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Research Article

POTENTIOMETRIC DETERMINATION OF GATIFLOXACIN & CIPROFLOXACIN IN PHARMACEUTICAL FORMULATIONS

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ABSTRACT

An accurate potentiometric titration is proposed for the determination of gatifloxacin (GTFX) & ciprofloxacin(CPFX) in pure drug and in its dosage forms. This method was based on the oxidation reaction of GTFX & CPFX with cerium(lV) in acid media (HCl & HNO_3). The reactions were found to be quantitative with stiochiometry 1:4 (GTFX: Ce^{4+} & CPFX: Ce^{4+}) in presence 0.25M HNO_3 medium, at temperature 25°C and the methods are applicable over the ranges 0.0125-2.500 mM (0.05–10 mN) and 0.0250-2.500mM (0.10–10 mN). The relative standard deviation did not exceed of ± 5.13% and ± 4.2%. GTFX & CPFX using Potentiometric and differential Potentiometric titrations respectively. There for the proposed methods can be used for routine determination of GTFX & CPFX in pharmaceutical formulations with high accuracy and the results have been statistically compared with the spectrophotometric methods.

Keywords: Gatifloxacin, Ciprofloxacin, Potentiometric titration, Cerium(IV), Redox reaction, Dosage forms.

INTRODUCTION

Ciprofloxacin (CPFX): (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)- 3-quinoline carboxylic acid) and Gatifloxacin (GTFX): (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid (Scheme-1) belongs to the fourth generation of a new class of synthetic antibacterial fluoroquinolone agents[1-3].

Several methods have been reported for the quantitative analysis of the cited drugs, such as spectrophotometric method, based on the oxidation of CPFX with alkaline potassium permanganate in alkaline medium[4], atomic absorption spectrometric, it is based on the oxidation CPFX with iron(III). The excess of iron(III) was extracted into diethyl ether and then the iron(II) in the aqueous layer was determined by AAS[5], high-performance liquid chromatography[6-14], spectrofluorimetry[15-18], voltammetry[19], polarography[20,21]. Square-wave adsorptive voltammetry on a glassy carbon electrode[18], spectrophotometric methods [22-27].

Differential electrolytic potentiometric titration was developed for the determination of CPFX. The work is based on the fast complexation reaction between iron(III) and CPFX in a ratio of 1:3, in sulfuric acid media of 0.09 mol dm^{-3}. Among the electrodes tested silver amalgam electrodes were found to be a suitable indicating system[28].

CPFX was titrated in pyridine with tetrabutyl ammonium hydroxide in methanol: isopropanol, the end point being detected potentiometrically using combined glass electrode. An acid-dye biphasic titrimetric method was described for CPFX. The sample was dissolved in water, mixed with phosphate: citrate buffer of pH 7, chloroform was then added. The mixture was titrated with 0.4 mM bromothymol blue to a light blue colour in the aqueous layer[29].

One titrimetric and two spectrophotometric methods are using for the determination of CPFX in bulk drug and in formulations using cerium (IV) sulphate as the oxidimetric agent and methyl orange and indigo carmine as chromogenic agents. In titrimetry, CPFX is treated with a measured excess of cerium (IV) sulphate in acid medium and the unreacted oxidant is back titrated with standard ammonium ferrous sulphate using ferroin indicator. In spectrophotometric methods, CPFX is treated with a known excess of cerium (IV) sulphate and the residual oxidant is determined by treating with a fixed amount of either methyl orange, and measuring the absorbance at 520 nm or indigo carmine, and measuring the absorbance at 610 nm[21].

Conductometric method were using for the determination of GTFX. The methods depend upon the reaction of ammonium reineckate with the studied drugs to form stable precipitate of ion-pair complexes, which was dissolved in acetone. Using conductometric titration, the studied drugs could be evaluated in 50% (v/v) acetone. The optimizations of various experimental conditions were described. Optimum concentration ranges for the determination of GTFX, 40–440 μg mL^{-1} [27].

An accurate potentiometric titration is proposed for the determination of norfloxacin in pure drug and in its dosage forms. This method was based on the oxidation reaction of norfloxacin with cerium(lV) in 0.3 M HCl. The reaction was found to be quantitative with stiochiometry 1:4 (norfloxacin: Ce^{4+}) and the method are applicable over the range 63-3130 μM. The limits of quantifying were about 63 μM. The relative standard deviation did not exceed of 4.8 % using differential Potentiometric titration [30].

The present paper, describes the applicability of potentiometric titrations and differential potentiometric titrations of CPFX and GTFX by titrating it with cerium(IV) in nitric acid medium using combined platinum electrode. The proposed method offers many advantages such as; sensitivity, simple, rapid. Also, it has been successfully applied for the determination of CPFX and GTFX in pure and pharmaceutical forms, and this paper provides a full discussion of the interaction mechanism.

MATERIALS AND METHODS

Reagents

GTFX & CPFX hydrochloride standard were supplied from Andromaco S.A. (Madrid, Spain). All reagents were analytical grade were purchased from Merck. Stock standard solutions 10^{-2} M were prepared by dissolving accurately measured amounts of GTFX & CPFX hydrochloride in double-distilled deionised water. During the experiments, this solution was found to be stable for several weeks if kept in the dark and at 4C°. Working standards were prepared daily from the stock solution dilutions. All solutions and reagents were prepared with double-distilled deionised water.

Standard cerium (IV) sulfate 0.01M 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.

Instruments and apparatus

A KEM station Automatic potentiometric titration AT 510, KEM Combined platinum electrode, All measurements were done at room temperature 25±2°C.

Sample preparation

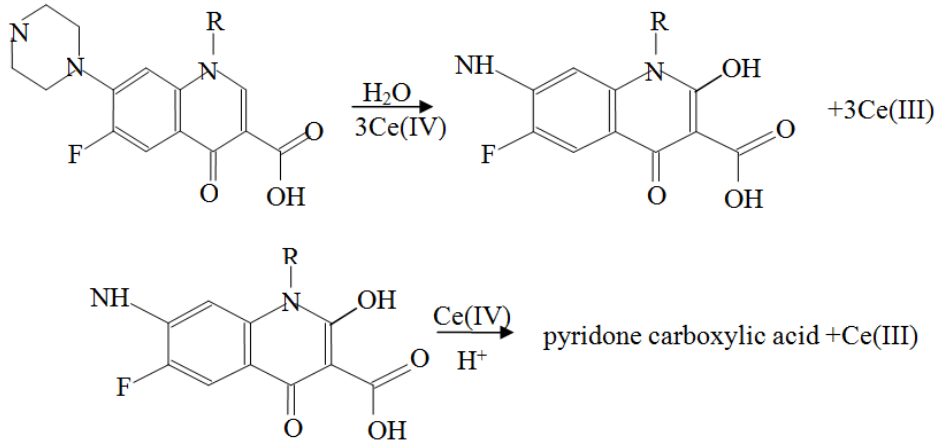
A commercial formulations (ciproxene; Bahri Labs, Damascus-Syria. ciprocin; Racha Labs, Ciproz; Alsaad, Ciprotob; Future, Aleppo-Syria) to contain 250, 500,750 mg of CPFX, and (gatifloxacin; Kanawati, Damascus-Syria, Tequinine; National Company for Pharmaceutical Industry, Gati; Sandy Pharma for Pharmaceutical Industry, Aleppo – Syria) to contain 400 mg of GTFX and Gatymar 0.3%: drop) were used for the analysis of CPFX or GTFX by potentiometric titrations. Eight tablets of pharmaceutical formulations were weighed and grind to a fine powder. A quantity equivalent to one tablet was weighed, dissolved in distilled deionised water with shaking for 5 min. Each of those solutions was filtered through an ordinary filter-paper, washed with the water several times, transferred to 100 mL volumetric flask and diluted to the mark with distilled deionised water. Known volumes (2 mL) of the prepared solution or drop (Gatymar) were dilute to 50 mL with 0.25M HNO_3 or 0.30M of HCl.

Analytical Procedure

A 2.0 mL of CPFX standard solution containing (25.0 – 2000.0µ M) or GTFX standard solution containing (12.5–2000.0µM) was transferred to the titration cell. Then, it was diluted to about 50 mL with hydrochloric acid or nitric acid solution. The platinum electrode was immersed into the sample solution. The titration performed by using (0.001 M) cerium(IV) solution from 10.0 mL micro burette, graduated at 0.02mL slow intervals and constant stirring of the reactants was continued with an electromagnetic stirrer throughout the course of titration. The potential measurements were recorded at a stable reading after each addition. The exact volume of the titrate was read from graph, plotted between the values of E (mV) and volume of the titrant.

RESULTS AND DISCUSSION

The method is based on the oxidation of GTFX & CPFX to the Pyridone carboxylic acid with cerium (IV) in hydrochloric acid and nitric acid media through the following reaction:



Scheme 1: Chemical oxidation of GTFX with cerium (IV) at PtE in 0.25M HNO_3 or 0.30M of HCl.

If potentiometric {E=f(V)} and differential potentiometric titration {dE/dv=f(v) } is applied to follow the titration of GTFX & CPFX 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 as an indicating system for this type of titrations. It was found that the differential curves are sharp, smooth and symmetric indicating the normal behavior of platinum electrode. This electrode was 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 effect of acid type

The effect of the acid media (CH_3COOH, H_2SO_4, HCl & HNO_3) in the calibration curve of GTFX & CPFX with Ce(IV) was studied. It was found that the calibration curve in the presence CH_3COOH isn't clear, in the presence H_2SO_4 was observed of noise in the calibration curve, but in the presence HCl and HNO_3 observed jump clear in the end point of calibration normal as well as the top clear for the calibration of differential. The HCl & HNO_3 were found to have a significant effect on the shape of the differential curve as shown in Fig. 1. The HNO_3 solution was used as an optimum supporting electrolyte.

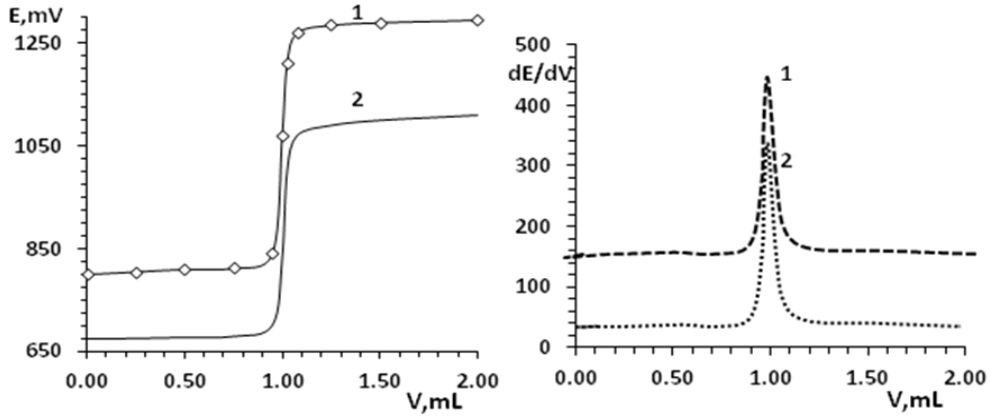


Fig. 1: Curves of E=f (V) and dE/dv=f(v) of (2ml of 5.000x10^{-4}N) *GTFX* with 0.001N of cerium (IV) in acid solution, (1) 0.15M of HNO_3, (2) 0.30M of HCl.

The effect of acid concentration

The effect of the concentration of HNO_3 & HCl solution from 0.05 to 0.50 M were investigated. Changing the concentration of acid solution was found to have a significant effect on the shape of the differential Calibration curve of GTFX & CPFX with Ce(IV) using PtE. The concentration of acid affect was observed clearly in the ratio of the reaction between Ce(IV) and GTFX or CPFX, where the ratio is 1:3 for the concentration of acid between 0.02 -0.10 M and becomes 1:4 at the concentration acid between 0.15 - 0.35 M and becomes 1:5 at the concentration acid ≥0.40 M. Curve as shown in Fig. 2. However, a smooth titration curve similar to the one shown in Fig.2 curves a & b was obtained in 0.20 - 0.3 M HCl and HNO_3 solution and was applied in all of the titrations.

The effect of Temperature

The effect of the temperature from 15 to 45°C were studied. The temperature affect was observed clearly in the ratio of the reaction between Ce(IV) and GTFX or CPFX in 0.25M HNO_3, where the ratio is 1:3 for the temperature between 15 -20°C and becomes 1:4 at temperature 22 -35°C and becomes 1:5 at the temperature >35 °C. Curve as shown in Fig. 3. curves 2 was obtained in 25-30°C was applied in all of the titrations.

Ce(IV) has been used for the quantitative determination of GTFX & CPFX in 0.25M HNO_3. Due to its high oxidation potential and excellent solution stability, this reagent has been utilized to develop a quantitative method for the analysis of GTFX in dosage forms. The method depends on measuring the E=f(v) & dE/dv=f(v). Fig.4.

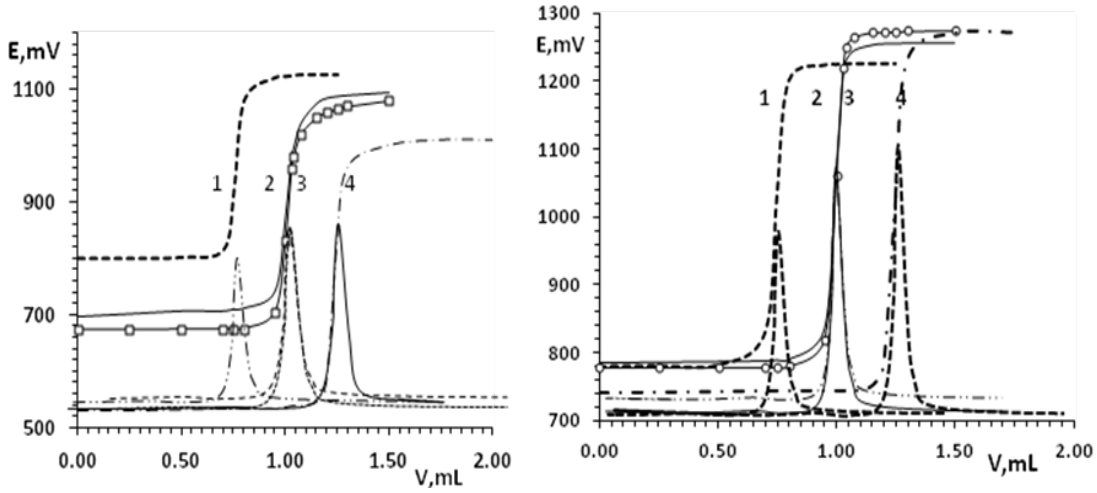


Fig. 2: Curves of E=f(V) and dE/dv=f(v) of (2.0 ml of 5.000x10^{-4}N) *GTFX* with 0.001N of Ce(IV) in concentrations of HCl (a) and HNO_3 (b), 1- 0.05M, 2- 0.15 M, 3- 0.30M, 4- 0.40M.

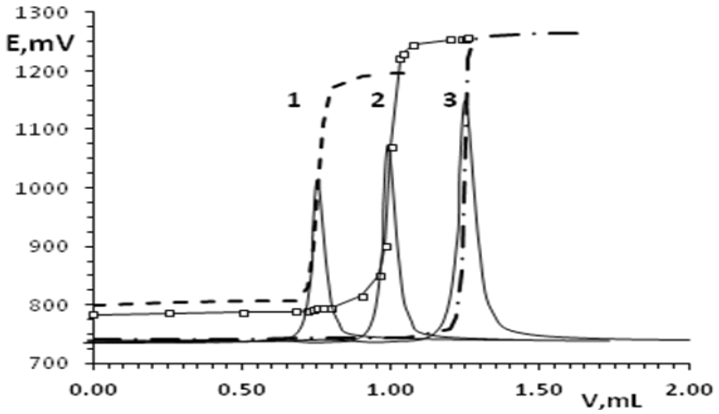


Fig. 3: Curves of E=f(V) and dE/dv=f(v) of (2.0 ml of 5.000x10^{-4}N) *GTFX* with 0.001N of Ce(IV) in 0.25 M HNO_3 in the temperature : 1- 18°C, 2- 30°C,, 3- 45°C.

Titrations were performed using different concentrations of GTFX & CPFX in 0.25M HNO_3, at temperature 25°C to examine the response of the applied electrodes and also to detect the lowest concentration that can be determined. The E=f(v) and dE/dv=f(v) curves can be easily used to locate the end-points. Concentrations of 0.0125-2.500 mM (0.05–10 mN) and 0.0250-2.500mM(0.10–10 mN) of GTFX & CPFX respectively, can be titrated with Ce(IV) by the E=f(v) and dE/dv=f(v) with good results in the pure GTFX & CPFX its pharmaceutical preparations. Tables 1 and 2 indicate the successful applicability of this technique. The reaction was found to be quantitative with a stoichiometry of 4:1 (Ce^{4+}: GTFX or Ce^{4+}: CPFX).

The amount of GTFX & CPFX in the aliquot was computed from the relationship:

$$M_{GTFX\ or\ CPFX} = \frac{N_{Ce}.V_{Ce}}{V_{GTFX\ or\ CPFX}.n}$$

$$m, mg.L^{-1} = \frac{N_{Ce}.V_{Ce}.M_w.10^3}{V_{GTFX\ or\ CPFX}.n}$$

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

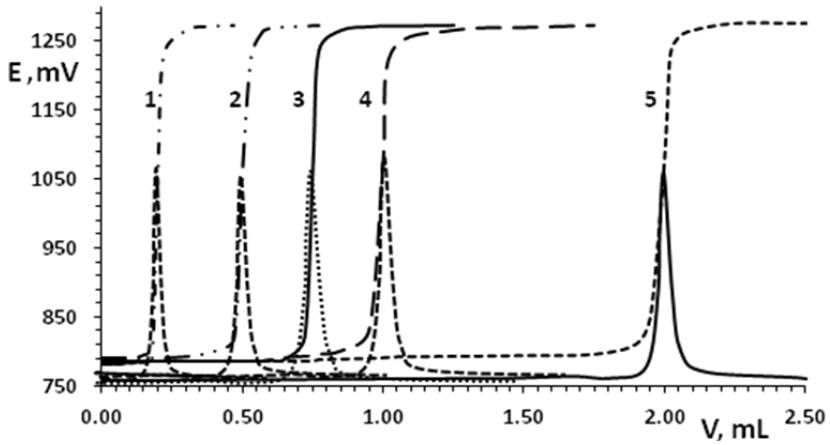


Fig. 4: Curves of E=f(V) and dE/dV=f(V) of 2ml GTF with concentration of (1) 1.250×10^{-4}N, (2) 2.504×10^{-4}N, (3) 3.750x10^{-4} N, (4) 5.000x10^{-4}N, (5)1.000×10^{-3}N,.in 0.25M of HNO_3 with 0.001M of Ce(IV)

Table 1: Evaluation of accuracy and precision of the proposed method for determination of GTFX in 0.25m hno_3, at temperature 25^{o}c by potentiometric titration (*reference electrode* Ag/AgCl).

Concentration of Ce(IV), 0.001 M								
	E=f(V)				dE/dv=f(v)			
C_{GTFX} taken, x10^5, M	$C_{GTFX.}$ found, $\overline{X}^*$ x10^5, M	$C_{GTFX.}$ found, $\overline{X}^*$ x10^5, N	Confidence limits ($\overline{X} \pm \frac{SD}{\sqrt{n}}$ t) x10^{-5},N	RSD %	$C_{GTFX.}$ found, $\overline{X}^*$ x10^5, M	$C_{GTFX.}$ found, $\overline{X}^*$ x10^5, N	Confidence limits ($\overline{X} \pm \frac{SD}{\sqrt{n}}$ t) x10^{-5},N	RSD %
1.250	1.285	5.140	5.140 ± 0.370	5.80	1.253	5.012	5.012 ± 0.319	5.13
2.500	2.550	10.20	10.20 ± 0.583	4.60	2.543	10.17	10.17 ± 0.436	3.45
3.125	3.144	12.58	12.58 ± 0.593	3.80	3.135	12.54	12.54 ± 0.420	2.70
6.250	6.280	25.12	25.12 ± 1.029	3.30	6.260	25.04	25.04 ± 0.808	2.60
12.50	12.58	50.32	50.32 ± 1.749	2.80	12.54	50.16	50.16 ± 1.432	2.30
25.00	24.95	99.80	99.80 ± 3.283	2.65	25.25	101.00	101.00 ± 2.633	2.10
50.00	51.20	204.8	204.8 ± 6.255	2.46	49.96	199.84	199.84 ± 4.590	1.85
100.0	102.0	408.0	408.0 ± 11.14	2.20	101.1	404.4	404.4 ± 7.732	1.54
200.0	202.5	810.0	810.0 ± 18.60	1.85	202.4	809.6	809.6 ± 12.56	1.25
250.0	252.5	1010	1010 ± 20.06	1.60	251.0	1004.0	1004.0 ± 12.46	1.00

* n=5, t=2.776

Table 2: Evaluation of accuracy and precision of the proposed method for determination of CPFX in 0.25m hno_3, at temperature 25^{o}C by potentiometric titration (*reference electrode* Ag/AgCl).

Concentration of Ce(IV), 0.001 M								
	E=f(V)				dE/dv=f(v)			
$C_{CPFX.}$taken, x10^5, M	$C_{CPFX.}$ found, $\overline{X}^*$ x10^5, M	$C_{CPFX.}$ found, $\overline{X}^*$ x10^5, N	Confidence limits ($\overline{X} \pm \frac{SD}{\sqrt{n}}$ t) x10^{-5},N	RSD %	$C_{CPFX..}$ found, $\overline{X}^*$ x10^5, M	$C_{CPFX.}$ found, $\overline{X}^*$ x10^5, N	Confidence limits ($\overline{X} \pm \frac{SD}{\sqrt{n}}$ t) x10^{-5},N	RSD %
2.500	2.600	10.40	10.40 ± 0.697	5.40	2.565	10.26	10.26 ± 0.535	4.20
3.125	3.112	12.45	12.45 ± 0.696	4.50	3.130	12.52	12.52 ± 0.566	3.64
6.250	6.280	25.12	25.12 ± 1.345	4.30	6.250	25.00	25.00 ± 0.931	3.00
12.50	12.58	50.32	50.32 ± 2.124	3.40	12.56	50.24	50.24 ± 1.746	2.80
25.00	24.95	99.80	99.80 ± 3.965	3.20	25.15	100.60	100.60 ± 2.748	2.20
50.00	51.20	204.8	204.8 ± 6.916	2.72	51.00	204.0	204.0 ± 4.863	1.92
100.0	102.0	408.0	408.0 ± 12.16	2.40	100.5	402.0	402.0 ± 8.734	1.75
200.0	202.5	810.0	810.0 ± 17.60	1.75	201.0	804.0	804.0 ± 14.37	1.44
250.0	252.5	1010	1010 ± 17.81	1.42	250.0	1000.0	1000.0 ± 14.90	1.20

* n=5, t=2.776

It is evident that comparable titration curves have resulted from the titration of GTFX & CPFX in 0.25M HNO_3, at temperature 25°C either in pure, A commercial formulations (ciproxene; ciprocin; Ciproz; Ciprotob;) to contain 250, 500,750 mg of ciprofloxacin, and (gatifloxacin; Tequinine; Gati) to contain 400 mg of gatifloxacin. and Gatymar 0.3%: drop) 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 GTFX & CPFX in pure form and in its pharmaceutical preparations are compared with the results obtained by the spectrophotometric and spectrofluorimetric methods[31,32] in Table 3. 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.

Application to pharmaceutical preparations

The proposed methods have been successfully applied for the analysis of GTFX & CPFX, in its commercial tablets and droop. Pharmaceutical preparations (ciproxene; ciprocin; Ciproz; Ciprotob;) to contain 250, 500,750 mg of ciprofloxacin, and (gatifloxacin; Tequinine; Gati) to contain 400 mg of gatifloxacin. and Gatymar 0.3%: drop) determined using E=f(v) and dE/dv=f(v) using 0.25M HNO_3 medium, at temperature 25°C. The results of quantitative analysis for GTFX & CPFX were calculated by the relationship(1), see Tables3&4.

CONCLUSION

A novel potentiometric titration{ E=f(V) and dE/dv=f(v)} of GTFX & CPFX, with cerium(IV) in both pure form and pharmaceutical formulations using 0.25M HNO_3 medium, at temperature 25°C The reaction was found to be quantitative with stiochiometry 1:4 (GTFX: Ce^{4+} or CPFX: Ce^{4+}).This titration was quite accurate compared with the conventional ones such as UV and manual titration. The limits of quantifying were about 0.0125 mM or 0.050 mN, 0.025 mM or 0.100 mN with RSD% ±5.13 and ±4.2 respectively. The proposed method was successfully applied to the determination of GTFX & CPFX in pharmaceutical preparations and the results have been statistically compared with the spectrophotometric methods.

Table 3: Determination of ciprofloxacin in some pharmaceutical formulations using potentiometric titration method in 0.25m HNO_3 medium, at temperature 25°C (reference electrode Ag/AgCl)

Commercial name	Contents, mg in tablet	$\overline{X}$, mg in tablet	RSD%	Recovery %
Ciprocin,Tablet Racha Labs. (Aleppo – Syria)	500	507	2.00	101.4
Ciproxene,Tablet Bahri Labs. Dammascus – Syria	500	514	2.10	102.8
Ciprotob;	750	765	1.86	102.0
Future, Aleppo-Syria	500	518	2.30	103.6
	250	254	3.00	101.6

Table 4: Determination of ciprofloxacin and ceprofloxacin in some pharmaceutical formulations using potentiometric titration method in 0.25m HNO_3 medium, at temperature 25°C (reference electrode Ag/AgCl)

Commercial name	Contents,mg in tablet	$\overline{X}$, mg in tablet	RSD%	Recovery %
Gatifloxacin,Tablet Kanawati Labs. Dammascus– Syria	400	408	2.20	102.0
Tequinine, Tablet National Company for Pharmaceutical Industry, Aleppo – Syria	400	412	1.90	103.0
Gati, Tablet Sandy Pharma for Pharmaceutical Industry, Aleppo – Syria	400	404	2.35	101.0
Gatymar, drop Delta for Medicament, Aleppo – Syria	0.3%	0.31%	2.00	103.3

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