca. 0.60 mm^2 drop area) and constant stirrer speed 2000 rpm, were used.

2.6. Procedure for spectrofluorimetric analysis

Into a set of 5 ml volumetric flasks, the reaction products were completed to the volume with dimethylformamide to obtain a final concentration range of 2–20 ng ml^{-1}. The fluorescence intensities were measured at λ_{em} 450 nm ($\lambda_{ex} = 400$ nm) against blank.

2.7. Procedure for spectrophotometric analysis

Into a set of 5 ml calibration flasks, the previously prepared reaction solutions were completed to the final volume with ethanol to obtain acidic-ethanol solutions with a final concentration range of 0.2–8.0 μg ml^{-1}. Into a second series of 10 ml volumetric flasks, to each 1 ml of ethanol was added to the prepared reaction solutions and the volume was diluted with 2 N sodium hydroxide solution to give alkaline-ethanol solutions with a final concentration range of 0.2–8.0 μg ml^{-1}. The first and the second UV derivative spectra for all the solutions were recorded against the corresponding blank. For the acidic-ethanol solutions the D_1 and the D_2 values were measured at 257–235 and 258–240 nm, respectively. For the alkaline-ethanol solutions the D_1 values were measured at 268–243 nm and the D_2 values at 270–258 nm.

It should be noted that in all techniques, the diluting solvent was added to the reaction solution gradually whilst keeping the reaction mixture in an ice-water bath.

2.8. Pharmaceutical preparation

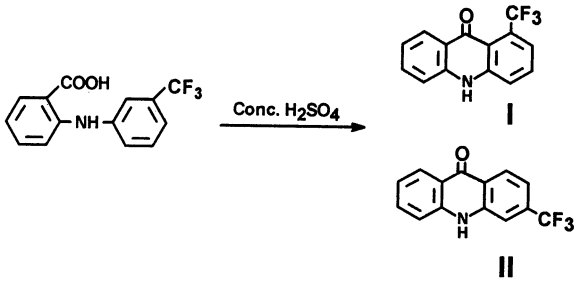
A quantity of the mixed contents of 20 capsules equivalent to 100 mg of FF was dissolved in 50 ml of ethanol with stirring. The solution was filtered into a 100 ml calibrated flask, the residue washed several times with ethanol and the solution diluted to the mark. Suitable dilution steps were made with ethanol. For the analysis, the experimental work described in Sections 2.4, 2.5, 2.6 and 2.7 was followed using the ethanolic pharmaceutical sample solution instead of the standard one.

3. Results and discussion

Scheme 1 represents the dehydration cyclisation reaction of FF (anthranilic acid derivative) when heated with concentrated sulphuric acid. The reaction is based on the presence of a –COOH group and *N*-(*o*-unsubstituted phenyl ring). The reaction products are a mixture of two isomeric acridones; 2-trifluoromethyl acridone (I) and 4-trifluoromethyl acridone (II) [18].

3.1. Voltammetric analysis

Preliminary study of the voltammetric behaviour of the acridone derivative at HMDE using DP mode was started with 2 μg ml^{-1} FF in an aqueous-methanol solution (50% v/v organic solvent). A peak current of ~ 50 nA was obtained which indicated low sensitivity. The study was directed to decrease the organic solvent content which is added to allow for the solubility of the acridone. A 5-fold enhancement in the peak current was attained upon lowering the methanol from 50 to 10% v/v. The matter was promising to continue the study of adsorption behaviour using a nanogram level of the analyte in an aqueous solution with no organic solvent added.



Scheme 1.

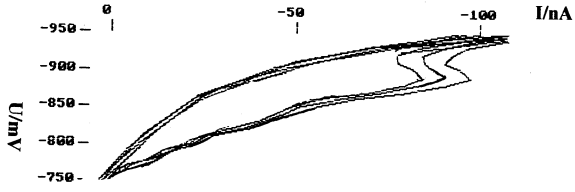


Fig. 1. Cathodic sequential cyclic voltammogram of acridone derivative of FF (200 ng ml^{-1} FF) in aqueous sulphuric acid solution using a scan rate of 500 mV s^{-1}. $t_{acc} = 20$ s. Accumulation potential = − 0.50 V.

3.1.1. Adsorptive behaviour

Adsorption of the analyte was confirmed by the results obtained with cyclic voltammetry. Fig. 1 shows cyclic voltammograms of acridone derivative of FF (200 ng ml^{-1} FF), only a cathodic peak is observed at − 0.85 V with 60 s stirring period (− 0.50 V accumulation potential). The peak decreased upon repetitive scan, indicating rapid desorption of the compound from the surface. No peaks are observed upon scanning in the positive direction indicating the irreversibility of the reduction reaction at the electrode surface.

3.1.2. Factors influencing the accumulation step

The spontaneous accumulation of the acridone derivative can be exploited for effective preconcentration prior to the voltammetric scan. Fig. 2(A) displays the resulting peak current versus preconcentration time plot for (a) 40 and (b) 80 ng ml^{-1} acridone derivative of FF. The rapid increase of the current observed at short preconcentration time, is followed by a levelling-off for longer periods. Hence to maximise sensitivity, a 60 s accumulation time was generally used for subsequent quantitative determinations. However, the ultimate choice of accumulation time should depend on the concentration range studied.

It should be noted that the peak potential moves towards less negative values (~ 40 mV shift) as the accumulation time increases from 0 to 120 s. This is attributed to the dependence of the concentration of analyte at the electrode surface on the accumulation time. Such a finding proves an irreversible electrode reaction.

The effect of the accumulation potential on the adsorptive stripping peak current was evaluated over the range 0 to − 0.900 V (Fig. 2(B)). Larger peaks were obtained over the range from − 0.400 to − 0.600 V, the peak decreased rapidly at lower and higher potentials. Therefore an adsorption potential of − 0.500 V was adopted for analytical determination of acridone derivative of FF.

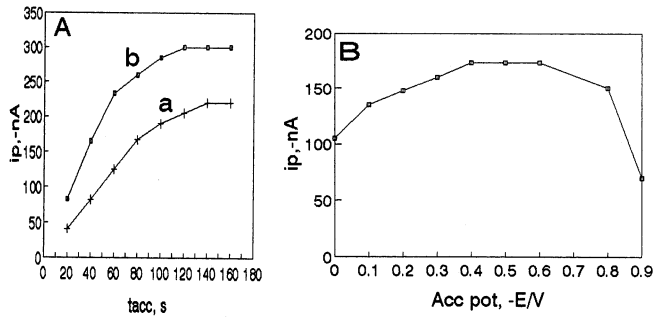


Fig. 2. (A) Effect of accumulation time on the peak current of acridone derivative of FF. (a) and (b) correspond to 40 and 80 ng ml^{-1} FF, respectively, in aqueous sulphuric acid solution (scan rate = 10 mV s^{-1}, accumulation potential = −0.50 V, pulse amplitude = −100 mV). (B) Effect of accumulation potential on the response to 80 ng ml^{-1} FF. t_{acc} = 40 s, other conditions as in (A).

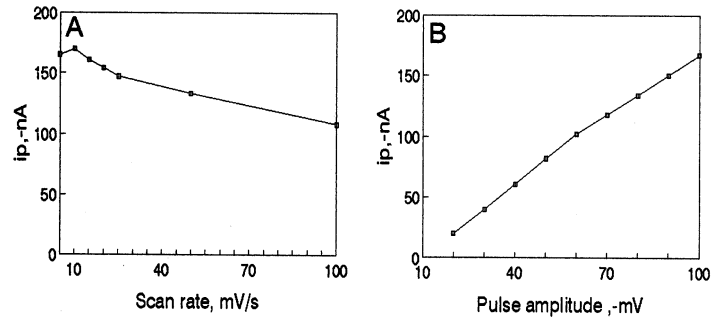


Fig. 3. Stripping peak current dependence of acridone derivative of FF (40 ng ml^{-1} FF) on scan rate (A) and pulse amplitude (B). t_{acc} = 80 s, other conditions as in Fig. 2(A).

3.1.3. Instrumental parameters

Fig. 3(A) displays the resulting peak current versus scan rate plot. Maximum response was obtained at a scan rate 10 mV s^{-1}.

Fig. 3(B) shows the dependence of peak current on the pulse amplitude. The plot is linear up to an amplitude of −100 mV.

3.2. Spectrofluorimetric analysis

In the early studies performed by Dell et al. [18] on FF–acridone derivatives, the excitation and emission maxima in methanol, methanol–HCl and methanol–NaOH were identified, for a product separated and crystallised from pyridine, with no further quantitative data. In our work following up the procedure cited in Section 2.6, the fluorescence emission of the acridone derivative in methanol–sulphuric acid (at λ_{ex} = 400 nm and λ_{em} = 465 nm) shows no linear correlation with concentration. However, using dimethylformamide as a diluting solvent for the fluorescent product, a maximum emission band was shown at

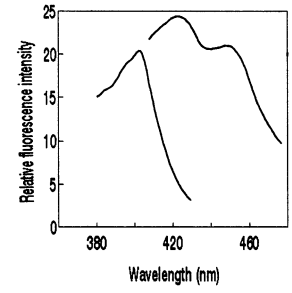


Fig. 4. Excitation and emission spectra of acridone derivative of FF (10 ng ml^{-1} FF) in acidic-dimethylformamide solution.

Table 1
Analytical data of the calibration graphs for the determination of flufenamic acid using different methods

Method	Linearity range	Wavelength (nm)	Regression equation ($A = a + bC$)[a]	r	S_a	S_b
Voltammetry	8.0–60.0 ng ml^{-1}		$I = 0.55 + 3.087C$	0.9990	1.748	0.0507
Spectrofluorimetry	2.0–20.0 ng ml^{-1}	$\lambda_{em} = 450$ ($\lambda_{ex} = 400$)	$F = -0.037 + 2.042C$	0.9997	0.208	0.0171
Spectrophotometry						
Acidic-ethanol	0.20–8.0 μg ml^{-1}					
D_1		257–235	$D = 0.0012 + 0.062C$	0.9998	0.00140	0.00035
D_2		258–240	$D = 4.3 \times 10^{-6} + 0.0048C$	0.9999	0.00010	0.000025
Alkaline-ethanol	0.20–8.0 μg ml^{-1}					
D_1		268–243	$D = 6.6 \times 10^{-4} + 0.082C$	0.9990	0.00099	0.00025
D_2		270–258	$D = -2.7 \times 10^{-5} + 0.008C$	0.9998	0.00010	0.000025

[a] Analytical signal (I, F or D) versus concentration; standard specimens: $n = 5$. r, correlation coefficient; S_a, standard deviation of intercept of regression line; S_b, standard deviation of slope of regression line.

450 nm ($\lambda_{ex} = 400$ nm) (Fig. 4). The intensity of the fluorescence in an acidic dimethylformamide medium was found to be linearly related to the concentration over the range cited in Table 1.

3.3. Spectrophotometric analysis

Fig. 5 shows the zero-order UV spectra of FF–acridone derivative in acidic- and alkaline-ethanol. The apparent molar absorptivities (ε) obtained for the acridone derivative in acidic and alkaline-ethanol were calculated to be 54833 ($\log \varepsilon = 4.74$) (256 nm) and 64675 ($\log \varepsilon = 4.81$) (268 nm), respectively.

The first- and second-derivative UV spectra of FF–acridone derivative in acidic and alkaline-ethanol exhibited several maxima and minima at different wavelengths (Fig. 6(A,B)). These maxima and minima were used for quantitation of FF in bulk powder and capsule forms. At the chosen wavelengths (Table 1) peak-to-peak measurement technique was used which provided greatest values of D_1 and D_2 and thereby the sensitivity of the method was increased.

3.4. Stability of solutions

The standard ethanolic solution of FF was prepared and stored in a refrigerator for 10 days. This FF solution was re-analysed (voltammetric assay) together with a freshly prepared FF solution of similar composition. Consistent voltam-

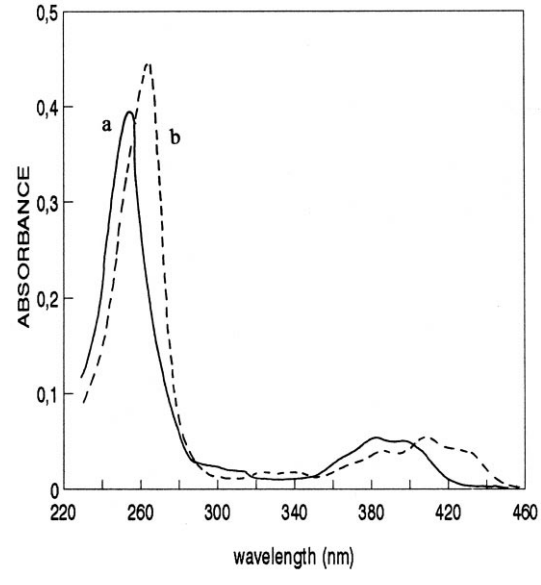


Fig. 5. Absorption spectra of acridone derivative of FF (2.0 μg ml^{-1} FF) in (a) acidic-ethanol and (b) alkaline-ethanol media.

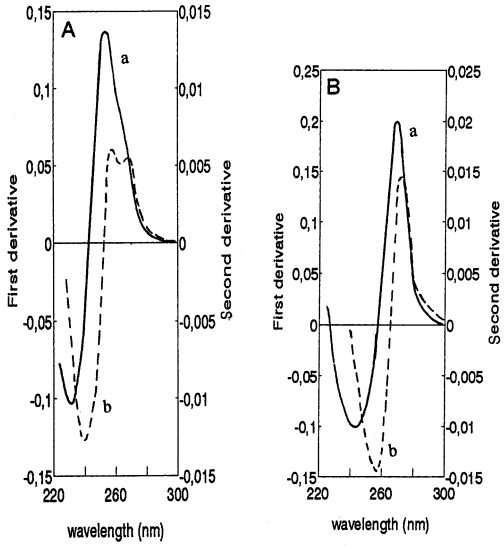


Fig. 6. (a) First- and (b) second-derivative spectra of acridone derivative of FF (4.0 μg ml^{-1} FF) in (A) acidic-ethanol and (B) alkaline-ethanol media.

metric peak heights (measured for the prepared acridone) were obtained for both the 'fresh' and 'stored' FF solution. No additional peaks were obtained in the 'stored' solution and this indicates good solution stability.

The stability of the acridone derivative was examined in various solutions used in the three analytical techniques. The investigation revealed that the voltammetric, fluorimetric and spectrophotometric measurements show no variations up to 24 h.

3.5. Calibration graphs

Table 1 represents the analytical data for the three procedures (voltammetry, spectrofluorimetry and spectrophotometry). These include linear regression equations, concentration ranges, correlation coefficients (r) and standard deviations of the intercept (S_a) and slope (S_b).

In the voltammetric method, the peak current observed at -0.90 V was found to be proportional to the FF–acridone derivative concentration over the range examined (8–60 ng ml^{-1}), under the optimised conditions of a preconcentration potential of -0.50 V for 60 s, a scan rate of 10 mV s^{-1} and pulse amplitude of -100 mV.

Concerning fluorimetric and spectrophotometric analyses, the fluorescence emission intensity at 450 nm and the derivative values (D_1 and D_2) at the selected wavelengths, respectively, were found to be linearly correlated to the concentration of acridone derivative of FF over the ranges 2–20 ng ml^{-1} and 0.2–8 μg ml^{-1}, respectively.

3.6. Detection and quantitation limits

According to IUPAC [19], the limit of detection, $LOD = 3s/k$, where s is the standard deviation of replicate determination values under the same conditions as for the sample analysis in the absence of the analyte; k is the sensitivity, namely the slope of the calibration graph. In accordance with the latter formula, the detection limits obtained for the voltammetric, spectrofluorimetric analyses were found to be 1.02 and 0.17 ng ml^{-1}, respectively. The limit of quantitation, LOQ, defined as 10 s $slope^{-1}$, were found to be 3.4 and 0.566 ng ml^{-1} for the voltammetric and spectrofluorimetric measurements, respectively.

3.7. Precision and accuracy

In order to assess the precision, as percentage relative standard deviation (RSD%) and the accuracy, as percentage relative error (E_r%) of the proposed methods, five replicate determinations were carried out on calibration samples. The data shown in Table 2 indicate good accuracy and precision of the proposed procedures for the analysis of FF.

3.8. Interferences

It was shown that the excipients such as starch, lactose and magnesium stearate, which are commonly formulated in capsule dosage form, do not interfere with the proposed methods. The results of determination of FF by the proposed procedures (previously described in Section 2.8) in the presence of the aforementioned ingredients indicate good recovery $\sim$ 99%.

3.9. Ruggedness

Concerning voltammetric analysis, the effect of various analysts (two analysts) on the results for 40 ng ml^{-1} standard sample, was evaluated. The results show good agreement, within 2% (within day assay).

3.10. Robustness

The robustness of the voltammetric assay was evaluated to show the reliability of the analysis with respect to deliberate variations in method parameters. The objective was to identify the method parameters which affect the response (voltammetric peak height) and determine the ranges over which they can be varied, without unduly affecting the method performance characteristics. In this work the factors studied were: accumulation potential, adsorptive time, pulse amplitude, scan rate, pulse duration, drop size and the reaction heating time. Section 3.1 deals with a part of this study. Table 3 shows the ranges over which the previous parameters were varied in the robustness study. The method was assessed using prepared acridone derivative of FF of 40 ng ml^{-1}.

3.11. Pharmaceutical applications

The different proposed methods were applied to the determination of FF in pure form and in

Table 2
Precision and accuracy for the determination of flufenamic acid by the proposed methods

Method	Nominal value	Found ± S.D.[a]	R.S.D. (%)[b]	E_r(%)[c]
Voltammetry	40 ng ml^{-1}	40.13 ± 0.66	1.64	0.33
Spectrofluorimetry	20 ng ml^{-1}	20.13 ± 0.14	0.70	0.65
	8 ng ml^{-1}	7.94 ± 0.10	1.26	0.75
Spectrophotometry				
Acidic-ethanol				
D_1 (257–235 nm)	4 μg ml^{-1}	4.03 ± 0.05	1.24	0.75
D_2 (258–240 nm)	4 μg ml^{-1}	4.06 ± 0.05	1.23	1.50
Alkaline-ethanol				
D_1 (268–243 nm)	4 μg ml^{-1}	4.07 ± 0.07	1.72	1.80
D_2 (270–258 nm)	4 μg ml^{-1}	3.92 ± 0.08	2.0	2.0

[a] Mean ± standard deviation for five determinations.
[b] Percentage relative standard deviation.
[c] Percentage relative error.

Table 3
Ranges of method parameters evaluated in method robustness study

Parameter[a]	Method level	Low level	% Difference[b]	High level	% Difference[b]
Pulse amplitude (mV)	100	98	2	–	–
Pulse duration (ms)	30	–	–	32	4
Drop size (a.u)	9	8	40	–	–
Accumulation potential (V)	−0.50	−0.49	0.01	−0.51	0.02
Accumulation time (s)	60	58	3.5	62	3.4
Scan rate (mV s^{-1})	10	5	2.9	16.6	5.9
Reaction heating time (min)	15	12	0.02	18	0.03

[a] The studied parameter is varied whilst the others are kept at the method level.
[b] As calculated with reference to the response obtained at the method level.

Table 4
Assay results for flufenamic acid in capsules using different methods

Mean[a] (±S.D.)	100.15 (±0.52) Method	Spectroflourimetry	Spectrophotometry	100.54 (±0.56)	Alkaline-ethanol	101.16 (±0.59)
	Voltammetry	Spectrofluorimetry	Spectrophotometry			
			Acidic-ethanol		Alkaline-ethanol	
			D_1	D_2	D_1	D_2
Mean[a] (±S.D.)	100.15 (±0.52)	99.49 (±0.80)	100.65 (±0.29)	100.54 (±0.56)	101.05 (±0.67)	101.16 (±0.59)
t (2.31)[b]		1.546	1.887	1.142	2.370	2.872
F (6.39)[b]		2.37	3.33	1.16	1.66	1.29

[a] Refers to the average of five experiments.
[b] Values in parenthesis are the theoretical values at $P = 0.05$.

capsule dosage form. The recoveries were calculated with reference to the calibration graphs (Table 1). As can be seen from the results shown in Table 4, the methods give satisfactory recovery data with no significant differences between the declared and experimental data. The standard deviations for the assays results show good precision.

In comparing the results obtained by the three methods, the t- and F-test were applied. There were no significant differences between the calculated and theoretical values at $P = 0.05$, demonstrating the high accuracy and precision of the three proposed methods. This suggested that the three methods are equally applicable.

4. Conclusion

Well adopted procedures for FF measurement using different analytical methods (voltammetry, spectrofluorimetry and spectrophotometry) were described. The voltammetric and spectrofluorimetric methods proved good sensitivity. Although the conventional spectrophotometric method measures higher concentration ranges, it is a simple and rapid tool. The proposed methods are accurate and precise and can be applied to the quality control analysis of FF in pharmaceutical formulations.

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