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Design and Fabrication of PVC Membrane Electrode Based on Netural Ligand (E)-N'-(1-(2-Hydroxyphenyl)Ethylidene)Benzohydrazi for Teramadol hydrochloride Measurement in Drugs and Biological Fluids

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Here, a simple, quick and sensitive potentiometric method is described for tramadol hydrochloride measurement using PVC membrane electrode based on neutral ligand (E)-N'-(1-(2-hydroxyphenyl)ethylidene)benzohydrazid. Besides, effect of various parameters like ionic additives, membrane solvent and pH on the potentiometric response of the electrode are investigated. The best electrode performance was observed with membrane composition of PVC 30%, DBP 60%, carrier 7% and additive 3% within pH range of 3-6. This electrode showed Nernstian slope about -60.24 ± 0.2 mV dec^{-1}, detection limit of 1.75×10^{-6} M and response time about 15 s over the concentration range of 1.0×10^{-1}-3.16×10^{-6} M. The lifetime of electrode was about 40 days. Finally, to evaluate the performance of the electrode, the amount of tramadol hydrochloride were measured in three samples, including urine, cow's milk and tablet. The results showed that the mentioned electrode has the more appropriate performance compared to the other usual approaches.

Keywords: Ion-selective electrode, Carrier, PVC membrane electrode, Tramadol hydrochloride, Biological fluids

INTRODUCTION

Pharmaceutical companies are among the recent environmental problems due to disposing the pharmaceutical waste into the nature. Hence, nowadays, drug residues in nature and aqueous systems are of the major pollutants causing many problems for biological systems.

Tramadol hydrochloride, [(±-trans-2-(dimethlamino-methyl)-1-(3-methoxy phenyl)-cyclohexanol (Fig. 1), is a synthetic drug which is usually synthesized as hydrochloride salt and is presented in edible (tablet, capsule and drop) and injecting forms. This is a sedative which is used for chronic pains. Its sedation is about 10 times slower than morphine. Also, it inhibits reuptake of norepinephrine causing alacrity unlike morphine. Tramadol can decrease muscular inflation in some consumer [1]. The dosage of tramadol should be adjusted to the intensity of pain and to

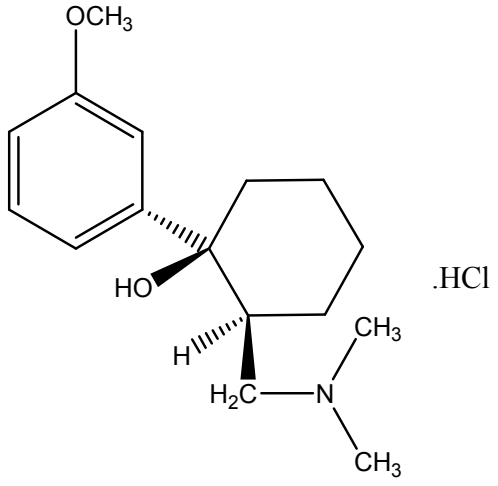

Fig. 1. Structure of tramadol hydrochloride (TDH).

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the response of an individual patient in the range of 100-300 ng l^{-1}. Its absolute bio availability is only 65-70% due to first-pass metabolism, and almost 10-30% of the parent drug is excreted un-metabolized in urine [2]. So far, several analytical techniques, such as thin layer Chromatography (TLC) [3], gas Chromatography (GC) [4], high efficiency liquid chromatography (HPLC) [5], fluorescence [6-7], electrophoresis [8], electrochemical methods [9] and spectrophotometry methods [10-12] have been employed to-determine the amount of tramadol in various biological and pharmaceutical samples. However, most of these methods are expensive and require complicated technologies. Using the potentiometric method with PVC membrane electrode, though, has several advantages over these techniques such as simplicity, low response time, low cost, proper detection limit, and acceptable linear range [13]. Ion-selective electrodes have been widely used for drugs measurements like tramadol hydrochloride in bio samples [14-17].

The goal of this study is to design and prepare a PVC membrane electrode with good response characteristics to measure tramadol. The response mechanism of the liquid membrane electrodes is based on the ion exchange function. In such a way that the liquid membrane electrode response is due to the potential generated along the interface level between the solution containing an analyte and an ion exchanger, that in this membrane, analyte is selectively bonded to the ion exchange. This electrode has reasonably high sensitivity and selectivity for tramadol hydrochloride measurement in the presence of many organic and mineral compounds.

EXPERIMENTS

Reagents and Materials

Ligand (E)-N'-(1-(2-hydroxyphenyl)ethylidene)benzo-hydrazide (HL), as ionophore, was produced and purified in Kerman mineral chemistry research laboratory, Iran [18]. Tramadol hydrochloride 100 g tablet was provided from two pharmaceutical corporations, Bakhtar biochemistry and Tehran chemistry, Iran.

Tramadol hydrochloride, aceton, tetrahydrofuran (THF), dimethylformamide (DMF), heavy polyvinyl chloride polymer and sodium tetraphenylborate (Na-TPB) were purchased from Sigma-Aldrich company.

Various plasticizers including: bis(2-ethylhexyl) phosphate (BEHP), bis(2-ethylhexyl sebacate (BEHS), dioctyl phthalate (DOP), dibutyl phthalate (DBP) and tris(2-ethylhexyl) phosphate(TEHP) were purchased from Sigma-Aldrich company. All used nitrate metal cation salts, acids and bases were purchased from Merck

Apparatus

A pH meter (Jenway pH-meter, UK 3020), digital-scale with 0.0001 accuracy (Shimadzu-AEL-200, Japan), glass double water distiller (Fusion, UK), saturated calomel (SCE), Hamilton microliter syringe (Hamilton, Switzerland) and Ag/AgCl electrode were purchased from Azar electrode, Iran..

Emf Measurements

The measurements were performed with the following cell assembly:

Ag/AgCl, KCl (saturated)|internal solution, 1.0×10^{-3} M TDC|PVC-membrane|test solution |Hg/Hg_2Cl_2, KCl (saturated).

In this study, all measurements were carried out in a 100 ml glass beaker with constant stirring of the desired solution through a magnet. Ion activities were calculated according to the Debye-Huckel formula (Eq. 1) [19]

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$$\log \gamma = -0.511 z^2 \, [\mu^{1/2} / (1 + 1.5\mu^{1/2}) - 0.2\mu)] \qquad (1)$$

Preparation of the Electrode

For the synthesis of PVC-based membrane electrode [20], 30 mg of PVC powder, 60 mg of DBP, as plasticizer, 7 mg of HL ligand, as natural carrier, 0.5 ml DMF of solvent, as ligand solvent, and 3 mg of Na-TPB, as additive, were mixed completely in a suitable container. Then about 3 ml of THF solvent was added to obtain a clear solution. After wards, the resulting solution was kept in a quiet place to be evaporated slowly in the room temperature and an oily solution was resulted. After that, the tip of PVC tube with 3 mm diameter was immersed in the solution for 15-20 s until a tin transparent membrane was formed. After that, the tip of PVC tube was kept in room temperature for an hour. Then, the half of the tube was filled with 1.0×10^{-3} M solution and as a final stage of preparation it was kept in the room temperature for 24 h. The Ag/Ag electrode was

selected as a reference electrode and different experiments were performed to optimize the membrane ingredients proportions, their concentrations and the contact time to have a stable and repeatable electrode.

RESULTS AND DISCUSSION

Ionophore Selection

The evaluation of results shows that the amount of neutral carrier has a great effect on the response of membrane electrode property. An ionophore or carrier is a complex agent which is in insoluble in water and could reversibly and selectively interact with particular ions [21-22].

Figure 2 shows the structure of the HL ligand. As seen in this figure, the presence of donor nitrogen and oxygen atoms in the structure of ligand makes it neutral for measuring ionized tramadol hydrochloride (Fig. 3)

Optimization of Membrane Components

Membrane compositions and the ratio of their amounts are effective in performance of the electrode. Therefore, the effect of each membrane composition on the hydrochloride tramadol measurement was studied and its value was optimized. The obtained results are summarized in Table 1. Using PVC texture for membrane structure has several advantages like increasing the mechanical resistance, stability of chemical indicator, inducing the semi permeability property which increases selectivity and sensitivity of electrode, as well as causing long life time, bio-compatibility and prevention of crystallization [23]. The other membrane component is membrane solvent, plasticizer, which is a lipophilic liquid with high viscosity. The addition of plasticizer to electrode improves the physical stability of the membrane and increases the mobility of membrane's components. However, it decreases the membrane resistance, so the proportion of the applied plasticizer must be optimized [23-24]. The DBP softener provided the best selectivity as plasticizer for membrane among the other used solvents in this study. The ionic additive is another membrane component which affects the electrode response *via* decreasing anionic interruptions and electrical resistance of membrane [25]. In this study, NaTPB was used as an ionic additive, and its amount was optimized. The obtained results showed that the best membrane composition was PVC 30%, DBP 60%, Carrier 7% and Additive 3%.

The pH Effect

For optimal usage of electrode and define the diversity of its application, it is always crucial to know the pH range in which the potential of electrode is constant. To study the pH effect on electrode performance, the potential of 1.0×10^{-3} M tramadol hydrochloride solution was measured in pH range of 2-9.

The HNO_3 and NaOH (1 M) solution were used for pH adjustment. According to Fig. 4, the response of electrode was stable and constant in pH range of 3-6. However, in solution with pH higher than 6, diminish of potential occurs which is due to the decrease in ionic form of tramadol and formation of free tramadol species in the solution. On the other hand, potential of electrode increases in pH less than 3 due to response of electrode to the released hydrogen ions.

Effect of Internal Reference Solution

One of the most effective ways for improving the detection limit in ion-selective electrodes is decreasing the influences of ion fields through increasing the activity of main ion in layers close to membrane surface [25].This can be done *via* adjusting the composition and structure of inner solution [26] or decreasing the thickness of diffusion layer [27]. The inner solution composition and its structure should be adjusted or the diffusion layer thickness must be reduced. As the inner solution may affect the electrode response when the diffusion potential is considerable, in this study, the effect of concentration of inner solution of PVC electrode is also investigated. Three membranes with optimized membrane compositions were prepared and each electrode was filled by solution with different tramadol hydrochloride concentrations in the range of 1.0×10^{-1}-1.0×10^{-3} M. Then, the electrodes were prepared by keeping them for 10 h. In 1.0×10^{-2} M tramadol hydrochloride solution and finally the curve of EMF versus TDH was plotted for each electrode. The results show that the variation of inner solution composition does not make a considerable difference in the potential signal. However, the working range for inner solution with 0.01 M

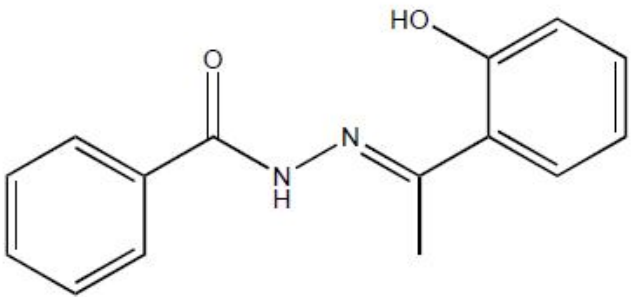

Fig. 2. Structure of HL ligand.

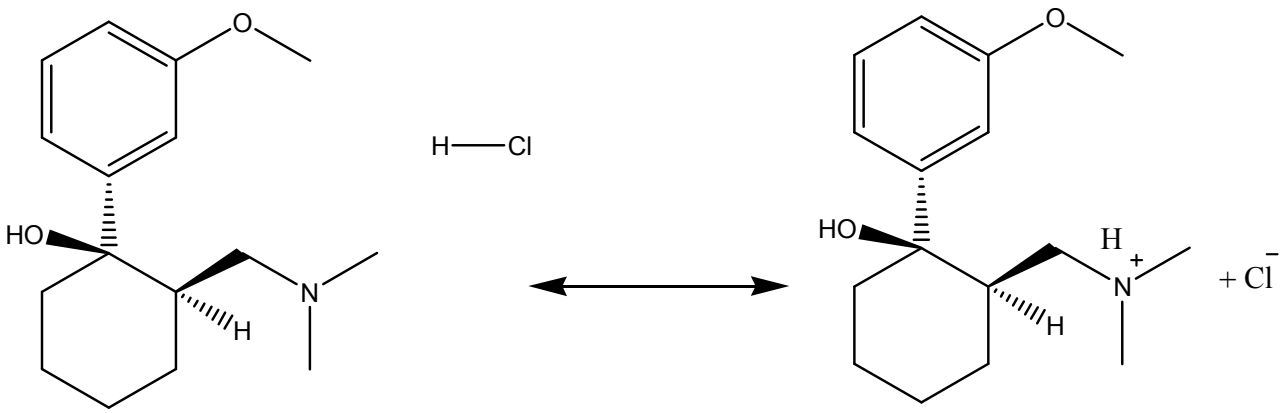

Fig. 3. Ionized state of tramadol hydrochloride.

concentration gets wider; therefore, it seems that 0.01 M concentration of solution is the most suitable concentration for the electrode system.

The Calibration Curve, Linear Range and Detection Limit

The sensitivity of ion selective electrode is defined as the slope of liner part of calibration curve which is 2.33RT/nF for ideal Nernstian electrode [28]. Also, the ion selective electrode measurement range includes the liner section of calibration curve. The electrode response potential in standards solutions with different tramadol hydrochloride concentrations was measured. These responses were located in 1.0×10^{-1}-3.16×10^{-6} M liner concentration part with almost Nernstian slope. The electrode detection limit was approximated from crossing two extrapolated sections of calibration curve from its lowest part [29]. The detection limit was calculated about 1.75×10^{-6} M from Fig. 5.

Response Time and Electrode Lifetime

The response time of the electrode is obtained by measuring the time required to achieve a steady state potential, which is 90% of final potential, after successive immersion of the indicator and reference electrodes in solution. The response time for this electrode (in 0.001 M tramadol hydrochloride solution) is obtained by intersection of two interpolated sections of response time curve [30]. Based on that, measured response time is 15 s (Fig. 6).The lifetime is the time span in which the properties of electrode like detection limit and selectivity be endured without a considerable change. To determine the lifetime, the electrode was used for about 1 hour per day for measurement of tramadol ion in standard tramadol

Table 1. Optimization of Membrane Ingredients

Electrode No.	Composition of the membrane (wt%)				Slope (mV dec^{-1})	Dynamic linear range (M)
	PVC	Plasticizer	Carrier	Additive		
1	30	BEHS, 62	5	3	-46.29 ± 0.4	1.0×10^{-1}-6.3×10^{-5}
2	30	BEHP, 62	5	3	-51.11 ± 0.2	1.0×10^{-1}-2.0×10^{-5}
3	30	TEHP, 62	5	3	-41.38 ± 0.3	1.0×10^{-1}-7.9×10^{-5}
4	30	DOP, 62	5	3	-52.35 ± 0.1	1.0×10^{-1}-1.6×10^{-5}
5	30	DBP, 63	5	2	-57.47 ± 0.2	1.0×10^{-1}-1.0×10^{-5}
6	30	DBP, 60	7	3	-60.24 ± 0.2	1.0×10^{-1}-3.16×10^{-6}
7	28	DBP, 62	7	3	-58.97 ± 0.4	1.0×10^{-1}-4.0×10^{-6}
8	32	DBP, 60	5	3	-55.64 ± 0.3	1.0×10^{-1}-5.1×10^{-6}
9	30	DBP, 60	6	4	-58.56 ± 0.1	1.0×10^{-1}-6.3×10^{-6}
10	30	DBP,68	9	3	-56.36 ± 0.3	1.0×10^{-1}-3.9×10^{-6}

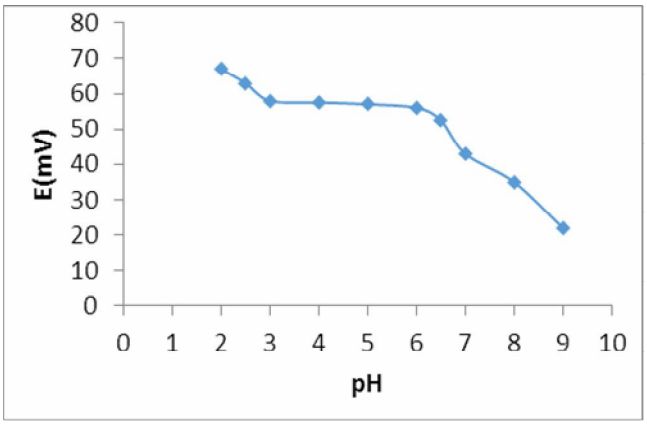

Fig. 4. The pH effect of the test solution (1.0×10^{-3} M) on the potential response of TDH sensor.

hydrochloride solutions in a period of 6 weeks. There was not a considerable change in the electrode performance after this time. Then, the electrode was used for 40 days, while no meaningful variation was detected in electrode response during 40 days, so the electrode lifetime was reported 40 days.

Reversibility and Reproducibility

In order to study the membrane electrode reversibility, the electrode is immersed in 10^{-5} and 10^{-3} M tramadol hydrochloride solutions and the values are recorded. The results which are shown in Fig. 7. indicates that this electrode has a good reversibility. The percentage of

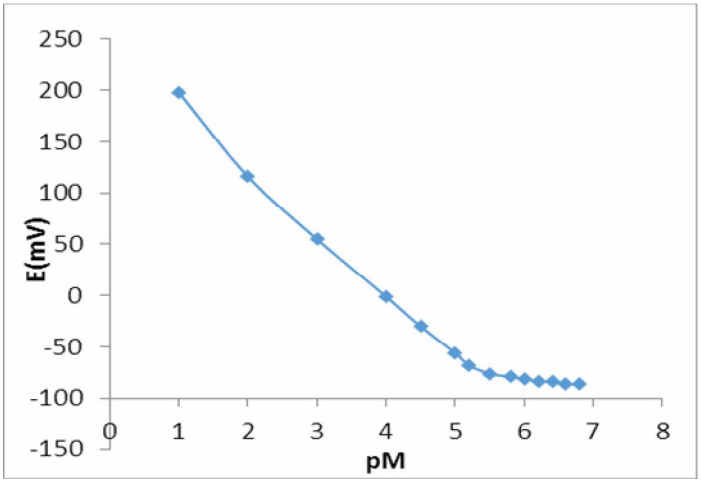

Fig. 5. The calibration curve of the TDH membrane electrode.

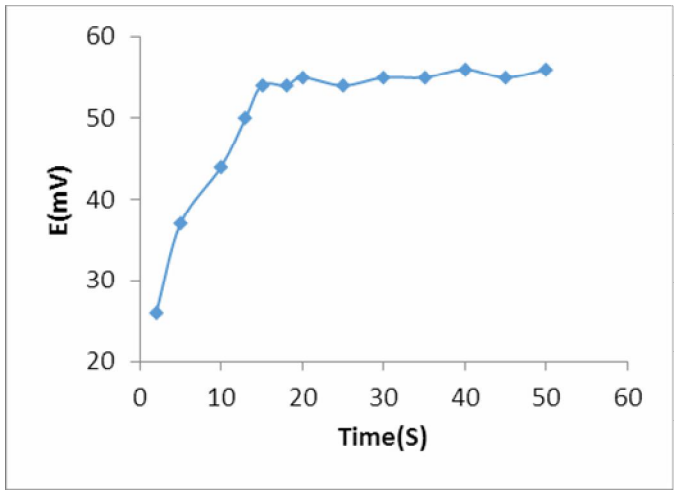

Fig. 6. The response time of the TDH membrane electrode.

Relative Standard Deviation, RSD%, for low and high tramadol hydrochloride concentrations was determined (5 times repetitions for each one). RSD% for 1.0×10^{-3} M concentration was ±0.14 and for 1.0×10^{-5} M concentration was ±0.17. The obtained value for RSD% showed that the measured potentials were remained constant irrelevant to increase or decrease of the concentration based on the obtained results; reproducibility of the electrode response can be confirmed for each concentration.

Selectivity

The selectivity of an electrode is defined by its relative response to the primary ion in the presence of other ions in the solution. The matched potential method (MPM) [31] and the Separate Solution Method (SSM) [32] were applied to determine the electrode selectivity.

In MPM, 50 ml of 1×10^{-4} M tramadol hydrochloride solution was added to 50 ml of 1×10^{-5} M standard tramadol hydrochloride solution to obtain 5.5×10^{-5} M

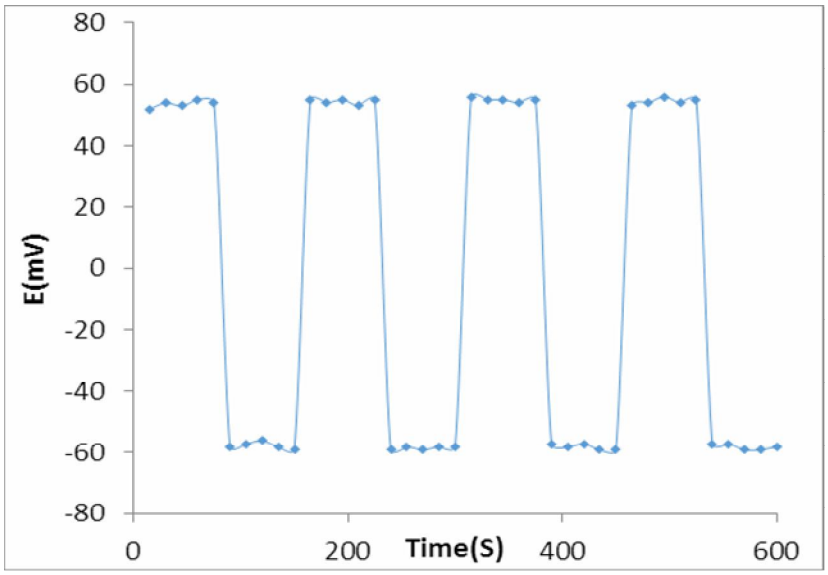

Fig. 7. Dynamic response time of the TDH electrode for two concentrations (1.0×10^{-3} M and 1.0×10^{-5} M).

Table 2. Determine the Selectivity Coefficient by Two Methods: (MPM), (SSM)

Interfering ion	$K_{A,B}^{pot}$ (MPM)	$K_{A,B}^{pot}$ (SSM)	Interfering ion	$K_{A,B}^{pot}$ (MPM)	$K_{A,B}^{pot}$ (SSM)
Na^+	7.6×10^{-3}	6.31×10^{-4}	Ascorbic acid	5.1×10^{-3}	3.9×10^{-2}
K^+	9.7×10^{-3}	5.12×10^{-4}	Maltose	9.3×10^{-4}	-
Mg^{2+}	4.2×10^{-3}	1.3×10^{-3}	D-fractose	7.4×10^{-4}	-
Ca^{2+}	4.5×10^{-3}	1.47×10^{-3}	Glucose	9.8×10^{-4}	-
Cu^{2+}	6.7×10^{-3}	2.94×10^{-3}	Sucrose	8.5×10^{-4}	-
Zn^{2+}	4.8×10^{-3}	1.06×10^{-3}	Glycine	2.3×10^{-3}	6.31×10^{-2}
Thiourea	3.4×10^{-3}	-	Galactose	9.6×10^{-4}	-

solution, and variations of solution potential were calculated. In next step, interfering species with 1×10^{-1} M concentration was continuously added to 1×10^{-5} M standard tramadol hydrochloride solution until the potential difference of solution became equal to its initial solution. Then, the final concentration of interfering species was calculated. For calculation of selectivity coefficient the following Eq. (2) was used:

$$\log K_{TD,J}^{pot} = \frac{a_{TD} - a_{TD_{ref}}}{a_j} \quad (2)$$

In this equation, a_j is activity of interfering species; a_{TD} is tramadol hydrochloride activity in 5.5×10^{-5} M solution

and $^{a}TD_{ref}$ is reference solution activity.

In SSM, the electrode response to primary ions and other ions was determined separately in concentration range of 0.01-1.0 × 10^{-6} M. The curve of solution potential versus the log of TDH concentration curve and the curve of solution potential *versus* the log of concentration of other species were plotted. Then, the same potential locations were found for the main ion and trouble one. The Eq. (3) was applied for calculation of selectivity coefficients:

$$K_{A,B}^{pot} = \frac{a_A}{(a_B)^{z_A/z_B}} \quad (3)$$

In above equation, Z_A and Z_B are the electrical charges of primary and other ions, respectively.

The experimental results are summarized in Table 2. According to results, the membrane electrode has a high selectivity with respect to tramadol in presence of different mineral and organic compounds with high concentration. This is a very applicable finding as most of tramadol drugs have other components like glucose, lactose, sucrose, Mg and cellulose micro crystals.

ANALYTICAL APPLICATIONS

Potentiometric Titration

The prepared electrode was utilized as indicator electrode for titration of 50 ml of 10^{-3} M tramadol hydrochloride solution with 10^{-3} M sodium tetra phenyl borate (Na-TPB) solution. The resulted titration curve (Fig. 8) showed a sharp peak and a reduction in the tetra phenyl borate ion potential upon addition of titrant which indicates the formation of free tetra phenyl borate species in the solution.

Actual Sample Analysis

To analyze the performance of modified liquid membrane electrode with ligand HL in tramadol hydrochloride measurement, two different 100 mg tramadol tablets from two companies, as well as urine and cow milk samples were used.

Tablet samples preparation. To prepare tablet samples, 5 tablets were selected from each pack and were separately grinded to form powder. Then, 100 mg from each powder sample was dissolved in 50 ml distillated water and purified by filtering. The resulted samples were poured in volumetric flasks and enough distillated water was added to obtain 1.0 × 10^{-3} M and 5.0 × 10^{-4} M solutions.

Preparation of biological fluids. To prepare urine sample, 10 ml of urine was placed in a test tube and put the tube in Centrifuges for 3 min. After filtration, a specific amount of tramadol hydrochloride was added and the mixture was mixed thoroughly for 5 min to obtain homogenous solution. Then, the mixture was diluted with enough distillated water in a volumetric flask to yield a 1.0 × 10^{-4} M solution and by further dilution its concentration became 5.0 × 10^{-5} M.

To prepare cow milk sample, 10 ml cow milk was poured in 50 ml beaker and a definite amount of tramadol hydrochloride was added into it. The resulting mixture was mixed by stirrer thoroughly for 5 min and transferred to a volumetric flask and was diluted with enough distillated water to yield 1.0 × 10^{-4} M and 1.0 × 10^{-5} M solutions. After preparation of samples, their tramadol contents were measured with membrane electrode using standard addition method [33] and calibration curve method [34]. Also, each test repeated 5 times.

The counter F test (Eq. (4)) was used to survey if there is meaningful difference between accuracy or repeatability of these two methods and to compare the results of calculations with critical values.

$$F\left(\frac{n_1 - 1}{n_2 - 1}\right) = \frac{S_1^2}{S_2^2} \quad (4)$$

To the point that all results were less than critical F values, there was not any meaningful difference between two selected methods for tramadol hydrochloride measurement.

Also, the T test (Eqs. (5) and (6)) was employed to compare systematic errors of two methods and to check if there is any considerable disparity between their mean values or not.

$$S^2 = \frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{(n_1 + n_2 - 2)} \quad (5)$$

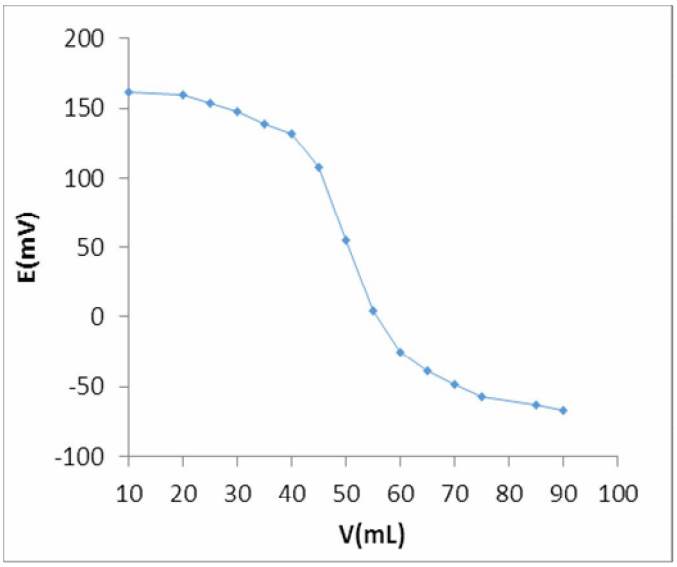

Fig. 8. Titration of 50 ml of 10^{-3} M TDH solution with 10^{-3} M (Na-TPB) solution.

Table 3. Tramadol Hydrochloride Measurements in Real Samples

Sample	Taken (M)	Found $(M)^S$	Found $(M)^C$	F-values	t-values
Tablet[a]					
A	1.0×10^{-3}	$9.84 (\pm 0.14) \times 10^{-4}$	$9.65 (\pm 0.23) \times 10^{-4}$	2.69	1.59
B	5.0×10^{-4}	$4.77 (\pm 0.19) \times 10^{-4}$	$4.59 (\pm 0.26) \times 10^{-4}$	1.187	1.28
Tablet[b]					
A	1.0×10^{-3}	$9.91 (\pm 0.09) \times 10^{-4}$	$9.78 (\pm 0.15) \times 10^{-4}$	2.7	0.59
B	5.0×10^{-4}	$4.83 (\pm 0.15) \times 10^{-4}$	$4.66 (\pm 0.23) \times 10^{-4}$	2.35	1.38
Urine					
A	1.0×10^{-4}	$1.08 (\pm 0.11) \times 10^{-4}$	$1.19 (\pm 021) \times 10^{-4}$	3.64	1.04
B	5.0×10^{-5}	$5.13 (\pm 0.15) \times 10^{-5}$	$5.22 (\pm 0.23) \times 10^{-5}$	2.75	0.52
Milk					
A	1.0×10^{-4}	$9.76 (\pm 0.21) \times 10^{-5}$	$9.45 (\pm 0.32) \times 10^{-5}$	2.33	1.82
B	1.0×10^{-5}	$9.70 (\pm 0.23) \times 10^{-6}$	$9.39 (\pm 0.35) \times 10^{-6}$	2.31	1.62

[a]Tablet from pharmacy corporations Bakhtar biochemistry.Iran. [b]Tablet from pharmacy corporations Tehran chemistry, Iran. The number of replicate measurements = 5. [C]Calibration curve. [S]Standard addition method. The critical value of F = 9.605 and the critical value of t = 2.31.

Table 4. Comparison of the Proposed Tramadol Sensor with other Works

No.	Plaxticizer	Slope	Linear range	LOD	Ref.
1	DBP	61.7	1.0×10^{-1}-7.3×10^{-6}	5.3×10^{-6}	[14]
2	NPOE	57.8 ± 0.4	1.0×10^{-1}-9.2×10^{-6}	6.2×10^{-6}	[15]
3	DBP	58.06	1.0×10^{-1}-1.0×10^{-5}	3.0×10^{-6}	[16]
	DBP	61	1.0×10^{-1}-5.5×10^{-6}	2.1×10^{-6}	[35]
4	DOP	57.1	1.0×10^{-2}-5.0×10^{-5}	1.0×10^{-5}	[36]
5		57.3	1.0×10^{-2}-2.5×10^{-5}	1.6×10^{-5}	[37]
6	DBP	58.5	1.0×10^{-2}-3.0×10^{-6}	5.0×10^{-6}	[38]
This work	DBP	-60.24 ± 0.2	1.0×10^{-1}-3.16×10^{-6}	1.75×10^{-6}	-

$$t = \frac{(X_{m_1} - X_{m_2})}{S\sqrt{\frac{1}{n_1} + \sqrt{\frac{1}{n_2}}}} \quad (6)$$

In these equations n is time measurements, S is variance, and X_m is measurement of mean value. There was not seen any important disparity between two methods by comparison of calculated results with critical T value.

The critical F value for counter test (P = 5%) is 9.605 and the absolute critical T value for a counter test (P = 5%) is 2.31. All this section results and calculations are summarized in Table 3.

COMPARISON WITH REPORTED ELECTRODES

Table 4 shows the comparison between performance characteristics of the designed electrode and electrodes reported in the literature for measuring tramadol hydrochloride. It can be clearly seen from this table that the detection limit of electrode, linear range and Nernstian slop are truly satisfactory

CONCLUSIONS

In conclusion, the achieved selectivity pattern of PVC-based liquid membrane with (*E*)-*N*'-(1-(2-hydroxyphenyl) ethylidene) benzohydrazide as a natural carrier can enable us to provide good selectivity requirements for tramadol hydrochloride analyses in drugs and biological samples, *e.g.*, urine.

Also, the designed electrode has advantages like simple preparation, quite vast working range, proper pH rang and good reproducibility. The electrode potentiometric measurements showed liner range of 1.0×10^{-1}-3.16×10^{-6} M, Nerstian slope of -60.24 ± 0.2 mV dec^{-1} and 1.75×10^{-6} M limit detection. Besides, this electrode has significant selectivity for tramadol hydrochloride measurement in the presence of mineral and organic species.

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