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New Diltiazem Potentiometric Membrane Sensor Stands on Theoretical Calculations as a Useful Device for Diltiazem Hydrochloride Analysis in Pharmaceutical Formulation and Urine

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Diltiazem, belongs to the group of drugs known as benzothiazepines, which are a class of calcium channel blockers, used in the treatment of hypertension, angina pectoris, and some types of arrhythmia. In this study, a potentiometric liquid membrane sensor for simple and fast determination of diltiazem hydrochloride in pharmaceutical formulation and urine were constructed. According to the theoretical calculation, diltiazem-tetraphenylborate (DTM-TPB) complexes were employed as electroactive material in the membrane. The best electrode performance was accomplished with a membrane composition of 30% PVC, 65% DBP, 5% (DTM-TPB). The wide linear range (10^{-5}-10^{-1} M), low detection limit (3.2 µg/ml), and fast response time (~12 s) are characterizations of the proposed sensors.

Keywords: Potentiometry; sensor; PVC membrane; Ion selective electrode; Diltiazem hydrochloride; Calculation chemistry

1. INTRODUCTION

Diltiazem, [(2S-*cis*)-3-(Acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,-5-benzolthiazepin-4(5H)-one) (Fig. 1), is a calcium ion influx inhibitor [1]. Calcium channel blockers (CCB) are widely used in the treatment of hypertension, angina pectoris and cardiac arrythmias [2–5]. Angina occurs when the muscular wall of the heart does not get enough oxygen.

Antianginal agents (AAs) typically increase blood flow by either increasing the oxygen supply or decreasing oxygen demand by the heart [6].

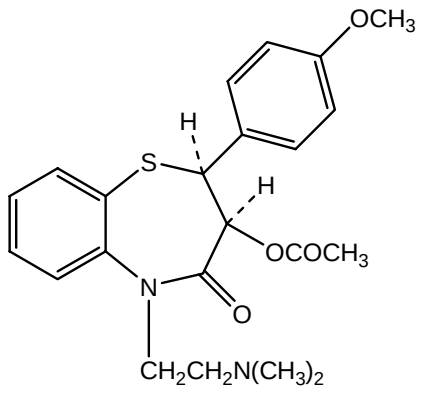

Figure 1. Chemical structure of diltiazem hydrochloride

There are several analytical techniques for the assay of diltiazem in pharmaceutical and in biological fluids, such as high performance liquid chromatography (HPLC) [7-12], gas chromatography [13-15], capillary electrophoresis [16,17], high performance thin layer chromatography (HPTLC) [18], spectrophotometry [19-21], voltammetry [22], polarimetry [23] and titrimetry [24].

Ion-selective electrodes are playing an important role in pharmaceutical analysis [25-31] due to its simplicity, rapidity and accuracy over some other analytical methods. One of the many existing principles for the construction of ion-selective membranes is the addition of a lipophilic ion-pair complex into a highly plasticized polymer membrane [27-30].

Computational chemistry and molecular modeling play an important role in the modern drug discovery [32-35]. 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 [36,37].

In present paper, a diltiazem ion-selective potentiometric PVC membrane electrode is developed based on ion-pair compound of diltiazem-tetraphenylbroate (DTM-TPB) as the electroactive substance and the accurate theoretical studies are performed for electronically study between DTM and TPB. The proposed electrode was successfully applied for the determination of diltiazem hydrochloride in the pharmaceutical tablet formulations and urine samples.

2. EXPERIMENTAL PART

2.1. Apparatus

The glass cell, where the diltiazem-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), high-molecular weight polyvinylchloride (PVC), tetrahydrofuran (THF), dibutylphthalate (DBP), benzyl acetate (BA), nitrobenzene (NB) and the chloride and nitrate salts of the used cations (Merck Co.). Diltiazem hydrochloride and its tablets were obtained from different local pharmaceutical factories. All solutions were prepared using triply distilled deionized water.

2.3. Preparation of Ion-Pair Compound

Ion-pair compound of diltiazem-tetraphenyl borate (DTM-TPB): About 20 mL of 0.01 M solution of diltiazem hydrochloride was mixed with 20 mL of 0.01 M solution of tetraphenyl borate under stirring. The resulting precipitates were filtered off, washed with water, dried at 60°C.

2.4. Preparation of the Membrane 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 diltiazem hydrochloride). The electrode was finally conditioned for 24 h by soaking in a 1.0×10^{-3} M diltiazem hydrochloride solution [38-41].

2.5. Standard Diltiazem Hydrochloride Solutions

A stock solution of 10^{-1} M diltiazem hydrochloride was prepared by dissolving the calculated weight of pure drug in 25 mL water. The working solutions (10^{-6} to 10^{-1} 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 [42];

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

These measurements were preceded by the calibration of the electrode with several diltiazem 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 DTM, L1-Drug for DTM-TPB and L2-Drug for DTM-TpClPB, are presented in Figs. 2 to 6, respectively.

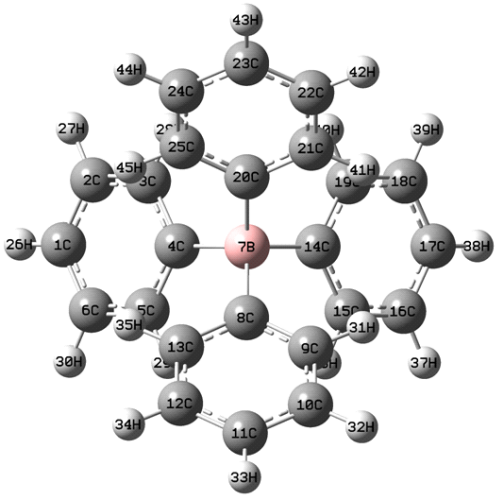

Figure 2. The full optimized structure of L1

To obtain a clue on metoclopramide tendency for L1 and L2 as potential ionophores, 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 [43,44].

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

which obtained to be -58.100 and -47.961 Kcal/mol for ΔE_{L1} and ΔE_{L2} , respectively that indicates L1 is a more appropriate ionophore for Diltiazem sensor in comparison to L2, which is due to its higher interaction energy.

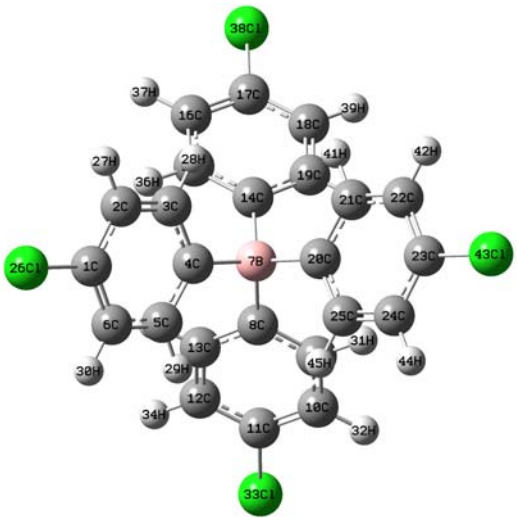

Figure 3. The full optimized structure of L2

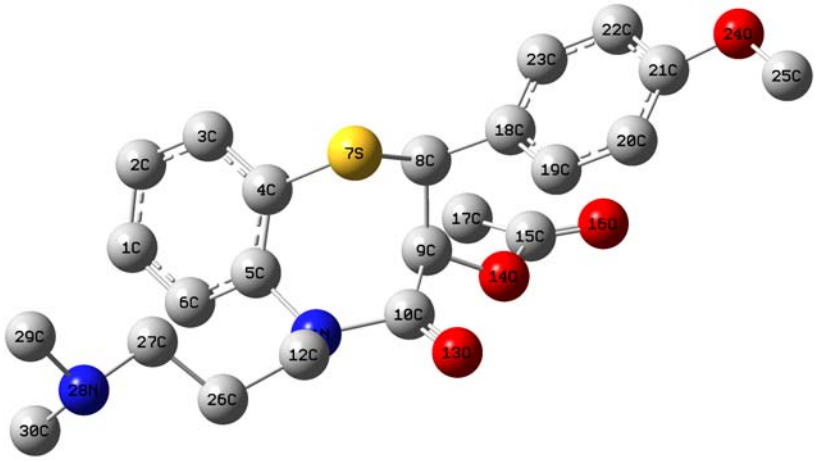

Figure 4. The full optimized structure of DTM

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.

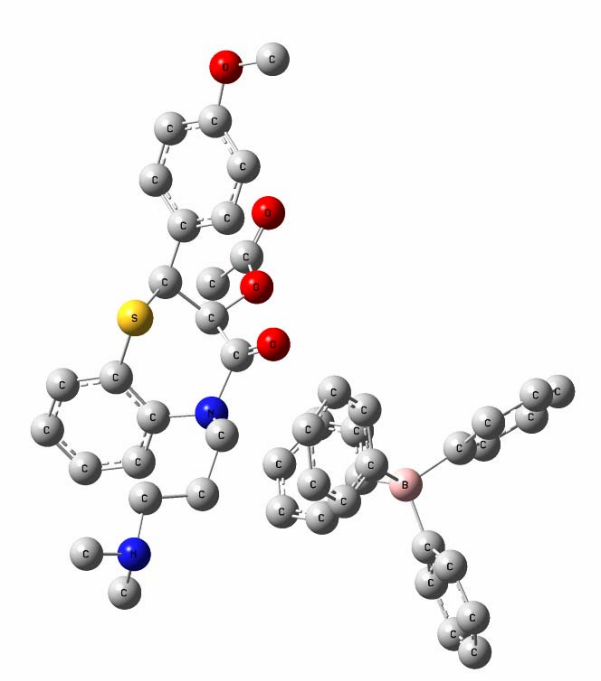

Figure 5. The full optimized structure of L1- DTM complex

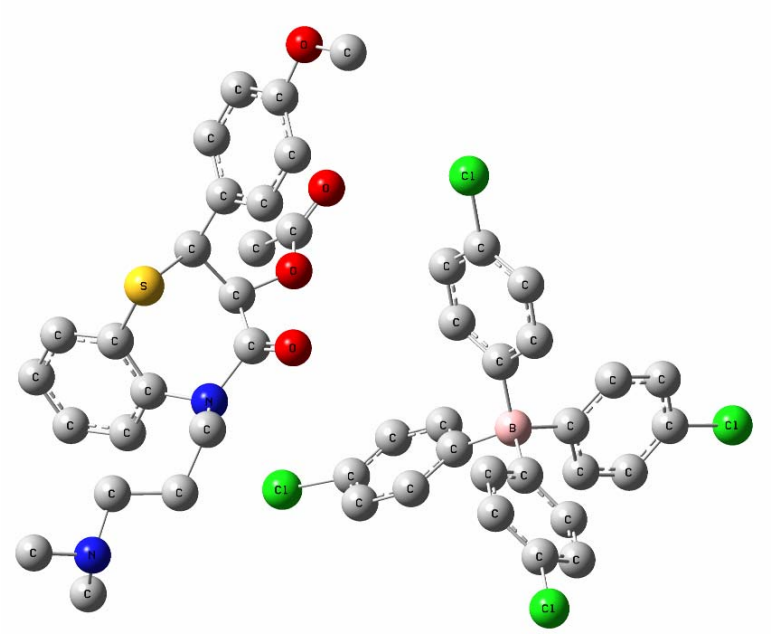

Figure 6. The full optimized structure of L2- DTM complex

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 [45–48]. As can be seen, hetero atoms (N, O and S) charges change more significantly in comparison to other atoms that confirm the hydrogen bonding and electrostatic interactions effective role in ion pair formation. In L1, remarkable atomic charge changes are seen for bohr (from 0.232 to 0.073) 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.

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

Charges				**Bonds**		
	NO.	Drug	Drug-complex B	NO.	Drug	Drug-complex B
7	S	0.199084	0.194719	R(5,11)	1.51	1.407
10	C	0.317911	0.314606	R(11,12)	1.0836	1.072
11	N	-0.24756	-0.255304	R(7,8)	1.8257	1.8468
13	O	-0.13902	-0.13369	R(8,9)	1.5844	1.5832
14	O	-0.24423	-0.240333	R(9,10)	1.5603	1.5589
16	O	-0.19622	-0.207255	R(15,16)	1.587	1.5975
21	C	0.14445	0.13796	R(10,13)	1.1995	1.251
24	O	-0.22568	-0.230386	R(12,26)	1.5499	1.5488
31	H	0.26865	0.292506	R(14,15)	1.4235	1.4489
	NO.	TPB	B-complex	NO.	TPB	B-complex
				R(1,2)	1.385	1.388
7	B	0.232	0.073	R(1,6)	1.385	1.391
8	C	-0.068	-0.082	R(2,3)	1.386	1.391
13	C	-0.086	-0.102	R(3,4)	1.401	1.393
				R(4,5)	1.400	1.408
18	C	-0.078	-0.066	R(5,6)	1.386	1.380
23	C	-0.093	-0.084	R(7,8)	1.643	1.662
28	H	0.042	0.017	R(7,14)	1.643	1.662
29	H	0.042	0.057	R(7,20)	1.643	1.662
30	H	0.033	0.051	R(14,19)	1.400	1.410
38	H	0.030	0.049	R(15,16)	1.386	1.389
39	H	0.033	0.057	R(16,17)	1.385	1.381
40	H	0.042	0.066	R(17,18)	1.385	1.392
				R(18,19)	1.386	1.380

Furthermore, high values of polarizability (155.772 and 214.793 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 (9.2730 for drug and 0.0 for L1). 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.

3.2. Membrane Composition Effect on the Potential Response of the Sensor

The sensitivity and selectivity degree of an ion selective electrode is greatly related to the membrane ingredients [49-51]. Thus, the membrane composition influence on the potential responses of the diltiazem hydrochloride sensor was studied. The main components of an electrode membrane of this type are PVC matrix, the plasticizer, the anionic lipophilic additive and the ion-pair (DTM-TPB) (C^+A^-). Each membrane component plays a special role in the membrane function. 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, 5% DTM-TPB, and 65 % DBP (no. 2) was the optimum one in the development of this sensor. This membrane composition was selected after many considerations.

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, 66	4, DTM-TPB	-	46.74	1.0×10^{-4} -1.0×10^{-1}
2	30	DBP, 65	5, DTM-TPB	-	55.48	1.0×10^{-5} -1.0×10^{-1}
3	30	DBP, 64	6, DTM-TPB	-	44.74	1.0×10^{-4} -1.0×10^{-1}
4	30	DBP, 64	5, DTM-TPB	1, NaTPB	47.2	5.0×10^{-4} -1.0×10^{-2}
5	30	DBP, 63	5, DTM-TPB	2, NaTPB	43.6	1.0×10^{-4} -5.0×10^{-2}
6	30	DBP, 62	5, DTM-TPB	3, NaTPB	42.8	1.0×10^{-4} -1.0×10^{-2}
7	30	BA, 65	5, DTM-TPB	-	19.65	5.0×10^{-3} -1.0×10^{-2}
8	30	NB, 65	5, DTM- TPB	-	11.34	1.0×10^{-4} -1.0×10^{-2}

The high diltiazem extraction into the liquid membrane was a result of the elevated ion-pair tendency to exchange with the diltiazem cations. From Table 2, 5 mg ion-pair (DTM-TPB) is the best amount for the best response.

The second factor which helps diltiazem ions to extract from an aqueous solution to the membrane as an organic phase is a plasticizer. 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 in order 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 also on the selectivity of the PVC membrane electrodes. 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 diltiazem ions as a hydrophobic ion.

The presence of lipophilic anions in a cation-selective membrane was also considered. 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 of 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 diltiazem solution (1.0×10^{-3} M) from the pH value of

1.0 up to 11.0 (concentrated NaOH or HCl solutions were employed for the pH adjustment). As it can be seen from Fig. 7, the potential remained constant despite the pH change in the range of 2.1 to 7.4, 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 fluctuations above the pH value of 7.5 might be justified by removing the positive charge on the drug molecule and the fluctuations below the pH value of 2.5 were attributed to the removing the ion-pair in the membrane.

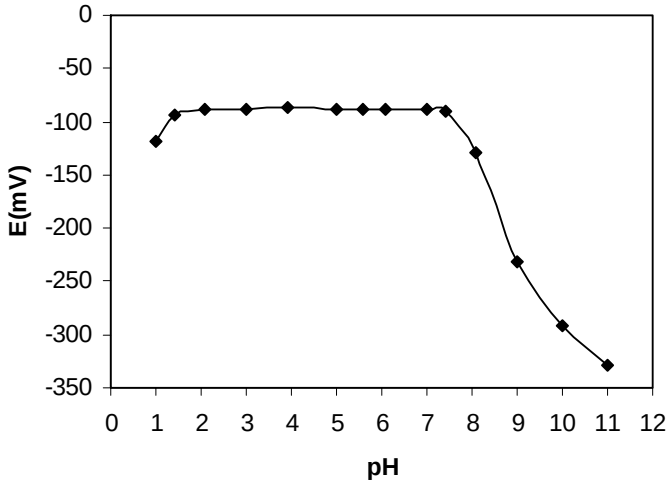

Figure 7. The pH effect of the test solutions (1.0×10^{-3} M) on the potential response of the diltiazem sensor with the composition of the membrane no. 2.

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. Calibration Graph and Measuring Range

The measuring range of an ion-selective electrode includes the linear part of the calibration graph as shown in Fig. 8. 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^{-1} M.

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 (3.2 μg/ml) which was calculated by extrapolating the two segments of the calibration curve (Fig. 8).

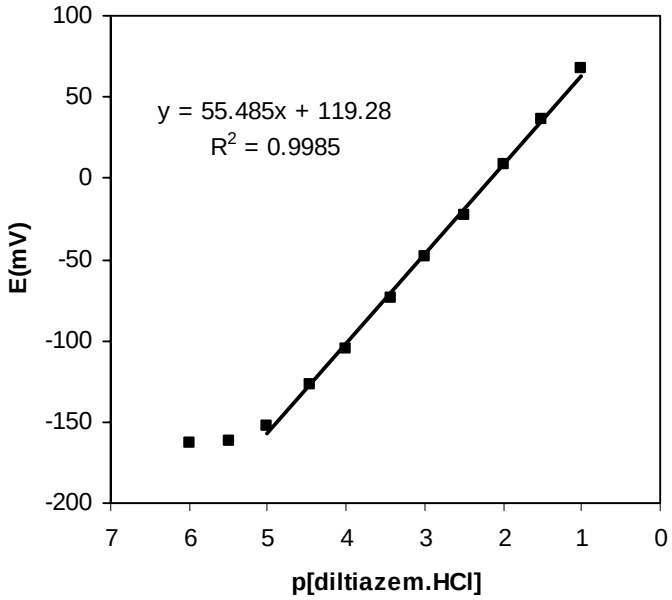

Figure 8. The calibration curve of the diltiazem hydrochloride membrane sensor (membrane no. 2).

3.4.2. 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 [52,53].

Its calculation involved the variation and the recording of the diltiazem hydrochloride concentration in a series of solutions from 10^{-5} to 10^{-1} M. In this work, less than 11 seconds response time was obtained for the proposed electrode when contacting different diltiazem solutions from 1.0×10^{-3} to 1.0×10^{-1} M, and about 15 seconds in low concentration solutions, which is due to the effect of analyte concentration on the response time of ion-selective electrode.

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 diltiazem sensor were evaluated by the matched potential method (MPM) [54-58].

The steps that need to be followed for the MPM method is certain; a) the addition of a specified concentration of the primary ions (A, 10^{-2} M of diltiazem solution) to a reference solution (10^{-5} M of diltiazem solution), b) the potential measurement. In addition, another experiment is conducted separately. For that experiment, the interfering ions (B, 10^{-2} M) are consecutively added to an identical 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, $K_{MPM} = a_A/a_B$.

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.

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

Interference ion	Log K_{MPM}
Na^+	-3.0
K^+	-3.4
Ca^{2+}	-2.7
Mg^{2+}	-3.1
HPO_4^{2-}	-3.9
NO_3^-	-3.8
CO_3^{2-}	-3.9
HCO_3^-	-3.5
Cl^-	-3.8
Br^-	-3.5
I^-	-3.5
NH_4^+	-2.9

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). The proposed sensors can be used for 7 weeks [59-61]. As can be seen from Table 4, at first there is a slight gradual decrease in the slopes (from 55.48 to 47.85 mV decade^{-1}) and then, an increase in the detection limit (from 7.0×10^{-6} M to 9.8×10^{-5} 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.

3.5. Analytical Application

3.5.1. Determination of diltiazem in formulations

A homogenized powder was prepared from 10 accurately weighed diltiazem 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 diltiazem content by using the calibration method. The results for determination of diltiazem amount in some pharmaceutical samples from local pharmacy are shown in Table 5. As it is seen, the results are in satisfactory agreement with the stated content on tablets.

Table 4. The life-time of the diltiazem membrane sensor

Week	Slope (mV decade^{-1})	Detection Limit (mol L^{-1})
First	55.48	7.0×10^{-6}
Second	55.1	8.3×10^{-6}
Third	54.63	8.7×10^{-6}
Fourth	54.14	9.2×10^{-6}
Fifth	53.7	1.4×10^{-5}
Sixth	53.15	2.6×10^{-5}
Seventh	52.94	4.3×10^{-5}
Eighth	51.82	5.2×10^{-5}
Ninth	50.46	8.1×10^{-5}
Tenth	47.85	9.8×10^{-5}

Table 5. Results of diltiazem assay in tablets by the diltiazem membrane sensor

Applied sample	Labeled amount (mg/tab.)	Found* (mg/tab.)
Diltiazem tablet, Aria	60	60.2±0.4
Diltiazem tablet, Amin	60	60.7±0.3
Diltiazem tablet, Daroupakhsh	60	60.3±0.2

* The results are based on triplicate measurements

3.5.2. Recovery of diltiazem from urine samples

In order to investigate the applicability of the new sensor to the determination of drug in the biological fluids, it was applied to the recovery of diltiazem from urine samples. A 2.5 mL of 10^{-3} M diltiazem 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 diltiazem 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 103.1%, 102.4% and 104.7% respectively.

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.

As mentioned before, the measuring range of the diltiazem sensor is between 1×10^{-5} and 1×10^{-1} M. The detection limit of the sensor was calculated 1.0×10^{-5} M (3.2 μg/mL).

3.6.1. Precision

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 3.02, 30.5, 303.5 μg/mL and with associated RSD values of 1.2, 1.05, and 0.43 %, respectively. Regarding the inter-day precision, the same three concentrations were measured for 3 consecutive days, providing mean diltiazem concentrations of 3.02, 30.5, 303.5 μg/mL and associated RSD values of 1.82, 1.02, and 0.26%, respectively.

3.6.2. Accuracy

The relevant error percentage and accuracy were calculated in each above case. The resultant concentrations were 3.02±0.03, 30.3±0.2, and 302.6±1.4 μg/mL with relevant error percentages of 3.53, 1.25, and 0.37 %, respectively.

3.6.3. Ruggedness/Robustness

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

4. CONCLUSIONS

After a series of experiments involving the usage of DTM-TPB ion-pair complexes along with several plasticizers in the membrane design, it was concluded that the diltiazem sensor exhibited

excellent analytical performance characteristics. It demonstrated an advanced performance with a fast response time (~12 s), a lower detection limit of 7.0×10^{-6} M and pH independent potential responses across the range of 2.1–7.4. This high sensitivity of the sensor enabled the diltiazem determination in pharmaceutical analysis.

It was noteworthy that this new diltiazem-selective electrode reliably and rapidly monitored the diltiazem concentration, in spite the simultaneous presence of other rare earth elements in the solution.

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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References

1. Budavari Susan, The Merck Index, 11th, Merck and Co., Inc, 1989, 505.
2. E. M. Sorkin, S. P. Clisold, and R. N. Brogden, *Drugs,* 30 (1985) 182.
3. H. Echizen, and M. Eichelbaum, *Clin. Pharmacokinet.*, 11 (1986) 425.
4. M. M. T. Buckley, S. M. Grant, K. M. Goa, D. McTavish,E.M. Sorkin, *Drugs*, 39 (1990) 757.
5. D. McTavish, and E. M. Sorkin, *Drugs,* 38 (1989) 19.
6. C. B. Cleveland, D. E. Francke, W. M. Heller, J.A. Kepler, G. P. Provost, and M. J. Reilly, American Hospital Formulary Service 98, Drug Information, American Society of Health-System Pharmacists, Bethesda, MD (1998).
7. R. E. Weins, D. J. Runser, J. P. Lacz, and D. C. Dimmitt, *J. Pharm. Sci.,* 73 (1984) 688.
8. J. P. Clozel, G. Caille, Y. Taeymans, P. Theroux, P. Biron, and F. Trudel, *J. Pharm. Sci.*, 73 (1984) 771.
9. S. C. Montamat, D. R. Abernethy, and J. R. Mitchell, *J. Chromatogr.*,415 (1987) 203.
10. K. Ishii, K. Minato, H. Nakai, and T. Sato, *Chromatographia,* 41 (1995) 450.
11. B. Artalejo-Ortega, A. Bamio-Nuez, C. Fauli Trillo, and A. Pozo Carrascosa, *Cienc. Pharm.* 7 (1997) 20.
12. M. Zhong, H. Wang, and J. Zhang, *Zhongguo Yiyuan Yaoxue Zashi*, 15 (1995) 355.
13. R.T. Sane, S.M. Purandare, V.G. Nayak, M.D. Joshi, and R. Nerurkar, *Indian Drugs*, 26 (1988) 623.
14. V. Rovie, M. Mitchard, and P. L. Morselli, *J. Chromatogr.*,138 (1977) 391.
15. F. Mikes, C. Boshart, and E. Gli-Av, *J. Chromatogr.*, 122 (1976) 205.
16. Y. Kuwahara, and H. Nishi, *Yakugaku Zasshi*, 118 (1998) 456.
17. H. Nishi, T. Fukuyama, M. Matsuo, and S. Terabe, *J. Chromatogr.*, 513 (1990) 279.
18. P. V. Devarajan, and V. V. Dhavse*, J. Chromatogr. B: Biomed.Sci. Appl.*, 706 (1998) 362.
19. C.S.P. Sastry, K. Sreedhar, M.N. Reddy, and D.G. Sankar, *Indian J. Pharm. Sci.*, 57 (1995) 170.
20. B. V. Kamath, K. Shivram, and A. C. Shah, *J. Pharm. Biomed. Anal.*, 11 (1993) 407.
21. K. Sreedhar, C. S. P. Sastry, M. N. Reddy, and D.G. Sankar, *Indian Drugs*, 32 (1995) 90.
22. Z. Z. Leng, X. Y. Hu, X. M. Jiang, R. J. Yu, and F. Huaxue, *Analytical Abstract*, 57 (1995) 332.
23. Y. Li, and Y. Qiu, *Zhongguo Yiyuan Yaoxue Zashi*, 18 (1998) 29.
24. Y. K. Agrawal, K. Shivramchandra, B.E. Rao, and G. N. Singh, *Indian J. Pharm. Sci.*, 23 (1991) 214.

25. F. Faridbod, M. R.Ganjali, R. Dinarvand, and P. Norouzi, *Combinatorial Chemistry & High Throughput Screening* 10 (2007) 527.
26. V. V. Cosofret, *Trends in Anal.Chem.,* 10 (1991) 298.
27. R. I. Stefan, G. E. Baiulescu, and H. Y. Aboul-Enein, *Tren. Anal.Chem.,* 27 (1997) 307.
28. C. Eppelsheim, R., Prubeck, N., Hampp, and C., Bruchle, *Analyst*, 116 (1991)1001.
29. A. Erdem, M. Ozsoz, L. Kirilmaz, E. Kilinc, and T. Dalbasti, *Electroanalysis*, 12 (1997) 932.
30. W. C. Ripka, and G. P. Vlasuk, *Annu. Rep. Med. Chem.*, 32 (1997) 71.
31. M. R. Ganjali, P. Norouzi, F. Faridbod, M. Rezapour, M. R. Pourjavid, *J. Iran Chem. Soc.,* 4 (2007) 1.
32. S. Riahi, M. R. Ganjali, P. Norouzi, and F. Jafari, *Sens. and Actuators B,* 132 (2008) 13.
33. S. Riahi, A. B Moghaddam, M. R Ganjali, and P. Norouzi, *Spectrochim. Acta A*, 71 (2008)1390
34. S. Riahi, M. R Ganjali, A. B. Moghaddamb, P. Norouzi, and S. S Hosseiny Davarani, *Spectrochim. Acta A*, 70 (2008) 94.
35. S. Riahi, P. Norouzi, A. B. Moghaddam, M. R. Ganjali, G. R. Karimipour, H. Sharghi, *Chem. Physics*, 337 (2007) 33.
36. S. Riahi, M. R. Ganjali, R. Dinarvand, S. Karamdoust, K. Bagherzadeh, P. Norouzi, *Chemical Biology & Drug Design*, 71 (2008) 474.
37. S. Riahi, M. R. Ganjali, and P. Norouzi, *J. Theor. Comput. Chem.*, 7 (2008) 317.
38. M. R. Ganjali, F. Faridbod, P. Norouzi, and M. Adib, *Sens. Actuators B,* 120 (2006) 119.
39. P. Norouzi, M. R. Ganjali, F. Faridbod, and M. Salavati-Niasari, *Bull. Korean. Chem. Soc.*, 27 (2006) 1439.
40. M. R. Ganjali, P. Norouzi, A. Daftari, F. Faridbod, and M. Salavati-Niasari, *Sens. Actuators B*, 120 (2007) 673.
41. M. R. Ganjali, R. Nemati, F. Faridbod P. Norouzi, and F. Darviche, *Int. J. Electrochem. Sci.,* 3 (2008) 1288
42. F. Faridbod, M. R. Ganjali, R. Dinarvand, P. Norouzi, and S. Riahi, Sensors, 8 (2008) 1645.
43. M. J. Frisch, J. E. Del Bene, J. S. Binkley, and H. F. Schaefer, *J. Chem. Phys.* 84 (1986) 2279.
44. D.W. Schwenke, and D. G. Truhlar, *J. Chem. Phys.,* 82 (1985) 2418.
45. M. R. Ganjali, P. Norouzi, F. Faridbod, S. Riahi, J. Ravanshad, J. Tashkhourian, M. Salavati-Niasari, and M. Javaheri, *IEEE Sensors J.,* 7 (2007) 544.
46. M. R. Ganjali, P. Norouzi, F. S. Mirnaghi, S. Riahi, and F. Faridbod, *IEEE Sensors J.*, 7 (2007) 1138.
47. F. Faridbod, M. R. Ganjali, B. Larijani, P. Norouzi, S. Riahi, and F. S. Mirnaghi, *Sensors*, 7 (2007) 3119.
48. M. R. Ganjali, P. Norouzi, F. Faridbod, S. Riahi, M. R. Yaftian, A. Zamani, and D. Matt, *J. Appl. Electrochem.,* 37 (2007) 827.
49. H. A. Zamani, M. R. Ganjali, and M. Adib, *Sens. Actuators B,* 120 (2007) 545.
50. M. R. Ganjali, Z. Memari, F. Faridbod, and P. Norouzi, *Int. J. Electrochem. Sci.,* 3 (2008) 1169.
51. H. A. Zamani, M. R. Ganjali, P. Norouzi, M. Adib, and M. Aceedy, *Anal. Sci.,* 22 (2006) 943.
52. M. R.Ganjali, P. Norouzi, and M. Rezapour, Encyclopedia of Sensors, Potentiometric Ion Sensors, American Scientific Publisher (ASP), 8 (2006)197.
53. F. Faridbod, M. R. Ganjali, R. Dinarvand, P. Norouzi, *African J. Biotechnol.*, 6 (2007) 2960.
54. P. R. Buck, and E. Lindneri, *Pure & Appl. Chem.,* 66 (1994) 2527.
55. V. K. Gupta, A. K. Jain, and G. Maheshwari, *Int. J. Electrochem. Sci.,* 2 (2007) 102.
56. H. A. Zamani, J. Abedini-Torghabeh, and M. R. Ganjali, *Electroanalysis*, 18 (2006) 888.
57. R. K. Mahajan and P. Sood, *Int. J. Electrochem. Sci.*, 2 (2007) 832.
58. M. R. Ganjali, M. Rahimi, B. Maddah, A. Moghimi, and S. Borhany, *Anal. Sci.,* 20 (2004) 1427.
59. M. R. Ganjali, P. Norouzi, F. Faridbod, N. Hajiabdollah, B. Larijani, and Y. Hanifehpour, Anal. Lett., 40 (2007) 2544.

60. M. R. Ganjali, P. Norouzi, B. Akbari-Adergani, S. Riahi, and B. Larijan, *Anal. Lett.*, 40 (2007) 1923.
61. M. R. Ganjali, M. Rezapour, M. R. Pourjavid, and S. Haghgoo, *Anal. Sci.*, 20 (2004) 1007.