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Design and Construction of a Naltrexone Selective Sensor Based on Computational Study for Application in Pharmaceutical Analysis

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Naltrexone is an opioid antagonist, which has been used for treatment of alcoholism and opiate dependence. In this study, the electronic and geometric properties of Naltrexone, sodium tetraphenyl borate and their complexes were studied by computational methods. Then, Naltrexone-tetraphenylborate complexes were employed as ion pair in construction of a potentiometric liquid membrane sensor for simple and fast determination of Naltrexone hydrochloride in pharmaceutical formulation and urine. The wide linear range (10^{-5}-10^{-2} mol L^{-1}), low detection limit (8.0×10^{-6} mol L^{-1}), and fast response time (~10 s) are characterizations of the proposed sensors. Validation of the method shows suitability of the sensors for application in the quality control analysis of naltrexone hydrochloride in pharmaceutical formulation. Also, the agreement mutually verifies the accuracy of experimental method and the validity of computational calculations.

Keywords: Potentiometric sensor, PVC membrane, Naltrexone hydrochloride, Computational Chemistry, Chemometrics, Density functional based tight binding (DFTB)

1. INTRODUCTION

Opiate antagonists are a class of drugs that can occupy opioid receptors but do not cause the physiological responses that agonists do. In general, a pure antagonist is devoid of pharmacological activity, but the actions of such drugs are evident not only in blocking the actions of opioid agonists, but also in reversing the effects caused by activation of endogenous opioid systems (e.g., pain or stress). Naltrexone (17-(cyclopropylmethyl)- 4,5a-epoxy-3,14- dihydroxymorphinan- 6-one) (Fig. 1) is a long-acting synthetic opiate antagonist with few side effects that is efficacious when administered

orally, either daily or three times a week for a sustained period of time. This opioid antagonist causes prompt reversal of the effects of morphine-like opioid agonists [1].

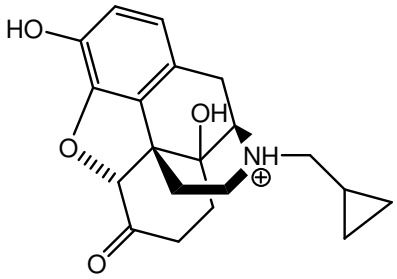

Figure 1. Chemical structure of Naltrexone

In order to study the clinical pharmacokinetics of a drug it is necessary to have a reliable, accurate, and sensitive analytical method for the determination of the compound in various body fluids. Several analytical methods have been reported for the determination of naltrexone in biological fluids and pharmaceutical preparations. The most widely used method seems to be liquid chromatography. Naltrexone was also determined by liquid chromatography-mass spectrometry (LC-MS) [2], LC-using amperometric and electrochemical detection [3,4], GC-MS [5,6], HPLC [7,8], spectrofluorimetric determination by a kinetic method using the stopped-flow technique[9], chemiluminescence determination based on potassium permanganate oxidation [10], and flow-injection method for the spectrophotometric determination [11], electrochemical method based on FIA and FFT Cyclic voltammetry for determination of naltrexone [12].

Potentiometric membrane sensors are playing an important role in pharmaceutical analysis [13-16] because of their 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 and electrochemical science [17-27]. 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 [28].

There are few studies to date in the literature which 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 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.

In this study we use density functional theory (DFT) atomic population analysis to measure a Ligand-Drug complexing by looking at the ability of the ligand to change in atomic charges and bond length of drug.

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

2. EXPERIMENTAL PART

2.1. Materials and Reagents

The chemical reagents (analytical grade) were: Sodium tetraphenyl borate (NaTPB), high-molecular weight polyvinylchloride (PVC), dibutyl phthalate (DBP), benzyl acetate (BA), nitrobenzene (NB), tetrahydrofuran (THF), and the chloride and nitrate salts of the used cations (Merck Co.). Naltrexone hydrochloride and its capsule were obtained from different local pharmaceutical factories. All solutions were prepared using triply distilled water.

2.2. Apparatus

The glass cell, where the Naltrexone-selective electrode was placed, consisted of an R684 model Analion Ag/AgCl reference electrode as the internal reference electrode and a calomel electrode (SCE, Philips). Both electrodes were connected to a Corning ion analyzer with a 250 pH/mV meter with ±0.1 mV precision.

2.3. Preparation of ion-pair compound

Ion-pair compound of Naltrexone-tetraphenylborate (Naltrexone-TPB): About 20 mL of 0.01 mol L^{-1} solution of naltrexone hydrochloride was mixed with 20 mL of tetraphenyl borate solution (0.01 mol L^{-1}) under stirring. The resulting precipitate was filtered off, washed with water and dried [15,16].

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} mol L^{-1} naltrexone hydrochloride). The electrode was finally conditioned for 24 h by soaking in a 1.0×10^{-3} mol L^{-1} naltrexone hydrochloride solution [29-32].

2.5. Standard naltrexone hydrochloride solutions

A stock solution of 10^{-1} mol L^{-1} naltrexone hydrochloride was prepared by dissolving the calculated weight of pure drug in 25 mL water. The working solutions (10^{-6} to 10^{-1} mol L^{-1}) 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} mol L^{-1} naltrexone hydrochloride| PVC membrane | sample solution | Hg–Hg_2Cl_2, KC1 (satd.)

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

2.7. Computational methods

Calculations on the isolated molecules and molecular complexes were performed within GAUSSIAN 98 package [33].

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 [34, 35].

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* [36,37].

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 [37-39]. 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 [40].

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 (Fig. 2), L2 for KTpClPB, NAL for Drug (Fig. 3) and Drug-L1 for NAL-TPB (Fig. 4) and Drug-L2 for NAL-TpClPB, are presented.

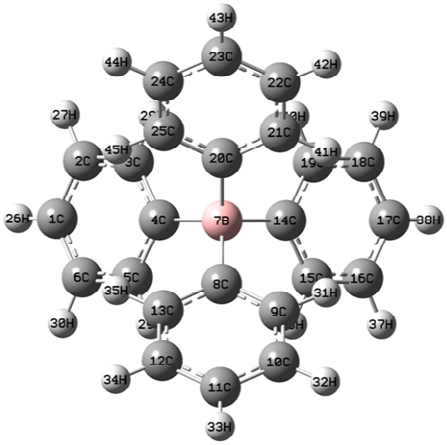

Figure 2. The full optimized structure of L1

To obtain a clue on Naltrexone tendency for L1 and L2 as potential ion pair, 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 the energies of the isolated partners. The interaction energies were corrected for the basis set superposition error using the counterpoise method [41,42].

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

which obtained to be -62.119 and -49.082 Kcal/mol for ΔE_{L1} and ΔE_{L2} , respectively that indicates L1 is a more appropriate ionophore for Naltrexone sensor in comparison to L2, which is contributed to its higher interaction energy. The main discussions are going to be on L1-NAL interaction afterward.

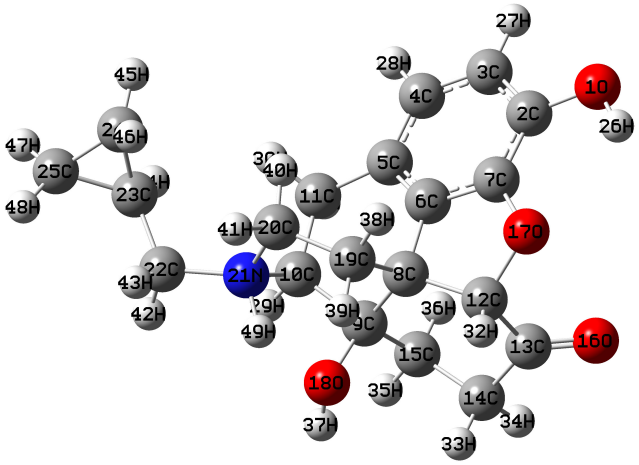

Figure 3. The full optimized structure of Naltrexone

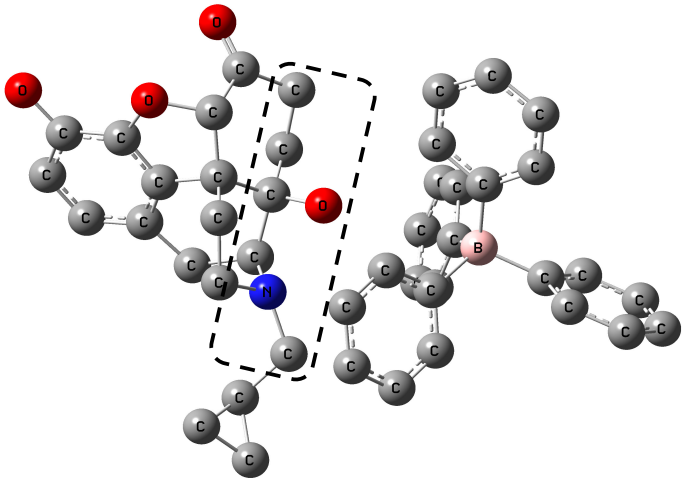

Figure 4. The full optimized structure of L1-Naltrexone complex

Results presented in Table 1, show that interactions exist between the drug and L1 are most electrostatic. Charge changes in the ion pairs are localized on specific atoms that interact together in each molecule [43-46]. The study of the atom charges and bond lengths in drug exhibits that the part, shown with dash marks (the only part which is going to be discussed afterwards), displays the highest changes. As can be seen, two hetero atoms (N21 and O18) 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 ligand concern to dash marks region results in the occurrence of the most significant changes in the atomic charges and also bond lengths. For example, for the drug, H37 atomic charge changes from 0.226 to 0.264 along with its bond length (O18-H37) which shifted from 0.987 to 1.070 or H43 atomic charge changes from 0.101 to 0.121 along with its bond length (C22-H43) which shifted from 1.527 to 1.541 and so on.

High values of polarizability (148.545 and 144.831 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=0.0) 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.

The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) and for L1 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. From Table 1, the results illustrate that charge transfer interaction have between L1 and drug, because the HOMO energy of L1 close to LUMO energy of drug.

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

Charges				**Bonds**		
	NO.	**Naltrexone**	**Drug-complex B**	**NO.**	**Naltrexone**	**Drug-complex B**
1	O	-0.260	-0.267	R(10,21)	1.537	1.529
18	O	-0.184	-0.220	R(18,37)	0.987	1.070
17	O	-0.227	-0.232	R(20,21)	1.522	1.516
21	N	-0.254	-0.280	R(21,22)	1.529	1.521
33	H	0.073	0.086	R(21,49)	1.073	1.136
35	H	0.071	0.085	R(22,23)	1.527	1.532
37	H	0.226	0.264	R(22,43)	1.527	1.541
43	H	0.101	0.118			
49	H	0.301	0.323			
	NO.	**tetraphenylborate**	**B-complex**	**NO.**	**tetraphenylborate**	**B-complex**
7	B	0.232	0.227	R(2,3)	1.386	1.388
9	C	-0.086	-0.096	R(3,4)	1.401	1.397
11	C	-0.093	-0.085	R(4,7)	1.643	1.641
14	C	-0.068	-0.080	R(14,19)	1.400	1.406
18	C	-0.078	-0.088	R(22,23)	1.385	1.387
31	H	0.042	0.019	R(24,25)	1.386	1.388
36	H	0.042	0.063			
37	H	0.033	0.052			
		Dipole moment	**Polarizability**	**HOMO**	**LUMO**	
Drug		11.328	144.831	-9.36	3.96	
L1		0.0	148.545	2.77	10.9	

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 naltrexone sensor was studied. For this purpose, different membrane compositions are tested which some of them are shown in Table 2. As it can be seen, the membrane with the composition of 30% PVC, 5% NAL-TPB, and 65% DBP (no. 2) was the optimum one in the development of this sensor.

The high Naltrexone extraction into the liquid membrane was a result of the elevated ion-pair tendency to exchange with the naltrexone cations. From Table 2, 5 mg ion-pair (Naltrexone-TPB) is the best amount for the best response. The second factor which helps naltrexone 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 naltrexone ions as a hydrophobic ion.

Table 2. Optimization of membrane ingredients

Membrane no.	NAL-TPB (% wt.)	Plasticizer (% wt.)	PVC (% wt.)	Linear range (mol L^{-1})	Slope (mV $decade^{-1}$)
1	4	DBP, 66	30	5.0×10^{-5} -3.0×10^{-2}	49.3
2	5	DBP, 65	30	1.0×10^{-5} -1.0×10^{-2}	57.8
3	6	DBP, 64	30	2.0×10^{-5} -1.0×10^{-2}	55.8
4	5	NB, 65	30	1.0×10^{-4} -3.0×10^{-2}	20.5
5	5	BA, 65	30	4.0×10^{-3} -1.0×10^{-2}	18.7

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 naltrexone solution (1.0×10^{-3} mol L^{-1}) from the pH value of 2 up to 10 (concentrated NaOH or HCl solutions were employed for the pH adjustment). As it can be seen from Fig. 5, the potential remained constant despite the pH change in the range of 3.2 to 7.0, 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 7.0 might be justified by removing the positive charge on the drug molecule and the fluctuation below the pH value of 3.2 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 [47-50].

The measuring range of an ion-selective electrode includes the linear part of the calibration graph as shown in Fig. 6. 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^{-5} and 1×10^{-2} mol L^{-1}.

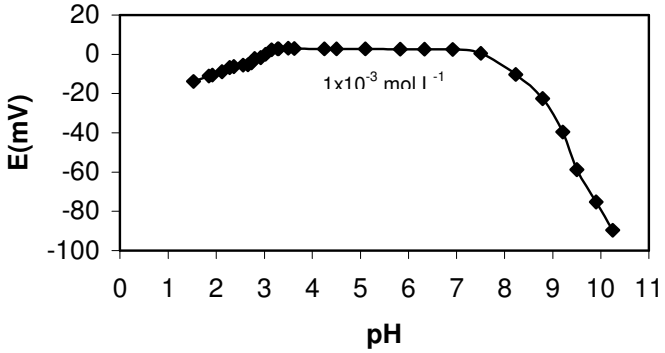

Figure 5. The pH effect of the test solutions (1.0×10^{-3} mol L^{-1}) on the potential response of the naltrexone sensor with the composition of the membrane no. 2.

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} mol L^{-1}.

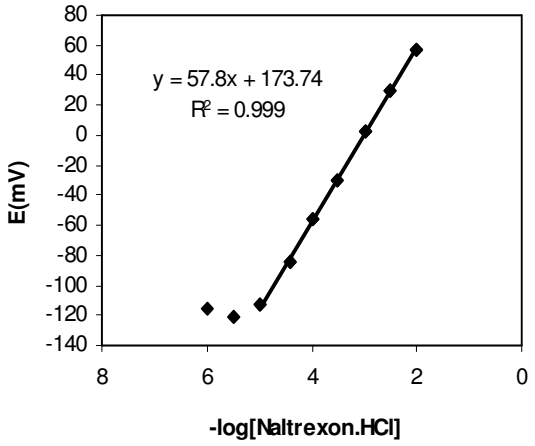

Figure 6. Calibration curve of the naltrexone membrane sensor with the composition of the membrane no. 2. The results are based on 8 measurements.

In this work the detection limit of the proposed membrane sensor was 8.0×10^{-6} mol L^{-1} which was calculated by extrapolating the two segments of the calibration curve (Fig. 6).

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 [51-54]. In this work, less than 10s response time was obtained for the proposed electrode when contacting different Naltrexone solutions from 1.0×10^{-5} to 1.0×10^{-2} mol L^{-1}.

The selectivity of an ion-pair based membrane electrode depends on the physico-chemical characteristics of the ion-exchange process at the membrane–sample solution interface, on the mobility of the respective ions in the membrane and on the hydrophobic interactions between the primary ion and the organic membrane [55].

The selectivity of the Naltrexone HCl membrane electrode is related to the free energy of transfer of the Naltrexone HCl 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) [56-58].

The steps that need to be followed for the MPM method is addition of a specified concentration of the primary ions (A, 10^{-2} mol L^{-1} of naltrexone solution) to a reference solution (10^{-5} mol L^{-1} of naltrexone solution), and the potential measurement. 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, the selectivity coefficient, 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 3, 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 Naltroxone-selective membrane sensor would not be greatly disturbed.

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

Interference	**Log K_{MPM}**
Na^+	-4.93
K^+	-4.88
Mg^{2+}	-4.55
Ca^{2+}	-4.73
Glucose	-5.21
NH_4^+	-4.33

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 8 weeks, during which time the electrodes were used extensively (one hour per day). The proposed sensors can be used for six weeks. First, there is a slight gradual decrease in the slopes (from 57.8 to 51.6 mV decade^{-1}) and, second, an increase in the detection limit (from 8.0×10^{-6} mol L^{-1} to 5.0×10^{-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.

3.5. Analytical application

3.5.1. Determination of Naltrexone in formulations

An appropriate amount of naltrexone capsule was transferred into a 10-mL volumetric flask. The solution was then diluted to the mark with water and the proposed electrode determined naltrexone content by using the calibration method. The results for determination of Naltrexone 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 capsule.

3.5.2. Recovery of Naltrexone from urine

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 naltrexone from urine samples. A 2.5 mL of 10^{-4} mol L^{-1} Naltrexone 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 naltrexone 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 104.2%, 103.3% and 102.2%, respectively.

Table 4. Results of Naltrexone HCl capsule assay by the Naltrexone selective sensor

Sample	**Stated content**	**Found ***
NALTREXONE-ALHAVI® 50MG CAP (smple 1)	50 mg	49.7±0.2 mg
NALTREXONE-ALHAVI® 50MG CAP (smple 2)	50 mg	51.1±0.2 mg
NALTREXONE HCL 50MG CAP-Iran Darou (sample 1)	50 mg	50.9±0.3 mg
NALTREXONE HCL 50MG CAP-Iran Darou (sample 2)	50 mg	50.7±0.2 mg

*The results are based on three measurements

3.6. Validation of the method

The linearity, limit of detection, precision, accuracy, and ruggedness/robustness were the parameters which were used for the method validation [59-61].

As mentioned before, the measuring range of the Naltrexone sensor is between 1×10^{-5} and 1×10^{-2} mol L^{-1}. The detection limit of the sensor was calculated 8.0×10^{-6} mol L^{-1} (2.7µg/mL).

The parameters of the repeatability and reproducibility were investigated in order to assess the precision of the technique. For the repeatability monitoring, 10 replicate standards samples 3, 30, 300 µg/mL were measured. Then, the mean concentrations were found to be 3.04, 30.3, 302.2 µg/mL and with associated RSD values of 1.3, 1.05, and 0.66%, respectively. Regarding the inter-day precision, the same three concentrations were measured for 3 consecutive days, providing mean Naltrexone concentrations of 3.04, 30.3, 302.2 µg/mL and associated RSD values of 1.74, 1.03, and 0.24%, respectively.

The relevant error percentage and accuracy were calculated in each above case. The resultant concentrations were 3.04±0.06, 30.3±0.2, and 302.25±1.4 µg/mL with relevant error percentages of 3.65, 1.32, and 0.35%, respectively.

For ruggedness of the method a comparison was performed between the intra- and inter-day assay results for naltrexone obtained by two analysts. The RSD values for the intra- and inter-day assays of naltrexone 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. Naltrexone recovery percentages were good under most conditions, not showing any significant change when the critical parameters were modified.

4. CONCLUSIONS

In the presented paper, types of interactions exist between a drug and ligands were studied. 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 theoretical calculations help selecting appropriate ionophores and also predicting their selectivity for different drugs. After a series of experiments involving the usage of Naltrexone-TPB ion-pair complexes along with several plasticizers in the membrane design, it was concluded that the naltrexone sensor exhibited excellent analytical performance characteristics. It demonstrated an advanced performance with a fast response time (~10s), a lower detection limit of 8.0×10^{-6} mol L^{-1} and pH independent potential responses across the range of 3.2–7.0. This high sensitivity of the sensor enabled the naltrexone determination in pharmaceutical analysis.

The theoretical calculations are 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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