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Preparation of a Naltrexone HCl Potentiometric Sensor and Its Application to Pharmaceutical Analysis and Drug Determination in Biological Fluids

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ABSTRACT

A novel ion selective electrode is fabricated for naltrexone HCl and used in pharmaceutical analysis and drug determination in biological fluids without complicated pretreatments and extractions, using direct potentiometry. The naltrexone complex with sodium tetraphenyl borate (NaTPB) is obtained by in situ soaking PVC membrane electrode in an 1×10^{-3} M naltrexone solution. The sensor exhibited fast, reproducible and linear sub-Nernstian response over concentration range of 1×10^{-5} - 1×10^{-3} M with a detection limit of 5×10^{-6} M. The membrane sensor was successfully applied to the determination of naltrexone in capsules as well as for its determination in urine and plasma samples.

Key words: Naltrexone HCl, ion selective electrode, direct potentiometry, pharmaceutical analysis, biological fluids

INTRODUCTION

Naltrexone, 17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one (Figure 1), first synthesized in 1965, is a potent mu opioid antagonist which reversibly blocks opioid receptors and has been approved by FDA for treating both alcohol and opioid dependence[(1)]. The blockade of opioid receptors is the basis behind its action in the management of opioid dependence. The mechanism of action in alcohol dependence is not fully understood, but as an opioid-receptor antagonist, it is likely to be due to the modulation of the dopaminergic mesolimbic which ethanol is believed to activate[(2)].

Naltrexone has been determined using a variety of quantitative analytical methods, including thin layer chromatography (TLC)[(3)], gas chromatography (GC)[(4,5)] with electron capture detector[(6-9)], tandem mass spectrometry[(10)] and mass spectrometry[(11-14)], high-pressure liquid chromatography (HPLC) with UV, electrochemical detection[(15-20)], mass spectrometry[(21)] and tandem mass spectrometry[(22,23)], chemiluminescence[(24)], flow injection analysis with amperometric detection[(25)], spectrofluorimety[(26)], voltammetry on carbon paste electrode[(27)], and electrochemical determination on the surface of glassy carbon electrode modified with nafion-doped carbon nanoparticles[(28)]. A nano-molar detection method based on fast fourier transforms continuous

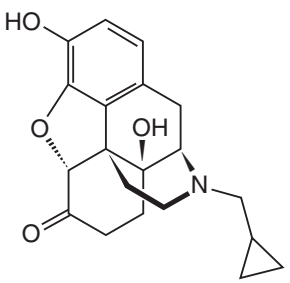

Figure 1. Chemical structure of naltrexone.

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cyclic voltammetry using gold ultra-microelectrode in a flow-injection system has been previously reported for the determination of naltrexone in pharmaceutical preparations[29]. Despite providing excellent sensitivity, these methods typically require extensive sample cleanup steps and derivatization prior to analysis, as well as the use of sophisticated and expensive instruments.

New requirements for the development of adequate analytical methods in the area of pharmaceutical analysis led many researchers to design and apply new potentiometric sensors involving ion-selective electrodes (ISEs). In many instances, even both the British and United States Pharmacopeias suggest assay methods requiring pretreatment and time-consuming manipulation steps, expensive equipment and special training. The development and application of potentiometric sensors based on ISEs have been investigated and continue to be of interest in the areas of chemical, pharmaceutical and biomedical analysis, because they offer the advantages of ease of preparation and procedures, simple instrumentation, design and handling, accuracy, low cost, wide concentration range, the possibility of direct application in colored and turbid solutions, reduced implementation time, fast response and long life span[30-39].

To the best of our knowledge, there are no reports in the literature on the use of ISE potentiometric sensors for determination of naltrexone in pharmaceutical preparations and biological fluids. The aim of this study is to develop and apply a naltrexone potentiometric sensor based on poly (vinyl chloride) (PVC) for direct determination of naltrexone in pharmaceutical preparations and biological fluids.

MATERIALS AND METHODS

I. *Materials and Reagents*

Naltrexone HCl of analytical grade was provided by Sun Pharma, Pharmaceutical Industries Ltd. Pharmaceutical formulation of naltrexone HCl (25 mg capsules, Alhavi Pharmaceutical Co., Tehran, Iran) was purchased from the local pharmacy. All other chemicals which were of analytical reagent grade were provided from Merck. Doubly distilled deionized water was used for all aqueous solution preparations. Stock solutions of naltrexone HCl were freshly prepared as required in 0.1 M phosphate buffer solutions (PBS) (pH 3, 6, 7 and 8) or 0.1 M acetate buffer solutions (ABS) (pH 4 and 5) as supporting electrolytes. Fresh frozen plasma was prepared by Iranian Blood Research and Fractionation Holding Company (IBRFC).

Urine was collected from healthy volunteers (males, about the age of 30).

PVC of high molecular weight was purchased from Aldrich. Sodium tetraphenyl borate (NaTPB), dioctyl phthalate (DOP) and tetrahydrofuran (THF) were prepared from Merck and were used without further purification, except THF, which was distilled before use.

II. *Apparatus*

Potentiometric and pH measurements of buffer solutions were made by a digital pH/mV/Ion meter Cyberscan model 2500. Potentials were measured by direct potentiometry at 25 ± 0.1°C and the cell set-up was as follows:

Ag/AgCl, KCl (sat.)// Sample solution/ Membrane/ Graphite electrode.

III. *Electrode Preparation*

Graphite electrodes (d = 3.0 mm and l = 15.0 mm) with spectroscopic purity was inserted in a PVC tube with almost the same inner diameter and length of 15.0 cm with the aid of epoxy glue. For electrical connection, a coated copper wire was used in PVC tube in connection with graphite electrode. The electrode was manually polished with 0.05 μm alumina slurry on a polishing cloth and rinsed thoroughly with doubly distilled water. In order to prepare the membrane of the electrode, PVC and NaTPB mixed with DOP as a solvent mediator in 3 mL of THF. The solvent was evaporated slowly until an oily concentrated mixture was obtained. The graphite electrode was dipped into the mixture for several times and then removed from the membrane mixture and dried at room temperature for about 3 h. Under these conditions, a transparent membrane of about 0.3 mm thickness was formed on the surface of the graphite electrode. The electrode was conditioned finally by soaking in 1.0×10^{-3} M solution of naltrexone for 24 h.

IV. *Validation Procedure*

The linear range, limit of detection (LOD), limit of quantification (LOQ), repeatability, intermediate precision, recovery and selectivity were evaluated in the determination of naltrexone. The linear range was evaluated by potentiometric analysis of naltrexone solutions in the range of 1×10^{-7} - 1×10^{-3} M. The LOD and LOQ were calculated from the intersection of two linear segments of the calibration graph. Repeatability (intra-day) and intermediate (inter-day) precision were assessed at three concentrations. To assess the repeatability, 3 replicate measurements of each solution were made in a short period of time. To determine intermediate precision, the solutions were each analysed three times per day for three consecutive days. The accuracy of procedure was verified by performing recovery assays in triplicate.

V. *Pharmaceutical Analysis*

The contents of 20 capsules of naltrexone (each capsule contains a labeled value of 25 mg) were transferred into a 100-mL volumetric flask and diluted with double distilled water. The mixture was sonicated for 15 min to complete dissolution and then made up to the volume. Suitable aliquots of solutions were taken and diluted with appropriate buffer to obtain the final concentrations. The recovery and precision studies in assay procedure were evaluated in low, middle and

Journal of Food and Drug Analysis, Vol. 19, No. 4, 2011

Table 1. Membrane compositions and their potentiometric response properties in naltrexone-selective electrode

Membrane No.	Composition (%)			Slope (mV decade^{-1})	Dynamic Range (M)
	PVC	DOP	NaTPB		
M1	32	64	4	-24.98	$1.0 \times 10^{-4} – 1.0 \times 10^{-3}$
M2	31.5	63	5.5	-27.91	$1.0 \times 10^{-5} – 1.0 \times 10^{-3}$
M3	31	62	7	-29.36	$1.0 \times 10^{-5} – 1.0 \times 10^{-3}$

high level concentrations of pharmaceutical solution. Quantitations were performed using the calibration curve method from the related calibration equations.

VI. *Analysis of naltrexone in Real Samples*

Aliquot volumes of plasma and urine samples were fortified with naltrexone. After 1 min of vortexing, the samples were diluted to obtain final concentrations of 1×10^{-5} - 1×10^{-3} M without extraction or further treatments. Quantitations were performed using the calibration curve method from the related calibration equations.

RESULTS AND DISCUSSION

I. *Influence of Membrane Composition*

Naltrexone HCl is a cationic substance which can aggregate with NaTPB to form a stable water-insoluble ion-pair association. In this study, ion-pair association of naltrexone was obtained in situ by conditioning the PVC membrane electrode containing NaTPB in 0.001 M naltrexone solution for 24 h. The selectivity and sensitivity of ISE is influenced by the nature of plasticizer. According to previous studies, in application of the PVC membrane electrodes for organic lipophilic ions, using of DOP as the membrane solvent produces better potential responses in comparison to other plasticizers like DBP (dibutylphthalate), AP (acetophenone), DOS (dioctyl sebacate), and O-NOPE (o-nitrophenyl octyl ether)[30,35,40,41]. Therefore, in this study, DOP was chosen as the membrane solvent. Several membrane compositions were investigated by varying the ratio of PVC, plasticizer, and the ion-exchanger. The potentiometric responses of the membranes are presented in Table 1. As observed, M3 has the best response and was selected in this study to investigate and characterize the potential response characteristics toward the naltrexone cation.

II. *Influence of pH*

In order to study the effect of pH on the electrode response, the membrane potentials were measured for a 1×10^{-3} M naltrexone solution over a pH range of 3.0 to 8.0 and the results are shown in Table 2. As observed, the potential response of the electrode shows the same behavior over a wide range of pH. The results showed that in the range of pH 6.0 to 8.0, the electrode response and the slope of the calibration curve (E versus - log $C_{naltrexone}$) remained constant. However, for lower pH values of the buffer solution, the slope increases and reaches a maximum value at pH 3.0. Therefore, phosphate buffer with pH 3.0 was chosen to achieve the best sensitivity in all measurements. The reason for this behavior can be ascribed to the increasing of the equilibrium concentration of the protonated (cationic) form of naltrexone on decreasing the pH of the solution. On the other hand, in basic solutions, hydroxide ions may react with naltrexone to produce the neutral form of naltrexone, which could not be extracted into the membrane.

Table 2. Influence of pH on the response of the naltrexone-selective electrode

pH	Slope (mV decade^{-1})	Linear Range (M)
3	-29.36	$1 \times 10^{-5} – 1 \times 10^{-3}$
4	-28.20	$1 \times 10^{-5} – 1 \times 10^{-3}$
5	-27.81	$1 \times 10^{-5} – 1 \times 10^{-3}$
6	-24.73	$1 \times 10^{-5} – 1 \times 10^{-3}$
7	-19.24	$1 \times 10^{-5} – 1 \times 10^{-3}$
8	-17.20	$1 \times 10^{-5} – 1 \times 10^{-3}$

III. *Selectivity Study*

The selectivity of a potentiometric sensor is one of the most important parameters. In order to study the selectivity of membrane ion selective electrode toward naltrexone with respect to different interfering ions, the selectivity coefficients $K_{A,B}^{pot}$ were evaluated according to IUPAC guidelines, using the separate solution method (SSM)[42]. The selectivity coefficients measured by separate solution method was calculated using the following equation:

$$\log K_{A,B}^{pot} = \frac{E_B - E_A}{S} + [1 - Z_A / Z_B] \log a_A \quad (1)$$

where a_A is the activity of naltrexone, Z_A and Z_B are the charges of naltrexone and interfering ion, S is the slope of the calibration graph (mV/-log $C_{naltrexone}$), and E_A and E_B are the potential values observed for the same concentration of naltrexone and interfering ion (1×10^{-3} M, pH 3.0), respectively.

The resulting selectivity coefficients are summarized in Table 3. As observed, none of the interfering drugs

significantly influence the potentiometric response of the proposed PVC-membrane sensor toward the naltrexone ion.

IV. *Calibration Curve, Response Time and Life Time*

The potentiometric responses of the prepared ion selective electrode were studied for naltrexone in the concentration range of 1.0×10^{-7} to 1.0×10^{-3} M, pH 3.0 at 25.0°C (Figure 2A). The calibration curve, as illustrated in Figure 2B, was achieved in the concentration range of 1.0×10^{-5} to 1.0×10^{-3} M with a sub-Nernstian slope of -29.36 ± 0.40 mV per decade. The limit of detection determined from the intersection of two linear segments of the calibration graph was 5×10^{-6} M. This relationship can be described with the following linear regression equation in the mentioned concentration range:

$$E = -29.36\ pC_{naltrexone} + 124.9 \qquad (R^2 = 0.998) \qquad (2)$$

The response time is an important factor for ion-selective electrodes. The response time was recorded at different concentrations of naltrexone in the sample solution. The potentiometric response of sensors was recorded by changing the solution from lower (1.0×10^{-5} M naltrexone) to higher (1×10^{-3} M naltrexone) concentrations (Figure 3). The response time for the electrode to reach the final equilibrium value was different in different concentrations. The response time of the sensors was found to be less than 7 s at various concentrations of the test solution.

Table 3. Values of selectivity coefficients of naltrexone-selective electrode

Interfering Ion	Log K
Na^+	-1.75
K^+	-2.00
Cu^{2+}	-3.23
Fe^{2+}	-3.20
Cr^{3+}	-3.56
Pb^{2+}	-3.09
Co^{2+}	-3.45
Morphine sulfate	-1.26
Naloxone HCl	-1.40
Codeine phosphate	-1.86
Tramadol HCl	-2.17
Dextromethorphan HBr	-4.97
Cetirizine diHCl	-4.54
Thioridazine HCl	-8.88
Propranolol HCl	-3.35
Lidocaine HCl	-1.67
Diltiazem HCl	-3.85
Diphenhydramine HCl	-4.57

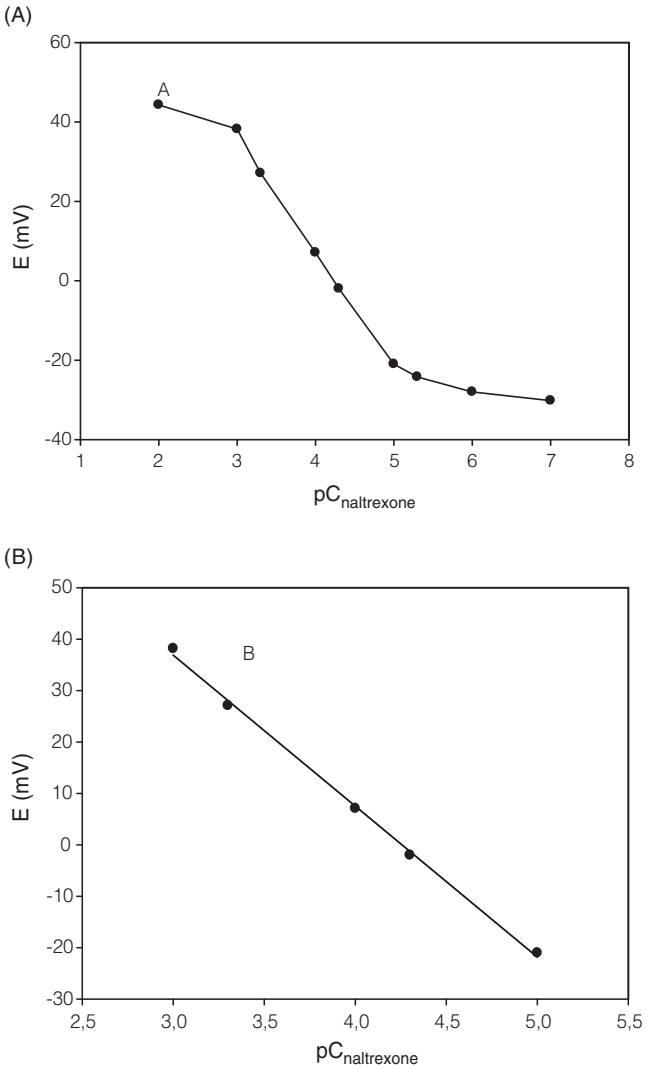

Figure 2. (A) Response behavior of naltrexone-selective electrode in different concentrations, (B) Calibration curve for the naltrexone -selective electrode.

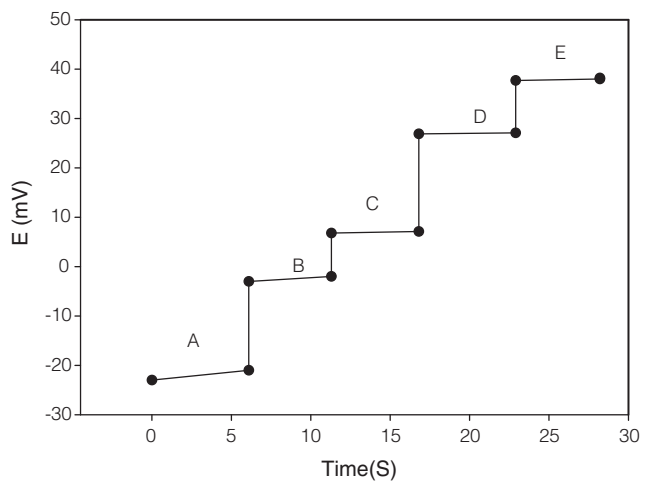

Figure 3. Response time of the electrode: (A) 1.0×10^{-5}, (B) 5.0×10^{-5} (C) 1.0×10^{-4} (D) 5.0×10^{-4}, and (E) 1.0×10^{-3} M of naltrexone.

The lifetime of ion-selective electrodes mainly depends on the type of ionophores and plasticizers used and the number of times it is used[43]. The lifetime of the sensor was worked out by performing calibrations periodically with standard solutions and calculating the slopes over the concentration ranges of 1.0×10^{-5} to 1.0×10^{-3} M of naltrexone. The experimental results showed that the lifetime of the present sensor was about 40 days. During this time, the detection limit and the slope of the electrode remained almost constant. Subsequently, the electrochemical behavior of the sensor gradually deteriorated, which may be due to aging of the polymer (PVC) and the plasticizers. Therefore, the sensor can be used for at least 40 days, without considerable change in its response towards naltrexone.

V. *Analytical Validation*

The analytical method was validated according to the International Conference for Harmonization (ICH) guidelines[44], under the optimized experimental conditions. Repeatability (intra-day) was tested with three EMF responses for each of the three sample solutions containing low, middle and high concentrations in linear ranges, and intermediate precision (inter-day) of the method was evaluated by considering low, middle, and high concentrations in linear range in three days. The CV (RSD%) values shown in Table 4 were satisfactory. The accuracy of the proposed method was studied by recovery experiments in low, middle and high concentrations in linear range (n = 9). The results showed good recoveries between 97.51% and 107.45% with %RSD values ranging from 2.34 - 9.83% across the concentration ranges studied.

VI. *Pharmaceutical Analysis*

The application of proposed method was evaluated for the determination of naltrexone HCl Capsules (Alhavi). For the analysis of a sample in capsule form with a labeled value of 25.00 mg, an amount of 24.24 mg was found, which represents a good recovery of 96.97% with RSD of 5.09% (n = 5).

Recovery and precision studies were evaluated in lower, middle and higher level concentrations of pharmaceutical solutions using standard addition method. For the added concentration of NAL in the range of 0.066 - 0.198 mM, recovery results between 97.92 ± 5.60% - 101.77 ± 6.27% were obtained (n = 5).

The naltrexone ion selective electrode using membrane was proven to be useful for the assay of naltrexone content of pharmaceutical preparations, using the direct reading of potential in turbid solutions without filtering or extraction.

VII. *Analysis of Naltrexone in Real Samples*

To assess the applicability of the proposed sensor to real samples, an attempt was made to determine naltrexone in urine and human plasma. Each sample was analyzed by standard addition, using the sensor without further pretreatment and extraction steps. Recovery and precision studies were evaluated in low, middle and high levels of concentration range. The results are given in Table 5, which show that the

Table 4. Precision (intra and inter day) in standard solutions of naltrexone HCl

Concentration (M)	Intra day (n = 3)		Inter day (n = 3)	
	Mean response ± SD	CV(%)	Mean response ± SD	CV(%)
1×10^{-5}	-21.1 ± 1.1	5.53	-21.7 ± 1.2	5.50
1×10^{-4}	7.1 ± 0.2	2.92	7.2 ± 0.2	3.96
1×10^{-3}	38.2 ± 0.9	2.35	37.7 ± 1.1	2.93

Table 5. Accuracy and precision in spiked human plasma and urine (n = 5)

Sample	Concentration (M)	% Recovery $(C_{exp}/C_{teo}) \times 100$	CV(%)
Plasma			
	1×10^{-5}	104.64	9.64
	1×10^{-4}	103.41	1.37
	1×10^{-3}	100.79	1.29
		Mean ± SD (102.95 ± 1.97)	
Urine			
	1×10^{-5}	105.87	2.99
	1×10^{-4}	106.59	2.79
	1×10^{-3}	104.44	1.34
		Mean ± SD (105.63 ± 1.10)	

amount of naltrexone recovered is good, thereby reflecting the usefulness of the proposed sensor. As can be seen in Table 5, the results are in the acceptable level according to US FDA Guidance for Industry; Bioanalytical Method Validation. The major advantage of the proposed sensor as applied to plasma and urine is that no prior extraction step is required.

CONCLUSIONS

The ion selective electrode based on plasticized PVC membrane containing NaTPB for naltrexone was prepared on the surface of graphite electrode and was revealed to have a sub-Nernstian response over a concentration range of 1×10^{-5} - 1×10^{-3} M with LOD of 5×10^{-6} M and accuracy of 102.34 ± 4.86%. The proposed potentiometric sensor offers other advantages of fast response, reasonable selectivity, low cost and elimination of pretreatments or separation steps before pharmaceutical and real samples analysis, which result in the successful and direct determination of naltrexone in pharmaceutical preparations and biological fluids.

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