



Use of Cerium(IV) in Potentiometric Titration of Norfloxacin in Pharmaceutical Preparations

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An accurate potentiometric titration is proposed for the determination of norfloxacin (NRF) in pure drug and in its dosage forms. This method was based on the oxidation reaction of norfloxacin with cerium(IV) in 0.3 M HCl. The reaction was found to be quantitative with stoichiometry 1:4 (norfloxacin: Ce⁴⁺) and the methods are applicable over the range 20-1000 $\mu\text{g mL}^{-1}$ (0.063-3.13 mM). The limits of quantifying was about 20 $\mu\text{g mL}^{-1}$ (0.063 mM). The relative standard deviation did not exceed of $\pm 5.6\%$ and $\pm 4.8\%$ using potentiometric and differential Potentiometric titrations respectively. There for the proposed methods can be used for routine determination of norfloxacin in pharmaceutical formulations with high accurate. The proposed method was successfully applied to the determination of norfloxacin in pharmaceutical preparations and the results have been statistically compared with the spectrophotometric methods.

Key Words: Norfloxacin, Potentiometric titration, Cerium(IV), Redox reaction, Dosage forms.

INTRODUCTION

Norfloxacin [NFLX, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid] is a synthetic, broad-spectrum antibacterial agent which exhibits high antimicrobial activity *in vitro* against a wide variety of Gram-negative and Gram-positive bacteria, including the gentamicin-resistant *Pseudomonas aeruginosa* and the β -lactamase positive *Neisseria gonorrhoeae*¹.

Various analytical techniques have been applied for the determination of norfloxacin such as kinetic spectrophotometric method, based on the oxidation of norfloxacin with alkaline potassium permanganate², atomic absorption spectrometric³, high-performance liquid chromatography⁴⁻¹², spectrofluorimetry^{3,13,14}, voltammetry¹⁵, polarography¹⁶, square-wave adsorptive voltammetry on a glassy carbon electrode¹⁷, spectrophotometric methods^{18,19}.

Norfloxacin, was titrated in glacial acetic acid with perchloric acid, the detection of the end point was accomplished potentiometrically. Conductimetric titration method for ofloxacin, norfloxacin and nalidixic acid based on the use of NaOH, AgNO₃ or tetrabutylammonium hydroxide¹⁶. Using conductometric titration, the studied drugs could be evaluated in 50 % (v/v) acetone in the range 5.0-65, 4.0-48, 5.0-56 and 6.0-72 $\mu\text{g mL}^{-1}$ of norfloxacin, ciprofloxacin, ofloxacin and enrofloxacin, respectively. The optimizations of various experimental conditions were described. The results obtained

showed good recoveries of 99.15 ± 1.15 , 99.30 ± 1.40 , 99.60 ± 1.50 and $99.00 \pm 1.25\%$ with relative standard deviations of 0.81, 1.06, 0.97 and 0.69 % for norfloxacin, ciprofloxacin, ofloxacin and enrofloxacin²⁰.

Chemiluminescence mechanisms between norfloxacin and cerium(IV) in an acidic medium were studied. Chemiluminescence spectra of the present system were recorded observing three maximum emissions at about 475, 550 and 620 nm, respectively. The results indicate that the chemiluminescence peaks located at 475 nm and 620 nm can be ascribed to the emission of a single oxygen, while the chemiluminescence emission at 550 nm occurred in course of the reaction between acidic cerium(IV) and the phenolic intermediate. Under optimum conditions, the chemiluminescence intensity was linear with the concentration of norfloxacin over the range of 2.0×10^{-8} - 1.0×10^{-5} g mL⁻¹ and the detection limit of 1.0×10^{-8} g mL⁻¹ (S/N = 3)²¹.

Differential electrolytic potentiometric titration was developed for the determination of ciprofloxacin. The work is based on the fast complexation reaction between iron(III) and ciprofloxacin in a ratio of 1:3, respectively, in sulfuric acid media of 0.09 mol dm⁻³. Among the electrodes tested silver amalgam electrodes were found to be a suitable indicating system²².

The present paper, describes the applicability of potentiometric titrations (EP) and differential potentiometric titrations (DEP) for the determination of norfloxacin by titrating it with

cerium(IV) in hydrochloride acid medium using combined platinum electrode. The proposed method offers many advantages such as sensitivity, simplicity and rapidity. It has also been successfully applied for the determination of norfloxacin in pure and pharmaceutical forms and this paper provides a full discussion of the interaction mechanism.

EXPERIMENTAL

Norfloxacin standard was supplied from Andromaco S.A. (Madrid, Spain). All reagents were analytical grade were purchased from Merck. Stock standard $2000.0 \text{ mg mL}^{-1}$ ($6.2638 \times 10^{-3} \text{ M}$) solutions were prepared by dissolving accurately measured amounts of norfloxacin in 0.02 M NaOH solution. During the experiments, this solution was found to be stable for several weeks if kept in the dark and at room temperature. Working standards were prepared daily from the stock solution dilutions. All solutions and reagents were prepared with double-distilled deionized water.

Standard cerium (IV) sulfate 0.01 M was prepared from cerium sulfate which was dissolved in 0.08 M sulfuric acid. The solution was stirred, filtered then diluted to 1 L . The solution was diluted appropriately before use. A automatic potentiometric titration AT 510, KEM combined platinum electrode, all measurements were done at room temperature $25 \pm 2 \text{ }^\circ\text{C}$.

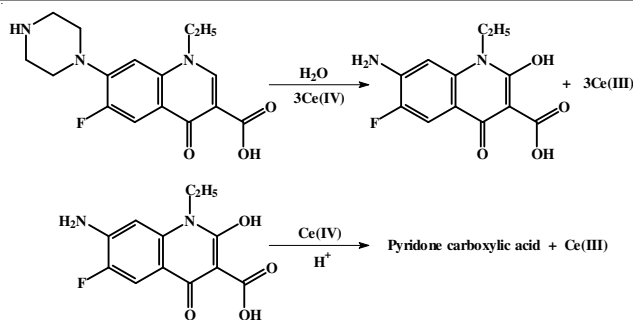
Sample preparation: Twenty tablets were weighed and finely powdered of (noroxacine, Razi labs, norflox, Alshahba labs and uriflox, EL Saad Pharma, Aleppo-Syria) to contain 400 mg of norfloxacin. A quantity equivalent 400 mg of norfloxacin was weighed and dissolved it in 10 mL of 0.02 M NaOH solution with shaken for 5 min . Each of those solutions was filtered through an ordinary filter-paper, washed with the same water solution several times. The filtrate plus washings were diluted to the mark in a 100 mL calibrated flask of the same solution.

Analytical procedure: A 2 mL of norfloxacin standard solution containing $20, 40, 50, 80, 100, 150, 200, 300, 400, 500, 800, 1000 \text{ } \mu\text{g mL}^{-1}$ ($0.063\text{--}3.13 \text{ mM}$) was transferred to the titration cell. Then, it was diluted to about 50 mL with 0.3 M hydrochloric acid solution. The platinum electrode was immersed into the sample solution. The titration performed by using (0.002 or 0.01 M) cerium(VI) solution from 10 mL micro burette, graduated at 0.02 mL slow intervals and constant stirring of the reactants was continued with an electromagnetic stirrer throughout the course of titration.

RESULTS AND DISCUSSION

Chemical system and optimization: The method is based on the oxidation of norfloxacin with cerium(IV) in 0.3 M hydrochloric acid media through the following reaction (**Scheme-I**).

If potentiometric $\{E = f(V)\}$ and differential potentiometric titration $\{dE/dv = f(v)\}$ is applied to follow the titration of norfloxacin with cerium(IV) in acid solution, a differential curve will be obtained and used to locate the end-point. The smoothness, the sharpness and the symmetry of the differential curve depend on the applying conditions, like the type of electrodes, acidic medium, the concentration of acid solution and temperature of the solution. To investigate the conditions, several titrations were performed using platinum electrodes



Scheme-I. Chemical oxidation of Norfloxacin with cerium (IV) at PtE in 0.3 M HCl

as an indicating system for this type of titrations. It was found that the differential curves are sharp, smooth and symmetric indicating the normal behaviour of platinum electrodes. These electrodes were found to be suitable for this type of oxidation-reduction titration and they were employed in this work. Other parameters that affect the shape of the differential curve, the sulfuric acid, hydrochloric acid, phosphoric acid, nitric acid and acetic acid were found to have a significant effect on the shape of the differential curve as shown in Fig. 1. The hydrochloric acid solution was used as an optimum supporting electrolyte.

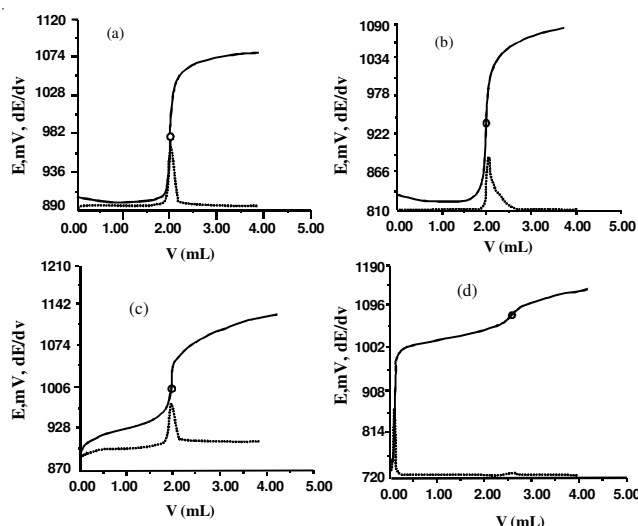


Fig. 1. Curves of $E = f(V)$ and $dE/dv = f(v)$ of (0.5 mL of 0.01 M) norfloxacin with 0.01 M of cerium(IV) in acid solution, (a) hydrochloric acid, (b) nitric acid, (c) sulfuric acid, (d) acetic acid

The concentrations of hydrochloric acid solution and the concentration of the analyte, were also investigated. Changing the concentration of hydrochloric acid solution from 0.10 M to 0.50 M was found to have a significant effect on the shape of the differential curve as shown in Fig. 2. However, a smooth titration curve similar to the one shown in Fig. 2 curves c and d was obtained in $0.30\text{--}0.4 \text{ M}$ hydrochloric acid solution and was applied in all of the titrations.

Titration were performed using different concentrations of norfloxacin to examine the response of the applied electrodes and also to detect the lowest concentration that can be determined. The results of those titrations are shown in Fig. 3 and the $E = f(V)$ and $dE/dv = f(v)$ curves can be easily used to locate the end-points. Concentrations of $20\text{--}1000 \text{ } \mu\text{g mL}^{-1}$ of

TABLE-1
EVALUATION OF ACCURACY AND PRECISION OF THE PROPOSED METHOD FOR DETERMINATION OF NORFLOXACIN BY POTENTIOMETRIC TITRATION (REFERENCE ELECTRODE Ag/AgCl)

Concentration of Ce(IV), 0.002 M							
E = f(V)				dE/dv = f(v)			
C _{Nfx} taken (µg mL ⁻¹)	C _{Nfx} found (µg mL ⁻¹)	\bar{X}	Confidence limits $\bar{X} \pm \frac{SD}{\sqrt{n}}t$, (µg mL ⁻¹)	RSD (%)	C _{Nfx} found \bar{X} (µg mL ⁻¹)	Confidence limits $\bar{X} \pm \frac{SD}{\sqrt{n}}t$, (µg mL ⁻¹)	RSD (%)
20.00	21.25		21.25 ± 1.477	5.6	21.00	21.00 ± 1.251	4.8
40.00	40.30		40.30 ± 2.201	4.4	40.20	40.20 ± 2.096	4.2
50.00	50.00		50.00 ± 2.359	3.8	50.00	50.00 ± 2.235	3.6
80.00	80.56		80.56 ± 3.000	3.0	80.33	80.33 ± 2.792	2.8
100.0	100.8		100.8 ± 3.35	2.5	100.2	100.2 ± 2.99	2.4
150.0	151.7		151.7 ± 4.14	2.2	150.9	150.9 ± 3.93	2.1
200.0	202.0		202.0 ± 5.02	2.0	200.0	200.0 ± 4.47	1.8
300.0	305.2		305.2 ± 5.68	1.5	302.0	302.0 ± 4.87	1.3
400.0	401.5		401.5 ± 5.68	1.2	400.6	400.6 ± 4.97	1.0
Concentration of Ce(IV), 0.01 M							
400.0	402.0		402.0 ± 4.24	0.85	400.0	400.0 ± 3.48	0.77
500.0	506.0		506.0 ± 4.77	0.76	504.0	504.0 ± 4.25	0.68
800.0	800.0		808.0 ± 6.52	0.65	805.0	805.0 ± 5.50	0.55
1000	1015		1015 ± 7.56	0.60	1010	1010 ± 6.27	0.50

*n = 5, t = 2.776

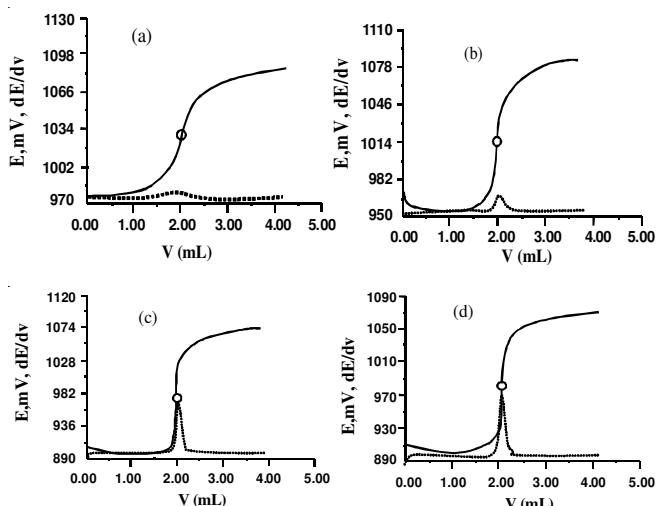


Fig. 2. Curves of E = f(V) and dE/dv = f(v) of (0.5 mL of 0.01M) norfloxacin with 0.01 M of cerium(IV) in concentration of hydrochloric acid solution, (a) 0.1 M, (b) 0.2 M, (C) 0.3 M, (d) 0.4 M

norfloxacin can be titrated with cerium(IV) by the E = f(V) and dE/dv = f(v) with good results in the pure norfloxacin its pharmaceutical preparations. Table-1 indicates the successful applicability of this technique. A set of the normal titration curves obtained was shown in Fig. 3. The reaction was found to be quantitative with a stoichiometry of 4:1 (Ce⁴⁺: norfloxacin) for the range studied 20-1000 µg mL⁻¹ (0.063-3.13 mM). The amount of norfloxacin in the aliquot was computed from the relationship:

$$m, \text{mg.L}^{-1} = \frac{N_{\text{Ce}} \cdot V_{\text{Ce}} \cdot M_w \cdot 10^3}{V_{\text{Nor}} \cdot n} \quad (1)$$

where, V = mL; Mw = relative molecular mass of drug, n = 4 number of electrons.

It is evident that comparable titration curves have resulted from the titration of norfloxacin either in pure norfloxacin, (noroxacine, norflox and uriflox contain 400 mg/tablet of norfloxacin) were found to require almost the same volumes

of cerium(IV) to reach the corresponding end-points. This indicates that no interferences from the excipients of the drug formulations. Results for the determination of norfloxacin in pure form and in its pharmaceutical preparations are compared with the results obtained by the spectrophotometric and spectrofluorimetric methods^{18-21,23} in Table-1. The results indicate no significant differences between the two methods with respect to accuracy and precision. Compared with the spectrophotometric method, the proposed method is simple and requires small amounts of drug.

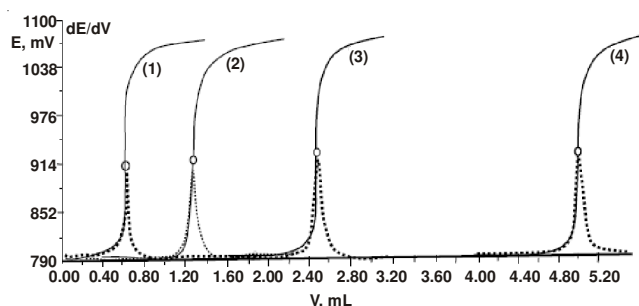


Fig. 3. Curves of E = f(V) and dE/dv = f(v) of 2mL norfloxacin with concentration of (1) 50 mg L⁻¹, (2) 100 mg L⁻¹, (3) 200 mg L⁻¹, (5) 400 mg L⁻¹ in acid media 0.3 M of HCl with 0.002 M of cerium (IV)

Application to pharmaceutical preparations: The proposed methods have been successfully applied for the analysis of norfloxacin in its commercial tablets. Pharmaceutical preparations noroxacine, norflox and uriflox tablets contain 400 mg of norfloxacin determined using E = f(V) and dE/dv = f(v) in 0.3 M hydrochloride acid medium. The results of quantitative analysis for norfloxacin were calculated by the relationship (1), (Table-2).

Conclusion

A novel potentiometric titration {E = f(V) and dE/dv = f(v)} of norfloxacin with cerium(IV) in both pure form and pharmaceutical formulations using hydrochloride acid medium. The reaction was found to be quantitative with stoichiometry

TABLE-2
DETERMINATION OF NORFLOXACIN IN SOME
PHARMACEUTICAL FORMULATIONS USING
POTENTIOMETRIC TITRATION METHOD AT ACID
MEDIUM (REFERENCE ELECTRODE Ag/AgCl)

Commercial name	Contents (mg in tablet)	\bar{X} (mg in tablet)	RSD (%)	Recovery (%)
Noroxacine, tablet Razi labs. (Aleppo-Syria)	400	406	1.2	101.5
Norflox, tablet Alshahba labs. Aleppo-Syria	400	408	1.3	102.0
Uriflox, tablet ELSaad pharma Aleppo-Syria	400	402	1.0	100.5

1:4 (norfloxacin: Ce^{4+}). This titration was quite accurate compared with the conventional ones such as UV and manual titration. The limits of quantifying was about $20 \mu\text{g mL}^{-1}$ (0.063 mM). The proposed method was successfully applied to the determination of norfloxacin in pharmaceutical preparations and the results have been statistically compared with the spectrophotometric methods.

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