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SIMULTANEOUS POTENTIOMETRIC DETERMINATION OF CIPROFLOXACIN-METRONIDAZOLE-MINOCYCLINE IN TRIAD COMBINATION USING NOVEL DRUG SELECTIVE SENSOR

Amir ALHAJ SAKUR*, Hashem A. DABBEET, Imad NOURELDIN

Department of Analytical and Food Chemistry, Faculty of Pharmacy, Aleppo University, Syria

***Corresponding author E-mail:** profsakur@gmail.com

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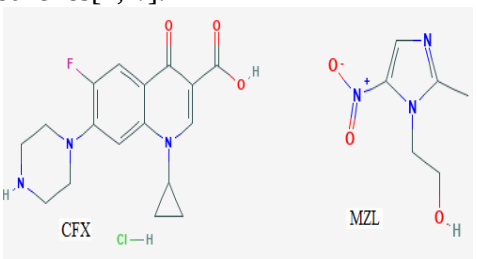
ABSTRACT

We investigated the capability of putting3 ion complex (pairs) in the same selective electrode's membrane, and so constructing an electrode sensitive to either Ciprofloxacin (CFX), Metronidazole (MZL), or Minocycline (MIN) according to the standard filling solution of the electrode, subsequently determine the three drugs CFX, MZL, and MIN Simultaneously in their combined solutions.Four PVC membrane drug selective sensors were constructed forCFX, MZL, and MINanalysis intended. The electroactive materials wereCFX- Tetraphenyl borate (CFX-TPB), MZL-Tetraphenyl borate (MZL-TPB), MIN-Tetraphenyl borate (MIN-TPB), and a composition of CFX-TPB +MZL-TPB + MIN-TPB. The characterization and analytical properties were determined,and the casting selective membranes of the selective electrodes were plasticized by Dioctylphthalate (DOP). Each of the assembled electrodes haveinternal reference Ag/AgCl electrode. Also, the gathered sensors haveexternal reference Ag/AgCl electrode. The developed sensors showed near NERNSTIAN response for ion pair percentagesof7%for both CFX-TPB andMZL-TPB, and 6% for MIN-TPB.The electrodes demonstrated a rapid responses of 9-14 sec for a period of 14-17days, with no changes that have meaningful results in the electrodes parameters. The suggested sensors have measurement pH ranges 2.0-6.0 for CFX, 2.0-5.25 for MZL, and 2.0-5.0 for MIN without using any buffers. The sensors were used asindicator electrodes for direct determination of CFX, MZL, and MIN in pharmaceutical preparations with mean relative standard deviation less than 2% that indicating good precision, as well as in pure form solutions with average recovery of 99.99, 99.94, 99.98 and 99.85% (CFX) or 99.86% (MZL) or 99.99% (MIN) and a mean relative standard deviation of 0.04%, 0.14%, 0.02 and 0.08% (CFX) or 0.20% (MZL)% or 0.02% (MIN) at 1 mM (367.8 µg/mL CFX, 171.2 µg/mL MZL, or 493.9 µg/mL MIN) for SENSOR-1, SENSOR-2, SENSOR-3, SENSOR-4, respectively. The acquire results were within the acceptance range of less than 2.0 % of RSD % for precision and more than 99.18 % of R % for the accuracy. ForCFX-TPB + MZL-TPB + MIN-TPB sensors respectively.

INTRODUCTION

Ciprofloxacin.HCL (CFX) {1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1, 4 dihydroquinoline-3-carboxylic acid hydrochloride} (Fig. 1) is a synthetic bactericidal 2nd generation fluoroquinolone that is widely used in the therapy of mild-to-moderate urinary and respiratory tract Infections caused by susceptible organisms. Ciprofloxacin exerts its bactericidal effect by interfering with the bacterial DNA gyrase, Thereby inhibiting the DNA synthesis and preventing bacterial cell growth [i,ii]. Metronidazole (MZL) {2-(2-methyl-5-nitroimidazol-1-yl)ethanol} (Fig. 1) is a synthetic nitroimidazole derivative with

antiprotozoal and antibacterial activities used For the treatment of anaerobic infections and mixed infections, surgical prophylaxis requiring anaerobic coverage, Clostridium difficile-associated diarrhea and colitis, Helicobacter pylori infection and duodenal ulcer disease, bacterial vaginosis, Giardia lamblia gastro-enteritis, amebiasis caused by Entamoeba histolytica, and Trichomonas infections. Reduced form of metronidazole causes DNA strand breaks, thereby inhibiting DNA synthesis and bacterial cell growth [1,iii]. Minocycline.HCL (MIN) {(4S,4aS,5aR,12aR)-4,7-bis(dimethylamino)-1,10,11,12a-tetrahydroxy-3,12-dioxo-4a,5,5a,6-tetrahydro-4H-tetracene-2-carboxamide;hydrochloride} (Fig. 1) is a broad-spectrum long-acting derivative of the antibiotic tetracycline, with antibacterial and anti-inflammatory activities which is used to treat many different bacterial infections, such as urinary tract infections, respiratory infections, skin infections, severe acne, chlamydia, tick fever, and others. It is also used for gonorrhoea, syphilis, and other infections as a second-line drug in those with a penicillin allergy. Minocycline binds to the bacterial 30S ribosomal subunit and interferes with the binding of tRNA to the ribosomal complex, thereby inhibiting protein translation in bacteria. In addition, minocycline inhibits the inflammatory enzyme 5-lipoxygenase (5LOX) and may impede T cell-microglia interactions; both activities may contribute to minocycline's neuroprotective effects. 5LOX catalyzes the synthesis of inflammatory mediators such as prostaglandins and leukotrienes[1,iv].



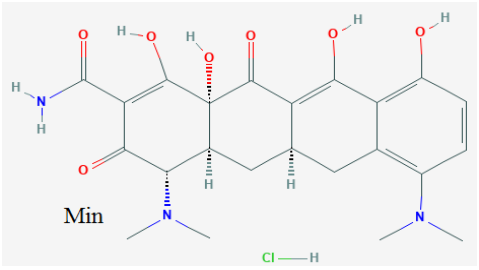


Fig. 1: Chemical Structure of Ciprofloxacin.HCL, Metronidazole, and Minocycline.HCL

The determination of CFX has been made by various analytical methods including HPLC and RP-HPLC [v], UV spectrophotometry [vi,vii,viii,ix,x], Derivative UV-Spectrophotometric [xi,xii], Spectroflourimetric [xiii], Rayleigh light scattering [xiv],Capillary Zone Electrophoresis [xv], Electrochemical Titrations [xvi], Electrical Micro-Titration [xvii], potentiometric methods using ion selective electrodes [xviii,xix]. While MZL determination has been made by various analytical methods including HPLC[xx],Spectrophotometric [xxi,xxii],cyclic voltammetric (CV) and differential pulse voltammetric (DPV) [xxiii,xxiv,xxv],Electrochemical Determination [xxvi].In addition, MIN determination has been made by various analytical methods including HPLC [xxvii],Semi-Differential Cyclic Voltammetry[xxviii],Spectrophotometric Determination [xxix], Electrochemical determination [xxx].Some analytical methods were state for the simultaneous determination of Ciprofloxacin HCL and Metronidazole including HPLC and UPLC [xxxi], HPLC and TLC-Densitometric [xxxii],Spectrophotometric [xxxiii],Potentiometric method using ion-selective electrodes (ISEs) [xxxiv]. We found ISEs which uses PVC as a matrix or a trap for one ion pair useful for the determination of a single drug providing fast result, simple analysis procedures, and over that offering high selectivity towards the drug in the presence of various pharmaceutical excipients [xxxv,xxxvi,xxxvii,xxxviii], andwe achieve a selective electrode for the determination of either CFX or MZL according to the electrode filling solution by making two ISE_s with the same membrane containing CFX-PTA (IP-1)+ MZL-PTA (IP-2) for each of them and differ in the filling solution, and according to this filling solution the electrode was selective for either of the two drugs CFX or MZL [xxxix]. In this work we assembled a novel electrode containing three different ion pairs of Ciprofloxacin, Metronidazole, and Minocycline. The analytical properties of the combined electrode was studied, and the

electrode was found to be selective for the three drugs in their triad mixture.

2.MATERIALS AND METHODS

2.1 Apparatus

All electrochemical measurementswere made withthreeIONcheck 10 pH/mV meter-RADIOMETER analytical S.A., France, with CFX-tetraphenyl borate (TPB), MZL-tetraphenyl borate (TPB), MIN-tetraphenyl borate (TPB), or CFX-TPB+MZL- TPB+ MIN-TPB –poly(vinyl chloride) (PVC)– Dioctylphthalate (DOP)plasticized membrane electrodes in conjunction withAg/AgCl wire as an external reference electrode. CRISON-GLP 21/EUpH-meterused for pH adjustment for all pH measurements.All potentiometric measurements were made at 25±1℃ with constant stirringusing hot-plate magnetic stirrer MS 300BANTE, China. All weights were taken by analytical balance (BP 221SSARTORIUS, Germany) with accuracy ±0.1mg. Conductivity meter (inoLab-cond 720, Germany)was used for bi-distill water quality. Oven (WTB binder-78532 TUTTLINGEN, Germany).

2.2 Reagentsand Materials

Ciprofloxacin CFX•HCL(Zhejiang Langhua Pharmaceutical Company, Linhai, China), with a purity proportion of 99.95%. Metronidazole MZL(Shaoxing hantai pharmaceutical co. ltd, China) 99.90%. Minocycline.HCL (Shaoxing hantai pharmaceutical co. ltd, China) 99.5%.High molecular weight poly vinyl chloride (PVC) (SABC, KSA).Sodium tetraphenyl borate $Na[(C_6H_5)_4B]$ (NaTPB) 99%, Dioctylphthalate (DOP) 99.0%,tetrahydrofuran (THF) 97.0%, hydrochloric acid, sodium hydroxide, potassium chloride(guarantee reagent grade,MERCK, Germany) were used.Bi-distilledwater (conductivity≤10 µS/cm),silverwire(Φ=1mm, Swiss, 99.99%) were used.

2.3 Standard Drug Solutions

Stock standard solutions (0.01 M) CFX.HCL(Mw=367.805 $g.mol^{-1}$), (0.01 M) MZL (Mw=171.156 $g.mol^{-1}$), (0.01 M) MIN.HCL (Mw=493.9 $g.mol^{-1}$)were prepared by dissolving accurate weightin 1 M KCL, this solutionswerestable for several weeks if kept in the dark at 4 ℃. Working solutions ranging 0.1-10000 µM were prepared by serial dilution of the previous stock solutions with 1 M KCL. These solutions are stable for 1 week if stored in a cool and dark place.BRITTON-ROBINSONuniversal buffers 0.2 M were used [xl].

3.ION SELECTIVE ELECTRODES

3.1 Preparation of Ion Pairs

The three ion-pairs were prepared by mixing equal volumes of 10 mM CFX, 10 mM MZL, 10 mM of MIN solutions with 20 mM sodium tetraphenyl borate (NaTPB) to form the three ion pairs (CFX-TPB, IP-1), (MZL-TPB, IP-2), (MIN-TPB, IP-3) respectively. Each mixture was stirred for 30 min and left in the darkover-night to settling down.Eachof the resulting precipitates wasfiltered, washed with bi-distilled water several times until the conductivity of the washed water is close to the conductivity of the usedbi-distilled water.After that, the precipitatewas dried at room temperature over-night away from light and dust. Using an agate mortarion pairsweregroundedinto a fine powder, then dried in the oven at 60 ℃ until the weight was stable. Ion pairs were stored in will-closed amber glass bottlesat 4 ℃. The molecular ratios of the complexes werefound to be 1:1 for CFX-TPB(IP-1), 1:1 for MZL-TPB(IP-2) , 1:1 for MIN-TPB (IP-3).

3.2 Casting of Ion Selective Membranes

The membraneswereprepared by dissolving equal weights of matrix PVC and the plasticizer (DOP), and the suitable weight of the ion pairs (IP-1, IP-2, IP-3 or IP-1+IP-2+IP-3) to have the target composition of ion selective membranes. Each mixture was dissolved by minimumvolume of THF,and the resulting solution was poured into a 9 cmglass PETRIdish and covered with a filter paper, avoided from air movement, dust and direct sunshine. The solvent was allowed to evaporate 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 twoaluminum foils, in will-closed container at 4 ℃.

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 ISEwas filled with internal reference solution consisting of 1 mM of CFX, 1 mM of MZL, or 1 mM of MIN in 1M potassium chloride (KCl) solution. Ag/AgCl wire electrode(lab. assembly) was used as an internal reference electrode[xli].The indicator electrode conditioned by soaking it in a 1 mM aqueous CFX, MZL, or MIN solution for 30 min.

3.4 Assembling of Ion Selective Electrode Cell: The cell assembled by attaching the above ISE in conjunction with Ag/AgCl wireas external reference electrode.The circuit closed by attaching the cell and outer reference electrode to temp./pH/mV-meter.The following electro-chemicalcells were accomplished [xlii]:

$SE_{CFX\text{-}TPB}$: Ag/AgCl-KCl (1M) +CFX (1mM) || CFX–TPB–DOP–PVC membrane ||Testsolution-KCl (1M) ||Ag/AgCl

$SE_{MZL\text{-}TPB}$: Ag/AgCl-KCl (1M) + MZL (1mM) || MZL–TPB–DOP–PVC membrane ||Testsolution-KCl (1M) ||Ag/AgCl

$SE_{MIN\text{-}TPB}$: Ag/AgCl-KCl (1M) + MIN (1mM) || MIN–TPB–DOP–PVC membrane || Testsolution-KCl (1M) || Ag/AgCl

$SE_{CFX+MZL+MIN\text{-}TPB}$: Ag/AgCl-KCl (1M) + CFX, MZL, or MIN (1mM) || CFX–TPB + MZL-TPB + MIN-TPB –DOP–PVC membrane ||Testsolution-KCl (1M) ||Ag/AgCl

3.5 ElectrodesCalibration: A suitablesample of 0.1-10000 µM standard solutions of CFX, MZL, or MIN in 1 M KCLwere transferred into a fitcompartment held in stable temperature jacket, and the membrane electrode in conjunction with Ag/AgClreference electrode was immersed in the test solution. All potentiometric measurements were performed using the cellsassembly mentioned above.The measured potential was plotted against the minus logarithmof drug concentration (pC_{CFX}, pC_{MZL}, pC_{Min}). The electrodes were washed with bi-distilled water and wiped with tissue paper between measurements.

3.6 Standard Addition Method: The electrode wasimmersed 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 ElectrodesSelectivity: Selectivity coefficients$K^{pot}_{CFX,B}$, $K^{pot}_{MZL,B}$, $K^{pot}_{MIN,B}$of the sensors towards different inorganic cations and some pharmacologically related compounds were determined according to IUPAC guidelines using the mixed solution method (MSM) [xliii,xliv]. The selectivitycoefficient by mixed solution method was definedas the activity ratio of primary and interfering ionsthat give the same potential change under identical conditions, and the following equations applied:

$$K_{CFX,B}=(a'_{CFX}-a_{CFX})/a_B$$

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

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

At first, a known activity (a'_{CFX}), (a'_{MZL}), or (a'_{MIN}) of the primary ion solution is added into a reference solution that contains a fixed activity (a_{CFX}), (a_{MZL}), or (a_{MIN}) 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[xlv].

3.8 Effect of pH: The effect of pH on the potential response of the prepared electrodes was studied using 0.01 and 0.001 M CFX, MZL, MIN solutions. The pH of this solutionswas 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 0.005 M BRITTON-ROBINSON universal buffers.

3.9 Determination of CFX, MZL, MIN in Pharmaceutical Dosage Forms: The following formulations were used for the analysis of CFX, MZL, MIN and CFX+MZL+MIN combination by direct potentiometric determinations:

Ciproflex (tablets, ALPHApharmaceutical, Syria):Each tablet contain 500 mg of CFX.
Flagyl (tablets, OUBARI pharma, Syria):Each tablet contain 500 mg of MZL.
Quatrocin (capsules, AL FARES pharmaceutical, Syria): Each capsule contain 100 mg of MIN
3 MIX Caps (Model Capsule Formulation Containing 500 mg of CFX, 500 mg of MZL, and 100 mg of MIN, lab.prepared).Ten tablets weighed and ground into a fine powder. A quantity equivalent to one tablet was weighed and dissolved in 50 mLKCL (1M) with shaking for 5 min., transferred to 100 mL volumetric flask and diluted to the mark with KCL (1M), 10 mL of the solution was transferred to 100 mL volumetric flask and diluted to the mark with KCL (1M).Each of the final solutions was analyzed as described under electrode calibration and standard addition methods. The results obtained were compared to those obtained fromHPLC[27,xlvi].

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 sensors based on the use of CFX-TPB, MZL-TPB, and MIN-TPB ion pairs in plasticized PVC matrix was evaluated according to IUPAC recommendations [xlvii]. The graphs were plotted for relation:

$$E(mV)=f(Pc_{CFX})$$
$$E(mV)=f(Pc_{MZL})$$
$$E(mV)=f(Pc_{MIN})$$

4. RESULTS AND DISCUSSIONS

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

The linear part of the calibration graph is taken as the analytical range of the potentiometric sensor(quantitative part) and found to be 10-10000µM for all electrodes. Where the total measuring range (TMR) which can be considered as qualitative part and includes the linear part of the graph plusthe lower curved partof the calibration graph.TMRs were 5.62-31623 µM for CFX-TPB (SENSOR-1), 3.16-17783 µM for MZL-TPB(SENSOR-2), and 5.62-17783 µM for MIN-TPB (SENSOR-3). In addition, TMRs for the combined electrode (SENSOR-4) were 5.62-31623 µM for CFX, 3.16-17783 µM for MZL, and 5.62-17783 µM for MIN (showed in Fig 2).In TMR the response of the electrode to changing concentration becomes gradually less as the concentration decreases. In order to measure Samples in this lower range we need to put in mind that more closely-spaced calibration points are needed to define the curve accurately,taking into consideration that Error% per mV will be incrementally higher as the slope reduces on the calculated concentration. We found that increasing IP percentage in the membrane of the selective electrode increasing the response of the electrode and the stability of potentiometric readings besides increasing the slope of the linear area for equation curve $E = f(Pc_{Drug})$ reaching -59.04 $mV.decade^{-1}$ at 7% CFX-TPB (SENSOR-1), -59.11 $mV.decade^{-1}$ at 7% MZL-TPB (SENSOR-2),and -58.99 $mV.decade^{-1}$ at 6% for MIN-TPB (SENSOR-3). At percentages of ion pair higher than those mentioned a decline in the electrode response, range and slope of the liner area was resulteddue to the kinetic of the ion pair inside the membrane (Fig. 3). The previously mentioned ion pair percentages were taken as the best percentage for the composition of ion selective membrane in the combined ion selective electrode (SENSOR-4), and the slopes of the linear area were -58.99 $mV.decade^{-1}$ for CFX-TPB, MZL-TPB, MIN-TPB, respectively. Table 1 summarized the least squares equations data.

4.2 Electrodes Selectivity

The obtain selectivity coefficients $K_{CFX,B}$, $K_{MZL,B}$, $K_{MIN,B}$of the four electrodeswith relation to several inorganic interruptings, some pharmaceutically related compounds, and the other drugs for each electrode were as given in Table 2. The results showed a trustworthy selectivity for CFX, MZL, and MIN in the presence of many related interferences.

4.3 Effect of pH on response: The potential found to remain constant despite of pH changes in the ranges of 2.0-6.0 for CFX-TPB (SENSOR-1), 2.0-5.25 for MZL-TPB (SENSOR-2), and 2.0-5.0 for MIN-TPB (SENSOR-3), suggesting the suitability of usingthe developed electrodes in the previous described ranges of pH. Using BRITTON-ROBINSON universal buffer;a fixed potentials were established in pH ranges of 2.0-6.5 for

CFX-TPB (SENSOR-1), 2.0-6.0 for MZL-TPB (SENSOR-2), and 2.0-5.5 for MIN-TPB (SENSOR-3) (Fig. 4). When pHdeclined under 2.0, the potential measured with allfour electrodesdeclined, which can be explained as the result of the of H^+ions migration out of themembranes of the ion selective electrode. At pH values higher than 6.5 the potential also declined caused by the progressive increase in the concentration of the non-protonated drugs in the solutions, or due to the effect mobility of the ion pair inside the ion selective membrane [xlviii,xlix].

4.4Lifetime Study: We estimated the lifetime of the electrodesfrom the calibration curves,for thatdaily-periodical tests of standard CFX, MZL, and MINsolutions (1–10000 µM)were taken and its response slopes were calculated. The calibration graphs were plotted after optimum soaking time of six hours in 1mM CFX, MZL, or MIN solution. The slopes of the calibration curves were -59.04 mV.decade^{-1} for CFX-TPB (SENSOR-1), -59.11 mV.decade^{-1}for MZL-TPB (SENSOR-2), -59.0 mV.decade^{-1} for MIN-TPB (SENSOR-3),and -58.99 mV.decade^{-1}for CFX-TPB, -59.21 mV.decade^{-1} for MZL-TPB, -59.03 mV.decade^{-1} for MIN-TPB in SENSOR-4 at temperature of 25°C. The electrodes were continuously soaked in 1mM solution of CFX, MZL, or MINfor about twenty days. A delicatelydeclining in the slopes of the calibration curvesappearedfrom day to dayreaching-53.14 mV.decade^{-1} for CFX-TPB after 17 days and that is the lifetime of SENSOR-1, -53.2 mV.decade^{-1} for MZL-TPB after 14 days and that is the lifetime of SENSOR-2, -53.1 mV.decade^{-1} for MIN-TPB after 15 days and that is the lifetime of SENSOR-3. In the same way, the slope reached -53.09 mV.decade^{-1} for CFX-TPB after 16 days, -53.29 mV.decade^{-1} for MZL-TPB after 14 days, -53.13 mV.decade^{-1} for MIN-TPB after 15 days in SENSOR-4, and so the lifetime for the combined sensor (SENSOR-4) is limited to 14 days. Thatdemonstratedthat soaking sensors in the drugs solution for a long time has a ruinous 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 of the three suggested electrodes, and the combined electrode were determined and the results summed up in Table 3. All four suggested sensors show near NERNESTIAN response over the concentration range 10-10000 µM (pC_{Drug} = 2-5).

4.6 Quantification of CFX, MZL, and MIN:

The researched sensors were useful in the potentiometric determination of CFX,MZL, and MINin pure solutions by calibration graph and standard addition method as well as in direct determination of the three drugs in both pure solutions(Table 4) and pharmaceutical medicinal (Table 5). The results obtained for pharmaceutical medicinal were compared with a reference HPLC method [28,33]; the $\bar{X} \pm SD$ (R%) values were 502.4 ± 0.89 mg (100.48%), 499.4 ± 1.14 mg (99.88%) for Ciproflex, and 3-MIX Caps,respectively using SENSOR-1 (CFX-sensor), 507.6 ± 1.52 mg (101.52%), 501.6 ± 1.14 mg (100.32%)for Flagyl, and 3-MIX Caps, respectively using SENSOR-2 (MZL-sensor), 102.4 ± 0.55 mg (102.4%), 100.1 ± 0.16 mg (100.1%) for Quatrocin, and 3-MIX Caps, respectively using SENSOR-3 (MIN-sensor). While the $\bar{X} \pm SD$ (R%) values using SENSOR-4 (combined sensor) were as the follow: 502.0 ± 0.71 mg (100.4%) for CFX in Ciproflex, 507.4 ± 1.52 mg (101.48%) for MZL in Flagyl, 102.2 ± 0.84 mg (102.2%) for MIN in Quatrocin, 503.4 ± 3.05 mg (100.68%), 502.6 ± 1.67 mg (100.52%), 100.06 ± 0.15 mg (100.06%) for CFX, MZL, MIN respectively in 3-MIX Caps. 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 [l].

5. METHOD VALIDATION

5.1 The linearity, LOD, and LOQ: We measured CFX, MZL, and MIN standard solutions of 0.1-10000 µM (Pc_{Drug}=1-6) using the four mentioned ISEs in conjunction with Ag/AgCl reference electrodes. Each of the different concentration of standard solution is checked five times. The obtained potentials of the five analyses were averaged at each concentration. The average potential was plotted versus Pc_{CFX}, Pc_{MZL}, or Pc_{MIN} according to the straight-line equation: $E = S \times Pc_{CFX} + b$,

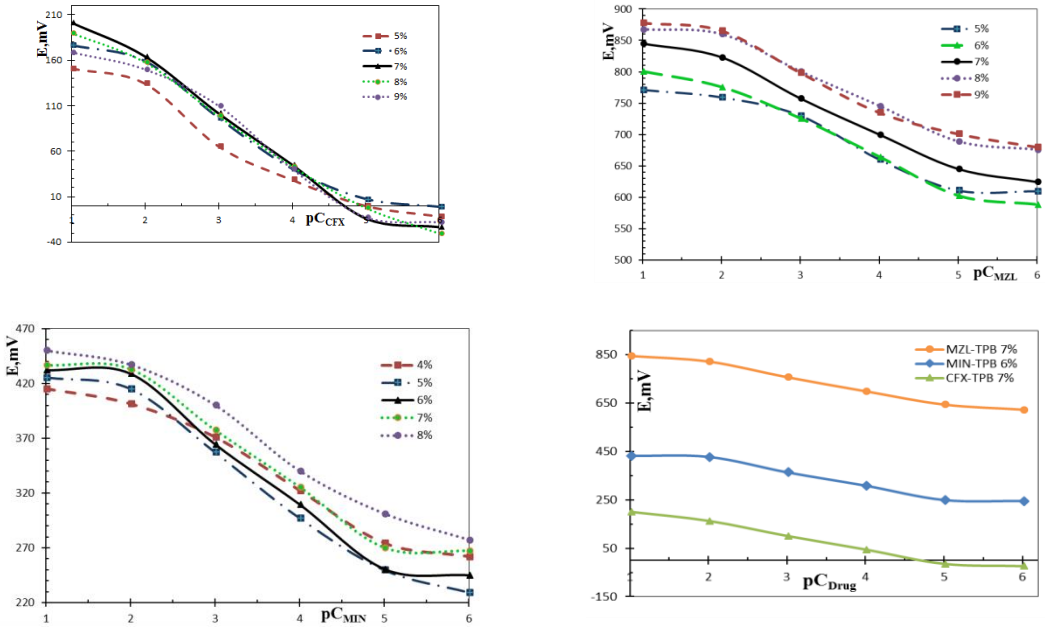


Fig. 2: Effect of IP content on CFX, MZL, MIN calibration curves

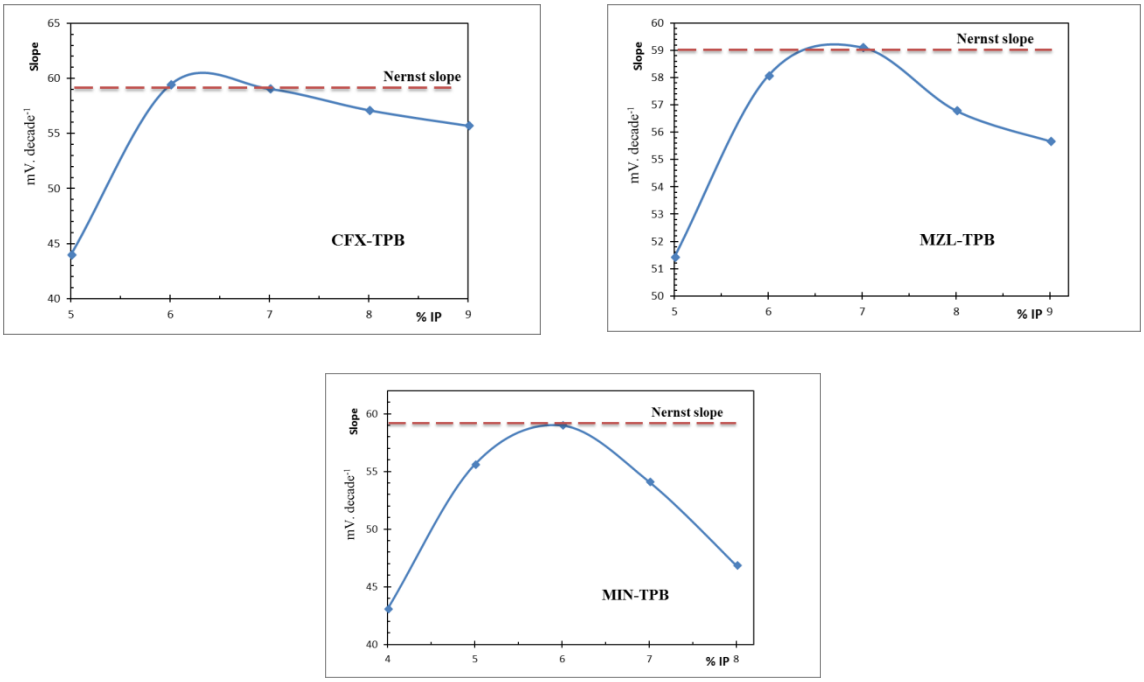


Fig. 3: Effect of IP percentage in the ion selective membrane on the slope of the liner area for equation curve: E = f(Pc_{Drug})

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

	SENSOR-1 CFX-TPB					SENSOR-2 MZL-TPB				
IP %	**5**	**6**	**7**	**8**	**9**	**5**	**6**	**7**	**8**	**9**
S, mV.decade^{-1}	-43.97	-59.4	**-59.04**	-57.1	-55.69	-51.42	-58.07	**-59.11**	-56.79	-55.67
b, mV.decade^{-1}	211.17	277.03	280.84	271.3	267.14	870.12	895.17	938.36	972.49	969.87
R^{2*}	0.957	0.999	0.9996	0.9997	0.9906	0.9786	0.9975	0.9983	0.9998	0.9805

	SENSOR-3 MIN-TPB					SENSOR-4 (combined sensor)		
IP %	**4**	**5**	**6**	**7**	**8**	**CFX**	**MZL**	**MIN**
S, mV.decade^{-1}	-43.07	-55.6	**-58.99**	-54.1	-46.85	-58.99	-59.21	-59.03
b, mV.decade^{-1}	493.02	524.4	544.84	540.9	533.75	280.19	938.01	544.23
R^{2*}	0.9897	0.9975	0.9991	0.9998	0.991	0.9996	0.9986	0.9992

***** Correlation coefficient

Table 2: Selectivity coefficient of some interfering ions by suggested ISEs

Interfering, B	**K_{pot} $K_{Drug,B}$**		
	SENSOR-1 CFX-TPB	**SENSOR-2 MZL-TPB**	**SENSOR-3 MIN-TPB**
Sodium chloride	5.7×10^{-3}	4.7×10^{-3}	3.9×10^{-3}
Potassium chloride	5.5×10^{-3}	3.7×10^{-3}	4.1×10^{-3}
Calcium chloride	7.3×10^{-3}	6.1×10^{-3}	5.2×10^{-3}
Magnesium chloride	4.3×10^{-3}	5.3×10^{-3}	4.9×10^{-3}
Magnesium stearate	5.1×10^{-3}	5.1×10^{-3}	5.1×10^{-3}
Microcrystalline Cellulose	4.1×10^{-3}	3.7×10^{-3}	4.2×10^{-3}
Glucose	3.8×10^{-3}	3.3×10^{-3}	3.1×10^{-3}
Starch	3.8×10^{-3}	3.3×10^{-3}	4.1×10^{-3}
Lactose monohydrate	2.3×10^{-3}	2.1×10^{-3}	2.5×10^{-3}
Ciprofloxacin. HCL	----	1.7×10^{-4}	1.9×10^{-4}

Metronidazole	1.4×10^{-4}	----	1.8×10^{-4}
Minocycline.HCL	1.8×10^{-4}	1.6×10^{-4}	----
		SENSOR-4	
	CFX-TPB	**MZL-TPB**	**MIN-TPB**
Sodium chloride	5.8×10^{-3}	4.8×10^{-3}	4.0×10^{-3}
Potassium chloride	5.7×10^{-3}	3.9×10^{-3}	4.3×10^{-3}
Calcium chloride	7.4×10^{-3}	6.2×10^{-3}	5.3×10^{-3}
Magnesium chloride	4.4×10^{-3}	5.4×10^{-3}	5.1×10^{-3}
Magnesium stearate	5.3×10^{-3}	5.4×10^{-3}	5.2×10^{-3}
Microcrystalline Cellulose	4.2×10^{-3}	3.9×10^{-3}	4.4×10^{-3}
Glucose	4.0×10^{-3}	3.4×10^{-3}	3.3×10^{-3}
Starch	3.9×10^{-3}	3.5×10^{-3}	4.2×10^{-3}
Lactose monohydrate	2.5×10^{-3}	2.3×10^{-3}	2.7×10^{-3}
Ciprofloxacin.HCL	----	1.8×10^{-4}	2.1×10^{-4}
Metronidazole	1.6×10^{-4}	----	1.9×10^{-4}
Minocycline.HCL	1.1×10^{-4}	1.7×10^{-4}	----

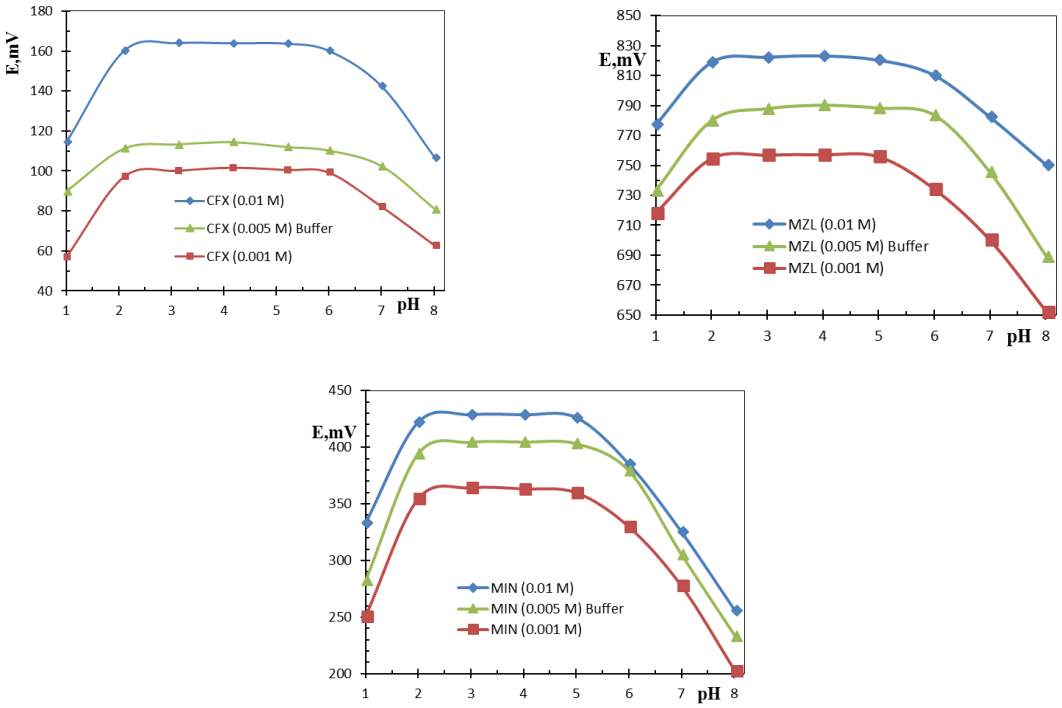


Fig. 4: Effect of pH on the potential response of the CFX, MZL, and MIN sensors using 10 mM, 1 mM drug solution, or 5 mM BRITTON-ROBINSON universal buffer solution.

Table 3: Response characteristics of CFX, MZL, MIN or CFX+MZL+MINsensors[a].

Parameter	SENSOR-1	SENSOR-2	SENSOR-3	SENSOR-4 (Combined Sensor)		
	CFX-TPB	MZL-TPB	MIN-TPB	CFX	MZL	MIN
IP%	7%	7%	6%	7%	7%	6%
Slope, mV.decade^{-1}	-59.04 ± 0.12	-59.11 ± 0.06	-58.99 ± 0.11	-58.99 ± 0.07	-59.21 ± 0.12	-59.03 ± 0.03
Intercept, mV.decade^{-1}	280.84	938.36	544.84	280.19	938.01	544.23
Correlation coefficient (R^2)	0.9996	0.9983	0.9991	0.9996	0.9986	0.9992
Linear range, µM	10-10000	10-10000	10-10000	10-10000	10-10000	10-10000
TMR, µM	5.62-31623	3.16-17783	5.62-17783	5.62-31623	3.16-17783	5.62-17783
LOD, µM	0.105	0.217	0.160	0.100	0.194	0.144
LOQ, µM	0.319	0.658	0.486	0.304	0.588	0.435
Response time for 1 mM, sec	10 ± 2	11 ± 1	12 ± 1	11 ± 1	12 ± 1	12 ± 2
Life time, day	17	14	15	14 (the shorter life time)		
Working pH range	2.0-6.0*	2.0-5.0*	2.0-5.0*	2.0-5.0*	2.0-6.0*	2.0-5.0*
	2.0-6.5**	2.0-6.0**	2.0-6.0**	2.0-6.0**	2.0-6.5**	2.0-6.0**

[a] Five replicate measurement.

* Without buffer.

** Using BRITTON-ROBINSON universal buffer.

Table 4: Direct determinations of CFX, MZL, and MIN in bulk solutions using proposed sensors

Taken $C_{CFX\cdot HCl}$		SENSOR-1*			Taken $C_{CFX\cdot HCl}$		SENSOR-4*		
(µg/mL)	mol/L	R%	SD	RSD%	(µg/mL)	mol/L	R%	SD	RSD%
0.3678	**1×10^{-6}**	99.95	0.0017	0.46	**0.3678**	**1×10^{-6}**	99.24	0.0026	0.69
3.678	**1×10^{-5}**	99.62	0.0365	0.99	**3.678**	**1×10^{-5}**	99.18	0.0327	0.89

36.78	**1×10^{-4}**	99.56	0.4087	1.12	**36.78**	**1×10^{-4}**	99.29	0.3114	0.85
367.8	**1×10^{-3}**	99.99	0.1517	0.04	**367.8**	**1×10^{-3}**	99.85	0.2881	0.08
3678	**1×10^{-2}**	99.97	3.3615	0.09	**3678**	**1×10^{-2}**	100.01	1.5166	0.04

Taken C_{MZL}		**SENSOR-2***			**Taken C_{MZL}**		**SENSOR-4***		
(µg/mL)	**mol/L**	**R%**	**SD**	**RSD%**	**(µg/mL)**	**mol/L**	**R%**	**SD**	**RSD%**
0.1712	**1×10^{-6}**	99.92	0.0007	0.42	**0.1712**	**1×10^{-6}**	99.77	0.0016	0.96
1.712	**1×10^{-5}**	100.07	0.0041	0.24	**1.712**	**1×10^{-5}**	99.88	0.0158	0.92
17.12	**1×10^{-4}**	100.02	0.0541	0.32	**17.12**	**1×10^{-4}**	99.65	0.0524	0.31
171.2	**1×10^{-3}**	99.94	0.2345	0.14	**171.2**	**1×10^{-3}**	99.86	0.3435	0.20
1712	**1×10^{-2}**	99.98	1.1402	0.07	**1712**	**1×10^{-2}**	99.94	1.5811	0.09

Taken $C_{MIN\cdot HCl}$		**SENSOR-3***			**Taken $C_{MIN\cdot HCl}$**		**SENSOR-4***		
(µg/mL)	**mol/L**	**R%**	**SD**	**RSD%**	**(µg/mL)**	**mol/L**	**R%**	**SD**	**RSD%**
0.4939	**1×10^{-6}**	99.21	0.0071	1.44	**0.4939**	**1×10^{-6}**	100.02	0.0055	1.11
4.939	**1×10^{-5}**	99.62	0.0212	0.43	**4.939**	**1×10^{-5}**	99.78	0.0130	0.26
49.39	**1×10^{-4}**	99.96	0.0187	0.04	**49.39**	**1×10^{-4}**	99.97	0.0152	0.03
493.9	**1×10^{-3}**	99.98	0.1095	0.02	**493.9**	**1×10^{-3}**	99.99	0.0894	0.02
4939	**1×10^{-2}**	99.98	0.8367	0.02	**4939**	**1×10^{-2}**	99.98	1.3038	0.03

*Average of fivereplicates.

Table 5: Determinations of CFX, MZL, and MIN in pharmaceutical preparations using proposed sensor

Commercial Name	**Composition**	**$\bar{X}$ ± SD, mg[a]**	**R%**	**t-value[b]**	**F-value[c]**
			SENSOR-1		
			CFX-TPB		
Ciproflex	Ciprofloxacin	502.4 ± 0.89	100.48	1.5	1.1429
	Ciprofloxacin	499.4 ± 1.14	99.88	0.7845	1.8571
3 MIX Caps	Metronidazole	----	----	----	----

	Minocycline	----	----	----	----
			SENSOR-2		
			MZL-TPB		
Flagyl	Metronidazole	507.6 ± 1.52	101.52	1.1795	2.875
	Ciprofloxacin	----	----	----	----
3 MIX Caps	Metronidazole	501.6 ± 1.14	100.32	1.1767	2.6
	Minocycline	----	----	----	----
			SENSOR-3		
			MIN-TPB		
Quatrocin	Minocycline	102.4 ± 0.55	102.4	1.6329	0.6
	Ciprofloxacin	----	----	----	----
3 MIX Caps	Metronidazole	----	----	----	----
	Minocycline	100.1 ± 0.16	100.1	2.5456	1.4706
			SENSOR-4		
			CFX-TPB + MZL-TPB + MIN-TPB		
Ciproflex	Ciprofloxacin	502.0 ± 0.71	100.4	0.6325	0.7143
Flagyl	Metronidazole	507.4 ± 1.52	101.48	1.4744	2.875
Quatrocin	Minocycline	102.2 ± 0.84	102.2	0.5345	1.4
	Ciprofloxacin	503.4 ± 3.05	100.68	0.2933	0.9588
3 MIX Caps	Metronidazole	502.6 ± 1.67	100.52	0.5345	0.3294
	Minocycline	100.06 ± 0.15	100.06	2.0642	1.3529

[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.

$E = S \times Pc_{MZL} + b$, or $E = S \times Pc_{MIN} + b$. The four suggested sensors presented a linear response all over the concentration range 10-10000 µM over a pH range of 2.0-6.0 for CFX determination, 2.0-5.25 for MZL determination, and 2.0-5.5 for MIN determination. The limit of detection (LOD) and limit of quantification (LOQ) were determined according to the IUPAC recommendation [45]. LOD and LOQ values were 0.105 µM, 0.319 µM, respectively for ciprofloxacin in SENSOR-1 (CFX-TPB), 0.217 µM, 0.658 µM, respectively for metronidazole in SENSOR-2 (MZL-TPB), 0.160 µM, 0.486 µM, respectively for minocycline in SENSOR-3 (MIN-TPB). While the LOD and LOQ values

for SENSOR-4 (combined sensor) were 0.100 µM, 0.304 µM ,respectively for ciprofloxacin, 0.194 µM, 0.588 µM, respectively for metronidazole, 0.144 µM, 0.435 µM, respectively for minocycline (Table 3).

5.2 Recovery and Precision: We calculate the recovery by comparing the potential of the found CFX, MZL, or MIN concentration to direct added standard in BRITTON-ROBINSON universal buffer (pH=2-6). Precision reported as RSD %. Its values of inter-a-day (three replicates) and inter-day (three different days) studies for the repeated determination were less than 2% which indicating good precision (Table 4).

6. CONCLUSION

We concluded that CFX-TPB-PVC, MZL-TPB-PVC, MIN-TPB-PVC,and CFX-TPB+MZL- TPB+MIN-TPB-PVCmembrane ion selective sensors offers a precious technique for direct determination of CFX, MZL, and MIN in pure solutions and pharmaceutical preparations. The construction of sensors issomewhat simple, fast, and can be re-create easily. The sensors showedanexcellent selectivity towards the drug in presence of various pharmaceutical excipients, and it can be used as indicator electrodes in potentiometric titrations of CFX, MZL, and MIN. Three electro-active ion pairs of CFX, MZL, and MINwith TPB werecarried outas foursensors for the determination ofCFX, MZL, and MIN.The four membrane sensorsshowed good analytical performance. The sensors exhibit a rapid, steady, and nearNERNESTIANresponse over a comparative wide drug concentration range of 10-10000 µM(pC_{Drug}=2-5). Using CFX-TPB + MZL-TPB + MIN-TPBas a combined electro-activematerials in the same membrane we could arrange a novel electrode that is sensitive to either CFX, MZL, or MIN according to the standard filling solution of the electrode, and in this way; when we use three of this combined electrodes (the first filled with CFX standard solution "ciprofloxacin selective electrode" and the second filled with MZL standard solution "Metronidazole selective electrode", and the third filled with MIN standard solution "minocycline selective electrode" each in conjunction with Ag/AgCl external reference electrode) connected to three separate mV-meters, we can take three readings for CFX, MZL, and MIN simultaneously and in this way we could determine the three drugs (CFX, MZL, and MIN) in their combined solutions. The suggested sensors accomplishedLOD and LOQ values of 0.105 µM, 0.319 µM, respectively for ciprofloxacin in SENSOR-1 (CFX-TPB), 0.217 µM, 0.658 µM, respectively for metronidazole in SENSOR-2 (MZL-TPB), 0.160 µM, 0.486 µM, respectively for minocycline in SENSOR-3 (MIN-TPB), 0.100 µM, 0.304 µM ,respectively for ciprofloxacin in SENSOR-4, 0.194 µM, 0.588 µM, respectively for metronidazole in SENSOR-4, and 0.144 µM, 0.435 µM, respectively for minocycline in SENSOR-4, with response time of less than 14 sec for all four sensors.The suggested sensorshavea measurement pH ranges 2.0-6.0 for CFX, 2.0-5.25 for MZL, 2.0-5.0 for MIN without using any buffer. The direct determination of CFX and MZL showed an average recovery of 99.99, 99.94, 99.98 and 99.85% (CFX) or 99.86%(MZL) or 99.99% (MIN) and a mean relative standard deviation of 0.04%, 0.14%, 0.02 and 0.08% (CFX) or 0.20% (MZL)% or 0.02% (MIN) at 1 mM (367.8 µg/mL CFX, 171.2 µg/mL MZL, or 493.9 µg/mL MIN)for SENSOR-1, SENSOR-2, SENSOR-3, SENSOR-4, respectively. The acquire results were within the acceptance range of less than 2.0 % of RSD % for precision and more than 99.18 % of R % for the accuracy. The sensors wereused as indicator electrodes for direct determination of CFX, MZL, MINin there pharmaceutical preparations as well as in pure form solutions.

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