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Full Paper

Ion-Selective Membrane Sensors for the Determination of Ciprofloxacin Hydrochloride in Water and Pharmaceutical Formulation

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Abstract- The construction and electrochemical response characteristics of six Ciprofloxacin-selective electrodes were investigated using precipitation based technique with sodium tetraphenyl borate (TPB), phosphomolybdate (PMA) and phosphotungstate (PTA); respectively upon using polyvinyl chloride (PVC) matrix and dibutyl phthalate (DBP) as a plasticizer. The resultant sensors have different forms, either as membrane electrodes (sensors 1, 3 and 5) or as coated wire electrodes (sensors 2, 4 and 6). Linear responses of CIP within the concentration ranges of 10^{-6} to 10^{-2} mol/L for sensors 1, 2 and 5 while for sensors 3 and 4, the linear responses were within the concentration ranges of 10^{-5} to 10^{-2} mol/L and for sensor 6 it shows linear responses within the concentration ranges of 10^{-7} to 10^{-2} mol/L. Nernstian slopes of 51.7, 50.7, 58.3, 57.7, 44 and 41.8 mV/decade were observed over the pH range of (5–9) for sensors 1, 2, 5 and 6 and over range of (5-7) for sensor 3 and 4 respectively. The selectivity coefficients of the developed sensors indicated excellent selectivity for CIP. The proposed sensors displayed useful analytical characteristics for the determination of CIP in water samples and pharmaceutical preparation.

Keywords- Ciprofloxacin HCl, Phosphomolybdic acid, Phosphotungestic acid, Tetraphenyl borate, Water samples

1. INTRODUCTION

Pharmaceutical compounds are widespread contaminants of the aquatic environment. Since traditionally they have not been viewed as environmental contaminants, the study of their presence in the environment is in some ways a new area of research which has taken recent years. Our current knowledge indicates that residues of pharmaceuticals at trace quantities are widely spread in aquatic systems [1]. Antibiotics constitute a large group of pharmaceuticals, which are widely administered in human and veterinary medicine. The extensive use of these antibiotics may result in their presence in the environment. Antibiotics are believed to be of greatest concern among all pharmaceuticals due to the potential risk of antibiotic resistance. Studies in the United States of America and Europe have detected antibiotic resistant bacteria in drinking water supplies [2,3]. According to previous studies and publications, one of the most prevalent groups of antibiotics found in the environment, and particularly in surface waters, is that of the widely used, highly potent fluoroquinolones [4,5]. They are largely excreted as unchanged compounds in urine, and consequently discharged into hospital sewage or municipal wastewater. Despite lots of studies with positive detection of antibiotics and other pharmaceuticals in soils and environmental waters and despite of their negative effects on human health, there is no defined limit value for the occurrence of these pollutants in soils or natural waters [6].

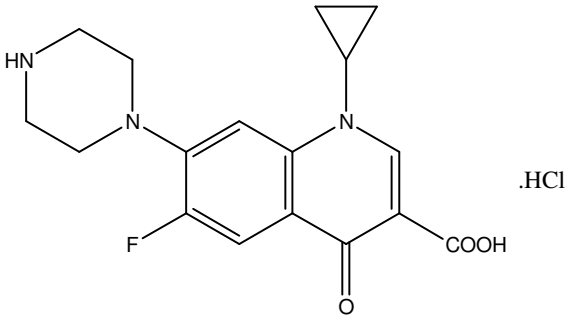
Therefore, more monitoring and surveillance studies are needed at local level to determine exactly how the antibiotics make their way into public waterways, and to obtain a better understanding of the transport and environmental fate of antibiotics.

Ciprofloxacin HCL (CIP) is 1-Cyclopropyl–6–fluoro–1,4–dihydro–4–oxo–7-(1–piperazinyl)-3–quinolone carboxylic acid it is a bactericidal fluoroquinolone. It acts by inhibiting the A subunit of DNA gyrase (topoisomerase) which is essential in the reproduction of bacterial DNA [7], its chemical structure was shown in Fig. 1.

Different analytical techniques were reported for CIP determination in pharmaceutical preparations, biological fluids and waste water such as: Spectroscopic methods [8-11], spectrofluorimetric methods [11-13], TLC [14,15], HPLC [6,16-19], Capillary electrophoresis [20], ion selective electrode [21-24].

Here in we report the novelty of electrochemical determination of CIP in production waste water sample by using the developed sensors without the need of preliminary extraction or cleaning up procedures of the samples.

The developed sensors were also successfully applied for the electrochemical determination of ciprofloxacin hydrochloride in pharmaceutical formulation. The method has the advantages of high sensitivity, accuracy, selectivity and the possibility of direct determination of the drug in turbid and colored solutions.



($C_{17}H_{18}FN_3O_3$•HCl, formula weight 367.8 g/mol)

Fig. 1. Structural formula of ciprofloxacin hydrochloride

2. EXPERIMENTAL

2.1. Apparatus

A Jenway digital ion analyzer model 3505 (Jenway, UK) with Ag/AgCl double junction reference electrode (Aldrich, USA) was used for potential measurements. A Jenway pH glass electrode (Jenway, UK) was used for pH adjustments.

2.2. Chemicals and Reagents

2.2.1. Pure Sample

Ciprofloxacin HCl powders were kindly supplied by Egyptian pharmaceutical industrial company (EPICO, EGYPT) and its percentage purity was found to be 100.1±0.95, according to official BP methods [25].

2.2.2. Chemicals and Reagents

All chemicals and reagents used were of analytical reagent grade. Polyvinyl chloride (PVC), Phosphomolybdic acid (PMA), Phosphotungestic acid (PTA), Sodium tetraphenyl borate (TPB), Dibutyl phthalate (DBP) and Tetrahydrofuran (THF) were obtained from Aldrich, USA. Hydrochloric acid, sodium hydroxide scales, potassium chloride were obtained from El-Nasr pharmaceutical chemicals, Cairo, Egypt. Starch, Lactose, CaCl2, NaCl, Glucose and Urea were obtained from Adwic, Cairo, Egypt.

2.3. Standard solutions

2.3.1. Stock Solutions

CIP was freshly prepared by transferring 0.1839 g of ciprofloxacin hydrochloride into a 50-ml volumetric flask. It was dissolved in 20 mL bi-distilled water, and the volume was then completed with the same solvent and protected from light.

2.3.2. Working solutions ($1\times10^{-}$-1×10^{-7}M)

Different solutions were freshly prepared by serial dilution from the stock solution using bi-distilled water. The prepared solutions were kept in well-closed tight containers and protected from light.

2.4. Procedures

2.4.1. Sample Collection and Preparation

A total of six wastewater samples were collected from pharmaceutical industries at different sites as shown in Table 1 and placed in 2 L amber glass bottles, Water samples were filtered through 0.45µm nylon membrane filter to eliminate fine particulate matter, and stored in the dark at 4^0C to avoid any degradation or deterioration [18].

2.4.2. Precipitation of the Ion Exchangers

In two different beakers, ten ml aliquot of 10^{-2} M aqueous standard CIP solution was treated separately with 10 ml of aqueous 10^{-2} M of each of TPB, PMA and PTA solutions, respectively. The prepared solutions were shaken well for 5minutes. The precipitates formed were filtered using Whitman filter papers, washed with cold water till chloride free (tested by $AgNO_3$ solution), dried at room temperature (~25°C) and then ground to fine powder. The formation and purity of the ion-associates and the chemical compositions of the precipitates were checked by elemental analysis for carbon, hydrogen and nitrogen, IR and mass spectroscopy.

2.4.3. Fabrication of PVC Based Membrane Sensors

For the preparation of sensor 1, 3 and 5, amounts of 10 mg of ion exchangers were separately mixed with 0.35 ml of DBP and 0.19 g PVC respectively in three separate glass petri dish (5 cm diameter), and then the mixtures were dissolved in 5 ml THF. The petri dishes were covered by a filter papers and left to stand overnight to allow solvent evaporation at room temperature. These ratios of components added will form a master membrane with a thickness of 0.1 mm which is wanted. From the formed master membranes, disks (≈10 mm diameter) were cut using a cork borer and pasted using THF to interchangeable PVC tips that were clipped into the end of the electrodes glass bodies. Equal volumes of 10^{-2} M CIP and 10^{-2} M KCl were mixed and this obtained solution was used as an internal reference solution. Ag/AgCl wire (1mm diameter) was immersed in the internal reference solution as an internal reference electrode. The electrodes were preconditioned by immersing in 10^{-2} M CIP solution for 24 h. The electrochemical cell for potential measurements was: Ag/AgCl (internal reference electrode)/ 1.0×10^{-2} M CIP solution, 1.0×10^{-2} M KCl (internal reference

solution)//PVC membrane//test solution (pH 4-9)//Ag/AgCl double junction reference electrode. The sensors were stored in distilled deionized water between measurements.

2.4.4. Fabrication of PVC Based Coated Wire Electrode

The previously prepared (CIP–ion exchangers, DPB, PVC and THF) mixtures were left at room temperature to allow solvent evaporation to obtain colloidal solutions. Three electrodes were prepared by applying layers of the pervious mixtures onto a silver wires tip at 10minutes interval until a globular membrane of about 3 mm diameter around the wire ends were formed. The electrodes were left standing at room temperature for 24 h to dry. The resultant dry coated wires membrane sensors had to be conditioned by soaking in 1.0×10^{-2} M CIP for 3 h and stored in the same solution when not in use. The electrochemical cell for potential measurements was: silver wire//PVC membrane//test solution (pH 4-9)//Ag/AgCl double junction reference electrodes.

2.4.5. Sensors Calibration

The conditioned sensors were calibrated by separately transferring 50 ml aliquots CIP solutions prepared in distilled water with concentration range of (1×10^{-7}–1×10^{-2} M) into a series of 100 ml beakers starting from the low to the high concentrations. The membrane sensors in conjunction with a reference electrode were immersed in each solution, allowed equilibrating with constant stirring using a magnetic stirrer, then recording the stable potential within ±2 mV. The electrode potential (EMF) was plotted versus each negative logarithmic concentration of CIP. The response time of the investigated electrodes was calculated.

2.4.6. Effect of pH

The effect of pH on the potential values of the four investigated sensors was studied over pH range of 3-10 at 1 pH interval by using 10^{-4} M and 10^{-3} M CIP solutions. The pH was gradually increased or decreased by adding aliquots of dilute sodium hydroxide or dilute hydrochloric acid solutions respectively. The potential obtained at each pH value was recorded.

2.4.7. Sensors Selectivity

The potentiometric selectivity coefficient log $K^{pot.}$ (Primary ion, interferent) was used to evaluate the extent to which a foreign ion would interfere with the response of an electrode to its primary ion. Selectivity coefficients were calculated by the separate solutions method, where potentials were measured for 10^{-3} M aqueous CIP solution and then for 10^{-3} M aqueous

interferent solution separately then potentiometric selectivity coefficients were calculated using the following equation:

$$\log K_{pot\ A,B} = \frac{(E_B - E_A)}{S} + \left(1 - \frac{Z_A}{Z_B}\right) \log a_A \quad (1)$$

Where $K_{pot\ A.B}$ is the potentiometric selectivity coefficient, E_A and E_B are the potentials of the drug and the interfering solutions respectively, S represents the slope of the calibration plot, a_A is the activity of the drug, Z_A and Z_B are the charges on the drug and the interfering ions, respectively.

2.4.8. Application to Pharmaceutical Dosage Forms

2.4.8.1. Ciloxan Eye Drops®

Five milliliters of Ciloxan® eye drops 0.3%were transferred into 50 mL volumetric flask, the volume was completed with distilled water to get 300 µg mL^{-1} of CIP. The potentiometric measurements were performed using the proposed sensors in conjunction with the Ag/AgCl reference electrode, and the potential readings were compared to the calibration plots.

2.4.9. Determination of CIP in Spiked Water Samples

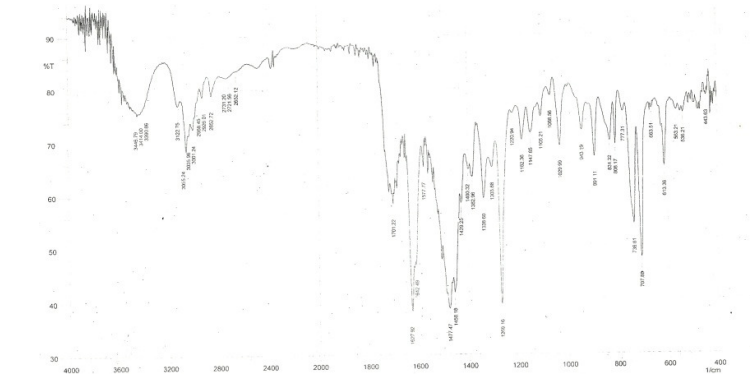
Volume of 2.5 mL of 10^{-3} M standard drug solution was added into 50 mL beaker containing 22.5 mL of the filtered water, and vortex for 1 min. The membrane sensors were immersed in conjunction with the reference electrode in this solution and then washed with water between measurements. The emf value of this spiked water sample was measured by the proposed sensors, and the concentration of CIP was calculated from the corresponding regression equation.

3. RESULTS AND DISCUSSION

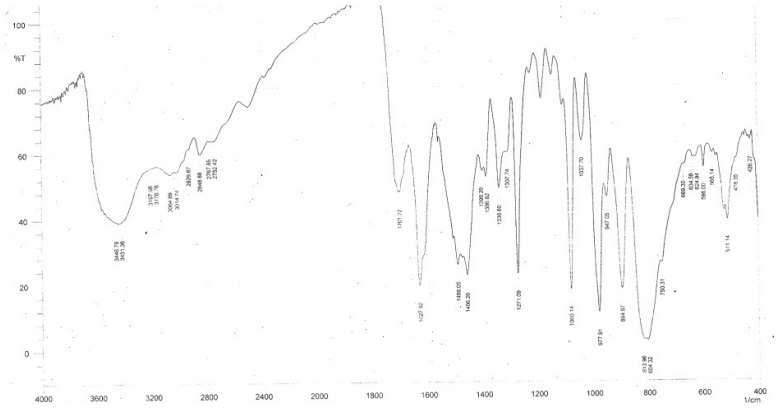
The present work evaluated the possibility of quantitative determination of CIP by using selective membrane sensors with ion exchanger TPB, PMA and PTA in its composition using PVC as a polymeric matrix to immobilize the sensors and to attain the formation of highly stable complexes. It was found that the three ionic exchangers have low solubility product and suitable grain size. CIP was found to form 3:1 ion association complex with a PTA, 3:1 with PMA and 1: 1 with TPB as proven by elemental analysis (as monovalent cation) and the obtained Nernstian slopes as mentioned in Table 1 and also using IR as shown in Fig. 2. The proposed sensors were used for the determination of CIP in bulk powder, pharmaceutical formulations and in water samples such as wastewater from pharmaceutical companies.

One of the problems in the determination of antimicrobials in the aquatic products is the sample treatment, due to the presence of other organic contaminants in the matrix, which can

interfere with the analytical procedures. It was found that ion selective electrodes (ISEs) offer several advantages over other methods for environmental analysis [26], particularly its ability for direct measurements in troubled, viscous solutions and in complex matrices without the need for samples pretreatment. In addition to its expense is considerably lowered than of the other methods, easy to use, time saving and non-destructive.



(a)



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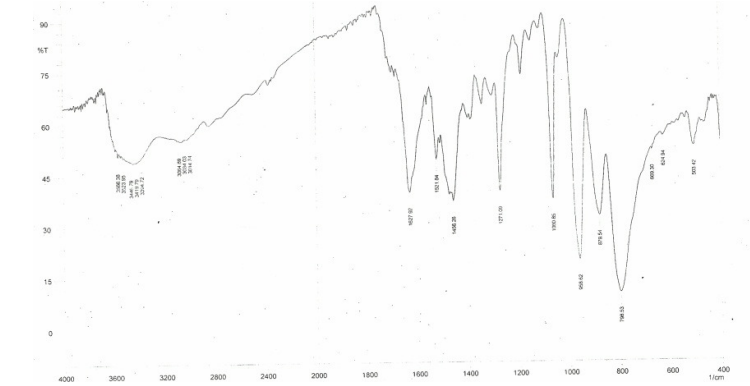

(c)

Fig. 2. Profile of IR of ion association complexes of CIP with (a) TPB, (b) PTA and (c) PMA

Table 1. Elemental analysis of the ion-associates

Ion associates	Tentative formulae	Percentage	C%	H%	N%
CIP-TPB	$(C_{17}H_{18}FN_3O_3)(C_6H_5)_4B$	Found	75.83	5.94	6.57
		Calculated	75.69	5.89	6.46
CIP-PMA	$(C_{17}H_{18}FN_3O_3)(H_3PMo_{12}O_{40})$	Found	21.23	2.18	4.42
		Calculated	20.9	2.15	4.3
CIP-PTA	$(C_{17}H_{18}FN_3O_3)(H_3PW_{12}O_{40})$	Found	15.58	1.37	3.23
		Calculated	15.5	1.4	3.26

3.1. Performance Characteristics of CIP Sensors

The electrochemical performance characteristics of the investigated CIP–selective sensors were evaluated according to the IUPAC recommendation data [27] and it was summarized in Table 2. It has been reported that PVC matrix is a regular support and reproducible trap for ion association complexes in membrane sensors. Nevertheless, its use creates a need for plasticization and places a constraint on the choice of mediator [28].

Table 2. Electrochemical response characteristics of the six proposed sensors used for the determination of ciprofloxacin hydrochloride

Parameters	Sensor1	Sensor 2	Sensor 3	Sensor 4	Sensor 5	Sensor 6
Slope (mV/decade)[a]	-51.7	-50.7	-58.3	-57.7	-44	-41.8
Intercept (mV)	101.4	87.3	158.8	162.7	181.2	180.19
LOD (mol. L^{-1})[b]	3×10^{-7}	2×10^{-7}	2×10^{-5}	3×10^{-5}	3×10^{-6}	9×10^{-6}
Response time (s)	10	10	15	15	10	10
Working pH range	5-9	5-9	5-7	5-7	5-9	5-9
Concentration range (M)	10^{-2}-10^{-6}	10^{-2}-10^{-6}	10^{-2}-10^{-5}	10^{-2}-10^{-5}	10^{-2}-10^{-6}	10^{-2}-10^{-7}
Stability (weeks)	4 weeks	4 weeks	4 weeks	4 weeks	5 weeks	5 weeks
Average recovery (%) ± S.D[a]	99.9±2.09	101±1.154	100.55±1.884	99.68±2.2	99.8±1.39	100.2±1.433
Correlation coefficient (r)	0.9987	0.997	0.9976	0.997	0.999	0.9974

[a] Result of five determinations
[b] Limit of detection (measured by interception of the extrapolated arms of figure 2)

In the present study, the use of the plasticizers, dibutyl phthalate (DBP) has been used in the fabrication of the proposed membrane sensors sensor. It adjusted the permittivity of the final organic membranes and mobility of the ion exchanger sites. The membranes constituents were dissolved in THF that was slowly evaporated at room temperature leading to membrane formation. Sensor 6 showed best sensitivity, where linearity was obtained in the range of (10^{-2}–10^{-7} M); sensors 1, 2 and 5showed also good sensitivity as their linearity was in range of (10^{-2}–10^{-6} M); while sensors 3 and 4 fell short in the limit of linearity (10^{-2}–10^{-5} M). Sensors 1, 2, 3 and 4 had good slope 51.7, 50.7, 58.3 and 57.7mV/decade, while the slopes of the calibration plots were 44 and 41.8 mV/decade for sensors 5 and 6, respectively. Typical calibration plots are shown in Fig. 3. Deviation from the ideal Nernstian slope (60 mV) is due to the electrodes responding to the activity of the drug cations rather than its concentration. The sensors displayed constant potential readings for day to day measurements, and the calibration slopes did not change by more than ±2 mV/decade over a period of 28 days. The detection limits of the three sensors were estimated according to the IUPAC definition [27]. The slopes of the calibration plot did not change significantly but show a gradual decrease in sensitivity.

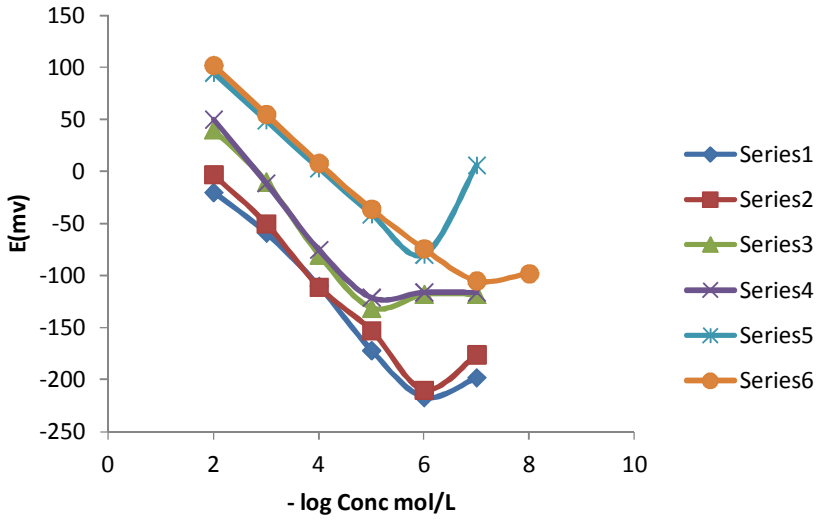

Fig. 3. Profile of the potential in mV to -log concentration of CIP using the two proposed ion selective electrode method

3.2. Dynamic Response Time

Dynamic response time is an important factor for analytical applications of ion-selective sensors. In this study, practical response time was recorded by increasing CIP concentration by up to 10-fold. The required time for the sensors to reach values within ±2 mV of the final

equilibrium potential was 10-15 sec. for the sensors. The response time increases with increasing the concentrations.

3.3. Effect of pH

For quantitative measurements with ion selective electrodes, studies were carried out to reach the optimum experimental conditions. The potential pH profile obtained indicated that the responses of the sensors 1, 2, 5 and 6 were fairly constant over the pH range 5–9; at pH less than 4 drop in reading occurs. Therefore, the pH range from 5 to 9 was assumed to be the working pH range of these sensors. While for sensor 3 and 4, the constant working pH is 5-7 as less than 5 and more than 7 potential readings were not constant as shown in Fig. 4.

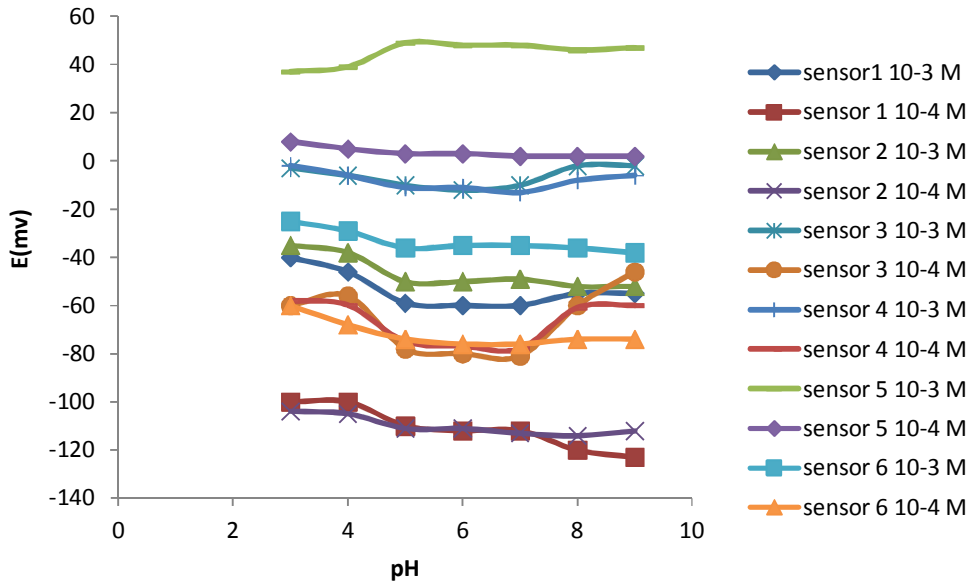

Fig. 4. Effect of pH on the response of the six sensors at 10^{-3} M and 10^{-4} M

3.4. Sensors Selectivity

Sensors 5 and 6 showed the highest selectivity coefficient values that correspond with more attack by interfering cations on the electrode membrane. The higher the selectivity coefficient value, the more the electrode membrane is attacked by the interfering cations. Table 3 shows the potentiometric selectivity coefficients of the proposed sensors in the presence of other pharmaceutical contaminants and inorganic cations (K^+, Na^+ and Ca^{2+}) that are usually found. Glucose, lactose and starch those are usually present in dosage forms. The

results reveal that the proposed membrane sensors display high selectivity; sensors 3 and 4 are at least 10 times more selective than sensors 1 and 2.

Table 3. Potentiometric selectivity coefficients of by separate selectivity method (SSM)

Interferent[a]	Selectivity coefficient[b]					
	Sensor1	**Sensor 2**	**Sensor 3**	**Sensor 4**	**Sensor 5**	**Sensor 6**
NaCl	1.8×10^{-2}	1.4×10^{-2}	2.7×10^{-3}	2.5×10^{-3}	3×10^{-3}	2.32×10^{-3}
Glucose	1.9×10^{-2}	1.3×10^{-2}	5.8×10^{-3}	5.3×10^{-3}	1.4×10^{-2}	1.7×10^{-2}
Urea	2.4×10^{-2}	1.4×10^{-2}	9.8×10^{-3}	9×10^{-3}	5.3×10^{-3}	5.6×10^{-3}
Lactose	4.6×10^{-2}	2.8×10^{-2}	2.8×10^{-2}	2.6×10^{-2}	5.9×10^{-3}	6.3×10^{-3}
$CaCl_2$	1.5×10^{-2}	1.06×10^{-2}	2.67×10^{-2}	2.4×10^{-3}	3.3×10^{-3}	3.9×10^{-3}
Starch	1.2×10^{-2}	1.68×10^{-2}	1.2×10^{-2}	1.19×10^{-2}	3.6×10^{-3}	4.02×10^{-3}
KCl	1.6×10^{-2}	1.06×10^{-2}	3.25×10^{-3}	2.7×10^{-3}	4.3×10^{-3}	3.2×10^{-3}

[a] Aqueous solutions of 1×10^{-3} M were used
[b] Each value is the average of three determinations

3.5. Potentiometric Determination of CIP in Pharmaceutical Formulations

The proposed sensors were applied for the analysis of CIP pharmaceutical formulations in buffered solutions. The results prove the applicability of the six sensors for the determination of pharmaceutical formulations containing CIP. These data are shown in Table 4. To examine the validity of the proposed sensors, the obtained results were compared to HPLC method and no significant difference was observed. Moreover, the proposed Sensors do not require preliminary drug extraction.

Table 4. Determination of Ciprofloxacin hydrochloride in pharmaceutical formulation by the six proposed sensors

Pharmaceutical preparation	Added	R%±SD*					
Ciloxan 0.3%	8.13×10^{-4} M	**Sensor 1**	**Sensor 2**	**Sensor 3**	**Sensor 4**	**Sensor 5**	**Sensor 6**
		102.21±0.21	101.70±0.25	102.09±0.31	100.91±0.34	101.20±0.36	100.20±0.76

* Average of three determinations

3.6. Potentiometric Determination of CIP in Water Samples

For determination of CIP in spiked wastewater sample (as concentration of CIP may be lower than LODs of the used sensors), it was found that four of the six sensors (sensor 1, 3, 5

and 6) are reliable and give stable results with very good accuracy and high Percentage recovery without preliminary extraction procedures, that's due to their low LODs which is shown in Table 5. The pH of these samples was measured and was found to be 6.2±0.5, which is within the pH working range of the proposed sensors.

The response times of the proposed sensors are instant (within 15 s). It is concluded that the proposed four sensors can be successfully applied in environmental analysis.

Statistical comparison was done between the proposed sensors and the official method, and no significance difference was observed as shown in Table 5. One way ANOVA was performed to prove that no significance difference was present between the results of the proposed sensors (Table 6 and 7).

Table 5. Determination of Ciprofloxacin hydrochloride in spiked wastewater samples by the six proposed sensors

Added (ppm)	**R% ± SD***					
1×10^{-4} M (36.78)	**Sensor 1**	**Sensor 2**	**Sensor 3**	**Sensor 4**	**Sensor 5**	**Sensor 6**
	104.23±1.34	118±2.3	101.6±2.04	102±1.87	96.5±1.4	94.1±1.87

* Average of three determinations

Table 6. Statistical comparison of the results obtained by the proposed sensors and the official method on pure form

Items	**Official Method**	**Sensor 1**	**Sensor 2**	**Sensor 3**	**Sensor 4**	**Sensor 5**	**Sensor 6**
Mean	100.206	99.94	101.33	100.55	99.83	99.85	100.2
± SD	0.9502	2.051	1.153	1.884	2.2	1.396	1.434
Variance	0.902	4.206	1.3317	3.55	4.48	1.9488	1.96
n	5	5	5	4	4	5	5
SEM	0.425	0.9353	0.516	0.9421	1.126	0.6243	0.6412
Student's *t*-test (2.306)[b]		0.2502	1.692	0.3638 **(2.364)[b]**	0.3617 **(2.364)[b]**	0.4594	0.0072
***F* value (6.3882)[b]**		4.844	1.475	3.932 **(6.5914)[b]**	5.614 **(6.5914)[b]**	2.158	2.276

[a] BP method is HPLC method.
[b] Figures between parentheses represent the corresponding tabulated values of t and F at P=0.05

Table 7. ANOVA for the proposed methods for the determination of CIP in pure form

Source of Variation	Degree of freedom	Sum of Squares	Mean square	F critical	F
Between Groups	6	8.984936	1.497489	2.49041	0.424685
Within Groups	25	88.15286	3.526114		
Total	31	97.1378			

4. CONCLUSION

The described sensors are sufficiently simple and selective for the quantitative determination of CIP in pure form, pharmaceutical formulations and water samples. PTA as ionophores increased the membrane sensitivity of sensors 5 and 6 in comparison with other sensors. High selectivity and rapid response make these electrodes suitable for measuring the concentration of ciprofloxacin hydrochloride in a wide variety of samples without the need for pretreatment or clean up steps and without significant interference from other anionic or cationic species present in the waste water.

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