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Citalopram Analysis in Formulation and Urine by a Novel Citalopram Potentiometric Membrane Sensor

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ABSTRACT

Citalopram is an antidepressant drug used to treat depression associated with mood disorders. This research introduces the design of an ion-pair based polyvinylchloride (PVC) membrane sensor for the citalopram determination based on theoretical investigations. For the membrane preparation, citalopram-tetraphenyl borate ion-pair was employed as an electroactive material in the PVC membrane. In parallel, several plasticizers were studied, i.e. dibutyl phthalate (DBP), acetophenon (AP), nitrobenzene (NB) and nitrophenyloctyl ether (*o*-NPOE). After a series of experiments, the best electrode performance was accomplished with a membrane composition of 30% PVC, 66% DBP, and 4% ion-pair. This electrode illustrated a fast (~5 s), stable and Nernstian response (58.6 ± 0.3 mV/decade) across a relatively wide citalopram concentration range 1×10^{-5} to 1×10^{-2} M and in the pH range of 3.0-5.5. Validation of the method showed suitability of the sensors for the quality control analysis of citalopram hydrobromide in pharmaceutical formulation and urine. The proposed method was simple, accurate and precise and can be used as a detector for HPLC.

Key words: potentiometric sensor, PVC membrane, ion-pair, citalopram, Density Functional Theory, chemometrics

INTRODUCTION

Citalopram (Figure 1), 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-5-phthalan carbonitrile, is an antidepressant drug used to treat depression associated with mood disorders. It is also used on occasion for the treatment of body dysmorphic disorder and anxiety. Citalopram belongs to a class of drugs known as selective serotonin reuptake inhibitors (SSRIs). It is primarily used to treat the symptoms of depression but can also be prescribed for social anxiety disorder, panic disorder, obsessive-compulsive disorder, the Huntington's disease, and premenstrual dysphoric disorder.

Citalopram affects neurotransmitters, the chemical transmitters within the brain. Neurotransmitters manufactured and released by nerves attached to adjacent nerves and alter their activities. Thus, neurotransmitters are considered the communication system of the brain. Many experts believe that an imbalance among neurotransmitters is the cause of depression. Citalopram works by preventing the uptake of serotonin by nerve cells after it has been released. Such uptake is an important mechanism for removing released neurotransmitters and terminating their actions on adjacent nerves. The reduced uptake caused by citalopram results in stimulation of the nerve cells by the free serotonin in the brain[(1)].

A number of research describe the determination of citalopram in biological fluids[(2,3)] and pharmaceutical formulation[(4,5)] by several methods. However, potentio-

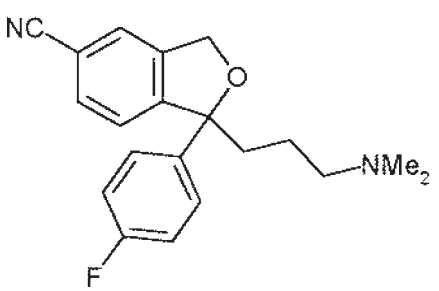

Figure 1. Chemical structure of citalopram.

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metric detection based on ion–selective electrodes (ISEs) offers the advantages of speed and ease of preparation and procedures, relatively fast response, reasonable selectivity thorough judicious choice of the membrane active materials, wide linear dynamic range, and low cost. These characteristics have inevitably led to the preparation of numerous sensors for several ionic species, and the list of available electrodes has grown substantially over the past years[6].

Computational chemistry and molecular modeling play important roles in the modern drug discovery[7-11]. Computational work is also valuable in the drug development, where medium-sized organic pharmaceuticals are selected as candidates and 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 ligand. Several energy contributions may be responsible for the binding, with electrostatic interactions playing a dominant role in the process, at least in sequence preferences and the target molecules positioning[12,13].

No studies to date in the literature have used computational methods to evaluate drug selective ligands by electronic properties. The lack of work in this area is probably due to the inherent difficulties associated with calculations on a Drug-Ligand complex, including the lack of parameters for semi-empirical or empirical methods even though the numbers of atoms in typical drug complexes indicate the use of these lower level calculations would be appropriate.

Furthermore, literature survey shows no reported sensor for citalopram. In this work, we report a membrane sensor based on an ion-pair to determine citalopram in its formulation samples and urine with a Nernstian response over a relatively wide working range. Also, in this study we used DFT (Density Functional Theory) atomic population analysis to measure a Ligand-drug complexing by examining the ability of the ligand to change in atomic charges and bond length of drug. This method was found to be simple, accurate and precise and can be used as a detector for HPLC[14-17].

EXPERIMENTAL SECTION

I. *Apparatus*

The glass cell, where the citalopram-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, Netherlands). 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.

II. *Materials and Reagents*

The necessary chemicals (of analytical reagent grade) were: high-molecular weight polyvinylchloride (PVC) (Fluka Co., USA), sodium tetraphenylborate (NaTPB), acetophenon (AP), dibutyl phthalate (DBP), nitrobenzene (NB), nitrophenyloctyl ether (*o*-NPOE) and tetrahydrofuran (THF) (Merck Co., Germany). All materials were of the highest available purity without further modification. Citalopram hydrobromide and its tablets were obtained from different local pharmaceutical manufacturers.

III. *Preparation of Ion-pair Compound*

Ion-pair compound of citalopram-tetraphenylborate (CP-TPB) was prepared as follows: about 20 mL of 0.01 M solution of citalopram hydrobromide was mixed with 20 mL of 0.01 M solution of tetraphenylborate under stirring. The resulting precipitate was filtered, washed with water and dried[18-20].

IV. *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 in thickness was formed. The tube was then pulled out from the mixture and kept at room temperature for about 10 h. Afterwards, the tube was filled with an internal filling solution (1.0×10^{-3} M citalopram hydrobromride). The electrode was finally conditioned for 24 h by soaking in a 1.0×10^{-3} M citalopram hydrobromide solution[21-25].

V. *Standard Citalopram Solutions*

A stock standard solution of 0.02 M citalopram hydrobromide was prepared by dissolving 0.405 g of pure drug in 100 mL of distilled water. The working solutions (1×10^{-6} to 1×10^{-2} M) were prepared by appropriately diluting of the stock solution with water.

VI. *The emf Measurements*

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

Ag-AgCl | internal solution, 1×10^{-3} M citalopram. HBr | PVC membrane | sample solution | Hg-Hg_2Cl_2, KCl (satd.)

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

VII. *Computational Methods*

Calculations on the isolated molecules and molecular complexes were performed within GAUSSIAN 98 package[26]. Each species was initially optimized with the parametric method three (PM3)[27-29] and then the optimized structures were again optimized with density functional theory using the 6-31G* basis set. Full geometry optimizations and frequency calculations were performed and each species was found to be minimal amounts without any negative values in the frequency calculation. The calculations gave internal energies at 0 K. In order to obtain gas phase free energies at 298.15 K, it was necessary to calculate the zero-point energies and thermal corrections together with entropies to convert the internal energies to Gibbs energies at 298.15 K[27,28].

Frequency calculations on these structures verified that they were true minima and provided the necessary thermal corrections to calculate H (Enthalpy) and G (Gibbs free energy). Finally, full optimization and frequency calculation for each species were performed with the DFT/6-31G*[30,31].

Additional one-electron properties (dipole moment, polarizability, energies of the frontier molecular orbital) were also determined at the B3LYP/6-31G* level (Becke, three-parameter, Lee-Yang-Parr)[30,31]. For the charged species, the dipole moment was derived with respect to their mass center since the non-neutral molecules' calculated dipole moment depended on the origin of the coordinate system.

The stabilization energies of the selected complexes were determined using the DFT calculations and estimated with a recently introduced method based on the combination of the approximate tight-binding DFTB (Density Functional based Tight Binding) with the empirical dispersion energy. The DFT methods are known to be inherently very deficient for stacking interactions, as they ignore the dispersion attraction[32-34]. As a consequence, their enlargement by an empirical dispersion terms allows the DFT method to be used for the evaluation of the molecular complexes. Note that the interaction energies were obtained as the difference between the complex energy and the combined energies of the molecules in isolation[35].

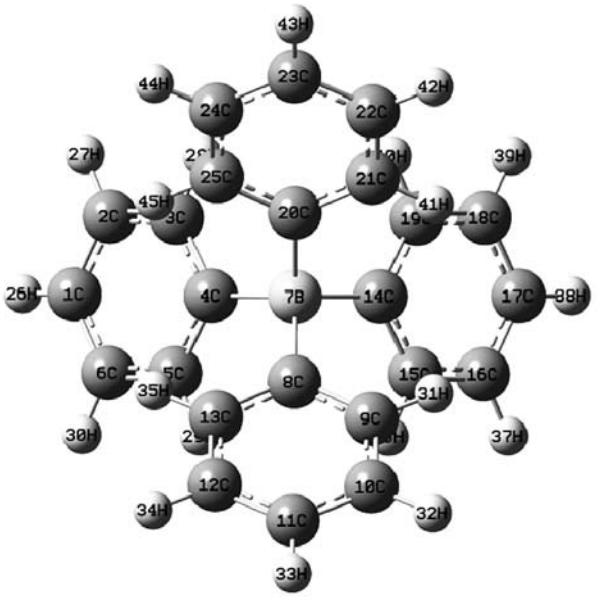

Figure 2. The full optimized structure of L1.

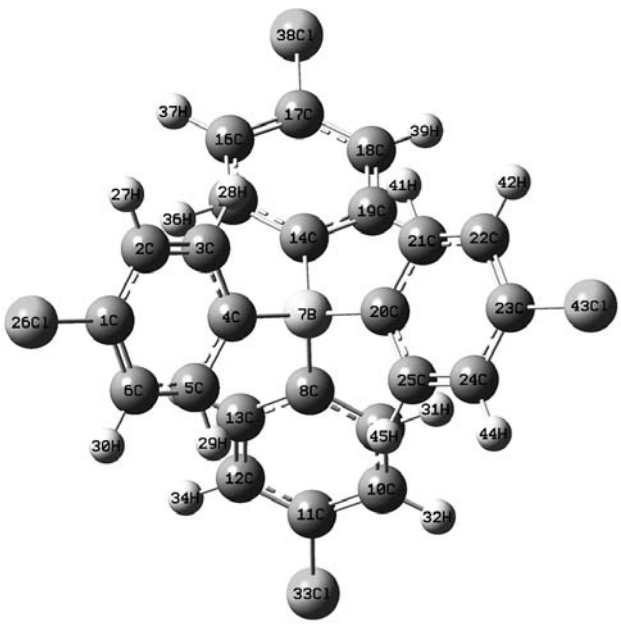

Figure 3. The full optimized structure of L2.

RESULTS AND DISCUSSION

I. *Computational 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, i.e. L1 for NaTPB, L2 for KTpClPB, Drug for CP, Drug-L1 for CP-TPB and Drug-L2 for CP-TpClPB, are presented in Figs. 2 to 6, respectively.

To obtain a clue on citalopram tendency for L1 and L2 as potential ionophores, DFTB 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 that of the isolated partners. The interaction energies were corrected for the basis set superposition error using the counterpoise method[36,37].

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

which was found to be -67.716 and -52.007 Kcal/mol

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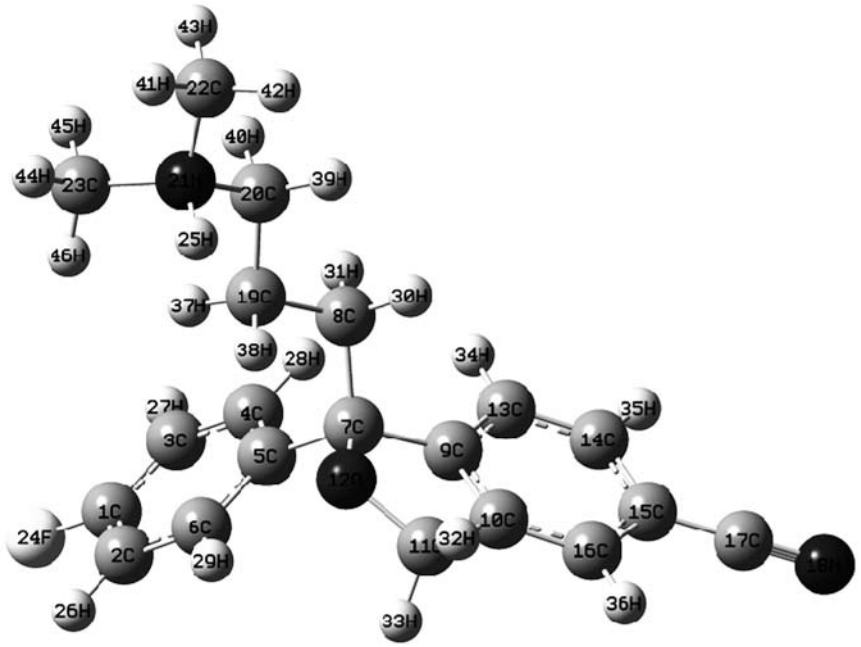

Figure 4. The full optimized structure of CP.

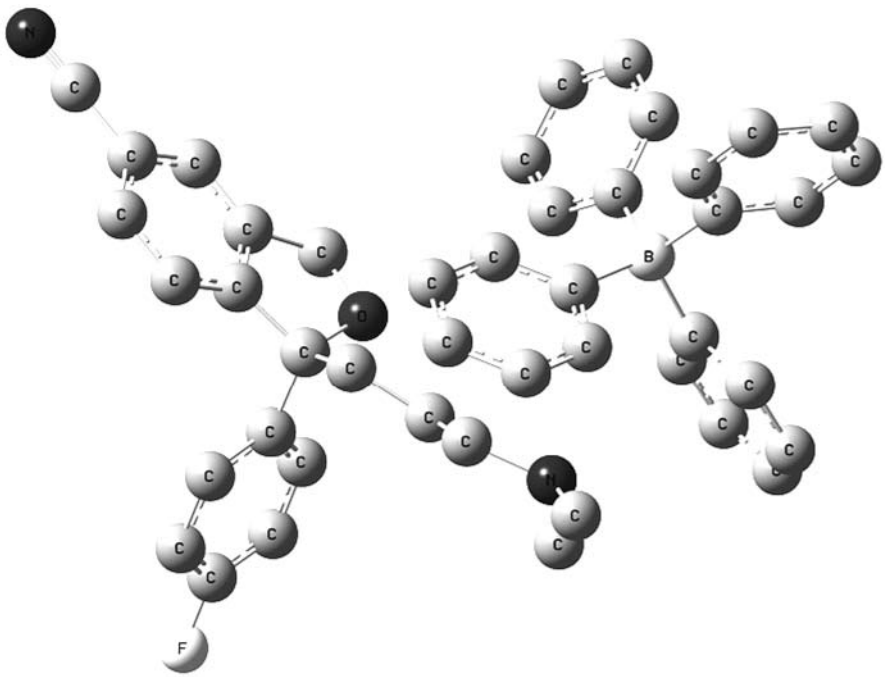

Figure 5. The full optimized structure of L1-CP complex.

for ΔE_{L1} and ΔE_{L2}, respectively. This result indicated that L1 is a more appropriate ionophore for citalopram sensor in comparison to L2 due to its higher interaction energy. The main discussions are going to be on L1-CP interaction afterward.

Results in Table 1 (the most noticeable Mulliken atomic charge changes) show that electrostatic interactions are the most dominant force between the drug and L1. Furthermore, charge changes in the ion pairs are localized on specific atoms that interact with each molecule[38,39]. Hetero atoms (N, O and F) significant charge changes confirm hydrogen bonding and electrostatic interactions effective role in ion pair formation, e.g. N21 (from -0.216 to -0.223), N18 (from -0.321 to -0.188), O12 (from -0.295 to -0.256), F24 (from -0.140 to -0.100), Moreover, significant changes were seen for carbon and

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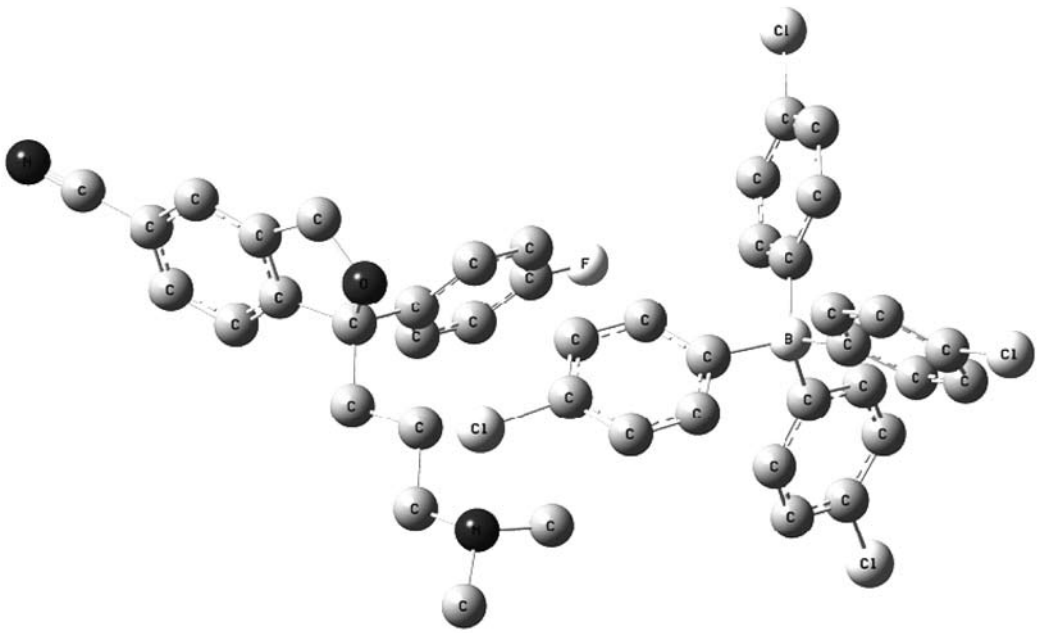

Figure 6. The full optimized structure of L2-CP complex.

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

Atom No.	Some important atomic charges (unit of electric charge)	
	CP	CP-L1
C9	-0.072	-0.001
O12	-0.292	-0.256
C17	0.005	0.068
N18	-0.321	-0.188
C20	0.001	-0.007
N21	-0.216	-0.223
C22	-0.080	-0.087
C23	-0.080	-0.082
F24	-0.140	-0.100
H25	0.282	0.300
No.	L1	L1-CP
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
Bond lengths (Å)		
R(1,24)	1.357	1.355

Atom No.	Some important atomic charges (unit of electric charge)	
	CP	CP-L1
R(7,12)	1.450	1.450
R(11,12)	1.448	1.444
R(17,18)	1.182	1.157
R(20,21)	1.544	1.522
R(20,39)	1.091	1.092
R(21,22)	1.520	1.508
R(21,23)	1.520	1.414
R(21,25)	1.042	1.096
R(22,41)	1.0895	1.088
R(23,44)	1.089	1.088
Bond lengths	L1	L1-CP
R(4,7)	1.643	1.656
R(7,8)	1.643	1.655
R(7,14)	1.643	1.657
R(7,20)	1.643	1.656
HOMO (eV)	-4.52	2.77 for L1
LUMO (eV)	3.12	10.94 for L1

hydrogen atoms, especially for H25 (from 0.282 to 0.300). In L1, which is connected to carbon atoms, remarkable atomic charge changes are seen for boron (from 0.232 to 0.027). Additionally, the bond lengths also changed as a result of ion pair formation (Table 1). According to Table 1, the maximum bond length change occurred in N21-H25 drug which indicates the interaction between the hydrogen (the most positive charge) and L1 (negative charge). Other bond length changes are localized on N21, (N21-C20 and N21-C23 and N21-C22). For L1, B7-C4 and B7-C20 are the most significant bond length changes.

High values of polarizability (155.772 and 144.088 for L1 and drug, respectively) have proven L1's effective role in the interactions between L1 and the drug. On the other hand, the low values of dipole-dipole interactions (especially for that of L1 = 0.0 and for drug = 0.6D) show that the dipole-dipole interactions do not play a significant role on interactions existing among L1 and the studied drug. As for the electrostatic interactions, atom charges are delocalized on L1 while they are localized on the drug (Table1).

The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) for L1 and drug were calculated at the B3LYP/6-31G(d) level (Table 1). The eigen values of LUMO and HOMO and their energy gap reflect the chemical activity of the molecule. LUMO as an electron acceptor shows the ability to obtain an electron, while HOMO as an electron donor represents the ability to donate an electron. The results in Table 1 illustrate the charge transfer interaction between L1 and drug, because the HOMO energy of L1 was close to that of LUMO energy of the drug.

II. *Membrane Composition Influence and Selection*

Because the sensitivity and selectivity degree of an ion-pair based electrode is greatly related to the membrane ingredients, the membrane composition influence on the potential responses of the citalopram sensor was determined. The operating characteristics of the ISEs can be significantly modified by changing the relative proportions of the electrode membrane components. The main components of an electrode membrane of this type are PVC matrix, the plasticizer and the ion-pair. Each membrane component plays a special role in the membrane function[40-45].

The plasticizer mainly acts as a fluidizer, allowing homogeneous dissolution and diffusional mobility of the ion-pair inside the membrane. The nature and/or the amount of the plasticizer must be properly controlled to minimize the electrical asymmetry of the membrane and to limit fouling of the sensor. The nature of the plasticizer has a marked influence on the response slope, linear domain and selectivity of the PVC membrane electrodes. Here, many plasticizer types were tested, namely acetophenon (AP), dibutyl phthalate (DBP), nitrobenzene (NB) and nitrophenyloctyl ether (*o*-NPOE), as listed in Table 2. In this study, DBP was chosen for the sensor construction. It had the lowest dielectric constant and provided an effective linear range and a lower detection limit due to the better extraction of the citalopram in the organic layer[46-48].

As it can be seen from Table 2, the absence of the ion-pair in the membrane resulted a very poor response (membrane no. 7), suggesting significance of the ion-pair. As a conclusion, membrane no. 2 with the composition of 30% PVC, 4% ion-pair, and 66% DBP was the optimum one for the sensor design.

III. *Calibration Graph and Statistical Data*

The measuring range of an ion-selective electrode included the linear part of the calibration graph as shown in Figure 7. Measurements could be performed in this lower range, but noted that more closely spaced calibration points are required for more precise determinations. For many electrodes the measuring range can extend from 1 molar to 10^{-6} or even 10^{-7} molar concentrations. According to another definition, the measurment range of an ion-selective electrode is defined as the activity range between the upper and lower detection limits[46-48]. In line with the membrane no. 2 performance, a calibra-

Table 2. Optimization of the membrane ingredients

Detection Limit (M)	Linear range (M)	Slope (mV/decade)	Ion-pair (% w)	Plasticizer (% w)	PVC (% w)	Membrane no.
1.0×10^{-5}	1.0×10^{-5} -1.0×10^{-2}	52.7 ± 0.4	3	DBP, 67	30	1
7.9×10^{-6}	1.0×10^{-5} -1.0×10^{-2}	58.6 ± 0.3	4	DBP, 66	30	2
9.0×10^{-6}	5.0×10^{-5} -1.0×10^{-2}	56.5 ± 0.3	6	DBP,64	30	3
1.0×10^{-5}	1.0×10^{-5} -1.0×10^{-2}	41.2 ± 0.3	5	NB, 63	30	4
5.0×10^{-5}	5.0×10^{-5} -1.0×10^{-2}	39.2 ± 0.2	5	NPOE, 63	30	5
8.2×10^{-6}	1.0×10^{-5} -1.0×10^{-2}	45.7 ± 0.4	5	AP, 63	30	6
3.0×10^{-4}	6.0×10^{-4} -2.0×10^{-3}	4.3 ± 0.2	-	DBP, 70	30	7

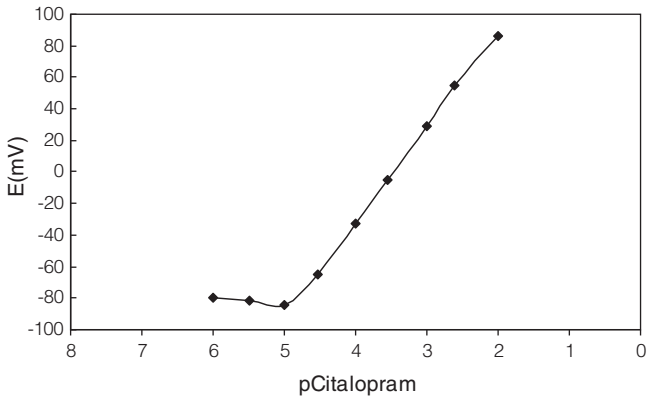

Figure 7. Calibration curve of the citalopram membrane sensor with the composition of membrane no. 2. The results are based on 8 measurements.

tion graph slope of 58.6 ± 0.3 mV/decade of the citalopram concentration and a standard deviation of ± 0.3 mV after eight replicate measurements. Also, electrode with composition of membrane no. 2 presented a linear response towards the citalopram.HBr concentration from 1.0×10^{-5}-1.0×10^{-2} M of the citalopram.HBr solution (Figure 7).

The detection limit was calculated from the intersection of the two extrapolated segments of the calibration graph. In this work, the detection limit of the proposed membrane sensor was 7.9×10^{-6} mol/L which was calculated by extrapolating the two segments of the calibration curve (Figure 7).

IV. *Dynamic Response Time of the Citalopram-based Sensor*

Dynamic response time is the required time for the sensor to reach values within ±1 mV of the final equilibrium potential, after successive immersions in the citalopram solutions. Its calculation involved the variation and the recording of the citalopram concentration in a series of solutions from 1.0×10^{-5} to 1.0×10^{-2} M. The sensor was able to quickly reach its equilibrium response (~5 s) in the whole concentration range.

V. *pH Effect on the Electrode Response*

To examine impact of pH on the electrode response, the potential was measured at two specific concentrations of the citalopram 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 results showed that the potential remained constant despite the pH change in the range of 3.0 to 5.5, which indicates the applicability of this electrode in the specified 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 5.5 might be justified by removing the positive charge on the drug molecule. Fluctuations below the pH value of 3.0 were caused by removal of the ion-pair in the membrane.

VI. *Life-time Study*

The citalopram-selective electrode lifetime was estimated with the calibration curve, periodical test of a standard solution (1.0×10^{-5}-1.0×10^{-2} M, citalopram.HBr) and calculation of its response slope.

For this estimation, four electrodes were employed extensively (2 hour per day) for 10 weeks. After 8 weeks of utilization, two changes were observed: a slight gradual decrease in the slope (from 58.6 ± 0.3 to 53.2 ± 0.4 mV/decade) and an increase in the detection limit (from 7.9×10^{-6} M to 3.5×10^{-5} M).

VII. *Analytical Applications*

(I) *Recovery Test from the Citalopram Tablet*

The proposed sensor was evaluated by measuring the drug concentration in some pharmaceutical formulations. The recovery results are shown in Table 3. The drug concentration was determined with the calibration method. The results are in satisfactory agreement with the labeled amounts. The RSD was equivalent to 2.0% with a corresponding recovery percentage value of 99.86%.

(II) *Recovery of Citalopram from Urine Samples*

In order to investigate the applicability of the new sensor to determination of drug in biological fluids, the proposed sensor was applied to recover citalopram from urine samples. Two milliliter of 10^{-4} M citalopram solution was transferred into a 10 mL volumetric flask. After addition of 2.5 mL of urine samples, the solution was diluted to the mark with water. The citalopram content of the solution was then determined by the proposed elec-

Table 3. Potentiometric determination of citalopram in pharmaceutical formulations

Sample	Labeled amount (mg/tab.)	Found* (mg/tab.)
Citalopram tablet, Bakhtar Biochemistry	10	10.2 ± 0.3
Citalopram tablet, Sobhan Darou	10	9.9 ± 0.2
Citalopram tablet, Osveh	10	10.3 ± 0.4

* The results are based on triplicate measurements

trode, using the calibration method. The recovery from three replicate measurements was found to be 105.3%, 103.2% and 104.4%, respectively.

VIII. *Validation of the Method*

The linearity, limit of detection, selectivity, precision, accuracy, and ruggedness/robustness were the parameters used for the method validation. As mentioned before, the citalopram sensor was measured between 1×10^{-5} and 1×10^{-2} M. The calculated detection limit of the sensor was 7.9×10^{-6} M (3 μg/mL).

(I) *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 citalopram sensor were evaluated by the matched potential method (MPM)[48,49]. The resulting values of the selectivity coefficients are shown in Table 4. Note that all selectivity coefficients are about 10^{-3}, suggesting were interferences negligible in the performance of the electrode assembly.

Table 4. Selectivity coefficients of various interfering compounds for citalopram sensor

Interference	Log K_{MPM}
Na^+	-3.33
Cl^-	-3.42
Br^-	-3.61
I^-	-3.75
CO_3^{2-}	-2.80
NO_3^-	-3.21
Mg^{2+}	-3.57
HPO_4^{2-}	-3.15
Ca^{2+}	-3.14
K^+	-2.91
glucose	-2.53
histamine	-3.43
ammonium	-3.17

(II) *Precision*

Repeatability and reproducibility were investigated in order to assess precision of the technique. For the repeatability monitoring, 8 replicate standard samples in 3, 30, 300 μg/mL were measured. The mean concentrations were found to be 3.05, 30.7, 303.3 μg/mL with respective RSD values of 1.6, 1.05, and 0.30%. Regarding the inter-day precision, the same three concentrations were measured for three consecutive days, providing mean citalopram concentrations of 3.04, 30.5, 303.6 μg/mL and associated RSD values of 1.72, 1.02, and 0.27%, respectively.

(III) *Accuracy*

The relevant error percentage and accuracy were calculated in each case above. The resultant concentrations were 3.04 ± 0.02, 30.5 ± 0.4, and 303.6 ± 1.2 μg/mL with relevant error percentages of 3.53, 1.34, and 0.33%, respectively.

(IV) *Ruggedness/Robustness*

For ruggedness of the method a comparison was performed between the intra- and inter-day assay results for citalopram obtained by two analysts. The RSD values for the intra- and inter-day assays of citalopram in the cited formulations performed in the same laboratory by the two analysts did not exceed 3.2%. On the other hand, the robustness was examined while the parameter values (pH of the solution and the laboratory temperature (changed slightly. Citalopram recovery percentages were good under most conditions, not showing any significant change when the critical parameters were modified.

CONCLUSIONS

In the present paper, types of interactions between a drug and ligands were studied. Since the studied molecules were in the form of ions that resulted in ion pair formation, DFTB method which also considers dispersion energies in addition to those calculated using DFT was used for further investigations. These theoretical calculations help select appropriate ionophores and also predict their selectivity for different drugs. After a number of experiments involving the usage of CP-TPB ion-pair complexes along with several plasticizers in the membrane design, it was concluded that the citalopram sensor yielded good analytical performance. Citalopram sensor demonstrated an advanced performance with a fast response time (~5 s), a lower detection limit of 7.9×10^{-6} M and potential responses across the range of 1.0×10^{-5}-1.0×10^{-2} M. This sensor enabled the citalopram determination in laboratory titrations and measurement of the drug rate release from its formulation.

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