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NEW PVC ELECTRODES FOR THE DETERMINATION OF GATIFLOXACIN IN PHARMACEUTICAL FORMULATIONS AND HUMAN FLUIDS BASED ON GATIFLOXACIN-BROMOPHENOL BLUE AS ION-PAIR

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Abstract

A simple, fast and easy potentiometric method for the determination of gatifloxacin in pharmaceutical formulations and human fluids was constructed. Three PVC membranes for gatifloxacin (GAF) were prepared based on the use of ion-pair compound gatifloxacin-bromophenol blue (GTF-BPB) as the ion-association substance with different plasticizers: Tri-ethyl phosphate (TEP), Tris (2-Ethylhexyl)phosphate (TEHP) and Di-butyl phthalate (DBPH). These electrodes gave a Nernstain response equal to 41.76, 49.21 and 57.31mV/decade with linear ranges 5×10^{-6} - 1×10^{-2}, 1×10^{-4} - 1×10^{-2} and 1×10^{-4} - 1×10^{-2} M for membranes that depend on TEP, TEHP and DBPH as plasticizers, respectively. Detection limits were equal 4.5×10^{-6}, 9×10^{-5} and 8.9×10^{-5} M, respectively. pH range was also studied at different concentration of gatifloxacin solutions, equally were studied lifetime and selectivity. Potentiometric methods such as direct, standard addition and multiple standard addition methods were used. The proposed electrode based on DBPH was successfully applied in the determination of gatifloxacin in some pharmaceutical formulations and human fluids.

Key words: PVC membrane, Gatifloxacin, Potentiometric, pharmaceutical formulations, human fluids.

Introduction

gatifloxacin is fluoroquinolone, the fourth generation commonly used in the treatment of infections of the urinary tract, respiratory tract infections, osteomyelitis, gastrointestinal, skin and soft tissue (Pharmacopoeia, 2008). Gatifloxacin is chemically name ($C_{19}H_{22}FN_3O_4$)1-cyclopropyl-6-fluoro- 8-methoxy-7-(3-methylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid. Gatifloxacin is a crystalline powder and is white to pale yellow in colour with molecular weight of 375.39 g/mol. The solubility of the gatifloxacin in water is pH dependent. It has a maximum aqueous solubility of 40-60 mg/mL in the pH range of 2–5. It is slightly soluble in ethanol and water and freely soluble in acetic acid. Gatifloxacin melts at approximately 182-185°C Fig. 1 shown the structure of (GTF) (Sweetman, 2009).

A series of analytical methods have been reported for the determination of gatifloxacin including high performance liquid chromatography (HPLC) (Bera *et al.,* 2014, Aljuffali *et al.,* 2015, Razzaq *et al.,* 2012, Abbas and Rasheed, 2018, Seubert and Saad Rasheed, 2017, Al-Phalahy and Rasheed, 2016, Al-Phalahy *et al.,* 2016, Motwani *et al.,* 2006), potentiometric method (Mandil *et al.,* 2013) liquid chromatographic (Grace *et al.,* 2019, Yaqout Abd Al-Hakeem Hamed and Rasheed, 2020, Karabat *et al.,* 2020, Ashraf Saad Rasheed and Rashid, 2020, Ali and Rasheed, 2020b, Ali and Rasheed, 2020a) and UV–spectrophotometry (Madhuri *et al.,* 2010, Prathap *et al.,* 2011). For the determination of various electroactive drug components in pharmaceutical dosage forms and biological fluids, electrochemical methods have proven sensitive and effective (Hussien *et al.,* 2011). Ion selective electrodes have been commonly used in scientific, environmental and industrial applications because they have excellent advantages, such as: low detection limits, good selectivity, high speed as well as ease of preparation, easy instrumentation, wide dynamic range and low cost (Davies *et al.,* 1973). The main advantages of using Ion selective electrodes are that they are insensitive to colour, viscosity or suspended solids

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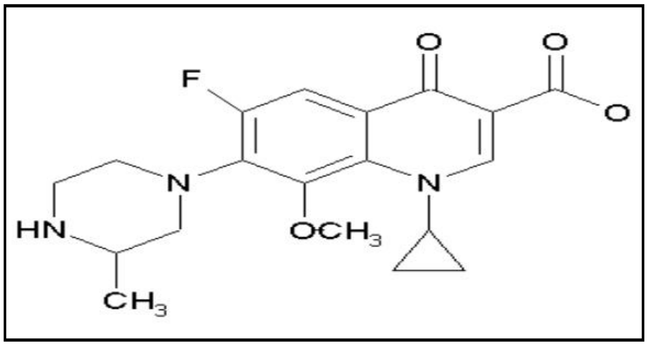

Fig. 1: Structure of Gatifloxacin.

(Shakir, 2016). The purpose of this study was to develop and validate a simple, accurate and economic potentiometric method for quantitative gatifloxacin determination by prepared PVC membrane based on the use of ion-pair Gatifloxacin - Bromophenol blue with different plasticizers

Materials and Methods

Instruments and equipment:

Expandable ion analyzer (Orion Research model EA940) was used in the potentiometry measurements in combination with a reference electrode (metrohm AG 9100 herisau). pH meter (pH professional benchtop model BP3001) was used to measure the pH of the solution and a magnetic stirrer was used to homogeneous of the solution.

Chemicals

Gatifloxacin standard ($C_{19}H_{22}FN_3O_4$) was obtained from the Sigma-Aldrich and the pharmaceutical formulations gatifloxacin (Gate eye drops) was supplied Ajanta pharma limited- India . Bromophenol blue was obtained from Fluka. The following plasticizers: Tri-ethyl phosphate (TEP) ($C_6H_{15}O_4P$), purity (99%), Tris (2-ethyl hexyl) phosphate (TEHP) ($C_{24}H_{51}O_4P$) , purity (97%), Di-butyl phthalate (DBPH) ($C_{16}H_{22}O_4$), purity (99%) were obtained from Fluka. Other chemicals such as Tetrahydrofuran (C_4H_8O; F.W. 72), Polyvinyl chloride CH_2-CHCl) n with high molecular weight, hydrochloric acid (HCl; F.W. 36.45; sp.gr. 1.19; 38% HCl; 12.4M), sodium hydroxide (NaOH; F.W. 40.00 pellets), sodium chloride (NaCl; F.W. 58.45), potassium chloride (KCl; F.W. 74.55), magnesium nitrate hexahydrate (($Mg(NO_3)_2.6H_2O$; F.W. 256.41), (LiCl; F.W. 42.4) , Calcium chloride ($CaCl_2$; F.W. 110.99), zinc chloride ($ZnCl_2$; F.W. 136.286), Ferric(III) chloride hexahydrate ($FeCl_3.6H_2O$; F.W. 270.30), Aluminium chloride (AlCl3; F.W. 133.34) and Chromium (III) Chloride Hexahydrate ($CrCl_3.6H_2O$; F.W. 266.44) were obtained from Fluka AG, (Switzerland). Other chemicals and reagents of analytical grade reagent were obtained from Fluka, BDH and Aldrich companies.

Preparation of standard solution:

All solutions were prepared in doubly distilled deionized water. Stock solutions of 0.01 M of LiCl, NaCl, KCl, $CaCl_2$, $ZnCl_2$, $Mg(NO_3)_2.6H_2O$, $FeCl_3.6H_2O$, $AlCl_3$ and $CrCl_3$.$6H_2O$ were prepared. More diluted solutions were prepared by subsequently dilution of the stock solutions.A standard solution of 0.01 M Gatifloxacin was prepared by dissolving 0.0938g standard and completing the solution up to 25 ml. The other Gatifloxacin standard solutions were prepared by subsequent dilution of the stock solution.

Preparation of ion-pair Compound

The preparation of ion-pair of (GTF-BPB) was performed by mixing 100 ml of 0.01 M solution of Gatifloxacin (GTF) with 100 ml of 0.01 M Bromophenol blue with stirring The resulting precipitate was filtered off and washed with water.

Fabrication of the sensors

As described by Davis *et al.,* (Moody and Thomas, 1980), the method of solidifying the Gatifloxacin into the PVC matrix membrane was developed. A 0.040 g of (GTF-BPB) matrix was mixed with 0.360 g of plasticizer and 0.17 g of PVC powder, then added (5.0 or 6.0) ml of THF with stirring until the formed viscous solution. The solution was poured into a glass casting ring about 30 mm in length and a diameter of 35 mm. It consists of two pieces; the glass cylinder is one of them and the glass plate is the other. The two pieces were pasted together using a viscous mixture (PVC-THF). The top side of the cylinder was covered with filter paper which put a heavyweight (~200 g). The assembly was left 2-3 days to permit graduate solvent evaporation.

Selectivity

Two methods were used in order to determine the selectivity coefficient of the potentiometric electrodes toward various species which are the separate solution method (SSM) (Umezawa *et al.,* 2000) and match potential method (MPM) (Tohda *et al.,* 2001). In the SSM method, the following equation was used:

$$K^{pot}_{A,B} = a_A^{(1 - zA/zB)}\, e^{(EB - EA)\, zA\, F / (R\, T)} \quad (1)$$

Where E_A is the potential of the drug and E_B for the interfering ions. While in the MPM method, the equation (2) was used:

$$K^{pot}_{A,B} = (a_A' - a_A) / a_B \quad (2)$$

Application to serum and urine:

A urine or blood sample was obtained from a healthy

Table 1: Effect of the plasticizer on the electrode response.

Parameters	DBPH	TEHP	TEP
Slope (mV/decade)	57.31	49.21	41.76
Detection limit (M)	8.9×10^{-5}	9×10^{-5}	4.5×10^{-6}
Linear range (M)	1×10^{-4} - 1×10^{-2}	1×10^{-4} - 1×10^{-2}	5×10^{-6} - 1×10^{-2}
Response time (min.)	1.1at 10^{-2}M 4.9at 10^{-6} M	0.8 at 10^{-2} M 3.9 at 10^{-6} M	0.5at 10^{-2} M 4.8at10^{-6} M
Life time (day)	45	18	14
pH	3-7	3-7	3-8
R	0.9960	0.9968	0.9965

volunteer and spiked with 1×10^{-2} M GTF standard solution. The synthetic urine or blood sample was centrifuged at 2500 rpm for 10 min. Then, the top layer was separated then directly analyzed using the proposed sensors (Hussien *et al.,* 2011).

Results and discussion

Effect of plasticizers

The characterization of three new electrodes based on ion pair with different plasticizers (DBPH, TEHP, TEP) were identified. Table 1 exhibits that DBPH is the best of the plasticizers examined due to high mixing between plasticizer and PVC that leads to the formation of homogeneous membrane. Therefore DBPH plasticizer gave near-Nernstian response as shown in Fig. 2. While TEHP and TEP show the poor sensitivity on the electrode response as shown in Fig. 3 and 4. The non-Nernstian slope behaviours could be attributed to the incompatibility of the plasticizer with the complex in PVC leads to leaching of the complex from the membrane or may have a high steric effect on methyl groups (Nassory *et al.,* 2008).

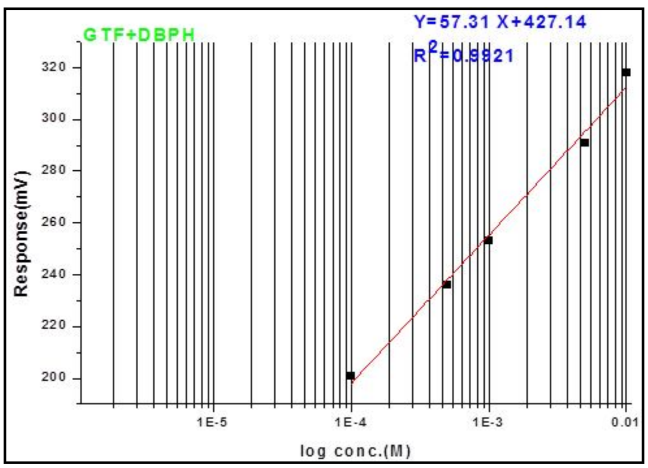

Fig. 2: Calibration curve of GTF-DBPH.

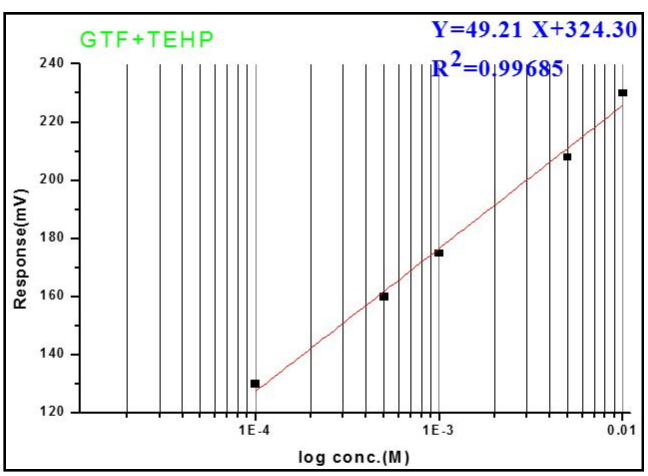

Fig. 3: Calibration curve of GTF-TEHP.

pH effect

The pH effect on the response of the electrode was studied by measuring the potentials of the electrode at 1×10^{-4} and 1×10^{-3} M of GTF solution, where the pH value was adjusted from (1) to (11) by adding HCl or NaOH as shown in Figs. 5, 6 and 7.

Figs. 5, 6 and 7 illustrates the GTF -BPB electrode can be used in the pH range of 3-7 and 3-8 with good

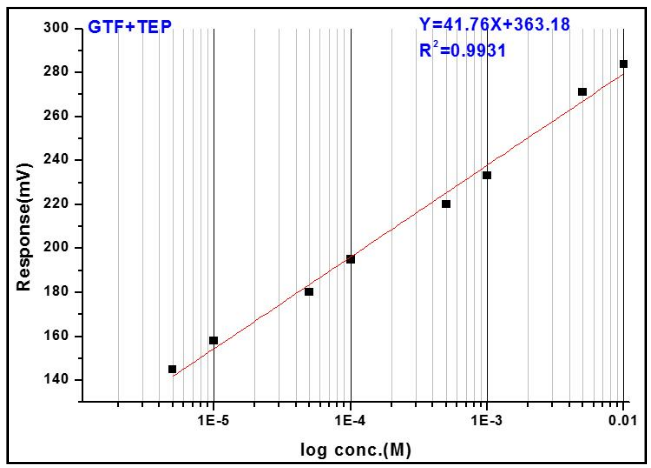

Fig. 4: Calibration curve of GTF-TEP.

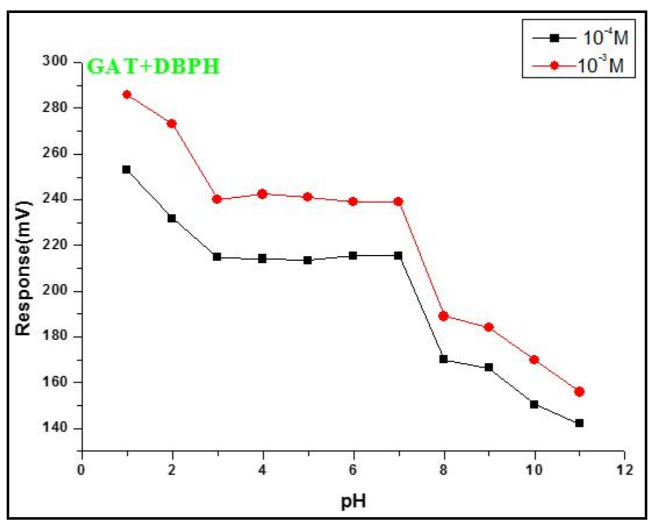

Fig. 5: Effect of pH on the GTF-DBPH electrode response

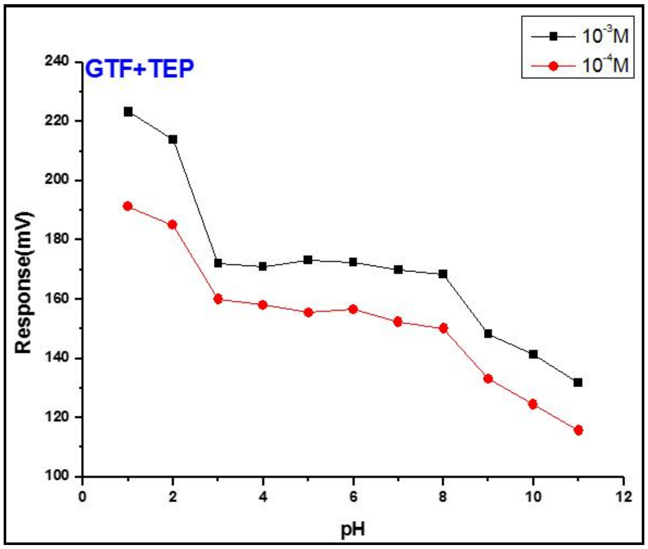

Fig. 6: Effect of pH on the GTF-TEHP electrode response.

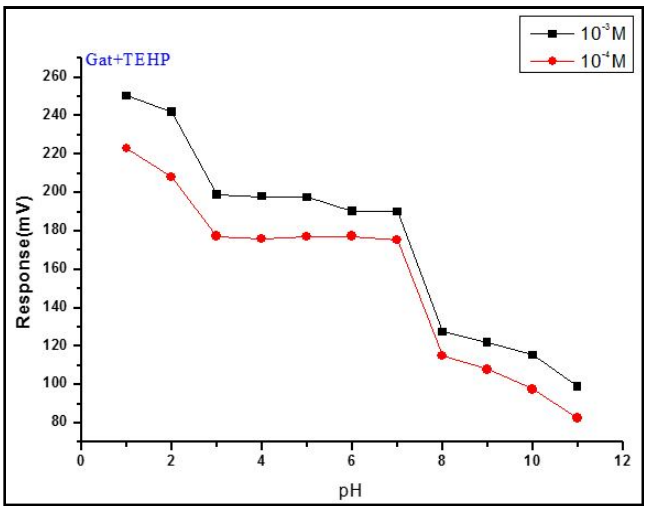

Fig. 7: Effect of pH on the GTF-TEP electrode response.

sensitivity (Shakir, 2016) . It should be noted increasing pH (pH >8) leads to decrease electrode response due to that gatifloxacin was insoluble in basic solution. The electrode response increases in strong acid (pH < 3) solution. This indicates that ion-pair (GTF -BPB) might probably respond to hydrogen ions (Nassory *et al.,* 2008).

Response time

The response time was measured for the Gatifloxacin electrode based on DBPH, TEHP and TEP for two concentrations (1×10^{-2}, 1×10^{-6}) M as shown in Figs. 8, 9 and 10.

From Figs. 8, 9 and 10, the values of response time increase as the concentration decrease. This is attributed to the need for more time to reach the equilibrium between the ion- pair in the membrane and the external solution when the concentration of the external solution is too low (Nassory *et al.,* 2008).

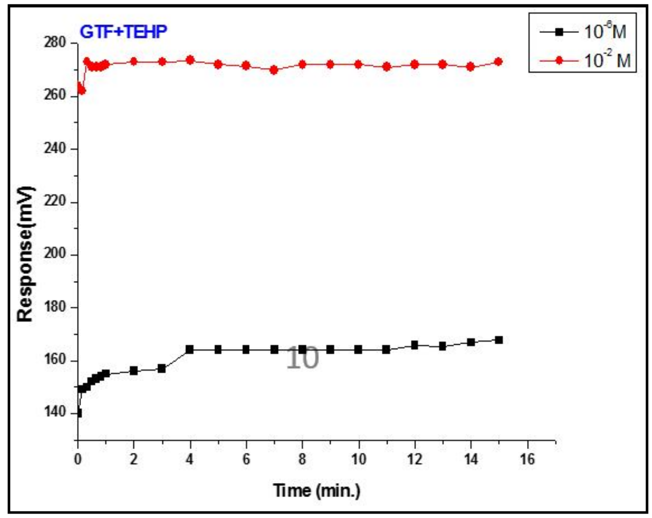

Fig. 8: Response time of GTF-TEHP electrode.

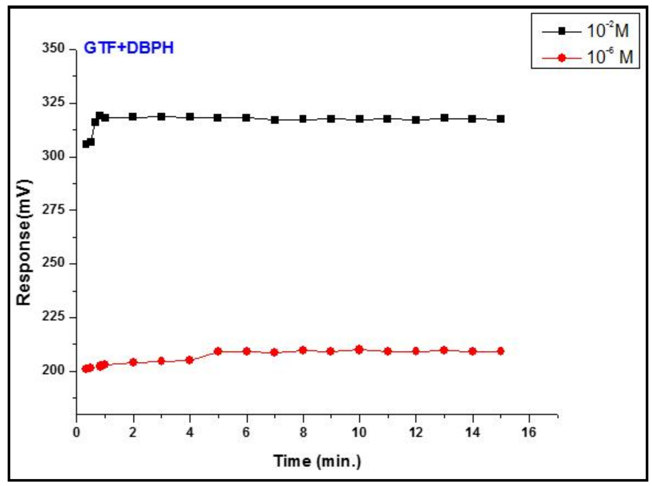

Fig. 9: Response time of GTF-DBPH Electrode.

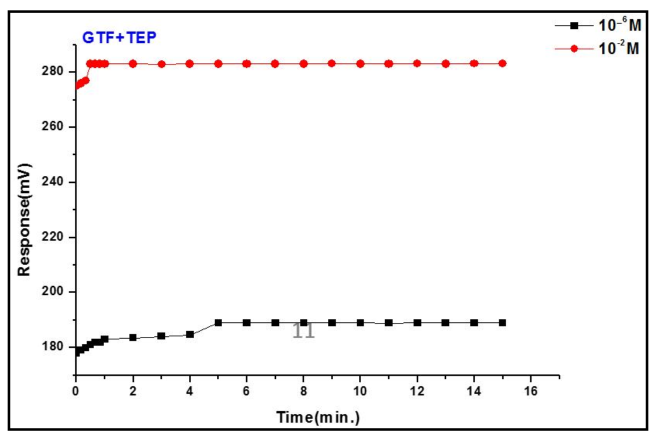

Fig. 10: Response time of GTF-TEP electrode.

Life time of electrode:

The three constructed electrodes required 2 hours for conditioning in 1.0×10^{-2} M GTF solution at room temperature to reach the stable potential. A calibration curve was created for electrode and the slope for the (GTF-DBPH), (GTF-TEHP) and (GTF-TEP) electrodes after 2 hours of soaking were 57.31, 49.21 and 41.76 respectively, but after 3 weeks of soaking the slope become 43.73 and 35.88 for electrodes (GTF-TEHP) and (GTF-TEP) respectively as shown in Figs. 12 and 13, while (GTF-DBPH) electrode, the slope become 50.87 after 5 weeks as shown in Fig. 11.

Selectivity

An important characteristic of an ion-selective electrode was responded to primary ions in the existing of other ions in the same solution, this measurement was expressed in the term of potentiometric selectivity coefficient. The influence of the interfering ions which are (Li^{+}, Na^{+}, K^{+}, Ca^{+2}, Mg^{+2},Zn^{+2}, Cr^{+3}, Fe^{+3}, Al^{+3}) on the electrode response using separate solution method (SSM) and match potential method (MPM) were examined, as shown in Fig. 14, 15 and 16. The selectivity coefficient values of the SSM are listed in the table 2.

From table 2, low values of selectivity coefficients

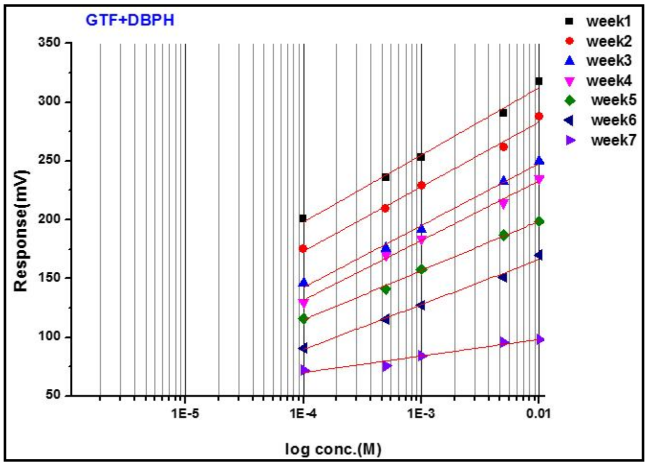

Fig. 11: Life time of the (GTF-DBPH) electrode.

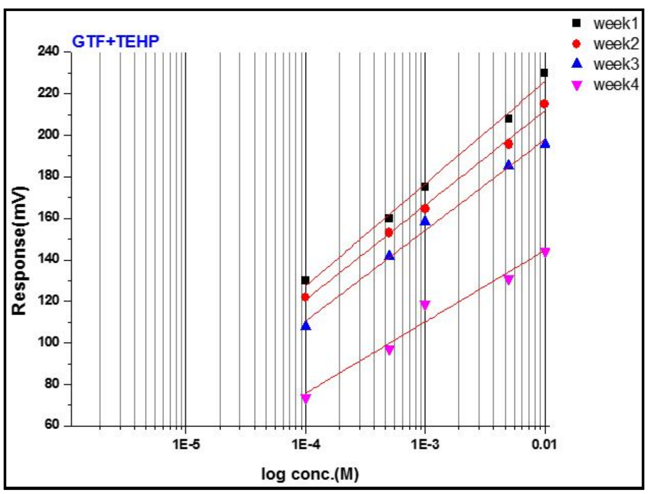

Fig. 12: Life time of the (GTF-TEHP)Electrode.

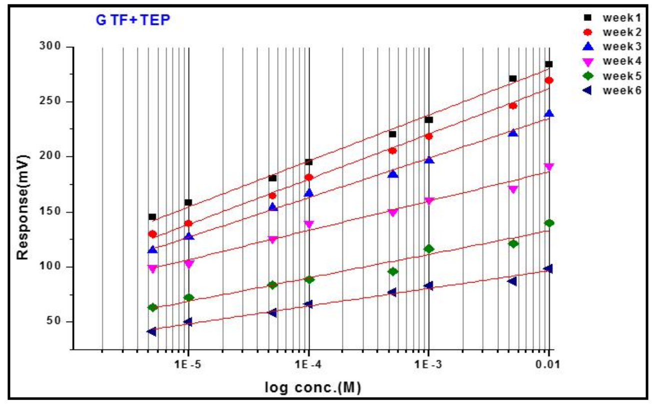

Fig. 13: Life time of the (GTF-TEP) electrode.

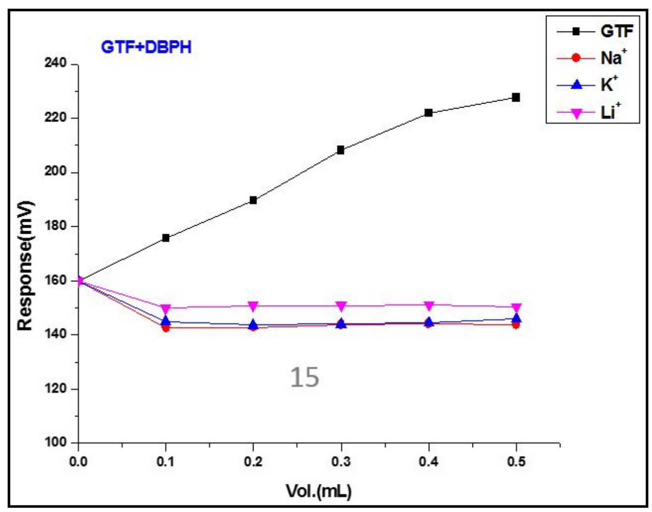

Fig. 14: Selectivity for GTF-DBPH mono-cations.

Table 2: Values of selectivity coefficient for different interfering ions using (GTF-BPB+DBPH) electrode.

Conc.M	$K_{A,B}$								
	Na^{+}	K^{+}	Li^{+}	Ca^{+2}	Mg^{+2}	Zn^{+2}	Fe^{+3}	Al^{+3}	Cr^{+3}
1.0×10^{-2}	2.83×10^{-3}	4.78×10^{-3}	5.11×10^{-3}	1.14×10^{-4}	1.19×10^{-4}	1.37×10^{-4}	4.43×10^{-5}	6.72×10^{-5}	3.21×10^{-4}
5.0×10^{-3}	5.84×10^{-3}	1.16×10^{-2}	1.19×10^{-2}	3.04×10^{-4}	2.49×10^{-4}	1.63×10^{-4}	9.74×10^{-5}	1.92×10^{-3}	5.59×10^{-4}
1.0×10^{-3}	1.86×10^{-2}	7.07×10^{-2}	6.16×10^{-2}	1.15×10^{-3}	1.86×10^{-4}	2.44×10^{-4}	1.30×10^{-4}	1.99×10^{-4}	1.01×10^{-3}
5.0×10^{-4}	5.33×10^{-2}	1.28×10^{-2}	1.35×10^{-1}	2.12×10^{-3}	4.64×10^{-4}	2.48×10^{-4}	2.40×10^{-4}	6.60×10^{-4}	7.81×10^{-4}
1.0×10^{-4}	4.02×10^{-2}	4.83×10^{-1}	4.72×10^{-1}	2.65×10^{-3}	5.26×10^{-4}	3.56×10^{-4}	2.09×10^{-4}	3.04×10^{-4}	2.14×10^{-4}
5.0×10^{-5}	2.88×10^{-1}	6.38×10^{-2}	3.11×10^{-1}	9.57×10^{-4}	1.59×10^{-4}	1.00×10^{-4}	1.39×10^{-4}	1.09×10^{-4}	5.71×10^{-5}
1.0×10^{-5}	2.08×10^{-1}	3.66×10^{-1}	9.86×10^{-2}	3.22×10^{-4}	1.26×10^{-4}	5.92×10^{-5}	3.17×10^{-5}	1.04×10^{-4}	2.72×10^{-5}
5.0×10^{-6}	1.71×10^{-1}	3.52×10^{-1}	5.05×10^{-1}	1.55×10^{-3}	1.08×10^{-4}	4.53×10^{-5}	2.09×10^{-5}	1.86×10^{-5}	2.32×10^{-5}
1.0×10^{-6}	1.41×10^{-1}	6.95×10^{-1}	8.99×10^{-2}	1.46×10^{-4}	1.99×10^{-4}	2.29×10^{-5}	1.39×10^{-5}	3.63×10^{-5}	8.62×10^{-6}

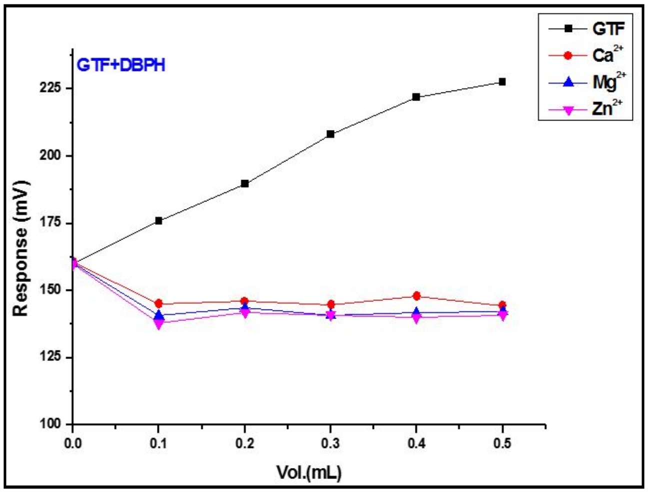

Fig. 15: Selectivity for GTF-DBPH for di-cations.

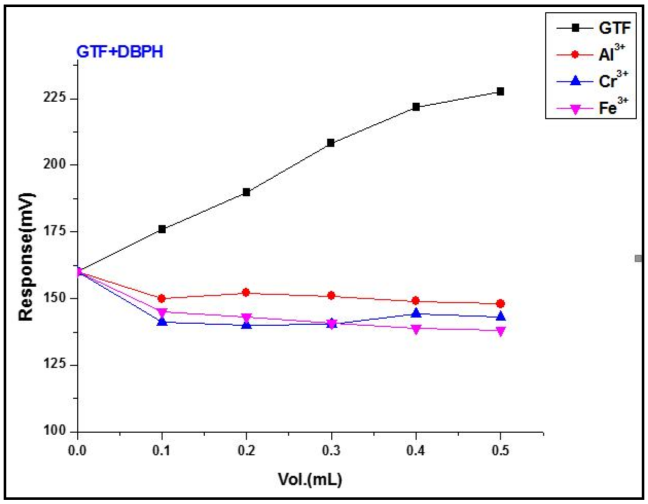

Fig. 16: Selectivity for GTF-DBPH for tri-cations.

Table 3: Estimation of the pharmaceutical application and human fluids by direct method.

Drug	Original Conc. (M)	Found Conc. (M)	RE %	RC %
Standard of gatifloxacin	1×10^{-4}	0.99×10^{-4}	-1.0	99.0
Gate eye drops	1×10^{-4}	0.98×10^{-4}	-2.0	98.0
Urine	1×10^{-4}	0.97×10^{-4}	-3.0	97.0
serum	1×10^{-4}	0.98×10^{-4}	-2.0	98.0

Table 4: Estimation of the pharmaceutical application and human fluids by standard addition method.

Drug	Original Conc. (M)	Found Conc. (M)	RE %	RC %
Standard of gatifloxacin	1×10^{-4}	0.99×10^{-4}	-1.0	99.0
Gate eye drops	1×10^{-4}	1.005×10^{-4}	0.5	100.5
Urine	1×10^{-4}	0.97×10^{-4}	-3.0	97.0
serum	1×10^{-4}	1.01×10^{-4}	1.0	101.0

Table 5: Estimation of the pharmaceutical application and human fluids by multi standard addition method.

Drug	Original Conc. (M)	Found Conc. (M)	RE %	RC %
Standard of gatifloxacin	1×10^{-4}	0.99×10^{-4}	-1.0	99.0
Gate eye drops	1×10^{-4}	1.03×10^{-4}	3.0	103.0
Urine	1×10^{-4}	0.98×10^{-4}	-2.0	98.0
serum	1×10^{-4}	1.008×10^{-4}	0.8	100.8

were obtained which means no interfering of these cations on the electrode (GTF -BPB+DBPH) response and Figs. 14, 15 and 16 show no interferences of the cations on Gatifloxacin at concentrations 10^{-4} M. Therefore, the selectivity coefficients cannot be determined because there is no difference in potential between the drug solution and interfering cation even at 5 mV or 10 mV (Nassory *et al.,* 2008).

Analytical application

In investigating electrode to the determination of gatifloxacin in pharmaceutical preparations (Gate eye drops) using direct and standard addition methods [14]. The results were summered up in table 3, 4 and 5. The suggested electrode was demonstrated to be useful in the potentiometric determination of GTF in the pharmaceutical products and human fluids by direct, standard addition and multi standard addition method.

Conclusion

New Gatifloxacin selective electrodes based on ion pair complex of GTF-BPB and with different plasticizers were constructed. The best Gatifloxacin electrode was based on DBPH. This electrode was used for drug determination in pharmaceutical preparations and human fluids. The electrode based on DBPH gave excellent electrode parameters and no interference with several cations. The proposed analytical method is proved to be simple and rapid, with good accuracy.

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