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A New Metoclopramide Potentiometric Membrane Sensor for Analysis in Pharmaceutical Formulation and Urine: Concerns to Theoretical Study

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Metoclopramide (MCP), 4-amino-5-chloro-N-(2-(diethylamino) ethyl**-(**2**-** methoxy benzamide, is usually marketed as the hydrochloride salt is a potent dopamine receptor antagonist used for its antiemetic and prokinetic properties. In this study, a potentiometric liquid membrane sensor for simple and fast determination of metoclopramide hydrochloride in pharmaceutical formulation and urine were constructed. Since Computational chemistry and molecular modeling play an important role in the modern drug discovery, after some theoretical calculations metoclopramide-tetraphenyl borate complex was used as electroactive material in the membrane preparation. The wide linear range (10^{-6}-10^{-1} M), low detection limit (0.3 µg/ml), and fast response time (10 s) are characterizations of the proposed sensors. Validation of the method shows suitability of the sensors for applies in the quality control analysis of metoclopramide hydrochloride in pharmaceutical formulation and urine. The proposed method was found to be simple, accurate and precise which can be used as a detector for HPLC.

Keywords: potentiometric sensor, PVC membrane, metoclopramide hydrochloride, chemometrics

1. INTRODUCTION

Metoclopramide (MCP), 4-amino-5-chloro-N-(2-(diethylamino)ethyl)-2-methoxy benzamide, is used as an anti-emetic in the treatment of some forms of nausea and vomiting and to increase gastrointestinal motility [1]. Many analytical methods have been developed for the determination of

metoclopramide, and most of them are based on fluorimetric [2], spectrophotometric [3] and chromatographic [4] techniques.

Potentiometric membrane sensors are playing an important role in pharmaceutical analysis [5-14] due to its simplicity, rapidity and accuracy over some other analytical methods like spectrophotometry and HPLC. Also, other mentioned methods are elaborate and time consuming methods and involve sophisticated equipment that might not be available in most analytical laboratories.

Computational chemistry and molecular modeling play an important role in the modern drug discovery [15-19]. Computational work is also valuable in the drug development, where medium-sized organic pharmaceuticals are selected as candidates and are made in larger quantities. Instead of modeling interactions with macromolecules, the prediction of molecular properties for small molecules is more essential in the development stage.

The strength of binding usually correlates with the target molecules tendency to the ionophore, and several energy contributions may be responsible for the binding which is believed that among these energies, electrostatic interactions play dominant role in the process, at least in sequence preferences and the target molecules positioning [20,21].

In present paper, interaction of metoclopramide with some ion-pair reagents was studied by theoretical and calculation methods and according to the obtained results a metoclopramide ion-selective potentiometric membrane electrode is developed based on ion-pair compound of metoclopramide-tetraphenylbroate (MCP-TPB) as the electroactive substance. The proposed electrode was successfully applied for the determination of metoclopramide hydrochloride in the pharmaceutical formulations and urine samples.

2. EXPERIMENTAL PART

2.1. Apparatus

The glass cell, where the metoclopramide-selective electrode was placed, consisted of an R684 model Analion Ag/AgCl double junction reference electrode as the internal reference electrode and a double-junction saturated calomel electrode (SCE, Philips). The cell chamber was filled with an ammonium nitrate solution and both electrodes were connected to a Corning ion analyzer with a 250 pH/mV meter with ±0.1 mV precision.

2.2. Materials and Reagents

The necessary chemicals (of analytical reagent grade) were: Sodium tetraphenyl borate (NaTBP), potassium tetrakis (*p*-chlorophenyl) borate (KTpClPB), polyvinylchloride (PVC), tetrahydrofuran (THF), dibutylphthalate (DBP), benzyl acetate (BA), nitrobenzene (NB) and the chloride and nitrate salts of the used cations (Merck Co.). Metoclopramide hydrochloride (Fig. 1) and

its tablets were obtained from different local pharmaceutical factories. All solutions were prepared using triply distilled deionized water.

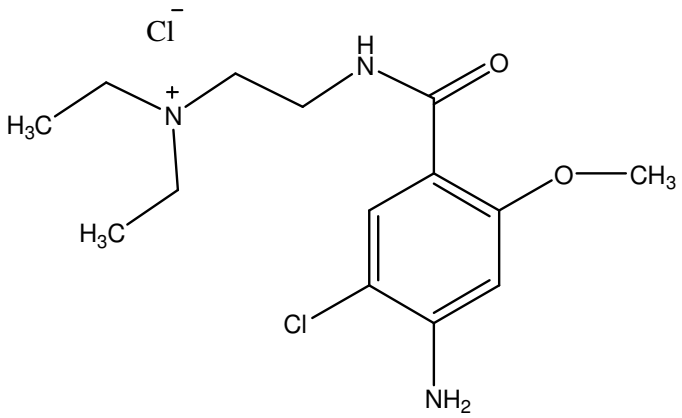

Figure 1. Chemical structure of metoclopramide hydrochloride

2.3. Preparation of ion-pair compound

Ion-pair compound of metoclopramide-tetraphenylborate (MCP-TPB): About 20 mL of 0.01 M solution of metoclopramide hydrochloride was mixed with 20 mL of 0.01 M solution of tetraphenylborate under stirring. The resulting precipitate was filtered off, washed with water and dried.

2.4. Preparation of the electrodes

The general procedure to prepare the PVC membrane was as follow: Different amounts of the ion-pair along with appropriate amounts of PVC, plasticizer and additive were dissolved in tetrahydrofuran (THF), and the solution was mixed well. The resulting mixture was transferred into a glass dish of 2 cm diameter. The solvent was evaporated slowly until an oily concentrated mixture was obtained. A pyrex tube (3-5 mm o.d.) was dipped into the mixture for about 10 s so that a transparent membrane of about 0.3 mm thickness was formed. The tube was then pulled out from the mixture and kept at room temperature for about 10 h. The tube was then filled with an internal filling solution (1.0×10^{-3} M metoclopramide hydrochloride). The electrode was finally conditioned for 24 h by soaking in a 1.0×10^{-3} M metoclopramide hydrochloride solution [22-24].

2.5. Standard metoclopramide hydrochloride solutions

A stock solution of 10^{-1} M metoclopramide hydrochloride was prepared by dissolving the calculated weight of pure drug in 25 mL water. The working solutions (10^{-7} to 10^{-2} M) were prepared by serial appropriate dilution of the stock solution.

2.6. The emf measurements

The following cell was assembled for the conduction of the emf (electromotive force) measurements;

Ag–AgCl | internal solution, 10^{-3} M metoclopramide hydrochloride | PVC membrane | sample solution | Hg–Hg_2Cl_2, KC1 (satd.)

These measurements were preceded by the calibration of the electrode with several metoclopramide hydrochloride solutions (working solutions).

3. RESULTS AND DISCUSSION

3.1. Theoretical Study

Molecular parameters are controlled by the molecular geometry; therefore geometry optimization is the most important step for the calculation of the interaction energy. The optimized geometries and numeration of the atoms of the studied molecules, L1 for NaTPB, L2 for KTpClPB, Drug for MCP, L1-Drug for MCP-TPB and L2-Drug for MCP-TpClPB, are presented in Figs. 2 to 6, respectively.

To obtain a clue on metoclopramide tendency for L1 and L2 as potential ionophors, DFT calculations (B3LYP/6-31G*) were carried out. The pair wise interaction energy ΔE_{A-B} between molecules A (L1 or L2) and B (the drug) was estimated as the difference between the energy of the formed complex and the energies of the isolated partners. The interaction energies were corrected for the basis set superposition error using the counterpoise method [25, 26].

$$\Delta E_{A-B} = E_{A-B} - E_A - E_B$$

which obtained to be -56.801 and -45.739 Kcal/mol for ΔE_{L1} and ΔE_{L2} , respectively that indicates L1 is a more appropriate ionophore for metoclopramide sensor in comparison to L2, which is due to its higher interaction energy.

Furthermore, charge changes are more significant in L1 atoms in compare with those of L2 that again confirms L1 molecules more significant tendency to interact with the drug. According to the obtained result it can be concluded that L1 is a better choice. It should also be mentioned that to avoid presenting large amount of data, only those atoms which show higher charge and bond length changes in L1 are given in the Table 1.

Results presented in Table 1, show that interactions exist between the drug and L1, L2 are electrostatic. Charge changes in the ion pairs are localized on specific atoms that interact together in each molecule [27, 28]. As can be seen, hetero atoms (N, O and Cl) charges change more significantly in comparison to other atoms that confirm the hydrogen bonding and electrostatic interactions effective role in ion pairs formation. The most noticeable atomic charge change belongs to N15 (from -0.223 to -0.429), N12 (from -0.380 to -0.348), O7 (from -0.251 to -0.244), O20 (from -0.303 to -0.282), and

Cl10 (from -0.142 to -0.158). In L1, remarkable atomic charge changes are seen for bohr (from 0.232 to 0.027) and it's connected carbon atoms. In addition, the bond lengths also changed as a result of ion pair formation (Table 1). According Table 1, the maximum bond length change occurred in those of heteroatom for example in drug: N15-C16, N15-C14 and N15-C18 and also in L2: B7-C4, B7-C20.

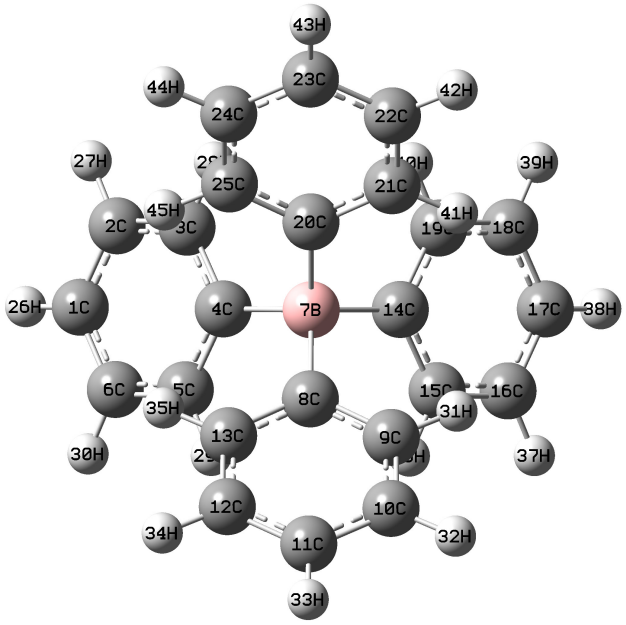

Figure 2. The full optimized structure of L1

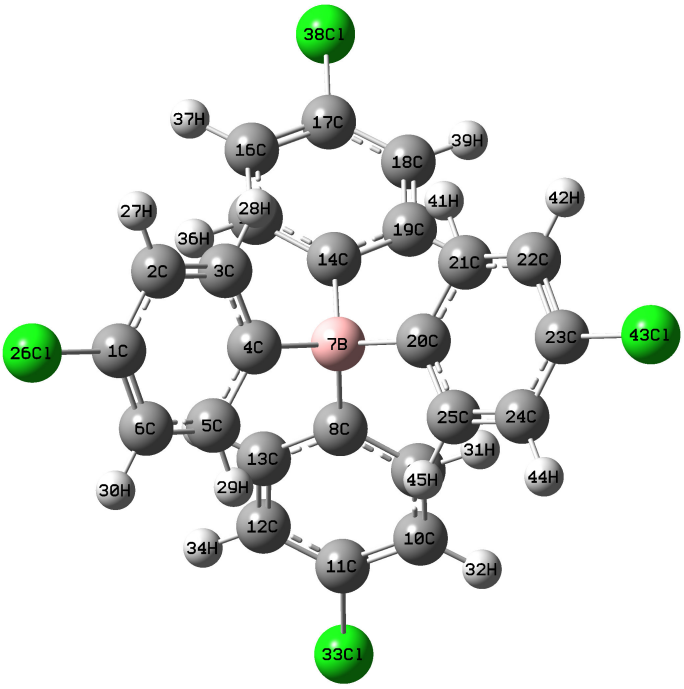

Figure 3. The full optimized structure of L2

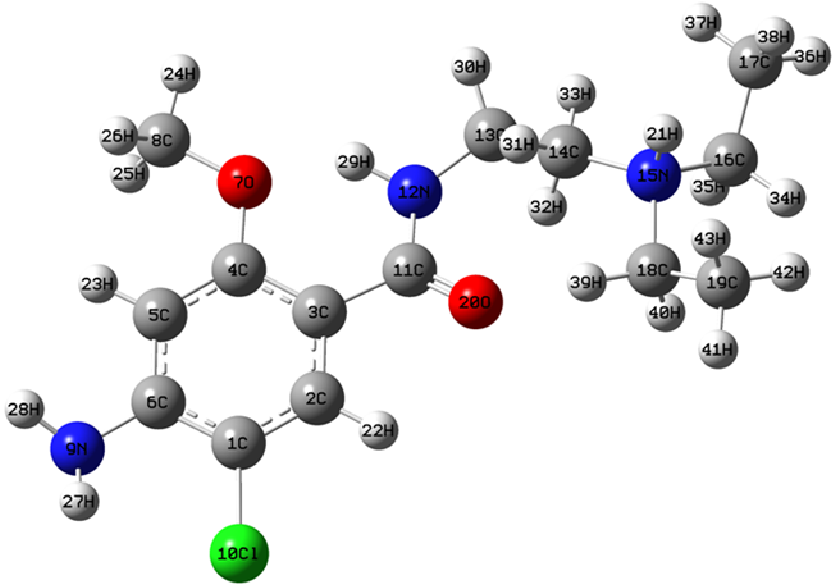

Figure 4. The full optimized structure of MCP

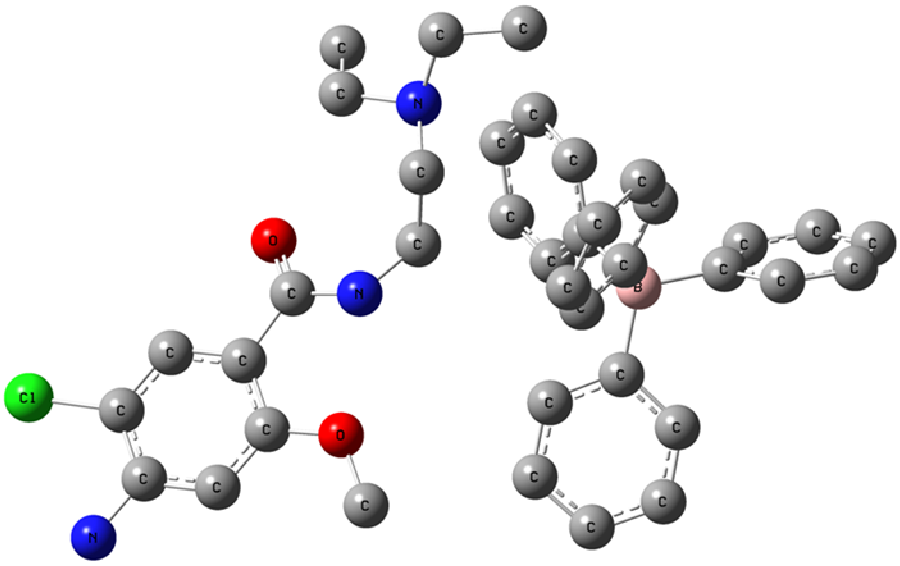

Figure 5. The full optimized structure of L1-MCP complex

Furthermore, high values of polarizability (155.772 and 151.356 for L1 and drug, respectively) prove its effect role on interactions among L1 and the drug. While the low values of dipole-dipole interactions (especially for that of L1) show that it does not play a significant role between L1 and the studied drug. Moreover, since the studied molecules are in form of ions, electrostatic interactions should also be considered. As can be seen in Table 1, atom charges are delocalized on L1 while they are localized on the drug.

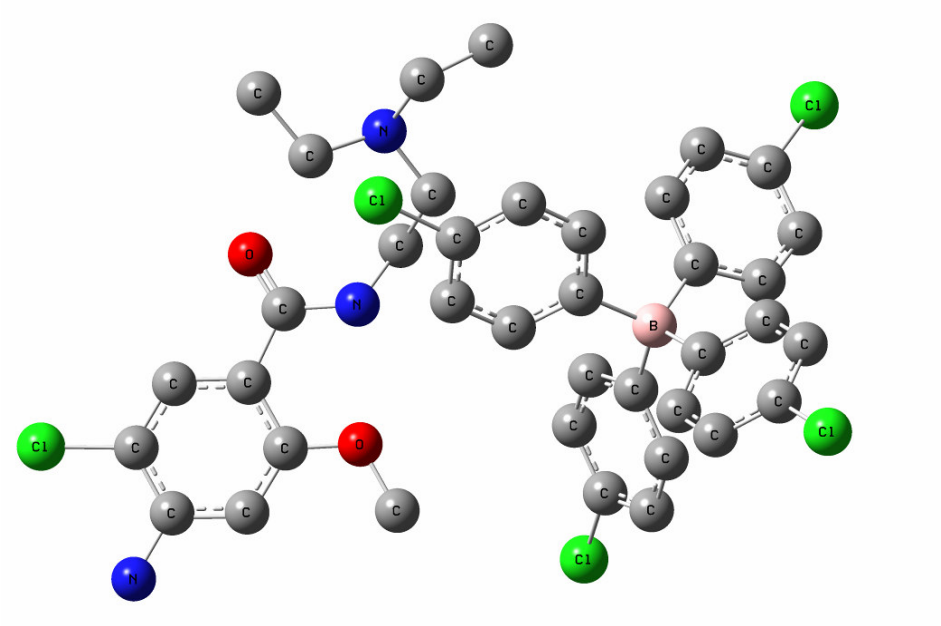

Figure 6. The full optimized structure of L2-MCP complex

Table 1. Significant computed atomic charges and bond length for metoclopramide and L1 before and after the complex formation

Charges			Bonds		
No.	Drug	Drug-complex B	No.	Drug	Drug-complex B
C6	0.149	0.139	R(1,2)	1.381	1.384
O7	-0.251	-0.244	R(1,6)	1.402	1.399
Cl10	-0.142	-0.158	R(1,10)	1.780	1.783
N15	-0.223	-0.429	R(2,3)	1.389	1.387
N12	-0.380	-0.348	R(3,11)	1.515	1.522
O7	-0.251	-0.244	R(4,7)	1.397	1.394
O20	-0.303	-0.282	R(5,6)	1.400	1.398
Cl10	-0.142	-0.158	R(6,9)	1.418	1.426
H21	0.264	0.286	R(11,12)	1.425	1.422
H24	0.088	0.099	R(12,13)	1.466	1.469
H27	0.209	0.199	R(13,14)	1.566	1.561
H28	0.194	0.186	R(14,15)	1.534	1.522
H30	0.094	0.122	R(15,16)	1.535	1.523
H32	0.117	0.101	R(15,18)	1.542	1.538
H33	0.102	0.116	R(15,21)	1.040	1.051
H34	0.11	0.098	R(18,39)	1.101	1.098
H35	0.109	0.097			
H36	0.108	0.092	No.	tetraphenylborate	B-complex
H37	0.085	0.098	R(4,7)	1.643	1.656
H41	0.108	0.094	R(7,8)	1.643	1.655
			R(7,14)	1.643	1.657
No.	tetraphenylborate	B-complex	R(7,20)	1.643	1.656
C4	-0.068	-0.075			
B7	0.232	0.027			
C8	-0.068	-0.075			
C14	-0.068	-0.077			
C50	-0.068	-0.073			

3.2. Membrane composition effect on the potential response of the sensor

The potential response of a sensor is greatly related to the membrane ingredients, the influence of membrane composition on the potential responses of the metoclopramide sensor was studied. For this purpose, different membrane compositions as shown in Table 2 were tested. As it can be seen, the membrane with the composition of 30% PVC, 7% MCP-TPB, and 63% DBP (no. 2) was the optimum one in the development of this sensor. This membrane composition was selected after many considerations.

The high metoclopramide extraction into the liquid membrane was a result of the elevated ion-pair tendency to exchange with the metoclopramide cations [29-31]. From Table 2, 7 mg ion-pair (MCP-TPB) is the best amount for the best response.

Table 2. Optimization of membrane ingredients

Membrane no.	PVC (% wt.)	Plasticizer (% wt.)	Ion-pair (% wt.)	Additive (% wt.)	Slope (mV decade^{-1})	Linear range (M)
1	30	DBP, 65	5, MCP-TPB	-	56.47	1.0×10^{-5} -5.0×10^{-2}
2	30	DBP, 63	7, MCP -TPB	-	59.25	1.0×10^{-6} -1.0×10^{-1}
3	30	DBP, 61	9, MCP -TPB	-	55.14	2.0×10^{-5} -1.0×10^{-1}
4	30	DBP, 61	7, MCP -TPB	2, NaTPB	57.28	4.0×10^{-6} -1.0×10^{-1}
5	30	DBP, 60	7, MCP -TPB	3, NaTPB	56.45	1.0×10^{-5} -5.0×10^{-2}
6	30	BA, 63	7, MCP -TPB	-	10.32	1.0×10^{-4} -1.0×10^{-2}
7	30	NB, 63	7, MCP -TPB	-	20.23	5.0×10^{-3} -1.0×10^{-2}
8	30	DBP, 63	7, MCP - TpClPB	-	43.34	1.0×10^{-5} -1.0×10^{-1}

Also, MCP-TpClPB was used as ion-pair in membrane composition. According to the theoritical calculations, interaction between metochlopramideand TpClPB anion is not so strong. The experimental data support the theoritical datas.

The second factor which helps metoclopramide ions to extract from an aqueous solution to the membrane as an organic phase is a plasticizer. After the evaluation of three solvent mediators (NB, BA and DBP), it was observed that they have not the same results if the optimum composition is used. DBP, which is a low-polar solvent mediator, shows better response than BA and NB. NB and BA have higher dielectric constant values than DBP, leading to the extraction of the polar ions, which have negative effects on the extraction of the metoclopramide ions as a hydrophobic ion [32].

The presence of lipophilic anions in a cation-selective membrane was also considered [33]. As it can be seen from Table 2, the presence of such anions in a cation-selective membrane, which is based on an ion-pair, decreases the response behavior of the sensor.

3.3. pH effect on the electrode response

In an approach to understanding the impact of pH on the electrode response, the potential was measured at two particular concentrations of the metoclopramide solution (1.0×10^{-3} M and 1.0×10^{-4} M) from the pH value of 2.0 up to 12.0 (concentrated NaOH or HCl solutions were employed for the pH

adjustment). The resulted data showed that the potential remained constant despite the pH change in the range of 3.5 to 8.0, indicating the applicability of this electrode in the specific pH range.

Relatively noteworthy fluctuations in the potential *vs.* pH behavior took place below and above the formerly stated pH limits. In detail, the fluctuations above the pH value of 8.0 might be justified by removing the positive charge on the drug molecule and the fluctuations below the pH value of 3.5 were attributed to the removing the ion-pair in the membrane.

3.4. Study of sensor properties

The properties of a potentiometric membrane sensor are characterized by parameters like these: measuring range, detection limit, response time, selectivity, lifetime, accuracy.

3.4.1. Measuring range

The measuring range of an ion-selective electrode includes the linear part of the calibration graph as shown in Fig. 7. Measurements can be performed in this lower range, but it must be noted that more closely spaced calibration points are required for more precise determinations. According to another definition, the measuring range of an ion-selective electrode is defined as the activity range between the upper and lower detection limits. The applicable measuring range of the proposed sensor is between 1×10^{-6} and 1×10^{-1} M.

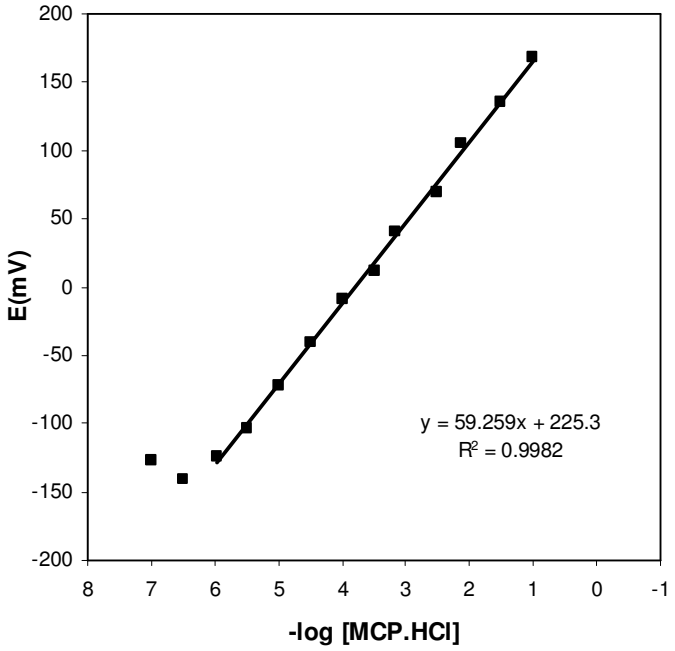

Figure 7. The calibration curve of the metoclopramide hydrochloride membrane sensor (membrane no. 2).

3.4.2. Detection limit

By extrapolating the linear parts of the ion-selective calibration curve, the detection limit of an ion-selective electrode can be calculated. In practice, detection limits for the most selective electrodes are in the range of 10^{-5}–10^{-6} M.

In this work the detection limit of the proposed membrane sensor was 1.0×10^{-6} M (0.3 µg/ml) which was calculated by extrapolating the two segments of the calibration curve (Fig. 7).

3.4.3. Response time

The response time of an electrode is evaluated by measuring the average time required to achieve a potential within ±0.1 mV of the final steady-state potential, upon successive immersion of a series of interested ions, each having a ten-fold difference in concentration. It is notable that the experimental conditions-like the stirring or flow rate, the ionic concentration and composition of the test solution, the concentration and composition of the solution to which the electrode was exposed before experiment measurement was performed, any previous usages or preconditioning of the electrode, and the testing temperature have an effort on the experimental response time of a sensor [10].

In this work, about 10 s response time was obtained for the proposed electrode when contacting different metoclopramide solutions from 1.0×10^{-3} to 1.0×10^{-1} M, and about 15 s in low concentration solutions, which is due to the effect of analyte concentration on the response time of ion-selective electrode.

Table 3. Selectivity coefficients of various interfering compound for metoclopramide sensor

Interference	Log K_{MPM}
Na^+	-3.35
Cl^-	-3.57
Br^-	-3.63
I^-	-3.42
CO_3^{2-}	-2.86
NO_3^-	-3.21
Mg^{2+}	-3.57
HPO_4^{2-}	-3.15
Ca^{2+}	-3.14
K^+	-2.94
Promethazine	-2.52
Imipramine	-3.32
Citaloperam	-3.02
Terazosine	-3.14

3.4.4. Selectivity

Selectivity, which describes an ion-selective electrode's specificity toward the target ion in the presence of interfering ions, is the most important characteristic of these devices. The potentiometric

selectivity coefficients of the metochlopramidesensor were evaluated by the matched potential method (MPM) [31-38].

The resulting values of the selectivity coefficients are given in Table 3. As can be seen from Table 3, in all cases the selectivity coefficients are about 10^{-3}, which seems to indicate negligible interferences in the performance of the electrode assembly.

3.4.5. Lifetime

The average lifetime for most of the reported ion-selective sensors is in the range of 4–10 weeks. After this time the slope of the sensor will decrease, and the detection limit will increase. The sensors were tested for 10 weeks, during which time the electrodes were used extensively (one hour per day). Fig. 8 shows the changes in the slope and detection limits of a sensor with time. The proposed sensors can be used for six weeks. First, there is a slight gradual decrease in the slopes (from 59.25 to 55.6 mV per decade) and, second, an increase in the detection limit (from 1.0×10^{-6} M to 1.2×10^{-4} M). It is well established that the loss of plasticizer, ionic site from the polymeric film due to leaching into the sample is a primary reason for the limited lifetimes of the sensors [39-41].

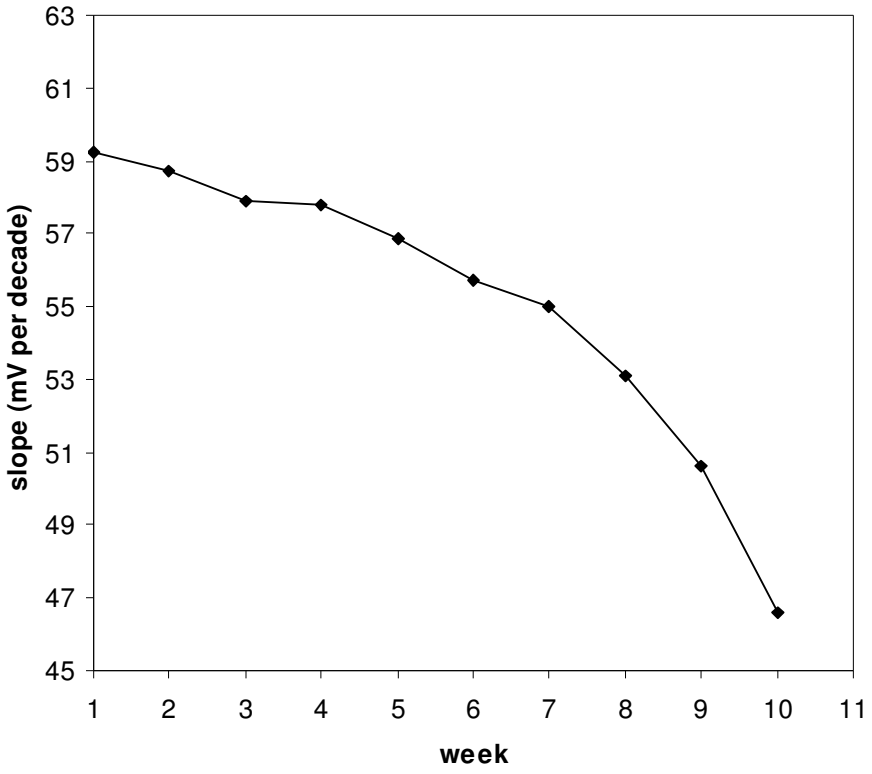

Figure 8. The lifetime of the metochlopramidemembrane sensor (membrane no. 2)

3.5. Analytical application

3.5.1. Determination of metoclopramide in formulations

A homogenized powder was prepared from 10 accurately weighed metoclopramide tablets. An appropriate amount of this powder (0.200 g) was transferred into a 100-mL volumetric flask. Dissolution of the drug was assisted by means of a magnetic stirrer. The solution was then diluted to the mark with water and the proposed electrode determined metoclopramide content by using the calibration method [42,43]. The results for determination of metoclopramide amount in some pharmaceutical samples from local pharmacy are shown in Table 4. As it is seen, the results are in satisfactory agreement with the stated content on tablets.

Table 4. Results of metoclopramide assay in tablets by the metoclopramide membrane sensor

Application sample	Stated content (mg/tab)*	Found (mg/tab)
AMI-METOCLOPRAMIDE®	10.0	10.4±0.2
METOCLOPRAMIDE-HAKIM®	10.0	10.5±0.3
PLAZILIN®	10.0	10.2±0.3

*Data obtained from three measurements

3.5.2. Recovery of metoclopramide from urine samples

In order to investigate the applicability of the new sensor to determination of drug in the biological fluids, it was applied to the recovery of metoclopramide from urine samples. A 2.5 mL of 10^{-3} M metoclopramide solution was transferred into a 10 mL volumetric flask. After addition of a 2.5 mL of urine samples, the solution was diluted to the mark with water. The metoclopramide content of the solution was then determined by the proposed electrode, using the calibration method. The recovery from three replicate measurements was found to be 102.3%, 105.2% and 103.4%, respectively.

3.5.3. Validation of the method

The linearity, limit of detection (LOD), precision, accuracy, ruggedness/robustness, and recovery was the parameters which were used for the method validation.

The measuring range of the metoclopramide sensor is between 1×10^{-6} and 1×10^{-1} M. The detection limit of the sensor was calculated 1.0×10^{-6} M (0.3 µg/ml).

The parameters of the repeatability and reproducibility were investigated in order to assess the precision of the technique. For the repeatability monitoring, 8 replicate standards samples 3, 30, 300

µg/ml were measured. Then, the mean concentrations were found to be 3.05, 30.7, 303.3 µg/ml and with associated RSD values of 1.6, 1.05, and 0.30%, respectively. Regarding the inter-day precision, the same three concentrations were measured for 3 consecutive days, providing mean metoclopramide concentrations of 3.04, 30.5, 302.6 µg/ml and associated RSD values of 1.72, 1.02, and 0.27%, respectively.

Additionally, the relevant error percentage and accuracy were calculated in each case. The resultant concentrations were 3.04±0.03, 30.5±0.4, and 302.6±1.2 µg/ml with relevant error percentages of 3.83, 1.34, and 0.34%, respectively.

For ruggedness of the method a comparison was performed between the intra- and inter-day assay results for metoclopramide obtained by two analysts. The RSD values for the intra- and inter-day assays of metoclopramide in the cited formulations performed in the same laboratory by the two analysts did not exceed 3%. On the other hand, the robustness was examined while the parameter values (pH of the eluent and the laboratory temperature) were being slightly changed. Metoclopramide recovery percentages were good under most conditions, not showing any significant change when the critical parameters were modified.

A known amount of metoclopramide standard powder was added to the tablet samples. Then, this amount was analyzed according to former reports. The RSD was equivalent to 2.0% with a corresponding recovery percentage value of 99.87%.

4. CONCLUSIONS

After a series of experiments involving the usage of MCP-TPB ion-pair complexes along with several plasticizers in the membrane design, it was concluded that the metoclopramide sensor exhibited excellent analytical performance characteristics. It demonstrated an advanced performance with a fast response time (~10-15 s), a lower detection limit of 1.0×10^{-6} M and pH independent potential responses across the range of 3.5–8.0. This high sensitivity of the sensor enabled the metoclopramide determination in pharmaceutical analysis.

The theoretical calculations are very accurate and suitable methods to obtain interaction energy and therefore choosing a better ion-pair. Additionally, employing these methods let us find centre of interactions in the target molecule and ionophore.

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