



## **Ion Selective Carbon Paste Electrode for Determination of Flavoxate Muscle Relaxant Drug in Pharmaceutical Formulation**

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### **Abstract**

The utility of carbon paste electrode for the determination of flavoxate HCl modified with flavoxate-tetraphenylborate (FLX-TPB) and flavoxate-phosphotungstic acid (FLX-PTA) ion-pairs in batch mode is demonstrated. The electrodes revealed a Nernstian response over a wide concentration ranges  $1.39 \times 10^{-5}$ - $1 \times 10^{-2}$  mol L<sup>-1</sup> and  $1 \times 10^{-5}$ - $1 \times 10^{-2}$  mol L<sup>-1</sup> using FLX-TPB and FLX-PTA, respectively. The detection limits of these sensors are  $1.39 \times 10^{-5}$  mol L<sup>-1</sup>, and  $1 \times 10^{-6}$  mol L<sup>-1</sup> using FLX-TPB and FLX-PTA, respectively. The best performance was obtained with carbon paste composition of 5% flavoxate-tetraphenylborate or flavoxate-phosphotungstate, 47.5% graphite and 47.5% o- nitro phenyl octyl ether (o-NPOE). The sensors exhibit a very fast response time (5-7 s) and good selectivity in presence of inorganic cations, sugars and aminoacids. The proposed sensors show great improvement in comparison with other previously reported sensors. The sensors were successfully applied to monitoring of flavoxate in pure solution and pharmaceutical formulation (Genurin tablet) with recovery ranges from 97.2 – 101.0% and 98.1-101.6% using FLX-TPB and FLX-PTA, respectively.

*Keywords:* Carbon paste electrode, Flavoxate, Potentiometry.

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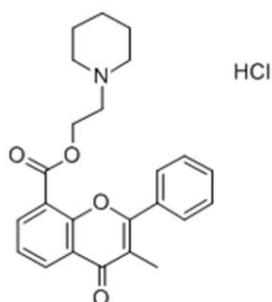
### **1. Introduction**

Flavoxate hydrochloride (FLX), 3-methylflavone-8-carboxylic acid (MFA) 6-piperidinoethyl ester hydrochloride, belongs to a series of flavones derivatives, which exhibit strong smooth muscle relaxant activity, with selective action on

the pelvic [1]. It is used for the symptomatic relief of pain, urinary frequency, and incontinence associated with inflammatory disorders of the urinary tract. It is also used for relief of vesico-urethral spasms resulting from instrumentation or surgery [2]. FLX is readily absorbed from the gastrointestinal tract and rapidly metabolized in plasma to MFA [3]. About 50-60% of a dose is being excreted in the urine within 24 h as MFA. MFA did not display antispasmodic activity. Determination of FX is described

in the British Pharmacopoeia [4] by a non-aqueous titration method. It is also determined by spectrophotometry [5], HPLC [6, 7, 8], and capillary electrophoresis [9].

The cationic properties of FLX suggested the use of anionic exchangers, such as phosphotungstic acid (PTA) and sodium tetraphenylborate (TPB) as counter ion association complexes. These complexes are plasticized with suitable solvent mediators to form chemically modified carbon paste electrodes (CMCPEs). These electrodes have been extensively used in pharmaceutical analysis. This type of ISEs has advantages over their counter parts plastic membrane ISEs with regard to simplicity in the assembly, no internal filling solution, and the ability of regeneration of the active surface easily.



**Scheme 1.** Chemical structure of flavoxate hydrochloride  $C_{24}H_{25}NO_4$ , HCl M.W 427.9.

## 2. Materials and Methods

### 2.1. Reagents and Materials

All chemicals and reagents used throughout the work were of analytical reagent grade and solutions were made

with double distilled water. Graphite powder, o-nitro phenyl octyl ether (o-NPOE), dioctylphthalate (DOP), dipropylphthalate (DPP), dibutylphthalate (DBP), phosphotungstic acid (PTA), acetone and potassium chloride (KCl) were from Aldrich, England. Sodium tetraphenylborate (NaTPB) was obtained from Fluka Chemical Co., Japan. Flavoxate hydrochloride (FLX) was kindly supplied by the Medical Union Pharmaceuticals (MUP), Ismailia, Egypt and also FLX was used as working standard. The purity of FLX was found to be  $99.2 \pm 0.5\%$  according to B.P 2012. Its commercial preparation, Genurin tablet, labeled to contain (200 mg FLX/tablet batch number 950207) was manufactured by MUP Co., Egypt.

### 2.2. Solutions

Aqueous solution of TPB ( $10^{-2}$  mol  $L^{-1}$ ) was prepared, and the exact concentration of this solution was determined by the appropriate recommended methods [10]. Na, K, Ca, and Mg solutions ( $1000 \mu g mL^{-1}$ ) were obtained from Merck, Germany. Glucose anhydrous, lactose monohydrate, L-serine, L-lysine, glycine, and L-alanine were obtained from Aldrich, England. Stock solutions  $10^{-2}$  mol  $L^{-1}$  of PTA, and NaTPB were prepared by dissolving the accurately weighed amounts of the pure solid in double distilled water. Solutions of sodium hydroxide and hydrochloric acid of concentrations within the range  $10^{-1}$ - $1.0$  mol  $L^{-1}$  were used for

adjusting the pH of the medium. FLX solution  $10^{-2}$  mol L<sup>-1</sup> was prepared by dissolving the accurately weighed amount in double distilled water stored in dark bottle and kept in a refrigerator for no more than ten days. All the solutions were prepared in de-ionized water.

### 2.3. Apparatus

Potentiometric and pH measurements were carried out using a digital HANNA meter, Model 211, USA. A saturated calomel electrode (SCE) was used as the external reference. The electrochemical system of the FLX carbon paste electrodes may be represented as carbon paste electrode/test solution/saturated calomel electrode.

### 2.4. Preparation of FLX-TPB and FLX-PTA Ion Exchangers

The precipitate of FLX-TPB and FLX-PTA ion exchangers were prepared by mixing aqueous solutions containing equimolar volumes of  $10^{-2}$  mol L<sup>-1</sup> NaTPB and  $10^{-2}$  mol L<sup>-1</sup> FLX whereas, FLX-PTA ion-associate was prepared by mixing three volumes of  $10^{-2}$  mol L<sup>-1</sup> of the FLX with one volume of  $10^{-2}$  mol L<sup>-1</sup> of PTA. The obtained precipitate was filtered, thoroughly washed with distilled water chloride-free and dried at room temperature.

The composition of ion-pair was confirmed by elemental analysis to be 1:1 (FLX-TPB) and 3:1 (FLX-PTA).

The precipitate of KTPB was prepared by mixing aqueous solutions containing equimolar amounts of NaTPB and KCl.

### 2.5. Preparation of carbon paste electrodes

Tetraphenylborate (FLX-TPB) mixed ion selective carbon paste electrode was prepared by mixing FLX-TPB (5% w/w) with spectroscopic graphite powder (Aldrich, 1-2 micron) and o-NPOE as pasting liquid [ratio graphite powder to pasting liquid was 1:1 (w/w)] in an agate mortar until it was uniformly wetted. The mixture was used for filling the electrode body, the electrode surface was polished using a filter paper to obtain a reproducible working surface and used directly for potentiometric measurements without preconditioning.

Tetraphenylborate/KTPB (FLX-TPB/KTPB) mixed ion selective carbon paste electrode was also prepared to improve the slope of the electrode (FLX-TPB) using 0.5% of KTPB as a selectivity promoter on the paste[11] with a ratio graphite powder to pasting liquid that was 1:1 (w/w), and filling the electrode body with the mixture.

Phosphotungstate (FLX-PTA) ion selective carbon paste electrode was prepared by mixing FLX-PTA (5% w/w) with spectroscopic graphite powder with the same ratio graphite: pasting liquid 1:1 (w/w) and filling the electrode body with the mixture.

### 2.6. Construction Calibration Graphs:

To 50-ml double distilled water in the titration cell, increments of  $10^{-2}$  mol L<sup>-1</sup> flavoxate hydrochloride were added to covering the concentration range  $1 \times 10^{-6}$ - $1 \times 10^{-2}$  FLX mol L<sup>-1</sup>. The potential values were measured at (25±1°C) and plotted vs. p [FLX] using carbon paste and saturated calomel electrodes. The constructed calibration graphs were extended to more concentrated solution ( $10^{-1}$  mol L<sup>-1</sup>) by measuring their solutions directly. The constructed calibration graphs were used for subsequent measurements of unknown flavoxate hydrochloride solutions.

### 2.7. Potentiometric Titration of Drug in Pure Solution

Aliquots of FLX, pure solution prepared previously containing 4.27-42.7 mg FLX was transferred into a 100-ml titration vessel and diluted to about 50 ml with water, then potentiometrically titrated with standard solutions of  $10^{-2}$  mol L<sup>-1</sup> TPB using any of the prepared FLX electrodes as indicator electrodes and calomel as reference electrode. The volume of titrant at equivalence point was obtained using the first derivative method.

### 2.8. Potentiometric Titration of Drug in Pharmaceutical Formulation

Twenty tablets were accurately weighed and finely powdered. Certain mass of the powdered tablets were weighed dissolved in about 30 ml double distilled water, transferred into a 50 ml-

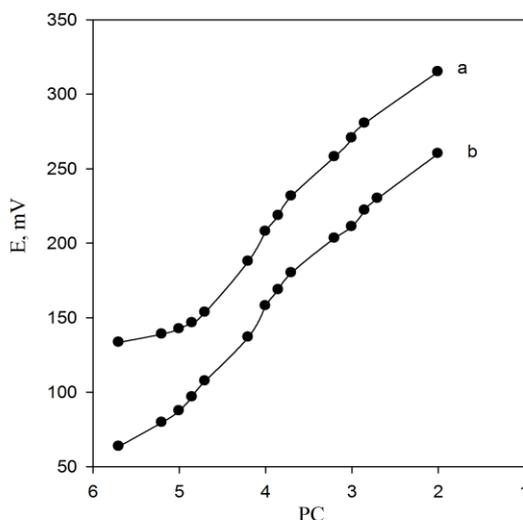
volumetric flask, the volume was completed with double distilled water. The potential values were recorded carbon paste electrodes in conjunction with saturated calomel electrodes. Potentiometric titration was applied in which an aliquot of FLX solution, containing 4.27-42.7 mg FLX, was transferred into a 100 ml beaker, diluted to approximately 50 ml with double distilled water, and then titrated against a standard solution of NaTPB using any of the prepared FLX-electrodes as an indicator electrode and using saturated calomel as a reference electrode. The end point was determined by first derivative plots.

## 3. Results and Discussion

### 3.1. Effect of Composition of Electrode

Flavoxate-tetraphenylborate (FLX-TPB) as an ion-sensor was found to be highly sensitive to FLX<sup>+</sup> with respect to several other cations. Therefore, the performance of the CPE containing this ion-exchanger in aqueous solutions was studied in details. It is well known that the selectivity, linear dynamic range and sensitivity obtained for a given CMCPE significantly depend on the paste composition [12], the nature of the solvent mediator [13, 14], and additives used [15].

The paste composition is changed, first using TPB to form ion pair with FLX and determine. The amount of ion-exchanger in the paste affects the response of the electrode, so three paste compositions were prepared by varying the percentage



**Figure 1.** Calibration graphs of FLX using (a) 5% FLX-TPB/KTPB and (b) 5% FLX-PTA CMCPEs for determination of FLX. All curves start at pC 5.7.

of FLX-TPB. The electrodes containing 5%, 7%, 10% have slopes of 50.34, 49.9, 43.65 mV/decade, respectively. Although, the three electrodes have the same linear range and almost the same detection limit and slope except the paste containing 10% of FLX-TPB has narrow linear range and lower detection limit.

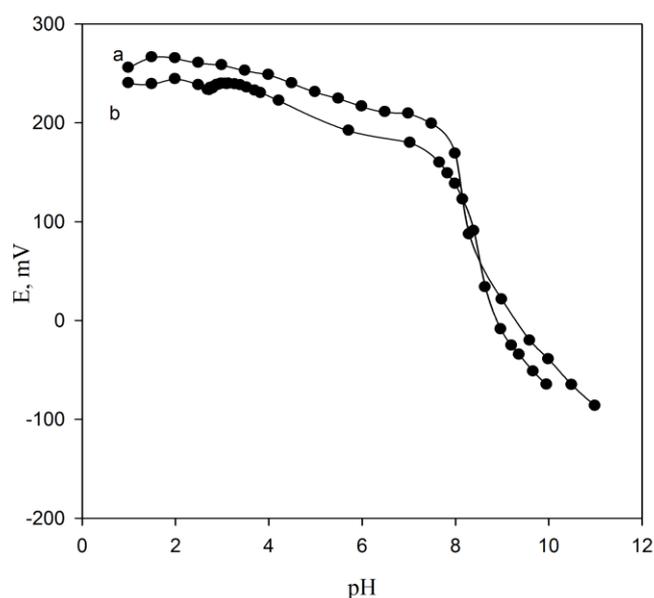
Due to lower slopes for FLX-TPB ion pair, KTPB (0.5% w/w) was added as a selectivity modifier and electrodes containing 5%, 7%, 10% TPB with 0.5 % KTPB were prepared to give slopes of 56.97, 56.27, 54.9 mV, respectively and so it improved the electrode response very well to obey Nernst equation.

The paste then is formed directly with FLX-PTA ion pair and the slopes is determined for different electrodes containing 5%, 7%, 10% PTA to give slopes 58.0, 56.3, 50.9, respectively. Figure

1 shows the best two electrodes obtained with 5% TPB/KTPB and PTA with slopes 56.97 and 58.0, respectively.

### 3.2. Effect of pH

Effect of pH on the potentials values of the electrodes system of FLX were tested by measuring the e.m.f. of the cell in the tested solution in which the pH was varied by adding appropriate amounts of HCl and/or NaOH solution (each  $10^{-1}$ -1.0 mol  $L^{-1}$ ). The results indicate that the electrode did not respond to the pH changes in the range 2-7.5 for FLX-TPB/KTPB electrode. The dissociation constant ( $pK_{ai}$ ) of FLX is 7.29. At pH values lower than 2, the electrodes become  $H^+$ -sensitive and the potential decreased gradually. This can be related to interference of hydronium ion, while the decrease that takes place at pH higher than 7.5 is most probably attributed



**Figure 2.** Effect of pH on  $10^{-3}$  Mol L<sup>-1</sup> FLX solutions on the potential response of FLX-TPB/KTPB (a) and FLX-PTA CMCPEs.

to the formation of the free flavoxate base leading to decrease in concentration of FLX cation (unprotonated species) in the test solution.

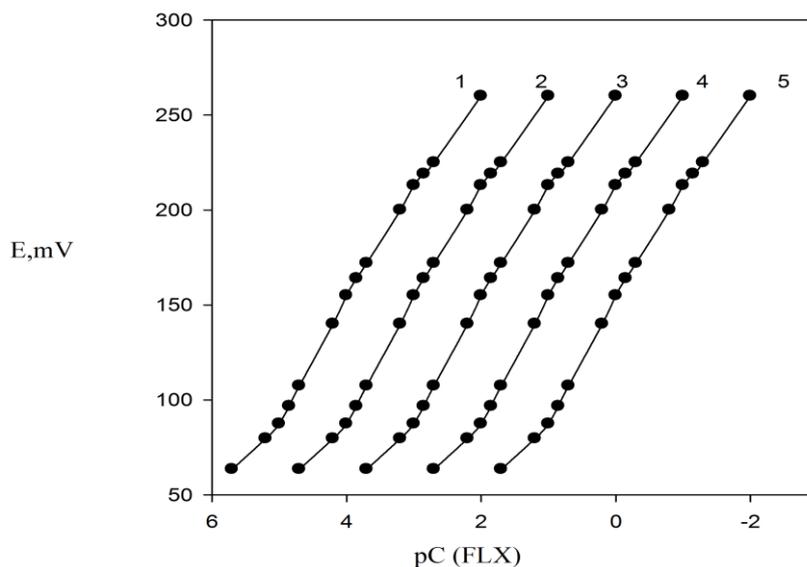
While the effect of pH on PTA ion pair, the electrode did not respond to pH in the range (1.5-7.5). It was also observed that a precipitate is formed with increasing of pH or time. This fact can be explained due to neutralization of HCl salt present in a bond with flavoxate. So, different pH values covering the acidic range (1.0-7.5 pH), at which the protonated form of flavoxate is present, were prepared and used as test solution. Representative curves for FLX-TPB/KTPB & FLX-PTA electrodes are shown in the figure 2 below.

### 3.3. Effect of Life Time of the Electrodes

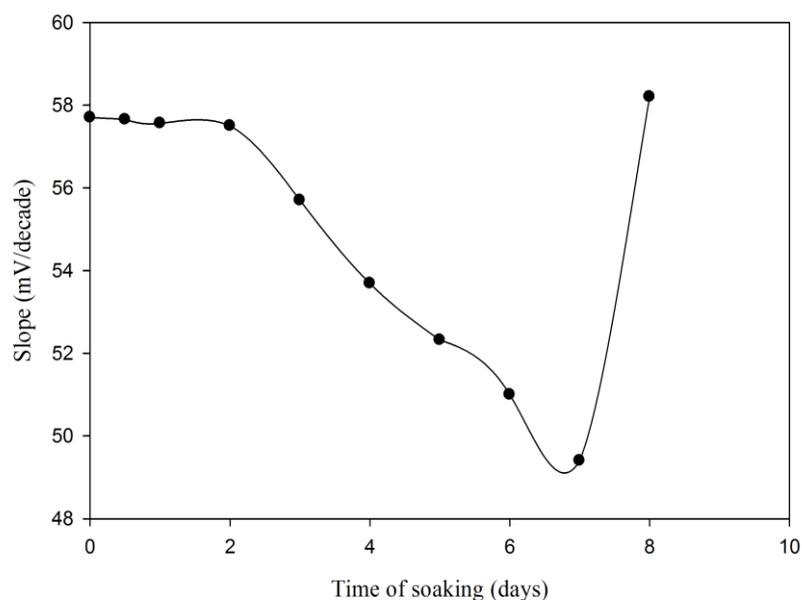
The performance of the electrodes was studied as a function of soaking time. Calibration plots (pFLX versus E (mV))

were obtained after the electrode was soaked continuously in  $1 \times 10^{-3}$  mol L<sup>-1</sup> FLX.Cl solution for 1/2, 1, 2, and 3 hours and 1, 5, and 7 days. The results indicate that the slope of the calibration graph was 57.97 mV/decade without preconditioning and then remained constant near 57.97 mV/decade for up to 2 days of soaking, then, decreased reaching 52.52, and 49.90 mV/decade after 4 and 6 days of soaking, respectively.

These results indicate that the life span of FLX-TPB electrode is 4 days. The main property of using modified carbon paste electrodes is that the electrode surface can be renewed, so by cutting the exhausted surface and using a new surface of electrode, the slopes of electrode increase again to reach about 58.30 mV/decade as shown in figures 3a and 3b.



**Figure. 3a.** Calibration graphs obtained at 25°C without soaking FLXPTA CMCP electrode after 0 min, (1), 1 day (2), 2 days (3), 3 days (4), and 4 days (5). All curves start at pC 5.7.

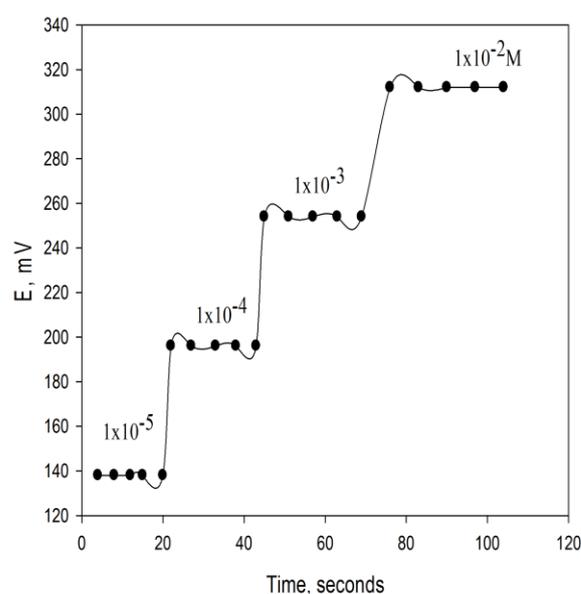


**Figure. 3b.** Effect of soaking  $1 \times 10^{-3} \text{ Mol L}^{-1}$  FLXCl solution on the performance of  $^1$  FLX-TPB CMCP electrode.

#### 3.4. Effect of Response Time

The dynamic response time of the electrode was tested by measuring the time required to achieve a steady state potential (within  $\pm 1 \text{ mV}$ ) after successive

immersion of the electrode in a series of  $\text{FLX}^+$  solutions, each having a 10-fold increase in concentration from  $1.0 \times 10^{-5}$  to  $1.0 \times 10^{-3} \text{ mol L}^{-1}$ . The electrode yielded steady potentials within 7-10 s as shown in



**Figure. 4.** Potential- time plot for the response of FLX-PTA CMCP electrode.

figure 4. The potential reading stays constant, to within  $\pm 1$  mV, for 1 minute.

### 3.5. Selectivity

The most important parameter of any potentiometric ion sensor is its response to the primary ion in the presence of other ions in solution, which is expressed in terms of the potentiometric selectivity ( $-\log K_{drug, j}^{pot}$ ) [16]. Two specialized

IUPAC committees were held concerning the determination of potentiometric selectivity coefficients. The selectivity coefficient values were calculated by applying the matched potential method (MPM) for methionine, leucine, histidine, lactose monohydrate, and glucose anhydrous. Separate simple method (SSM) is used for inorganic cations e.g.  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{+2}$ ,  $\text{Ca}^{+2}$ ,  $\text{Fe}^{+2}$ ,  $\text{Cu}^{+2}$ ,  $\text{Li}^+$ ,  $\text{Cr}^{+2}$  and the resulting values, presented in

Table 1 shows that the electrodes significantly display high selectivity for flavoxate over many common inorganic cations as well as amino acids.

In the SSM the EMF value ( $E_{drug}$  and  $E_j$ ) of the electrode in pure solution of each of the primary and the interfering ion of equal concentration are used for calculating the selectivity coefficient. The selectivity coefficient  $-\log K_{drug, j}^{pot}$  is calculated using Nicksky-Eisenman equation.

$$\log K_{drug, j}^{pot} = \frac{(E_j - E_{drug})}{2.303RT / Z_{drug}F} + (1 - \frac{Z_{drug}}{Z_j}) \log a$$

Potentiometric selectivity factor was evaluated using the matched potential method [17]. According to this method, the activity of the analyte was increased from  $a_A = 1.0 \times 10^{-5}$  mol  $\text{L}^{-1}$  (reference solution) to  $a^A = 1.39 \times 10^{-5}$  mol  $\text{L}^{-1}$ , and

**Table 1.** Selectivity coefficient values ( $-\log K_{drug, j}^{pot}$ ) for FLX-TPB/KTPB & FLX-PTA CMCPE.

Effect of Interferents	FLX-PTA	FLX TPB/KTPB
	( $-\log K_{drug, j}^{pot}$ )	( $-\log K_{drug, j}^{pot}$ )
Na <sup>+</sup>	0.3684	0.6701
K <sup>+</sup>	0.19298	0.684
Mg <sup>2+</sup>	1.59649	2.038
Ca <sup>2+</sup>	1.87543	2.094
Fe <sup>2+</sup>	0.42982	0.512
Cu <sup>2+</sup>	1.58245	1.894
Li <sup>+</sup>	0.18947	0.4789
Cr <sup>2+</sup>	1.819298	2.08
Glucose Anhydrous	4.85535	3.428
Lactose Monohydrate	5.189	3.984
Histidine	6.080	7.242
Leucine	5.435	6.57
Methionine	5.355	6.85
Degradate	4.19	5.19

**Table 2.** Composition, slope, linear ranges, and detection limits of calibration curves for flavoxate chemically modified carbon paste electrodes using 5% FLX-TPB at 25±1 °C without soaking.

Paste No.	Composition % w/w			Slope (mV/decade)	linear range (mol L <sup>-1</sup> )	LOD (mol L <sup>-1</sup> )
	graphite	placitser	% additive			
1	47.5	47.5(DOP)	---	42.39	1.99×10 <sup>-6</sup> - 9.09×10 <sup>-4</sup>	1.99×10 <sup>-6</sup>
2	47.5	47.5(DBP)	---	73.1	1.99×10 <sup>-6</sup> - 9.09×10 <sup>-4</sup>	1.39×10 <sup>-5</sup>
3	47.5	47.5(DPP)	---	28.3	1.99×10 <sup>-6</sup> - 1.228×10 <sup>-3</sup>	1.99×10 <sup>-6</sup>
4	47.5	47.5(o-NPOE)	0.5%KTPB	56.97	1.39×10 <sup>-5</sup> - 1.00×10 <sup>-2</sup>	1.39×10 <sup>-5</sup>

the change in potential ( $\Delta E$ ) corresponding to this increase in activity is measured. Then, 0.1 mol L<sup>-1</sup> solution of an interfering ion is added to a new 1.0×10<sup>-5</sup> mol L<sup>-1</sup> analyte reference solution until the same potential change ( $\Delta E$ ) is recorded [18], the concentration of the added amount is thus

a<sub>j</sub>. The selectivity coefficient  $K_{A, j}^{MPM}$  for each interferent was calculated using the following equation:

$$K_{A, j}^{MPM} = \frac{a_A^- - a_A}{a_j}$$

**Table 3.** Determination of flavoxate in pure solution and in pharmaceutical preparations using 5 % FLX-TPB/KTPB & FLX-PTA CMCPE by applying potentiometric method.

FLX -TPB/KTP electrode								FLX-PTA electrode							
In Pure Solution				In pharmaceutical Solution				In Pure Solution				In Pharmaceutical Solution			
sample	Taken (mg)	Found (mg)	Mean Recovery (%)±SD	sample	Taken (mg)	Found (mg)	Mean Recovery (%)±SD	sample	Taken (mg)	Found (mg)	Mean Recovery (%)±SD	sample	Taken (mg)	Found (mg)	Mean Recovery (%)±SD
1	4.27	4.15	97.20±0.09	1	4.27	4.18	97.90±0.08	1	4.27	4.19	98.13±0.04	1	4.27	4.21	98.59±0.02
2	12.81	12.48	97.42±0.13	2	12.81	12.51	95.00±0.17	2	12.81	12.81	100.00±0.30	2	12.81	12.81	100.00±0.20
3	21.35	21.39	100.18±0.11	3	21.35	21.40	100.23±0.17	3	21.35	21.55	100.94±0.36	3	21.35	21.52	100.80±0.29

### 3.6. Effect of Specificity

Flavoxate hydrochloride is degraded according to ICH guidelines for degradation of ester by refluxing using 0.1 mol L<sup>-1</sup> NaOH for 1 h and the degradate is confirmed using IR and mass spectroscopy. 10<sup>-3</sup> mol L<sup>-1</sup> of degradate is prepared and found having no interference using PTA or TPB/KTPB CMCPes, The selectivity coefficient found to be 4.19 & 5.19, respectively as shown in table 1.

### 3.7. Effect of Plasticizer

The use of plasticizers will give some permeable properties to the paste and will improve its mechanical stability by promoting binding between grains [19]. In addition, the solvent mediator, in particular, has a dual function; liquefying agent, enabling homogenous solubilization and modifying the distribution constant of the active ingredient used. The proportion of solvent mediator must be optimized in order to minimize the electrical asymmetry of the paste, to keep the sensor as clean as possible, and to stop leaching to the aqueous phase [20]. Different plasticizers are used and the slopes are calculated for each one. The optimum plasticizer is obtained using o-NPOE which gives best slope. The slope of each plasticizer and its range are calculated in table 2 using FLX-TPB ion pair.

In exploration for a suitable plasticizer for constructing this electrode, four plasticizers (DOP, DBP, DPP, and o-NPOE) were used, with different values of

dielectric constants, lipophilicity and molecular weight [21], to figure out the plasticizer with the best response. The sensor with o-NPOE as a solvent mediator produced the best response, as shown in table 2, likely due to better dielectric characteristics of o-NPOE comparing to other solvents, and the ability of o-NPOE to extract flavoxate ions from the aqueous solution to the organic paste phase [22]. It is well known that the sensitivity and selectivity of the ion-selective sensors not only depend on the nature of ion-exchanger used but also significantly on the paste composition, the nature of plasticizers and any additives used, so KTPB was tested as additives on the paste ingredients as shown in table 2. Addition of KTPB resulted in near Nernstian response with wide linear range and high detection limit.

Among the different compositions studied, a paste containing ion-exchanger complex 5.0 wt % FLX-TPB, 47.5 wt % graphite, and 47.5 wt % o-NPOE exhibited the best response characteristics and the low detection limit. Therefore, this composition was used to study various operation parameters of the electrodes. The electrochemical performance characteristics of this electrode were systematically evaluated according to the IUPAC recommendations [23].

**Table 4.** Statistical treatment of data obtained for determination of flavoxate using FLX-TPB/KTPB & FLX-PTA CMCPE in pure solution and pharmaceutical preparation in comparison with the BP method [4].

Sample	Reference method	potentiometric method					
		FLX-TPB/KTP electrode			FLX-PTA electrode		
	Recovery %	Recovery %	F value	t value	Recovery %	F value	t value
Pure solution	100.49±0.32	98.2±0.43	0.727	1.61	99.67±0.33	0.652	0.63
Genurin tab	102.20±0.21	98.6±0.14	0.089	3.83	99.76±0.29	0.133	3.07

F-tabulated = 9.28 at 95% confidence limit. t-tabulated = 2.447 at 95% confidence limit under n= 6 degrees of freedom.

### 3.8. Analytical Application

The investigated electrodes can be used in the determination of FLX in pure solutions and in pharmaceutical preparation potentiometric titration. Collective results are given in table 3.

Statistical treatment (F and t-tests) of the data was carried out to compare the experimental data with those of the reference method [4] (Table 4). It was found that values were lower than the tabulated ones, and 5% critical values (95% confidence level).

## 4. Conclusion

The proposed chemically modified electrodes based on flavoxate electro active ion tetraphenylborate with potassium tetraphenylborate or phosphotungstate have advantages over traditional ISEs of simple, cheap preparation, fast response, low detection limit, high sensitivity, good selectivity, resistance to change of pH over a wide

range. Moreover, they may be used for measurements of a wide concentration range over a long life span. Then, these electrodes might be an accurate alternative analytical tool for the determination of FLX+ in pure samples, dosage forms and in presence of its degradation products.

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