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Novel Moxifloxacin Ion Selective Electrodes for Potentiometric Determination of Moxifloxacin in Pure Form and Pharmaceutical Formulations

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ABSTRACT: *Moxifloxacin (MFX) is a synthetic broad-spectrum bactericidal 4th generation fluoroquinolone. At this study, three PVC membrane ion selective electrodes were constructed for MFX analysis purposes. The electro-active materials are MFX-tetraphenyl borate (MFX-TPB), MFX-REINECKATE (MFX-RNK) or MFX-NESSLER's (MFX-NSR). The characterization and analytical properties were determined. The casting membranes were plasticized by* di-n-butyl phthalate (DBP). *The constructed electrodes have inner reference Ag/AgCl electrode. In addition, the assembled sensors have outer reference Ag/AgCl electrode. The sensors were near NERNSTIAN response when the percentages ion pair at membranes were 6%, 4%, 6% for MFX-TPB, MFX-RNK, and MFX-NSR, respectively. The electrodes exhibited a fast dynamic response of 14-21 sec for a period of 10-13 days, without significant change in the electrodes parameters. The sensors worked at pH ranges 2.0-5.0, 2.0-5.5, and 2.0-6.0 for MFX-TPB, MFX-RNK, MFX-NSR sensors, respectively. The sensors have been used as indicator electrodes for direct determination of MFX in pharmaceutical preparations with mean relative standard deviation less than 2% indicating good precision, as well as in pure form solutions with average recovery of 98.58%, 99.09%, 99.27% and a mean relative standard deviation of 1.28, 1.81 and 1.91% at 0.438µg/ml MFX•HCl for MFX-TPB, MFX-RNK, and MFX-NSR sensors respectively.*

Keywords: *Ion Selective Electrodes, Moxifloxacin, NESSLER'S Reagent, Potentiometric Determination, REINECKATE Salt, Tetraphenyl Borate.*

1. INTRODUCTION

Moxifloxacin (MFX) {1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid, monohydrochloride} (Fig. 1) is a synthetic bactericidal 4th generation fluoroquinolone (fluorinated derivative of the quinolone) discovered in 1996 and reached the UK market in 2000 [1,2]. MFX is a broad spectrum important antibacterial agent used in human medicine which is active against many aerobic, anaerobic, gram positive (G^+) and gram negative (G^-) bacteria. It is also active against other microorganisms such as *Chlamydia pneumonia* and *Mycoplasma pneumonia*. It functions by inhibiting the two bacterial topoisomerases: DNA-gyrase (in G^- organisms) and topoisomerase IV (in G^+ organisms), the two enzymes are necessary to separate bacterial DNA, and the bactericidal action of MFX results from trapping of enzymes on DNA and lethal release of double-stranded breaks, thereby inhibiting of cell replication [3,4].

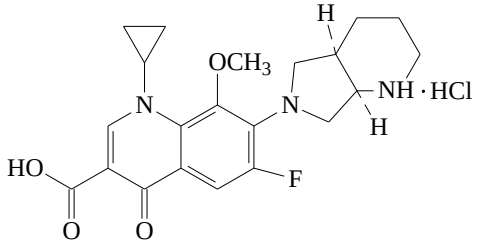

Fig. 1: chemical structure of MFX•HCl

Various analytical techniques have been applied for the determination of MFX including HPLC-UV [5,6], HPLC-fluorescence [7], HPLC-mass spectrometry [8], spectrophotometry [9], AA spectrometry [10], conductometry [10], spectrofluorimetry [11], voltammetry [12], potentiometry [13] and CE [14,15]. Most of these methods are complicated, involve derivation procedures, time and labor consuming, and require sophisticated expensive instruments. In recent years, interest to develop accurate analytical methods that are valid for the quantification of MFX in pharmaceutical forms and biological samples increased. Potentiometric methods, using ion selective electrodes (ISEs) have found wide application; providing fast results, simple analysis procedures, economical costs, applicable over a wide range of concentrations, good selectivity, preciseness, applicability to turbid and colored solutions, applicability to various drug forms, and offering enough selectivity towards the drug in the presence of various pharmaceutical excipients [16]. The proposed sensors based on the use of PVC membrane sensor of MFX-tetraphenyl borate (MFX-TPB), MFX-REINECKATE (MFX-RNK) or MFX-NESSLER's reagent (MFX-NSR) as electro-active materials.

2. MATERIALS AND METHODS

2.1 Apparatus

The electrochemical measurements were made with IONcheck 10 pH/mV meter-RADIOMETER analytical S.A., France, with MFX–tetraphenyl borate (TPB), –REINECKATE salt (RNK) or –NESSLER's reagent (NSR) - poly(vinyl chloride) (PVC) – di-n-butyl phthalate (DBP) plasticizer membrane electrodes in conjunction with double junction Ag/AgCl electrode as external reference electrode (Lab. assembly), containing 1M potassium chloride in the outer compartment. CRISON-GLP 21/EU pH-meter was used for pH adjustment for all pH measurements. All potentiometric measurements were made at 25±1°C with constant stirring using hot-plate magnetic stirrer MS 300 BANTE, China. All weights were taken by analytical balance (BP 221S SARTORIUS, Germany) with accuracy ±0.1mg. Conductivity meter (inoLab-cond 720, Germany) used for bi-distill water quality. The oven (WTB binder-78532 TUTTLINGEN, Germany) for drying. The charger (ZAIN 300 mA/ 3-12 V, China) used for Ag/AgCl electrodes assembling.

2.2 Reagents and Materials

Analytical grade Moxifloxacin (MFX•HCl) (ROCHE PHARMA AG, Germany), high molecular weight poly vinyl chloride (PVC) (SABC, KSA), sodium tetraphenyl borate $Na[(C_6H_5)_4B]$ (NaTPB) 99%, di-n-butyl phthalate (DBP) 99.0%, tetrahydrofuran (THF) 97.0%, hydrochloric acid, sodium hydroxide, potassium chloride (guarantee reagent grade, MERCK, Germany) were used. Bi-distilled water (conductivity≤10 µS/cm), silver wire (Φ=1 mm, Swiss, 99.9%), ammonium REINECKATE $NH_4[Cr(SCN)_4(NH_3)_2]•H_2O$ (NH_4RNK) (BDH Laboratory, England), mercury iodide (BDH Laboratory, England) and potassium iodide (ScP, England) were used.

2.3 Standard Drug Solutions

Stock standard solution (0.01 M) MFX•HCl (Mw=437.89 $g.mol^{-1}$) was prepared by dissolving accurate weight in bi-distilled water and analyzed by HPLC. During the work, this solution was found to be stable for several weeks if kept in the dark at 4 °C. Working solutions ranging 0.1-10000 µM were prepared by serial dilution of the stock solution. These solutions are stable for at least 1 week if stored in a cool and dark place. BRITTON-ROBINSON universal buffers 0.2 M were used [17].

2.4 Preparation of NESSLER's Reagent

THOULET'S solution $\{K[HgI_3]\}$ was prepared by mixing 1 mmol hot aqueous suspension of mercury (II) iodide with 2 mmol solution of potassium iodide. To have NESSLER's reagent $\{K_2[HgI_4]\}$, 2 mmol potassium hydroxide was added. Any precipitate was filtered. Then, the filtrate brought to room temperature and diluted to the required concentration [18]. Freshly prepared reagent was used for synthesis of ion accumulate.

3. ION SELECTIVE ELECTRODES

3.1 Synthesis of Ion Pairs

The ion-pairs were prepared by mixing equal volumes of 10 mM MFX solution with 10 mM tetraphenyl borate (NaTPB, IP-1), 10 mM ammonium REINECKATE (RNK, IP-2), or 20 mM NESSLER's reagent (NSR, IP-3). Each mixture was stirred for 30 min and left in the dark for over-night to settling down. The resulting precipitates were filtered, washed with bi-distilled water several times until the conductivity of the washed water is close to the conductivity of the bi-distilled water used. Then, the precipitates were air dried at room temperature over-night away from light and dust. Each ion pair was ground into a fine powder using an agate mortar, then dried in the oven at 50 °C until the weight was stable. The resulting products were yellowish white of MFX-TPB (IP-1), reddish of MFX-RNK (IP-2), yellowish of MFX-NSR (IP-3).

Ion pairs were stored in will-closed amber glass bottles at 4 °C. The molecular ratios of the complexes were found to be 1:1 for MFX-TPB (IP-1), 1:1 for MFX-RNK (IP-2), 1:2 for MFX-NSR (IP-3).

3.2 Casting of Ion Selective Membrane

The membrane was casted by dissolving equal weights of matrix PVC and the plasticizer (DBP), and the suitable weight of the ion pair (IP) to have the target composition of ion selective membrane. The mixture was dissolved by minimum volume of THF. The resulting solution was poured into a glass PETRI dish and covered with a filter paper, avoided from air movement, dust and direct sunshine. The solvent allowed evaporating slowly at room temperature, leaving the casted ion selective membrane that represents the electro-active part of ion selective electrode (ISE). Membranes were stored between two metal foils, in will-closed container at 4 °C.

3.3 Construction of Ion Selective Electrode (ISE)

Circular cut from casted membrane was glued to a polished polyethylene tube. The result bucket was attached to the end of a suitable glass tube. This body of the ISE was filled with internal reference solution consisting of 1 mM of MFX in 1M potassium chloride (KCl) solution. Ag/AgCl wire electrode (lab. assembly) was used as an internal reference electrode [19,20]. The indicator electrode conditioned by soaking it in a 1 mM aqueous MFX solution for 30 min.

3.4 Assembling of Ion Selective Electrode Cell

The cell assembled by attaching the above ISE in conjunction with double junction Ag/AgCl electrode as external reference electrode, containing 1 M potassium chloride in the outer compartment (lab. assembly). The circuit closed by attaching the cell and outer reference electrode to temp./pH/mV-meter. The following electro-chemical cells were accomplished [21]:

$\mathbf{SE_{MFX\text{-}TPB,\ RNK,\ or\ NSR}}$: Ag/AgCl-KCl (1M) + MFX (1mM) ||
MFX–TPB, MFX–RNK, or MFX–NSR –DBP–PVC membrane ||Test solution||Ag/AgCl-KCl (1M)

3.5 Electrodes Calibration

A suitable aliquot of 0.1-10000 µM standard solutions of MFX were transferred into a fit compartment held in stable temperature jacket, and the membrane electrode in conjunction with Ag/AgCl reference electrode was immersed in the test solution. All potentiometric measurements were performed using the cells assembly mentioned above. The measured potential was plotted against the minus logarithm of drug concentration (pC_{MFX}). The electrode was washed with bi-distilled water and blotted with tissue paper between measurements.

3.6 Standard Addition Method

The electrode was immersed into sample of 50 mL with unknown concentration and the equilibrium potential E_1 was recorded. Then 0.1 mL of 0.1 M of standard drug solution was added into the testing solution and the potential E_2 was recorded. The concentration of the testing sample was calculated from the change of potential $\Delta E=E_2-E_1$.

3.7 Electrodes Selectivity

Selectivity coefficients $K^{pot}_{MFX,B}$ of the sensors towards different inorganic cations and some pharmacologically related compounds were determined according to IUPAC guidelines using the mixed solution method (MSM) [22,23]. The selectivity coefficient by mixed solution method was defined as the activity ratio of primary and interfering ions that give the same potential change under identical conditions, and the following equation applied:

$$K^{pot}_{MFX,B}=(a'_{MFX}-a_{MFX})/a_B$$

At first, a known activity (a'_{MFX}) of the primary ion solution is added into a reference solution that contains a fixed activity (a_{MFX}) 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) recorded again. The change in potential produced at the constant background of the primary ion must be the same in both cases [24].

3.8 Effect of pH

The effect of pH on the potential response of the prepared electrodes was studied using 10 and 1 mM MFX solutions. The pH of this solution was adjusted between 1.0-8.0 using suitable amounts of 0.1 M KOH or HCl solution. The potential readings corresponding to different pH values were recorded and plotted using the proposed electrodes. On other hand, the study was repeated using BRITTON-ROBINSON universal buffers.

3.9 Determination of MFX in Pharmaceutical Dosage Forms

Three local manufacturing formulations (Aleppo-Syria): Moxicin (tablets, IBN-ALHAYTHAM), and Moxiflox (tablets, RAZI LABS) both contain 400 mg of MFX; Megamox (0.5% MFX eye drop, RAMA PHARMA) were used for the analysis of MFX by direct potentiometric determinations. Ten tablets weighed and ground into a fine powder. A quantity equivalent to one tablet was weighed, dissolved in 50 mL bi-distill water with shaking for 5 min. Each of the solutions was filtered through a common filter paper, washed with water several times, transferred to 100 mL volumetric flask and diluted to the mark with bi-distilled water. Otherwise, 2 mL of the eye drop was diluted with bi-distilled water into 50 mL volumetric flask. Each of the final solutions was analyzed as described under electrode calibration and standard addition methods. The results obtained were compared to those obtained from HPLC [25].

3.10 Effect of Ion Pair Percentage on Electrode Potential

Groups of electrodes containing 2-10% IP were constructed. The potentiometric response characteristics of the MFX sensors based on the use of MFX-TPB (IP-1), MFX-RNK (IP-2), or MFX-NSR (IP-3) ion pairs in plasticized PVC matrixes evaluated according to IUPAC recommendations [22]. The graphs plotted for relation $E(mV)=f(pC_{MFX})$.

4. RESULTS AND DISCUSSIONS

4.1 Calibration Graph and Effect of Ion Pair Percentage on Electrode Potential

The analytical range of a potentiometric sensor was the linear part of the calibration graphs (10^{-2}-10^{-5} M for three sensors). Where the total measuring range (TMR) includes the linear part of the graph (quantitative part) together with a lower curved portion of the calibration graphs (qualitative part) where the response to varying concentration becomes progressively less as the concentration reduces. Samples can be measured in this lower range but it must be noted that more closely spaced calibration points are required in order to define the curve accurately and the percentage error per mV on the calculated concentration will be progressively higher as the slope reduces. TMRs were 10^{-2}-5.62×10^{-6} for MFX-TPB, and 10^{-2}-10^{-6} M for MFX-RNK and MFX-NSR (Fig 2).

Increasing IP percentage in the membrane was found to increase the electrode response and the stability of potentiometric readings as well as increasing the slopes of the liner area for equation curve $E = f(pC_{MFX})$ reaching -59.5 $mV.decade^{-1}$ at 6% MFX-TPB (IP-1), -46.08 $mV.decade^{-1}$ at 4% MFX-RNK (IP-2),or -29.67 $mV.decade^{-1}$ at 6% MFX-NSR (IP-3). At percentages higher than those previously named a decreased in electrode response, range and slope of liner area was determined due to the kinetic of the ion pair inside the membrane (Fig. 3). Table 1 summarized the least squares equations data.

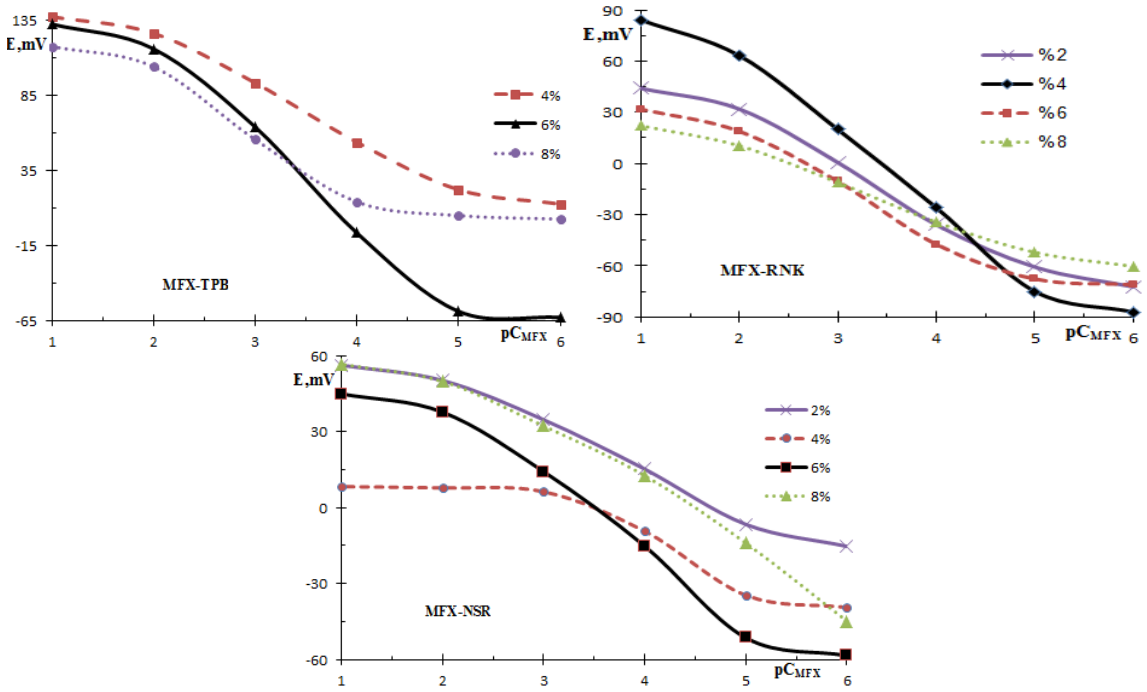

Fig. 2: Effect of IP content on MFX calibration curve

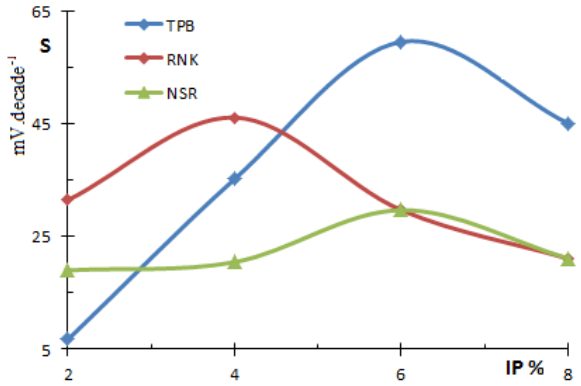

Fig. 3: Effect of IP percentage in the ion selective membrane on the slope of the liner area for equation curve: E = f(pC$_{MFX}$)

Table 1: The least squares equations data obtained from the liner equation

	MFX-TPB				MFX-RNK				MFX-NSR			
IP %	2	4	6	8	2	4	6	8	2	4	6	8
S, mV	-6.73	-35.18	**-59.50**	-45.05	-31.46	**-46.08**	-29.67	-21.08	-18.99	-20.45	**-29.67**	-21.10
b, mV	60.68	196.93	236.80	192.95	94.11	156.88	77.17	51.98	89.84	69.27	100.17	94.00
r^{2} *	0.9981	0.9982	0.9961	0.9980	0.9950	0.9992	0.9888	0.9972	0.9944	0.9816	0.9909	0.9904

***** Correlation coefficient

4.2 Electrodes Selectivity

The obtained selectivity coefficients $K^{pot}_{MFX,B}$ of the sensors towards different inorganic cations and some pharmacologically related compounds were results are given in Table 2. The result shows a reasonable selectivity for MFX in the presence of many related interferences.

Table 2: Selectivity coefficient of some interfering ions by MFX-ISEs

Interfering, B	$^{pot}K_{MFX,B}$		
	MFX-TPB	**MFX-RNK**	**MFX-NSR**
Sodium chloride	8.8×10^{-3}	2.3×10^{-3}	4.4×10^{-3}
Potassium chloride	7.7×10^{-3}	2.6×10^{-3}	2.4×10^{-3}
Calcium chloride	5.5×10^{-3}	5.3×10^{-3}	4.1×10^{-3}
Magnesium chloride	6.1×10^{-3}	5.5×10^{-3}	5.8×10^{-3}
Magnesium stearate	4.6×10^{-3}	4.8×10^{-3}	4.2×10^{-3}
Microcrystalline Cellulose	3.4×10^{-3}	5.3×10^{-3}	4.7×10^{-3}
Glucose	7.3×10^{-3}	1.9×10^{-3}	2.1×10^{-3}
Starch	5.5×10^{-3}	3.3×10^{-3}	3.9×10^{-3}
Lactose monohydrate	2.2×10^{-3}	1.9×10^{-3}	1.7×10^{-3}

4.3 Effect of pH on response

The results of studying pH effect on potential response showed that the potential remained constant despite the pH change in the ranges of 2.0-5.0 for MFX-TPB sensor, 2.0-5.5 for MFX-RNK sensor, and 2.0-6.0 for MFX-NSR sensor, which indicates the applicability of these electrodes in the pH specified ranges. By using BRITTON-ROBINSON universal buffers a constant potential was acquired in the ranges of 2.0-6.0 for MFX-TPB and MFX-RNK sensor, or 2.0-6.5 for MFX-NSR sensor (Fig. 4).

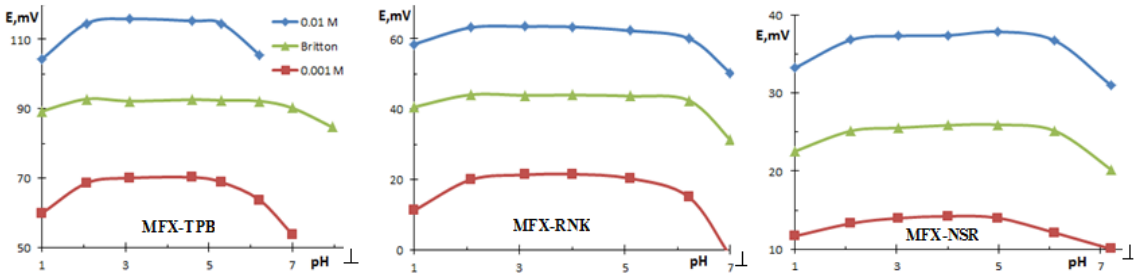

Fig. 4: Effect of pH on the potential response of the MFX sensors using 10 mM MFX solution, 1 mM MFX solution, or 5 mM BRITTON-ROBINSON universal buffers solution.

At pH lower than 2.0, the potential of the electrode decreased due to the migration of H^+ ions from membrane. On other hand, the potential decreased at higher pH values (> 6.5) due to the gradual increase in the concentration of the non-protonated MFX, or due to the influence of the ion pair mobility inside the ion selective membrane [26,27].

4.4 Lifetime Study

MFX electrodes lifetimes were estimated from the calibration curves. Periodical tests of standard MFX solutions (0.1–10000 µM) were made and its response slopes were calculated. For this purpose, two sensors were employed and the calibration graphs were plotted after optimum soaking time of 6 h in 1mM MFX solution. The slopes of the calibration curves were 59.47, 46.22 and 29.67 mV.decade^{-1} at 25 °C for MFX-TPB, MFX-RNK and MFX-NSR sensors, respectively. The electrodes were continuously soaked in 1mM solution of MFX for about 15 days. The calibration plot slopes decreased slightly to be 53.5, 41.49 and 26.80 mV.decade^{-1} after 10 days for MFX-TPB, MFX-RNK and 13 days for MFX-NSR sensors. This reveals that soaking 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.

4.5 Response characteristics and Statistical Data

The characteristics performance for the three proposed electrodes was determined and the results summarized in Table 3. The three proposed sensors show nearly NERNESTIAN response over the concentration range 10-10000 µM (pC_{MFX} = 2-5).

Table 3: Response characteristics of MFX-sensors[a].

Parameter	MFX-TPB	MFX-RNK	MFX-NSR
IP%	6%	4%	6%
Slope, mV.decade^{-1}	59.45 ± 0.15	46.19 ± 0.09	29.65 ± 0.02
Intercept, mV.decade^{-1}	236.80	156.88	100.17
Correlation coefficient (R^2)	0.9961	0.9992	0.9909
Linear range, µM	10-10000	10-10000	10-10000
TMR, µM	5.62-10000	1-10000	1-10000
LOD, µM	9.12	5.01	4.57
LOQ, µM	27.36	15.03	13.71
Response time for 1 mM, sec	17 ± 3	18 ± 2	19 ± 2
Life time, day	10	10	13
Working pH range	2.0-5.0* 2.0-6.0**	2.0-5.5* 2.0-6.0**	2.0-6.0* 2.0-6.5**

[a] Five replicate measurement
* Without buffer
** Using BRITTON-ROBINSON universal buffers

4.6 Quantification of MFX

The investigated sensors found to be useful in the potentiometric determination of MFX in pure solutions by calibration graph and standard addition method as well as in direct determinations of MFX in both pure form (Table 4) and pharmaceutical preparations (Table 5). The results obtained for pharmaceutical preparations were compared with a reference HPLC method [24]; the $\bar{X}$ ± SD (R%) values were 404.5 ± 5.7 mg (101.13%), 402.5 ± 3.9 mg (100.63%), and 5.247 ± 0.012 mg (104.94%) for Moxicin, Moxiflox, and Megamox respectively. Statistical analysis 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 [28].

Table 4: Direct determinations of MFX in bulk solution using proposed sensors

Taken $C_{MFX\cdot HCl}$		MFX-TPB*			MFX-RNK*			MFX-NSR*		
(µg/mL)	mol/L	R%	SD	RSD%	R%	SD	RSD%	R%	SD	RSD%
0.438	**1×10^{-6}**	98.58	0.0055	1.28	99.09	0.0078	1.81	99.27	0.0083	1.91
4.38	**1×10^{-5}**	99.32	0.0453	1.04	101.14	0.0552	1.25	101.14	0.0826	1.87
43.8	**1×10^{-4}**	99.22	0.3847	0.88	99.82	0.5310	1.21	99.41	0.7925	1.82
438	**1×10^{-3}**	99.22	3.3615	0.77	100.91	4.8477	1.10	99.45	7.4364	1.71
4380	**1×10^{-2}**	99.92	31.7223	0.72	99.89	33.2461	0.76	99.83	47.2948	1.08

*Average of five replicates.

Table 5: Determinations of MFX in pharmaceutical preparations using proposed sensors

Ion Pair	$\bar{X} \pm SD$, mg[a]	R%	t-value[b]	F-value[c]
	Moxicin, tablets			
MFX-TPB	403.8 ± 3.7	100.95	0.0452	2.372
MFX-RNK	405.8 ± 5.7	101.45	0.0508	1.009
MFX-NSR	400.9 ± 5.3	100.24	0.1516	1.065
	Moxiflox, tablets			
MFX-TPB	402.8 ± 3.4	100.70	0.1748	1.323
MFX-RNK	402.6 ± 2.7	100.65	0.1791	1.578
MFX-NSR	402.1 ± 2.3	100.53	0.1638	3.025
	Megamox, eye drop			
MFX-TPB	5.228 ± 0.022	104.56	0.2068	3.361
MFX-RNK	5.372 ± 0.098	107.44	0.3178	3.618
MFX-NSR	5.230 ± 0.027	104.60	0.1465	5.119

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

5. METHOD VALIDATION

5.1 The linearity, LOD, and LOQ

MFX standard solutions of 0.1-100000µM (pC_{MFX}=1-7) were measured using ISEs in conjunction with Ag/AgCl reference electrode. Each of different concentration of standard solution was tested five replicates. The potentials obtained for the five analyses averaged at each concentration. The average potential was plotted versus pC_{MFX} according to the straight-line equation: $E = S \times pC_{MFX} + b$. The three sensors displayed a linear response over the concentration range 10-10000 µM over a pH range of 2.0-5.5 (pC_{MFX}=2-5). The limit of detection (LOD) and limit of quantification (LOQ) were determined according to the IUPAC recommendation [28]. LOD and LOQ found to be 9.12, 5.01, and 4.57 µM, and 27.36, 15.03, and 13.71 µM for MFX-TPB, MFX-RNK, and MFX-NSR sensors, respectively (Table 3).

5.2 Recovery and Precision

The recovery was calculated by comparing the potential of the found MFX concentration to direct added standard in BRITTON-ROBINSON universal buffers (pH=2-6). Precision reported as RSD %. Its values of inter-a-day (three replicates, Table 4) and inter-day (three different days) studies for the repeated determination were less than 2% which indicating good precision.

6. CONCLUSION

It can be concluded that MFX-TPB-PVC, MFX-RNK-PVC, MFX-NSR-PVC membrane sensors offers a viable technique for the direct determination of MFX in pharmaceutical preparations as well as in pure form solutions. The sensors construction is simple, rapid, and reproducible. The sensors exhibit a good selectivity towards the drug in the presence of various pharmaceutical excipients, and it can be used as indicator electrodes in potentiometric titrations of MFX.

Three different electro-active complexes of MFX have been performed as sensors for MFX. The MFX membrane sensors displayed good analytical performance. The sensors display a fast, stable and near NERNESTIAN response over a relative wide MFX concentration range of 10-10000 µM (pC_{MFX}=2-5).

Using MFX-RNK, MFX-NSR as electro-active materials, the proposed sensors accomplished LOD of 5.01, 4.57 µM, comparing with 9.12 µM, LOQ of 15.03, 13.71 µM, comparing with 27.36 µM for MFX-RNK and MFX-NSR sensors comparing with MFX-TPB, respectively (TPB: most widely used for synthesis of ion pairs). However, the proposed sensors have response time of 18±2, 19±2 sec for MFX-RNK and MFX-NSR

sensors, comparing with 17±3 sec for MFX-TPB. In other hand, MFX-NSR accomplished a sensor life time 3 days longer, but in other work [13], 30±0.5 sec for MFX-TPB.

Concerning pH range of measurements, the proposed sensors have pH range up to 2.0-2.5, 2.0-6.0 without using any buffers, comparing with 2.0-5.0 for MFX-RNK and MFX-NSR sensors comparing with MFX-TPB, respectively. However, in [13] the pH range was 6.0-9.0 for MFX-TPB.

The direct determination of MFX showed an average recovery of 99.22, 100.91 and 99.45% and a mean relative standard deviation of 0.77, 1.10 and 1.71% at 1 mM (438 µg/mL) MFX•HCl for MFX-TPB, MFX-RNK, and MFX-NSR sensors, respectively. The results obtained are within the acceptance range of less than 3.0 % of RSD % for precision and more than 98.3 % of R % for the accuracy. The sensors have been used as indicator electrodes for direct determination of MFX in pharmaceutical preparations as well as in pure form solutions.

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