

NEW ION SELECTIVE ELECTRODE FOR POTENTIOMETRIC DETERMINATION OF GATIFLOXACIN IN PURE FORM AND PHARMACEUTICAL FORMULATIONS

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ABSTRACT

A new type of ion-selective electrode for the determination of gatifloxacin (GTFX) is presented. Ion selective coated wire sensors have been constructed from the incorporation of GTFX and tetraphenyl borate (TPB) with the ion-pairing agents (IP), plasticised polyvinyl chloride (PVC) and bis(2-ethylhexyl) phthalate (DOP) or dibutyl phthalate (DBP). The two sensors show nearly Nernstian response over the concentration range 1.0×10^{-5} – 1.0×10^{-2} mol L⁻¹ at 25° C over the pH range 2–6 with slopes of 59.12 ± 0.08 mV and 51.50 ± 0.14 mV decade⁻¹ for (GTFX-TPB-DBP) and (GTFX-TPB-DOP) coated wire sensors. The electrodes exhibit a fast dynamic response of 5.0 and 10 s for a period of 15 days for (GTFX-TPB-DBP) and (GTFX-TPB-DOP) coated wire sensors, respectively. The sensors exhibit good selectivity for GTFX with respect to some inorganic compounds. The sensor served as an end-point detector in ion-pair surfactant potentiometric titrations using TPB as titrant. The method is accurate and precise as indicated by the mean recoveries 99.00% with RSD less than 1.6% for (GTFX-TPB-DBP) or (GTFX-TPB-DOP) coated wire sensors. The proposed method was successfully applied for the determination of GTFX in pure form and its pharmaceutical formulations.

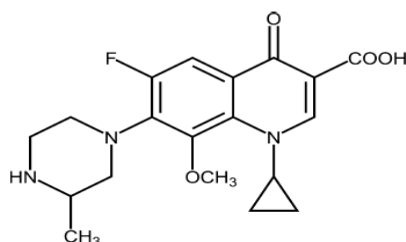
Keywords: Gatifloxacin; Ion-selective electrodes; potentiometric membrane sensor.

INTRODUCTION

Gatifloxacin (GTFX) is a fourth-generation synthetic broad spectrum 8-methoxy fluoroquinolone antibacterial drug derivative. It is (1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methylpiperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid) (Scheme 1) offer several advantages over previous generation antibiotics. It has enhanced in vitro activity against clinically important pathogens and resistant strains (especially penicillin-resistant *Streptococcus pneumoniae*), with better pharmacokinetics [1,2].

GTFX is prescribed for the treatment of acute bacterial exacerbation of chronic bronchitis, acute sinusitis, community acquired pneumonia, uncomplicated urinary tract infections (cystitis) and complicated urinary tract infections [1,2].

Various analytical techniques have been applied for the determination of GTFX, including high-performance liquid chromatography (HPLC) [3–9], spectrophotometry and fluorimetry [10–14], high-performance thin-layer chromatography (HPTLC) [15,16] and electrochemical (polarography, voltammetry and other) [17–24] methods most prevalent to identify different kinds of drugs in pure and pharmaceutical dosage forms.



Scheme 1: Chemical structure of Gatifloxacin.

Ion-selective electrodes (ISEs) are electrochemical transducers that respond selectively, directly, and continuously to the activity of the free ion of interest in solution. They are characterized by low cost, easy fabricate, accuracy, and can be used without previous extraction of samples. Because of these merits, the use of ISEs is increasing day by day in medicinal, environmental, agricultural and industrial fields [25–28]. The aim of this study was to develop and validate simple, selective and sensitive coated wire electrodes for the determination of (GTFX) in pure and dosage forms.

MATERIALS AND METHODS

Apparatus

The electrochemical measurements were carried out with Jenway 3010 pH/mV meter, with Gatifloxacin-tetraphenyl borate (TPB)-poly(vinyl chloride) (PVC) membrane electrode in conjunction with double junction Ag/AgCl electrode was used as external reference electrode, containing 1M potassium chloride in the outer compartment. Glass-calomel combination electrode was used for pH adjustment. All potentiometric measurements were carried out at $25 \pm 1^\circ\text{C}$ with constant magnetic stirring.

Reagents

Pure grade gatifloxacin supplied from Andromaco S.A. (Madrid, Spain), Poly vinyl chloride (PVC) high molecular weight, Sodium tetraphenyl borate (NaTPB) 99%, 1×10^{-2} M aqueous solution, dioctyl phthalate (DOP) 99.0%, Di n- Butyl phthalate (DBP), tetrahydrofuran (THF) 97.0%, hydrochloric acid, sodium hydroxide. All reagents were of analytical grade, Merck (Germany). Double-water was used.

Standard drug solutions

Stock standard solutions 0.1M GTFX ($\text{C}_{19}\text{H}_{22}\text{FN}_3\text{O}_4 \cdot 1\frac{1}{2}\text{H}_2\text{O}$, Mw=402.42) were prepared accurately weighed 4.03g standard sample was dissolved in double-distilled water. During the experiments, this solution was found to be stable for several weeks if kept in the dark and at 4°C . Working solutions ranging from 1×10^{-7} – 1×10^{-2} M were prepared by serial dilution of the stock solution. The solution is stable for at least 1 week if stored in a cool and dark place.

Preparation of gatifloxacin ion-pair and membrane composition

The ion-pair was prepared by mixing 50 mL of 1.0×10^{-2} M GTFX solution and 50 ml of 1.0×10^{-2} M aqueous NaTPB. The resulting precipitates were filtered, washed thoroughly with distilled water and air dried. The membrane was prepared by dissolving 1980–1800 mg of powdered PVC, 1980–1800 mg of the plasticizer (DOP) and 4.0–4.0 mg of the ion-pair (IP) in 5 ml THF, Table 1. The solution was poured into a petri-dish (7 cm in diameter) and covered with a filter paper. The solvent was allowed to evaporate slowly at room temperature. Punched circular membrane was attached to polyethylene tube (8 mm in diameter) in an electrode configuration

according to the procedure[25,26]. A mixture of equal volumes of 1.0×10^{-2} M solution of GTFX and 5×10^{-3} M potassium chloride (KCl) was used as internal reference solution in which Ag/AgCl reference

electrode was dipped. The constructed electrode was pre-conditioned after preparation by soaking for at least 24 h in 1.0×10^{-2} M drug solution and stored in the same solution, Table 1.

Table 1: Composition of GTFX -TPB-PVC Matrix Membrane Sensor

IP%	Amount of IP, g	amount of PVC, g	amount of DOP or DBP, g	Total amount, g
1	0.0040	0.1980	0.1980	0.4000
2	0.0080	0.1960	0.1960	0.4000
4	0.0160	0.1920	0.1920	0.4000
6	0.0240	0.1880	0.1880	0.4000
8	0.0320	0.1840	0.1840	0.4000
10	0.0400	0.1800	0.1800	0.4000

Electrode calibration

25 milliliter aliquots of 1×10^{-7} – 1×10^{-2} M standard solutions of GTFX were transferred into a 50 ml beaker and the membrane electrode in conjunction with Hg/Hg₂Cl₂ reference electrode were immersed in the solution. All potentiometric measurements were performed using the following cell Assembly: Ag–AgCl/KCl (0.005M) + GTFX (0.01M)// GTFX -TPB-PVC membrane//test solution/Hg -Hg₂Cl₂ reference electrode (Al/ membrane/test solution//KCl salt bridge//SCE).

The measured potential was plotted against the logarithm of drug concentration. The electrode was washed with deionised water blotted with tissue paper between measurements.

Standard addition method

The electrode was immersed into sample of 50 mL with unknown concentration and the equilibrium potential of E1 was recorded. Then 0.1 mL of 0.1 M of standard drug solution was added into the testing solution and E2 was recorded. The concentration of the testing sample was calculated from the change of potential ΔE (E2-E1).

Electrode selectivity

Selectivity coefficients $K^{Pot}_{GTFX, J^{z+}}$ of the sensors towards different cations, amino acids and some pharmacologically related compounds were determined by the separate solution method[28] in which the following equation was applied:

$$\log K^{Pot}_{GTFX, J^{z+}} = (E2 - E1)/S + \log [GTFX] - \log [J^{z+}] / z$$

Where, K^{Pot} is the selectivity coefficient, E1 is the sensor potential in 1.0×10^{-3} M GTFX solution. E2 is the electrode potential in 1.0×10^{-3} M solution of the interferent ion J^{z+} and S is the slope of the calibration plot in mV.

Effect of pH

The effect of pH on the potential response of the prepared electrodes was studied using 1×10^{-2} and 1×10^{-3} M GTFX solutions. The pH of this solution was adjusted between 1-8 by using suitable amounts of 0.1 M NaOH or HCl solution. The potential readings corresponding to different pH values were recorded and plotted using the proposed electrode(s). The results showed that, the potential remained constant despite the pH change in the range of 2-6 which indicates the applicability of this electrode(s) in the specified range.

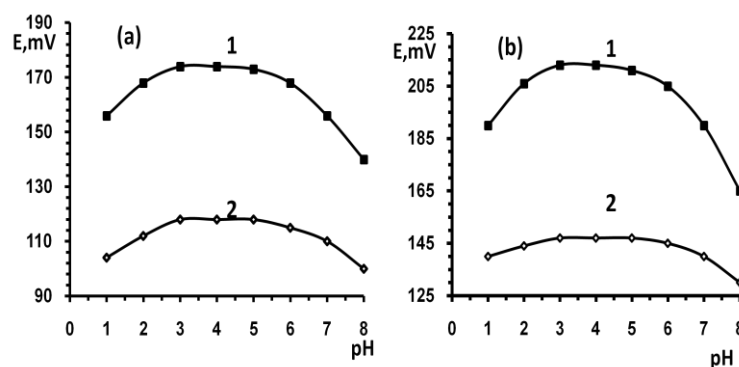


Fig. 1: Effect of pH on the potential response of the GTFX on (a) GTFX TPB-DOP, (b) GTFX-TPB -DBP with GTFX-PVC matrix membrane sensor (1×10^{-2} M, 1×10^{-3} M).

Determination of gatifloxacin in pharmaceutical dosage forms

A commercial formulations (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 Gatyamar 0.30%: drop were used for the analysis of 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 double-distilled water with shaking for 5 min. Each of the 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 double-distilled water. Known volumes (5

mL) of the prepared solution or drop (Gatyamar) were dilute to 50 mL with 0.1M CH₃COOH. Analyzed as described above under electrode calibration and standard addition methods. The results obtained were compared to those obtained with HPLC[6].

Analytical Procedure

A 5.0 mL of GTFX standard solution containing (2×10^{-3} - 10^{-2} M) was transferred to the titration cell. Then, it was diluted to about 50 mL with 0.1M CH₃COOH solution. The membrane electrode in conjunction with Hg/Hg₂Cl₂ reference electrode were immersed into the sample solution. The titration performed by using (10^{-2} M) NaTPB 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 DISCUSSIONS

Calibration graph and statistical data

The measuring range of a potentiometric sensor was the linear part of the calibration graph as shown in Fig. 2. The critical response coated wire sensor electrodes were determined and the results were summarized in Table 2. The Two sensors show nearly Nernstian response over the concentration range 1.0×10^{-7} - 1.0×10^{-2} M of the drug investigated. Calibration graph slopes for sensor electrodes were 59.12 and 51.50 mV decade⁻¹ and standard deviations of 0.52

and 0.41 after six replicate measurements for (GTFX-TPB -DBP) and (GTFX-TPB -DOP) coated wire sensors, respectively. The electrodes exhibited a fast dynamic response of 10 and 20 s for a period of 15 and 12 days for (GTFX-TPB -DBP) and (GTFX-TPB -DOP) coated wire sensors, respectively, without significant change in the electrodes parameters. To examine the effect of pH on the response of the two sensors, the potential was measured at a specific concentrations of GTFX solution (1.0×10^{-2} & 1.0×10^{-3} M) from the pH value of 2.0 up to 8.0 (0.1 M NaOH or 0.1 M HCl solution were employed for the pH adjustment). The results showed that the potential remained constant despite the pH change in the range of 2 – 6, which indicates the applicability of these electrodes in the specified pH range, Fig.1. Between pH 1.0-2.0, the potential of the electrode increased with increase of pH which may be described to extraction of H⁺ ions by membrane. While at pH more than 6.5, the response of the electrode decreased which may be attributed to deposition of GTFX.

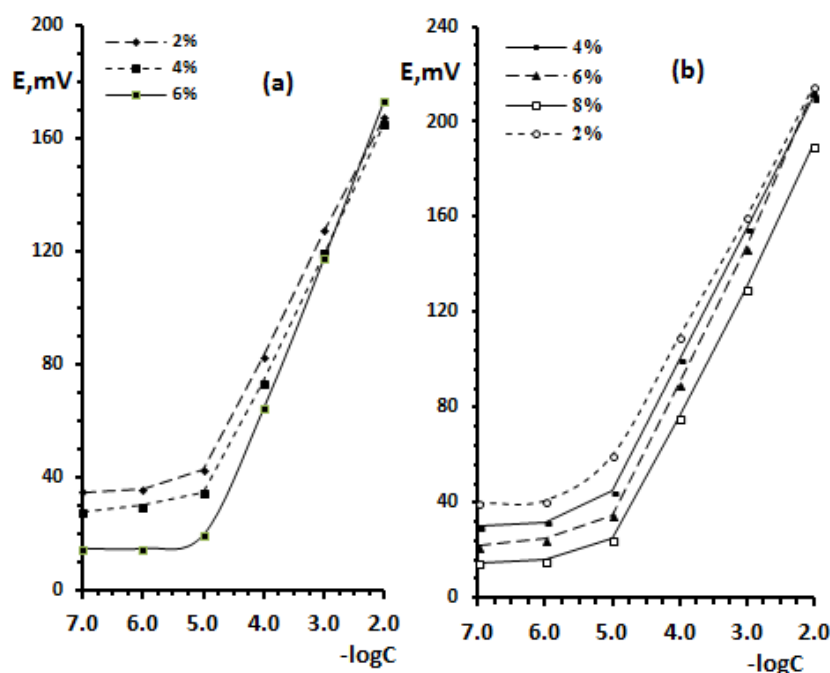


Fig. 2: Effect of IP content on calibration of modified (a) GTFX-DBP and (b) GTFX-TPB-DOP Electrodes (1.0×10^{-7} - 1.0×10^{-2} M).

Table 2: Response characteristics of GTFX-TPB -DBP -PVC matrix membrane sensor and GTFX -TPB-DOP-PVC matrix membrane sensor

Parameter	GTFX-TPB - DBP	GTFX-TPB - DOP
IP%	6%	6%
Slope (mV decade ⁻¹)	59.12±0.08	51.50±0.14
Intercept,	328.1	274.50
Correlation coefficient, (r)	0.9991	0.9976
Linear range (M)	1.0×10^{-5} - 1.0×10^{-2}	1.0×10^{-5} - 1.0×10^{-2}
LOD(3.3SD), M	1.52×10^{-6}	8.25×10^{-6}
LOQ (10SD), M	4.6×10^{-6}	2.5×10^{-5}
Response time for 10^{-3} M GTFX/s	20	10
Life time/day	15	12
Working pH range	2 - 6	2 - 6
Robustness ^a	99.00 ± 1.584	99.00±1.634

^aA small variation in method parameters were carried out as pH of acetate buffer (pH 3.5±1).

Lifetime Study

GTFX electrodes lifetimes were estimated with the calibration curve, periodical test of a standard solution (1.0×10^{-7} - 1.0×10^{-2} M) and calculation of its response slope. For this purpose, two sensors were employed and the calibration graphs were plotted after optimum soaking time of 6 h in 1.0×10^{-3} M GTFX solution. The slopes of calibration curves were 59.12 and 51.50 mV decade⁻¹ at 25°C for

(GTFX-TPB-DBP) and (GTFX-TPB-DOP) coated wire sensors, respectively. The electrodes were continuously soaked on 1.0×10^{-3} M solution of GTFX for about 15 days. The calibration plot slopes decreased slightly to be 50.25 and 41.60 mV decade⁻¹ after 15 and 12 days for (GTFX-TPB-DBP) and (GTFX-TPB-DOP) coated wire sensors, respectively. This reveals that soaking of sensors in the drug solution for a long time has a negative effect on the response of membrane. The same effect appears after working with the sensors for a long time.

Interference effect

The response of the electrode was also examined in the presence of some inorganic compounds ions by Matched potential method (MPM). This method does not depend on the Nicolsky-Eisenman equation. In this method, the potentiometric selectivity coefficient is defined as the activity ratio of primary and interfering ions that give the same potential change under identical conditions. At first, a known activity (a_A') of the primary ion solution is added into a reference solution that contains a fixed activity (a_A) of primary ions, and the corresponding potential change (ΔE) is recorded. Next, a solution of an interfering ion is added to the reference solution until the same potential change (ΔE) is recorded. The change in potential produced at the constant background of the primary ion must be the same in both cases.

$$K_{A,B}^{\text{pot}} = (a_A' - a_A) / a_B$$

Results obtained are given in Table 3 and reasonable selectivity for GTFX was observed in presence of many interferons.

Table 3: Selectivity coefficient for some common cations with GTFX -TPB-DBP-PVC matrix membrane sensor electrode

Interferential	$K_{\text{gati,B}}^{\text{pot}}$
Sodium chloride	8.33×10^{-2}
Potassium chloride	10×10^{-2}
Calcium chloride	4×10^{-2}
Magnesium chloride	5×10^{-2}

Quantification of gatifloxacin

The investigated sensors were found to be useful in the potentiometric determination of GTFX in pure solutions by calibration graph and standard addition method. The results obtained were listed in Fig.3. The results obtained were compared with a reference HPLC[6], as shown in Table 4. Statistical analysis[27] of the results obtained by the proposed and comparison methods using Student's t-test and variance ratio F-test, showed no significant difference between them regarding accuracy and precision, respectively.

Method validation

The linearity, limit of detection, selectivity, precision, accuracy and ruggedness/robustness were the parameters used for the method validation. For linearity and limit of detection as mentioned before, the investigated drug (GTFX) was measured using GTFX -electrodes over the concentration range 1×10^{-5} - 1×10^{-2} M at lower limit of detection 1.52×10^{-6} and 8.25×10^{-6} M for (GTFX-DBP) and (GTFX-DOP) coated wire sensors, respectively. The intraday and interday precision of the method was calculated in terms. The RSD% values of intraday and interday studies for the repeated determination were less than 2% which indicating good precision in Tables 4,5.

The robustness of proposed method was carried out by using acetic acid pH 3.5 ± 0.5 and the percentage recoveries were 99.00 ± 1.584 and 99.00 ± 1.634 for (GTFX-DBP) and (GTFX-DOP) coated wire sensors, respectively.

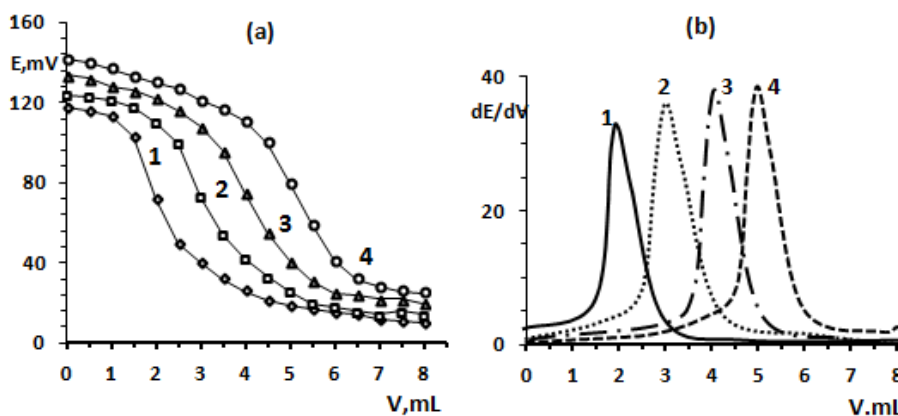


Fig. 3: Potentiometric titration of different concentrations of GTFX (0.01M) (1- 2mL, 2- 3mL, 3- 4mL, 4- 5mL) with 0.01M NaTPB using of GTFX-DBP - PVC matrix membrane sensor electrodes (a) $E=f(V)$, (b) $dE/dV=f(V)$.

Table 4: Evaluation of accuracy and precision of the proposed method for determination of GTFX IN 0.10M CH_3COOH , at temperature 25°C by potentiometric titration using of GTFX-TPB-DOP - PVC matrix membrane sensor electrode (reference electrode Ag/AgCl).

Concentration of TPB, 0.01 M				$dE/dV=f(V)$		
$E=f(V)$				$dE/dV=f(V)$		
C_{GTFX} taken, $\times 10^4$, M	C_{GTFX} found, $\bar{x} \times 10^4$, M	Confidence limits $\frac{SD}{\sqrt{n}}$ $(\bar{x} \pm \frac{SD}{\sqrt{n}} t) \times 10^4$, M	RSD %	C_{GTFX} found, $\bar{x} \times 10^4$, M	Confidence limits $\frac{SD}{\sqrt{n}}$ $(\bar{x} \pm \frac{SD}{\sqrt{n}} t) \times 10^4$, M	RSD %
0.50	0.510	0.510 ± 0.034	5.3	0.500	0.500 ± 0.031	5.0
1.00	1.032	1.032 ± 0.061	4.8	0.997	0.997 ± 0.056	4.5
2.00	2.10	2.10 ± 0.117	4.5	2.03	2.03 ± 0.103	4.1
4.00	3.97	3.97 ± 0.197	4.0	4.06	4.06 ± 0.181	3.6
6.00	6.00	6.00 ± 0.276	3.7	6.13	6.13 ± 0.213	2.8
8.00	8.12	8.12 ± 0.262	2.6	8.00	8.00 ± 0.238	2.4
10.00	10.4	10.4 ± 0.284	2.2	10.32	10.32 ± 0.256	2.0
20.00	21.2	21.2 ± 0.421	1.6	21.00	21.00 ± 0.365	1.4

* $n=5$, $t=2.776$

Table 5: Evaluation of accuracy and precision of the proposed method for determination of GTFX IN 0.10M CH₃COOH, at temperature 25°C by potentiometric titration using of GTFX-TPB- DBP - PVC matrix membrane sensor electrode (reference electrode Ag/AgCl).

Concentration of TPB, 0.01 M						
E=f(V)			dE/dV=f(V)			
C _{GTFX} taken, x10 ⁴ ,M	C _{GTFX} found, $\bar{X}^* \times 10^4, M$	Confidence limits $(\bar{X} \pm \frac{SD}{\sqrt{n}} t) \times 10^4, M$	RSD %	C _{GTFX} found, $\bar{X}^* \times 10^4, M$	Confidence limits $(\bar{X} \pm \frac{SD}{\sqrt{n}} t) \times 10^4, M$	RSD %
0.10	0.110	0.110 ± 0.007	5.3	0.100	0.100 ± 0.006	4.6
0.50	0.497	0.497 ± 0.031	5.0	0.510	0.510 ± 0.028	4.4
1.00	1.00	1.00 ± 0.056	4.5	1.00	1.00 ± 0.052	4.2
2.00	1.98	1.98 ± 0.105	4.3	2.00	2.00 ± 0.092	3.7
4.00	4.08	4.08 ± 0.177	3.5	4.05	4.05 ± 0.131	2.6
6.00	6.12	6.12 ± 0.213	2.8	5.98	5.98 ± 0.156	2.1
8.00	7.97	7.97 ± 0.228	2.3	8.04	8.04 ± 0.178	1.8
10.00	10.5	10.5 ± 0.196	1.5	10.20	10.20 ± 0.152	1.2
20.00	21.0	21.0 ± 0.288	1.1	20.60	20.60 ± 0.256	1.0

* n=5, t=2.776

Table 6: Determination of GTFX in some pharmaceutical preparations using GTFX-TPB-DBP- PVC matrix membrane sensor electrode (reference electrode Ag/AgCl). membrane sensor preparation

Commercial name	Labeled GTFX	$\bar{X} \pm SD,$ mg	Recovery %	F-value ^b	t-value ^b
Gatifloxacin , Tablet Kanawati Labs. Dammascus-Syria	400 mg per tablet	407 ± 4.07	101.75 ± 1.175	2.318	2.6395
Tequinine , Tablet National Company for Pharmaceutical Industry, Aleppo - Syria	400 mg per tablet	408 ± 6.12	102.00 ± 1.53	1.37	2.694
Gati , Tablet Sandy Pharma for Pharmaceutical Industry, Aleppo - Syria	400 mg per tablet	396 ± 6.34	99.00 ± 1.584	1.451	1.325
Gatymar , drop Delta for Medicament, Aleppo - Syria	300mg per100mL	303 ± 4.24	101.0 ± 1.414	1.600	1.396

^a Average of five replicates.^b Tabulated t-value at 95% confidence level is 2.776. Tabulated F-value at 95% confidence level is 6.39.

CONCLUSION

It can be concluded that GTFX - TBP-DBP- PVC membrane sensor offers a viable technique for the direct determination of GTFX in some pharmaceutical preparations. The sensor is simple, rapid, reproducible and exhibits a good selectivity towards the drug in the presence of various pharmaceutical excipients. The sensor can be used as indicator electrode in some potentiometric titrations.

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