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Potentiometric Sensor for Quantitative Analysis of Pioglitazone Hydrochloride in Tablets Based on Theoretical Studies

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Pioglitazone is a prescription drug of thiazolidinedione group with hypoglycemic action. Based on the computational studies, pioglitazone-tetraphenyl borate was selected as a suitable ion-pair reagent in making pioglitazone potentiometric PVC membrane sensor. A wide linear range of 10^{-5}-10^{-2} mol L^{-1}, low detection limit of 6.0×10^{-6} mol L^{-1}, and fast response time of ~20 s are characterizations of the proposed sensors. Validation of the method shows suitability of the sensor for application in the quality control analysis of pioglitazone hydrochloride in pure and pharmaceutical formulation.

Keywords: pioglitazone hydrochloride, potentiometric sensor, PVC membrane, geometry, density functional based tight binding (DFTB).

1. INTRODUCTION

Pioglitazone is a prescription drug of thiazolidinedione group with hypoglycemic (antidiabetic) action. Pioglitazone is used for the treatment of diabetes mellitus type 2 (previously known as non-insulin-dependent diabetes mellitus) in mono-therapy or in combination with a sulfonylurea, metformin, or insulin. Pioglitazone stimulates the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) selectively [1-3]. It modulates the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism in the muscle, adipose tissue, and the liver. As a result, pioglitazone reduces insulin resistance in the liver and peripheral tissues; increases the expense of insulin-dependent glucose; decreases withdrawal of glucose from the liver; reduces quantity of glucose, insulin and glycated haemoglobin in the bloodstream [2,3].

Many analytical techniques have been previously reported for pioglitazone analysis in biological fluids and pharmaceutical formulations including high performance liquid chromatography (HPLC) [4-9]. Although HPLC techniques analysis pioglitazone with very low detection limits, it is a time consuming and rather expensive method for use in quality control laboratories.

Recently, electrochemical methods for fast and online monitoring of drugs have been developed which are based on cyclic voltammetry and potentiometry [10-18]. Potentiometric sensors have been used in analysis of some pharmaceutics in their formulations [19-28] due to their simplicity, rapidity, accuracy, portability and cost-effectiveness over some instrumental methods like spectrophotometry and HPLC. Literature survey reveals that there are only two reports on pioglitazone potentiometric sensor [29,30]. Recently, our group has widely used computational methods to evaluate selectivity of sensing materials according to their electronic properties [31-36]. The lack of work in this area is probably due to the inherent difficulties associated with doing calculations on a Drug-Ligand complex. Some of these problems include 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.

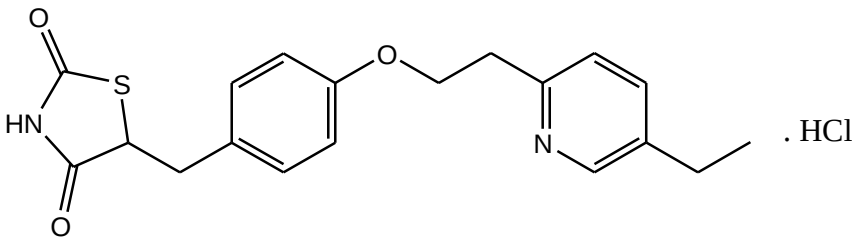

Figure 1. Chemical structure of Pioglitazone hydrochloride

Here, a simple potentiometric PVC-membrane sensor is introduced for determination of pioglitazone in its tablet. The membrane used in this electrode was made from liquid-plasticized PVC and was based on a water-insoluble pioglitazone–tetraphenyl borate ion-pair complex as an ion-exchanger. The ion-pair complex was selected based on preliminary computational studies.

2. EXPERIMENTAL PART

2.1. Computational methods

Calculations on the isolated molecules and molecular complexes were performed within GAUSSIAN 98 package [36].

Each species was initially optimized with PM3 method 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 minima by having no

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 is 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 [37, 38].

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 optimizations and frequency calculations for each species were performed with the DFT/6-31G* [39,40].

The other one-electron properties (dipole moment, polarizability, energies of the frontier molecular orbital) were also determined at the B3LYP/6-31G* level. For the charged species, the dipole moment was derived with respect to their mass center, because for the non-neutral molecules the calculated dipole moment depended on the origin of the coordinate system.

The stabilization energies of the selected complexes were determined with the help of the DFT calculations and calculated with a recently introduced method, based on the combination of the approximate tight-binding DFTB with the empirical dispersion energy. The DFT methods are known to be inherently very deficient for stacking interactions, as they basically ignore the dispersion attraction [40-42]. As a consequence; their enlargement by an empirical dispersion term currently appears to be a very reasonable way to improve the major deficiency of the DFT method for the evaluation of the molecular complexes. It should also be mentioned that the interaction energies were obtained as the difference between the complex energy and the combined energies of the molecules in isolation [43].

2.2. Apparatus

The glass cell where pioglitazone electrode was placed consisted of two Azar-Electrode Ag/AgCl reference electrode (Iran) as an internal and external reference electrodes. Both electrodes were connected to a Corning ion analyzer with a 250 pH/mV meter with ±0.1 mV precision.

2.3. The emf measurements

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

Ag–AgCl | internal solution (10^{-3} mol L^{-1} pioglitazone.HCl) | PVC membrane | sample solution | Ag–AgCl, KC1 (satd.)

These measurements were preceded by the calibration of the electrode with several pioglitazone hydrochloride solutions as working solutions.

2.4. Materials and Reagents

Pioglitazone hydrochloride and its tablet were obtained from local pharmaceutical factories in Iran. The analytical grade of chemical reagents, sodium tetraphenyl borate (NaTPB), potassium

tetrakis-parachlorophenyl borate (KTpClPB), high-molecular weight polyvinylchloride (PVC), dibutyl phthalate (DBP), nitrophenyl octyl ether (NPOE), nitrobenzene (NB), tetrahydrofuran (THF), and the chloride and nitrate salts of the used cations were all purchased from Merck Chemical Co. All solutions were prepared using deionized distilled water.

2.5. Ion-pair Preparation

Ion-pair complex of pioglitazone-tetraphenyl borate was prepared by mixing 20 mL of 0.01 mol L^{-1} solution of pioglitazone hydrochloride with 20 mL of tetraphenyl borate solution (0.01 mol L^{-1}) under stirring. Then, the resulting precipitate was filtered off, washed with water and dried in room temperature [16,17, 25,44-46].

2.6. Preparation of the electrode

The general procedure to prepare the PVC membrane was as follow: Different amounts of the pioglitazone-tetraphenyl borate 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} mol L^{-1} pioglitazone hydrochloride). The electrode was finally conditioned for 24 h by soaking in a 1.0×10^{-3} mol L^{-1} pioglitazone hydrochloride solution [44-46].

2.6. Stock solution of pioglitazone hydrochloride

A stock solution of 10^{-1} mol L^{-1} pioglitazone hydrochloride was prepared by dissolving the calculated weight of pure drug in 25 mL of distilled water. The working solutions (10^{-6} to 10^{-2} mol L^{-1}) were prepared by serial appropriate dilution of the pioglitazone stock solution.

3. RESULTS AND DISCUSSION

3.1. Computational Study

Molecular parameters are controlled by the molecular geometry; consequently geometry optimization is the most important step for the calculation of the interaction energy [47-54]. The optimized geometries and numeration of the atoms of the studied molecules, Drug for pioglitazone (Fig. 2), TPB for NaTPB (Fig. 3), PTK for KTpClPB, and Drug-TPB for pioglitazone -TPB (Fig. 4) and Drug-PTK for pioglitazone -TpClPB are presented.

To obtain a clue on PM tendency for TPB and PTK as potential ionophores, DFTB calculations (B3LYP/6-31G*) were carried out. The pair wise interaction energy ΔE_{A-B} between molecules A (TPB or PTK) 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 [36].

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

which obtained to be -66.251 and -89.853 kcal/mol for ΔE_{PTK} and ΔE_{TPB}, respectively that indicates TPB is a more appropriate ionophore for pioglitazone sensor in comparison to PTK, which is contributed to its higher interaction energy. Thus, the main discussions are going to be on Drug-TPB interaction afterward.

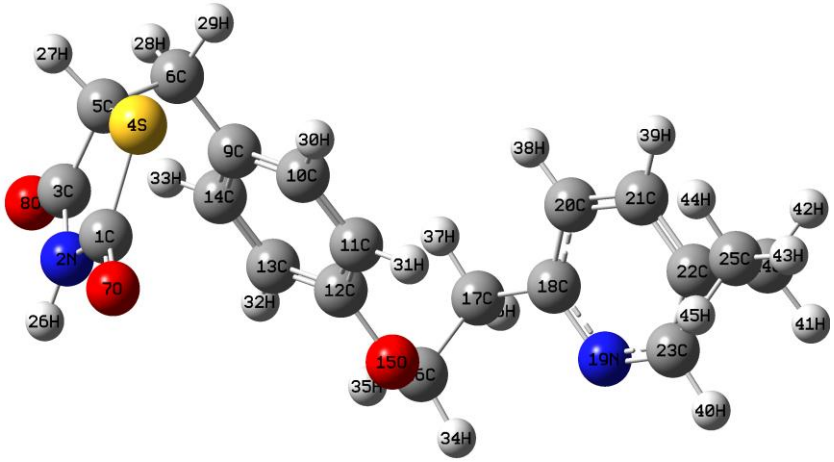

Figure 2. Full optimized structure of pioglitazone

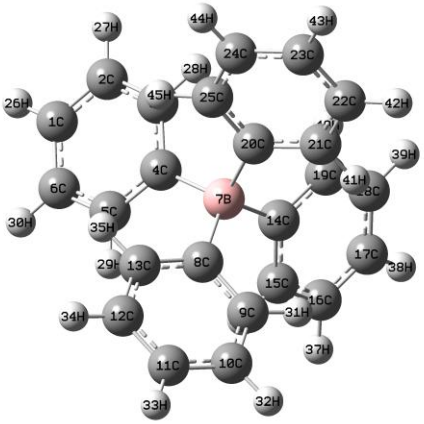

Figure 3. Full optimized structure of TPB

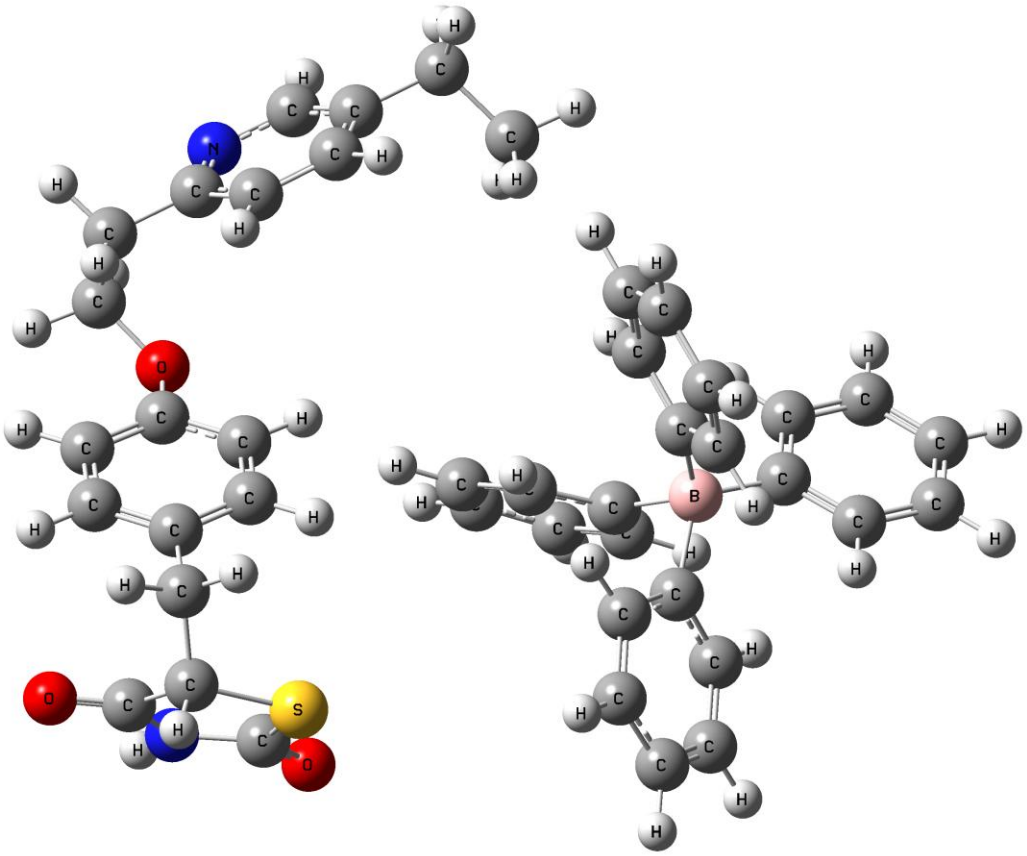

Figure 4. Full optimized structure of pioglitazone -TPB complex

Results presented in Table 1 (the most noticeable Mulliken atomic charge changes), show that interactions exist between the drug and TPB are most electrostatic. Furthermore, Charge changes in the ion pairs are localized on specific atoms that interact together in each molecule. As can be seen, all hetero atoms have charges change that confirm the hydrogen bonding and electrostatic interactions effective role in ion pair formation. The most noticeable atomic charge changes are shown in Table 1. Bond lengths and atomic charges have changed as a result of ion pair formation.

According to Table 1, interaction between Drug and TPB concern to thiol ring results in the occurrence of the most significant changes in the atomic charges and also bond lengths of those atoms that are bonded to them. For example, for the drug, S4 atomic charge changes from 0.490 to 0.187 along with its bond length (S4-C1) which shifted from 1.749 to 1.759. O7 atomic charge changes from -0.544 to -0.264, along with its bond length (C1-O7) which shifted from 1.211 to 1.223 or N2 atomic charge change from -0.703 to -0.374, along with its bond length (N2-C1) which shifted from 1.408 to 1.417. The study of atom charges in Drug and Drug-TPB shows that some atoms which have been shown in Table 1 (numbering is shown in Fig. 2,3) display the highest changes that are because of the interactions between Drug and TPB. For example, the charge of B has decreased (Table 1).The reason is, when B atom in TPB interact with hydrogen atom of Drug the charge density shifts from Drug

toward B atom in TPB, Since B atom of TPB molecule interacts with the nearest heteroatoms in the district, charge changes are not significant in other heteroatoms of Drug or TPB primary pairs. In this analysis, the effect of the TPB and drug charges change is considerably higher. The changes of the Drug-TPB charge density is much more important than the Drug-PTK.

High values of polarizability (160.606 and 194.57 for TPB and drug, respectively) prove its effect role on interactions among TPB and the drug. While the low values of dipole-dipole interactions (especially for that of TPB=0.0D and for drug 5.339D) show that it does not play a significant role between TPB and the studied drug. Moreover, since the studied molecules are in form of ions, electrostatic interactions should also be considered.

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

	Charges			Bonds(Å)		
	Atomic No.	**Drug**	**Drug-TPB**	**No.**	**Drug**	**Drug-TPB**
Drug	S4	0.490	0.187	R(1,4)	1.749	1.759
	O7	-0.544	-0.264	R(4,5)	1.794	1.890
	O8	-0.561	-0.267	R(1,7)	1.211	1.223
	N2	-0.703	-0.379	R(3,8)	1.216	1.215
	H26	0.442	0.228	R(2,3)	1.410	1.407
	O15	-0.749	-0.259	R(2,1)	1.408	1.417
	N19	-0.568	-0.251	R(2,26)	1.018	1.018
	C13	-0.218	-0.085	R(12,15)	1.363	1.362
	C1	0.445	0.216	R(15,11)	1.402	1.403
	C3	0.743	0.304	R(18,19)	1.363	1.363
	C5	-0.634	-0.275			
	HOMO	-8.681				
	LUMO	3.022				
	Atomic No.	**TPB**	**Drug-TPB**	**No.**	**TPB**	**Drug-TPB**
TPB	B7	0.232	0.214	R(7,8)	1.643	1.652
	C8	-0.068	-0.062	R(8,9)	1.400	1.421
	C9	-0.086	-0.168	R(9,10)	1.386	1.433
	C10	-0.078	-0.054	R(9,31)	1.082	1.068
	C11	-0.093	-0.081	R(10,32)	1.083	1.093
	C12	-0.078	-0.067	R(11,12)	1.384	1. 399
	C13	-0.086	-0.099	R(11,33)	1.081	1.089
	H32	0.033	0.049	R(12,13)	1.385	1. 378
	H33	0.030	0.047	R(12,34)	1.083	1.088
	H34	0.033	0.042	R(13,35)	1.082	1.089
	H35	0.042	0.057			
	HOMO	-2.777				
	LUMO	10.919				

The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) and for TPB and drug, calculated at the B3LYP/6-31G(d) level, are displayed in 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 represents the ability to obtain an electron, while HOMO as an electron donor represents the ability to donate an electron.

3.3. Membrane composition effect on potential response of the sensor

The potential response of a PVC sensor is related to its membrane composition [55-58]. Effect of membrane composition on the potential response of pioglitazone sensor was investigated. For this purpose, different membrane compositions are tested which most important ones are shown in Table 3. As it can be seen from Table 3, the membrane with composition of 30% PVC, 5% Pioglitazone-TPB, and 65% DBP (no. 3) showed the best potential response.

Pioglitazone extraction into the organic membrane was a result of ion-pair tendency to exchange with pioglitazone cation from aqueous solution. From Table 3, 5 mg ion-pair (pioglitazone-TPB) shows the best response. The second factor helps pioglitazone extract from an aqueous solution to organic membrane is a plasticizer or solvent mediator. After testing three plasticizers, NB, NPOE and DBP, it was observed that they have not the same results if the optimum composition is used. DBP, with lower dielectric constant, shows better response than NPOE and NB. NB and NPOE have higher dielectric constant values than DBP, leading to extraction of the polar ions. It has a negative effect on the extraction of pioglitazone ion which is a hydrophobic organic ion.

Table 3. Optimization of membrane ingredients

Membrane no.	PVC (% wt.)	Pioglitazone-TPB (% wt.)	Plasticizer (% wt.)	Linear range (mol L^{-1})	Response time	Slope (mV $decade^{-1}$)
1	30	1	DBP, 69	5.0×10^{-4} -5.0×10^{-2}	1.0±0.2 min	32.3±0.3
2	30	3	DBP, 67	4.5×10^{-5} -1.0×10^{-2}	32.0±2.0 s	48.5±0.4
3	30	5	DBP, 65	1.0×10^{-5} -1.0×10^{-2}	20.0±2.0 s	58.5±0.3
4	30	7	DBP, 63	4.0×10^{-5} -1.0×10^{-2}	25.0±2.0 s	54.3±0.3
5	30	5	NB, 64	5.0×10^{-4} -3.0×10^{-2}	43.0±3.0 s	31.1±0.2
6	30	5	NPOE, 64	1.0×10^{-3} -1.0×10^{-2}	1.0±0.3 min	22.7±0.4
7	30	5 (Pioglitazone-PTK)	DBP, 65	5.0×10^{-5} -1.0×10^{-2}	33.0±2.5 s	51.4±0.3
8	30	0	DBP, 70	5.0×10^{-3} -5.0×10^{-2}	3 min	18.5±0.4

3.4. Sensor properties

The properties of a potentiometric membrane sensor are characterized by parameters like measuring range, detection limit, response time, selectivity, lifetime, and accuracy [59-62].

The measuring range of a potentiometric membrane sensor includes the linear part of the calibration graph as shown in Fig. 5. The applicable measuring range of the proposed sensor is between 1×10^{-5} and 1×10^{-2} mol L^{-1}. By extrapolating the linear parts of the ion-selective calibration curve, the detection limit of an ion-selective electrode can be calculated. In this work, the detection limit of the proposed membrane sensor was 6.0×10^{-6} mol L^{-1} which was calculated by extrapolating two segments of the calibration curve (Fig. 5). The slope of the calibration curve was 58.5±0.3 mV $decade^{-1}$. The standard deviation of 10 replicate measurements is 0.3 mV $decade^{-1}$. The potential drift of the sensor is 0.1 mV after 2 minutes.

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 [62-66]. 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. In this work, 20.0±2.0 s response time was obtained for the proposed electrode when contacting different pioglitazone solutions from 1.0×10^{-5} to 1.0×10^{-2} mol L^{-1}.

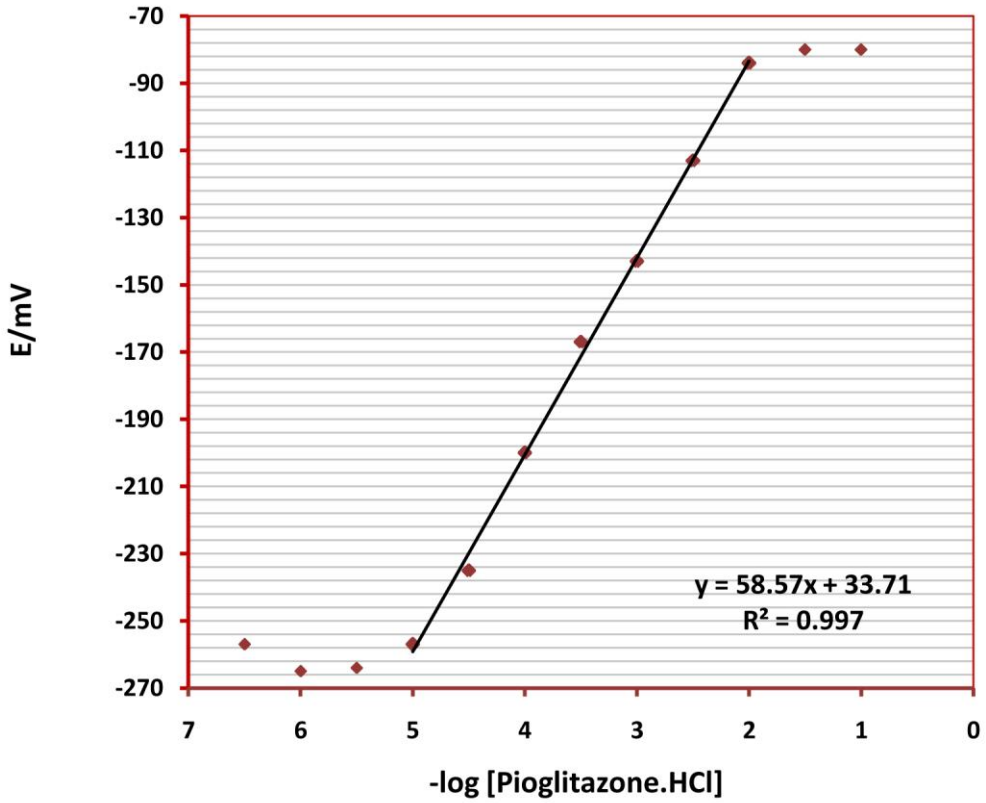

Figure 5. Calibration curve of pioglitazone membrane sensor with membrane composition of no. 3; the results are based on 10 replicate measurements.

Selectivity of an ion-pair based membrane electrode depends on the physico-chemical characteristics of the ion-exchange process at the membrane interface, on the mobility of the respective ions in the membrane and on the hydrophobic interactions between the primary ion and the organic membrane. Selectivity of pioglitazone membrane electrode is related to the free energy of transfer of pioglitazone cation between aqueous and organic phases. The response of the electrode towards different substances has been checked and the selectivity coefficient values K_{AB}^{Pot} were used to evaluate the interference degree. The selectivity coefficient values were obtained using the matched potential method (MPM) [67].

In MPM method, a specified concentration of the primary ions (A, 10^{-2} mol L^{-1} of pioglitazone solution) is added to a reference solution (10^{-5} mol L^{-1} of pioglitazone solution), and then the potential is measured. Then, the interfering ions (B, 10^{-2} mol L^{-1}) are consecutively added to the same reference solution, until the measured potential matches the one obtained before the addition of the primary ions. Then, selectivity coefficients, as defined by the matched potential method, K_{MPM}, is equal to the ratio of the resulting primary ion activity (concentration) to the interfering ion activity, $K_{MPM} = \Delta a_A/a_B$.

The respective results are summarized in Table 4, depicting that the selectivity coefficient values of the electrode for all the tested substances were in the order of 10^{-3} or smaller. Given the low coefficient values, it was considered that the function of the pioglitazone-selective membrane sensor would not be greatly disturbed.

Table 4. Selectivity coefficients of various interfering compound for pioglitazone sensor

Interference	Log K_{MPM}
Na^+	-3.11
K^+	-3.16
Mg^{2+}	-3.76
Ca^{2+}	-3.43
Glucose	-4.00
NH_4^+	-3.23
Lactose	-4.10
CO_3^{2-}	-4.33
NO_3^-	-3.89
Cl^-	-4.21

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 this time the electrodes were used extensively (one hour per day). The proposed sensors can be used for six weeks. After this time, there is a slight gradual decrease in the slopes (from 58.5 to 47.5 mV $decade^{-1}$) and, an increase in the detection limit (from 7.9×10^{-6} mol L^{-1} to 3.2×10^{-4} mol L^{-1}). 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.

Literature survey reveals that there are only two reports on pioglitazone potentiometric sensor [29,30]. A comparison between the proposed pioglitazone selective electrode and two reported in the literature (Table 5), revealed some superiority in terms of the easier ion-exchanger preparation, improved response time, lifetime, and sensitivity.

Table 5. Comparison Table of pioglitazone membrane sensors

Ref.	Detection Limit (mol L^{-1})	Linear range (mol L^{-1})	Response time	pH range	Slope (mV $decade^{-1}$)
29	4.0×10^{-6}	1.0×10^{-5} -1.0×10^{-2}	25 s	1-5	58.0±0.5
30	3.1×10^{-5}	3.1×10^{-5} -1.0×10^{-2}	-	-	48.5±0.4
This work	6.0×10^{-6}	1.0×10^{-5} -1.0×10^{-2}	20 s	1.5-5.5	58.5±0.3

3.5. pH effect on the electrode response

In an approach to understanding the impact of pH on the electrode response, the potential was measured at a particular concentrations of the pioglitazone solution (1.0×10^{-3} mol L^{-1}) from the pH value of 2 up to 10 (concentrated NaOH or HCl solutions were used for pH adjustment). As it can be seen from Fig. 5, the potential remained constant despite the pH changes in the range of 1.5 to 5.5, indicating the applicability of this electrode in the specific pH range. On the contrary, relatively noteworthy fluctuations in the potential *vs.* pH behavior took place below and above the formerly stated pH limits. In detail, the fluctuation above the pH value of 5.5 might be justified by removing the positive charge on the drug molecule.

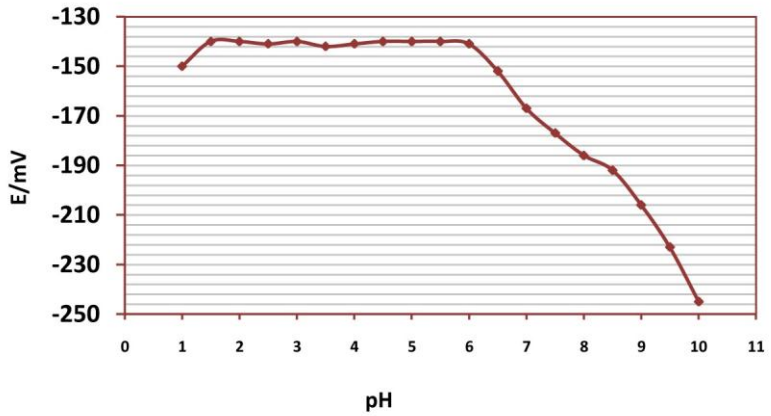

Figure 6. pH effect of the test solutions (1.0×10^{-3} mol L^{-1}) on the potential response of pioglitazone sensor with membrane composition of no. 3

3.6. Determination of pioglitazone in pharmaceutical formulations

20 tablets of pioglitazone were thoroughly milled and powdered. An appropriate amount of pioglitazone tablet powder (10 mg) was carefully weighed and transferred into a 10-mL volumetric flask. The solution was then diluted to the mark with water and the proposed electrode determined pioglitazone content by using the calibration method. The results for determination of pioglitazone amount in some pharmaceutical samples from local pharmacy in Iran are shown in Table 6. As it is seen, the results are in satisfactory agreement with the stated content on the tablets.

3.7. Method Validation

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

As mentioned before, the measuring range of the pioglitazone sensor is between 1×10^{-5} and 1×10^{-2} mol L^{-1}. The detection limit of the sensor was calculated 6.3×10^{-6} mol L^{-1} (2.47 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 standard samples 5, 50, 500 µg/mL were measured. Then, the mean concentrations were found to be 5.05, 50.7, 504.5 µg/mL and with associated RSD values of 1.3, 0.8, and 0.72%, respectively. Regarding the inter-day precision, the same three concentrations were measured for 3 consecutive days, providing mean pioglitazone concentrations of 5.06, 51.3, 505.2 µg/mL and associated RSD values of 1.45, 2.7, and 1.11%, respectively.

Table 6. Results of pioglitazone HCl tablet assay by the membrane sensor

Sample	Stated content (mg per tablet)	Found (mg per tablet) n=5	Official Method * (mg per tablet) n=5	t-test (P=0.05; $t_{theoritical}$=2.31)
Sample 1	15	15.18±0.03	15.15±0.03	$t_{experimental}$= 1.58
Sample 2	15	15.27±0.03	15.21±0.03	$t_{experimental}$= 2.11
Sample 3	15	15.02±0.04	14.97±0.02	$t_{experimental}$= 2.30
Sample 4	30	30.21±0.03	30.16±0.04	$t_{experimental}$= 2.23
Sample 5	30	30.23±0.02	30.18±0.03	$t_{experimental}$= 2.17
Sample 6	30	31.02±0.04	30.94±0.02	$t_{experimental}$= 2.27
Sample 7	45	45.18±0.03	45.13±0.03	$t_{experimental}$= 2.29
Sample 8	45	45.02±0.04	44.95±0.03	$t_{experimental}$= 2.25
Sample 9	45	45.01±0.04	44.93±0.04	$t_{experimental}$= 2.27

*HPLC method

For determination of method accuracy four different tablets of pioglitazone.HCl was analyzed with an official method (HPLC) and the proposed sensor. The results are shown in Table 6. At 95% confidence level the calculated t-value did not exceed the theoretical t-value indicating no significant difference between the four proposed methods and the reference method.

For ruggedness of the method a comparison was performed between the intra- and inter-day assay results for pioglitazone obtained by two analysts. The RSD values for the intra- and inter-day assays of pioglitazone in the cited formulations performed in the same laboratory by the two analysts did not exceed 3.15%. On the other hand, the robustness was examined while the parameter values (pH of the eluent and the laboratory temperature) were being slightly changed. Pioglitazone recovery percentages were good under most conditions, not showing any significant change when the critical parameters were modified.

4. CONCLUSIONS

There is a growing need to make electrochemical sensors for fast and economical monitoring of pharmaceutical compounds in their formulations. In this work, types of interactions exist between a pioglitazone compound and ion-pair reagents were studied by computational calculations. Since the studied molecules were in 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 computational methods help selecting appropriate ionophores and also predicting their selectivity for different drugs. After a series of experiments involving usage of pioglitazone-TPB ion-pair complexes along with several plasticizers in the membrane design, it was concluded that pioglitazone sensor exhibited excellent analytical performance characteristics. It demonstrated an advanced performance with a fast response time (~20 s), a lower detection limit (6.3×10^{-6} mol L^{-1}) and pH independent potential responses across the range of 1.5-5.5. This sensitivity of the sensor enables pioglitazone monitoring in pharmaceutical analysis.

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