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Potentiometric Sensor for Determination of Tramadol Hydrochloride in Pharmaceutical Preparations and Biological Fluids

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Abstract

A potentiometric tramadol-selective electrode based on the ion-association of tramadol hydrochloride (TDCl) with phosphomolybdic acid (TD-PM) is developed. The electrode exhibits a Nernstian slope of 58.3±0.7 mV/decade for tramadol ions in the concentration range 2.0×10^{-6} - 1.0×10^{-1} M with the limit of detection of 1.3×10^{-6} M. The electrode has a fast and stable response time 5-8 s, good reproducibility and it can be used in pH range of 1.8-6.1. The present electrode show good discrimination of tramadol hydrochloride from several inorganic, organic ions, sugars and some common drug excipients. These characteristics of the electrode enable it to be used successfully for determination of tramadol hydrochloride in its pharmaceutical preparations and biological fluids (urine and milk).

Keywords: Tramadol hydrochloride; Ion-selective electrode; Potentiometry; Ppharmaceutical analysis

Introduction

In recent years, the potentiometric membrane sensors have been widely used in pharmaceutical analysis. [1-3]. This is mainly because of low cost, simple design, wide linear concentration range, low detection limit, adequate selectivity, high accuracy, and applicability of the selective electrodes to colored and turbid solutions [4].

Tramadol hydrochloride, (1RS,2RS)-2-[(dimethylamino) methyl]-1-(3-methoxyphenyl) cyclohexanol HCl (Figure 1), is a centrally acting opioid analgesic in wide spread clinical use throughout the world. It is a synthetic analogue of codeine but has a relatively low affinity for opiate receptors and has not been classified as a controlled substance [5]. Few analytical methodologies, for determination of tramadol in pharmaceutical dosage forms were proposed. They are mainly based on spectrophotometry, HPLC, capillary isotachophoresis [6] and potentiometry [7-11]. Only a few reports [7-11] have been devoted to the construction of ion selective electrodes for tramadol hydrochloride. However, most of these electrodes have not been very fruitful as the developed electrodes have either one, two, or in some cases, all of the following problems, (1) high detection limit, (2) a narrow working concentration range, (3) long response time, (4) serious interferences from various cations, sugars, and amino acids.

This work describes the construction, performance characteristics and analytical application of a novel tramadol ion-selective sensor based on ion-association of tramadol hydrochloride with phosphomolybdic acid as electroactive materials and dibutyl phthalate as a plasticizer. The electrode presented in this paper shows a wide concentration range, low limit of detection, good Nernstain slope and high selectivity over a wide variety of other cations.

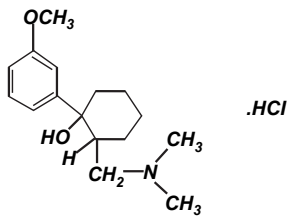

Figure 1: The chemical structure of tramadol hydrochloride.

Material and Methods

Chemicals

Tramadol hydrochloride TDCl was obtained from Pharmacare LTD company (Ramallah- Palestine). The pharmaceutical preparations containing TDCl (Tramal, tablets, capsules, drops and ampoules) were obtained from local drug stores. 2-nitrophenyl octyl ether (2-NPOE), dioctyl phthalate (DOP), dibutyl phthalate (DBP), tris(2-ethylhexyl) phosphate (TEPh), dioctyl sebacate (DOS), tributyl phosphate (TBPh) and dibutyl butyl phosphonate (DBBPh) as well as metal salts were purchased from Aldrich and used as received. Phosphomolybdic acid (PMA) were obtained from Sigma.

Apparatus

Potentiometric measurements were carried out with a digital millivoltmeter (SR-MUL-3800). pH measurements were made with a digital pH meter (Wissenschaftlich-Technische Werkstatten GmbH (WTW)- Germany) under stirring conditions at room temperature (25.0±1.0°C).

The performance of the electrode was investigated by measuring the emfs of TD solutions with a concentration range of 10^{-7}–10^{-1} M by serial dilution. Each solution was stirred and the potential reading was recorded when it became stable, and plotted as a logarithmic function of TD cation activities.

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Preparation of ion-pair

An ion-pair was made from tramadol hydrochloride (TD) with phosphomolybdic acid (PMA) according to a previously reported method [7]. This ion-pair was used as the active substance for preparing the PVC membrane electrode of tramadol hydrochloride.

Preparation of the electrode

The membranes were prepared as previously described [12]. In each case, after curing, a small disk (7.5 mm) was punched from the cast film and mounted on the body of a homemade electrode body. The electrode TD-PM was filled with a solution that is 10^{-1} M NaCl and 10^{-2} M TDCl and preconditioned by soaking in 10^{-3} M TDCl.

Selectivity coefficient determination

Separate solution method (SSM) and the Matched Potential Method (MPM) [13] were employed to determine the selectivity coefficients of the potentiometric sensor towards different species.

In the SSM, the potential of a cell comprising a working electrode and a reference electrode is measured in two separate solutions, one containing the drug ions, E_1, and the other containing the interferent ions (J), E_2, and S is the slope of the calibration graph. These values were used to calculate the selectivity coefficient from the following equation:

$$\text{Log } K^{pot}_{Drug,J^{z+}} = \frac{E_2 - E_1}{S} + \log[\text{Drug}] - \log[J^{z+}]^{1/z}$$

In MPM, specified amounts of TDCl in the range of $2x10^{-4}$ to $2x10^{-5}$ M were added to a reference solution of TDCl, and the corresponding potential change (ΔE) was measured. In a separate experiment, 1.0 x 10^{-1} M of the interfering ion (J) was successively added to an identical reference solution until the change in potential matched the ΔE value. The values of were then calculated using the following equation:

$$\text{Log } K^{pot}_{Drug,J^{z+}} = \frac{a_{Drug}}{a_J}$$

Where the a_j is the activity of the added interferent.

Sample preparation

Tramadol hydrochloride was determined in different formulations (100mg TDCl/capsule, 100mg TDCl/tablet, 100mg TDCl/2mL-ampoule and 100mg TDCl/1mL Tramal drops).

Samples of tramadol hydrochloride (ampoules, drops, capsules and tablets) ranging from 5.0 x 10^{-6} to 1.0 x 10^{-3} M TDCl were determined by the standard addition, potentiometric titration, and the calibration curve methods respectively. 1.5mL-ampoule or 5mL of drops solution were transferred to a 50mL volumetric flask and diluted to the mark with distilled water. 3 tablets or capsules were powdered and homogenized as described previously [14]. A portion of the powdered mass equivalent to about 150.0mg of TDCl was accurately weighed and dissolved in 50mL of distilled water. This procedure produced 0.01 M solutions of tramadol in these preparations (ampoules, drops and tablets or capsules). Different volumes of these solutions equivalent to 5.0 x 10^{-6} to 2.5 x 10^{-3} M were taken and analysed by the above methods using the present electrodes. Each analysis was repeated 5 times.

Sample analysis

The standard addition method in which small increments (10-100 μl) of (0.1 mol L-1) TDCl solution were added to 50.0mL aliquot-samples of various concentrations (5.0 x 10^{-6} to 2.5 x 10^{-3} M) TDCl was applied. The change in potential at (25 ± 0.1°C) was recorded after each increment and these data were used to calculate the concentration of TDCl in the drug samples using the following equation.

$$C_x = \frac{C_x X V_s}{(V_x + V_s)10^{\Delta E/S} - V_x}$$

where C_x is tramadol concentration in the testing sample, C_s is the concentration of the standard, V_x and V_s are the corresponding volumes, S is the slope of the electrode response, and ΔE is the change in potential [15]. The potentiometric titration of different volumes of 1.0 x 10^{-3} M and 1.0 x 10^{-2} M TDCl solution: 3-10mL equivalent to 0.9 -30mg, were transferred to a 25mL beaker, and titrated with a standard solution of Na-TPB using the prepared TD-PM as indicator electrode. The end points were determined from the S-shaped curve. In the calibration graph method, different amounts of TDCl were added to 50mL of water comprising a concentration range from 1.0 x 10^{-7} to 1.0 x 10^{-1} M and the potential was the measured recorded using the present electrode. Data were plotted as potential versus logarithm of the TD^+ activity and the resulting graph was used for subsequent determination of the concentration of drug samples [16].

Analysis of spiked urine and milk samples

The samples (5ml of urine and 10mL of humanized cow milk) were spiked with tramadol hydrochloride and left stirred for 5 min, transferred to a 25-mL volumetric flask and completed to the mark with distilled water to give 1.0×10^{-5} to 1.0×10^{-4} M TDCl. These solutions were subjected to the standard additions method or the calibration graph method for determination TDCl [12].

Results and Discussion

The key factor of the applicability of ion-sensitive electrodes, for tramadol cation, is the selectivity to the ion being determined compared to other ingredients of the medicinal forms. Therefore both the scientific and the practical challenge are the basis and the validation of the ways of the selectivity control by varying the membrane composition. Membranes of different compositions were prepared as shown in Table 1.

Electrode characteristics

In preliminary experiment, membranes with and without ion-exchanger were constructed. The membrane with no exchanger showed no measurable response toward TD^+, whereas, in the presence of the proposed ion-exchanger TD-PM, the optimized membrane demonstrated Nernstian response and remarkable selectivity for

$R_{(s)}$	LOD	S	Composition (%)			
			Plasticizer	PVC	I.P	No.
20	$6.5x10^{-5}$	46±2.1	53.0(DBP)	47.0	--	1-
10	$6.8x10^{-6}$	49±1.5	53.0(DBP)	46.9	0.1	2-
8	$4.1x10^{-6}$	56±0.9	53.2(DBP)	46.5	0.3	3-
5	$1.3x10^{-6}$	58±0.3	53.0(DBP)	46.5	0.5	4-
10	$2.0x10^{-6}$	57±1.4	53.0(2-NPOE)	46.5	0.5	5-
10	$2.8x10^{-6}$	55±0.5	53.0(DOP)	46.5	0.5	6-
15	$6.2\ x10^{-6}$	53±0.9	53.0(DOS)	46.5	0.5	7-
10	$3.1x10^{-6}$	57±0.2	53.0(TEPh)	46.5	0.5	8-
23	$4.1x10^{-5}$	47±2.3	53.0(DBBPh)	46.5	0.5	9-

I.P: Ion-pair, S: slope (mV/decade), LOD: limit of detection, R(s): response time(s)

Table 1: Composition and slope of calibration curves for TD-PM membrane electrode.

TD^+ over several common inorganic and organic cations. Thus, several membranes of varying nature and ratios of ion-exchanger/PVC/plasticizer were prepared for the systematic investigation of the membranes compositions. A few membranes with miscellaneous compositions were made and tested. The composition containing 0.5%, of the ion-pair (membrane No. 4) produced the best response as shown in Table 1. Higher ratios (> 0.5%) were insoluble in THF. Membrane with no ion-exchanger has lower sensitivity and selectivity with poor repeatability.

It is well known that the sensitivity and selectivity obtained for a given ion-selective electrode depends not only on the nature of ionophore used, but also significantly on the membrane composition and the properties of the plasticizer. After the evaluation of six solvent mediators (2-NPOE, DOP, DBP, TEPh, DOS, TBPh and DBBPh), it was observed that DBP with relatively moderate viscosity, lipophilicity, molecular weight and low dielectric constant, produced the best results as shown in table 1 and Figure 2. Therefore, DBP was used as a suitable plasticizer for further studies.

The results, given in Table 1, indicate that sensor no. 4, composed of 53.0% DBP, 46.5% PVC and 0.5% ion exchanger (TD-PM), gives the best sensitivity, with a Nernstian slope of 58±0.3 mV/decade and detection limit of $1.3x10^{-6}$ M over a relatively wide dynamic range ($2.0x10^{-6}$ to $1.0x10^{-1}$ M) of TD^+ ions. Therefore, this composition was used to study various operation parameters of the electrode. The electrochemical performance characteristics of this electrode were systematically evaluated according to the IUPAC recommendations [17].

Response time, reversibility and repeatability of the electrode

Dynamic response time is an important factor for an ion-selective electrode. In this study, the practical response time was recorded by changing solution with different TD^+ concentration from 1.0×10^{-5} to 1.0×10^{-1} M. The static response time of the electrode over the concentration range was ≈5 s as shown in Figure 3. To evaluate the reversibility of the electrode, a similar procedure in the opposite direction was adopted. with measurements performed in the sequence of high-to-low sample concentrations and the results are shown in Figure 4. It shows that the potentiometric response of the electrode is reversible and the time needed to reach the equilibrium is about 8s.

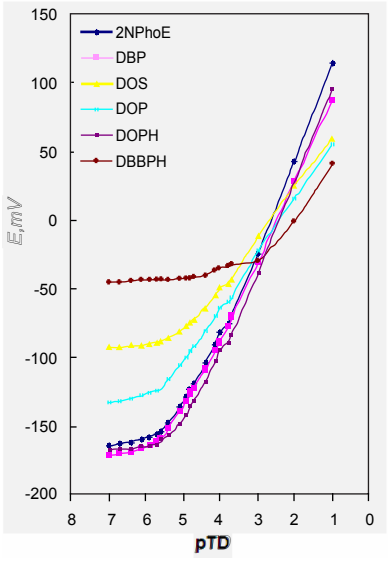

Figure 2: Effect of different plasticizers on the response of TD-PM electrode.

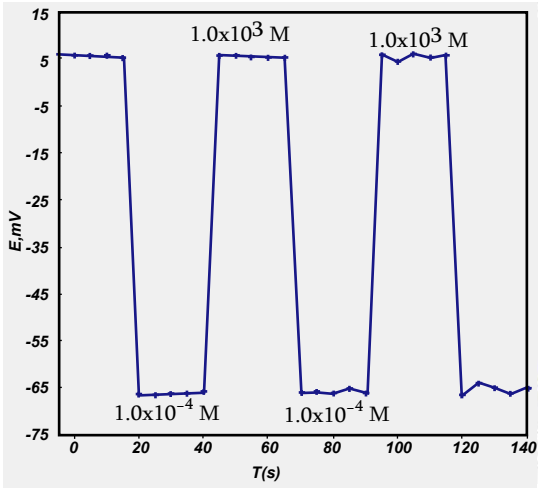

Figure 3: Dynamic response of the TD-PM electrode for several high-to-low sample cycles.

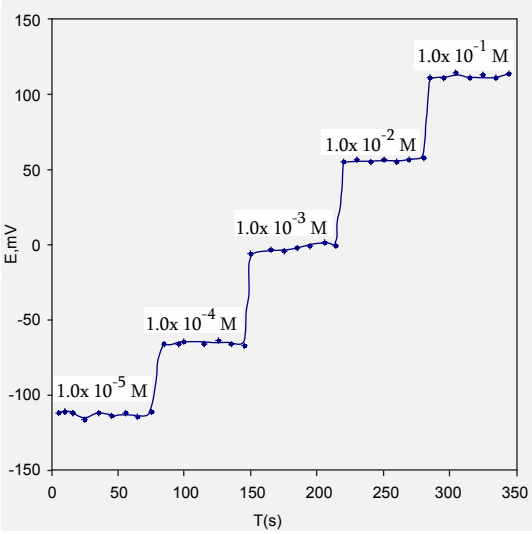

Figure 4: Typical potential-time plot for response of TD-PM electrode.

The reproducibility of the electrode was also examined by immersing the electrode alternatively in $1.0x10^{-4}$ and $1.0x10^{-2}$ M of tramadol hydrochloride solutions. The standard deviation of measuring emf for five replicate measurements was found to be 1.582 for 1.0×10^{-4} M solution and 0.305 for 1.0×10^{-2} M solution. This indicates the excellent repeatability of the potential response of the electrode.

Effect of temperature

To study the thermal stability of the electrode, calibration graphs were constructed at different test solution temperatures of the test solution covering the range 20–60°C [18]. The slope, response time, concentration range and the detection limit obtained from the calibration plots as corresponding to each temperature is given in

Table 3. From Table 2, it is obvious that no appreciable change in the calibration characteristics was observed in the temperature range 20–60°C.

Lifetime

A freshly prepared TD-PM electrode can be used after soaking in 1×10^{-3} M of drug solution for at least 15 min. The effect of soaking on the performance of the TD-PM was studied by soaking the electrode in 10^{-3} M solution of tramadol hydrochloride for variable intervals of time starting from 30 min reaching 37 days. The slopes of the electrode were observed to show gradual decrease after 30 days. Therefore, The proposed electrode can be used for one month without any considerable change in potential response.

Internal solution effect

The internal reference solution affected substantially the characteristics of the electrodes. High NaCl concentrations without TD^+ ions yielded electrode with no response. The best results in terms of characteristics of the sensor were obtained with an inner solution containing 1.0 x 10^{-2} M of TDCl and 1.0 x 10^{-1} M NaCl solution. These results might be due to the fact that the Donnan equilibrium was reached at the interface membrane/inner solution and an electrical potential was generated (Donnan potential) that is necessary to develop the membrane potential. This was probably not the case when the inner solution contained NaCl [19].

T(c)	S	C.R.	LOD	R(s)
20	57±0.8	2.2×10^{-6}-1.0×10^{-1}	1.7×10^{-6}	5
25	58±0.3	2.0×10^{-6}-1.0×10^{-1}	1.3×10^{-6}	5
30	58±0.7	2.0×10^{-6}-1.0×10^{-1}	1.3×10^{-6}	7
35	57±1.1	2.8×10^{-6}-1.0×10^{-1}	1.7×10^{-6}	7
40	56±0.9	3.1×10^{-6}-1.0×10^{-1}	2.1×10^{-6}	8
45	56±0.3	3.1×10^{-6}-1.0×10^{-1}	2.3×10^{-6}	7
50	56±1.1	3.5×10^{-6}-1.0×10^{-1}	2.5×10^{-6}	7
60	55±0.7	3.8×10^{-6}-1.0×10^{-1}	2.5×10^{-6}	10

T(c): temperature, S: slope (mV/decade), C.R.: concentration range (M) LOD: limit of detection (M), R(s): response time(s)

Table 2: characteristics of TD-PM electrode at different temperature.

Interfering ions	MPM	SSM
K^+	1.2×10^{-3}	2.8×10^{-3}
Na^+	9.6×10^{-5}	5.5×10^{-3}
Co^{2+}	7.5×10^{-4}	3.5×10^{-3}
Li^{2+}	5.7×10^{-4}	2.9×10^{-3}
Ni^{2+}	6.5×10^{-4}	3.8×10^{-3}
Mg^{2+}	5.4×10^{-4}	8.7×10^{-4}
Ca^{2+}	9.5×10^{-4}	4.1×10^{-3}
Cu^{2+}	8.4×10^{-4}	3.5×10^{-3}
Zn^{2+}	4.4×10^{-4}	2.8×10^{-3}
Cr^{3+}	7.2×10^{-4}	1.6×10^{-2}
Ampicilline sodium	4.5×10^{-4}	3.9×10^{-3}
Diclophinic sodium	2.6×10^{-4}	6.9×10^{-5}
Captopril	5.5×10^{-4}	3.3×10^{3}
Spiramycine	1.8×10^{-3}	1.7×10^{-2}
Dioctylsulfosuccinate	4.5×10^{-4}	9.6×10^{-4}
Spectinomycine Hcl	8.9×10^{-4}	1.5×10^{-3}
D-Fractose	-	2.5×10^{-5}
D- Galactose	-	5.5×10^{-5}
Maltose	-	6.9×10^{-5}
Glucose	-	2.8×10^{-5}
Ascorbic acid	5.4×10^{-4}	4.0×10^{-4}
L-Histidine	4.5×10^{-4}	3.7×10^{-3}
Glycine	4.9×10^{-4}	1.9×10^{-4}

Table 3: Selectivity coefficient for TD-PM electrode.

Selectivity of the electrodes

The potentiometric selectivity coefficient of an electrode, as one of the most important characteristics, is defined by its relative response for the primary ion over the other ions present in the solution [20]. The separate solution method (SSM) is recommended by IUPAC to determine the selectivity coefficient of the ISE [13]. SSM is based on Nickolsky-Eisenman equation. However, it has been shown that this method suffers some limitations in terms of the values for ions of unequal charges, a non-Nernstain behavior of interfering ions [21].

Therefore another method named the "matched potential method (MPM)" was recommended especially when the primary ion and/or the interfering ion dissatisfy with the Nernst response or when the involved ions are unequal in charge [22]. The resulting values, presented in Table 3, show that these sensors display significantly high selectivity for tramadol over many common organic and inorganic compounds, drugs, sugars, amino acids as well as some anions.

In pharmaceutical analysis, it is important to test the selectivity toward the excipients and the fillers added to the pharmaceutical preparations. Tramadol pharmaceutical formulations, mainly tablets, contain common excipients such as lactose, glucose, sucrose, starch, stearic acid, magnesium stearate and microcrystalline cellulose. The interference of some of these excipients was explored and measured. It is found that they cause minor effect on the function of the electrode as shown in Table 4. It is worth mentioning that measurements performed on tablets showed accurate results as high as 98.5% indicating that these excipients made negligible effect on the performance of the electrode. Comparing the selectivity coefficient values obtained for the investigated electrodes in both SSM and MPM methods collected in Table 3, makes obvious that there is a measurable difference between the values for each interfering ion obtained in both cases. The values of selectivity coefficients obtained using MPM method are more reliable. It is noticed that the results of selectivity tests on interfering monovalent ions are similar to those of tramadol ion. However, the bivalent and trivalent cations produce different results from the two methods. This is reasonable considering that the SSM depends on the charge and gives inaccurate results.

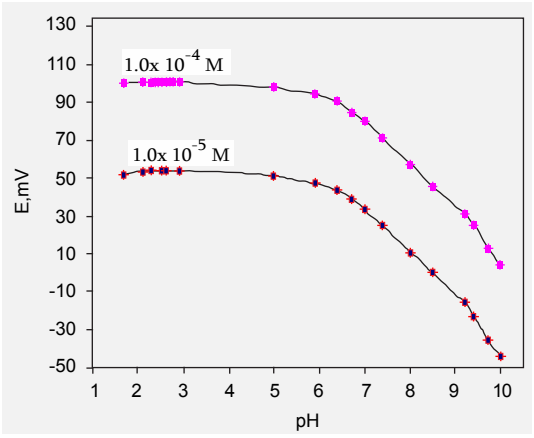

Figure 5: Effect of pH on response of TD-PM response.

samples	M				
	Taken	Found	X ± S.E	F-values	t-Values
Capsule					
P	1.00 x10^{-2}	1.03 x 10^{-2}	103.0 ± 0.035	3.25	1.25
S	5.00 x10^{-6}	4.88 x 10^{-6}	97.6± 0.019	2.54	2.13
C	7.50 x10^{-5}	7.41 x 10^{-4}	98.8 ± 0.079	1.58	2.55
Ampoule					
P	1.00 x10^{-3}	1.01 x 10^{-3}	101.0± 0.058	1.54	1.88
S	1.50 x10^{-5}	1.52 x 10^{-5}	101.3± 0.071	2.11	1.23
C	1.00 x10^{-4}	9.91 x 10^{-5}	99.1± 0.035	3.12	1.15
Tablet					
P	5.00x10^{-4}	4.93 x 10^{-4}	98.6 ± 0.012	3.56	2.45
S	1.00x10^{-5}	1.00x 10^{-5}	100.0± 0.015	2.89	1.58
C	2.00x10^{-5}	2.02 x 10^{-5}	101.0 ± 0.013	2.77	1.11
Drops					
P	1.00x10^{-3}	1.02x 10^{-3}	102.0± 0.045	3.87	2.51
S	1.00x10^{-5}	9.75 x 10^{-6}	97.5± 0.020	3.01	2.79
C	5.00 x10^{-4}	5.02 x 10^{-4}	100.4 ± 0.011	1.59	1.77
urine					
S	1.00 x10^{-5}	1.03 x 10^{-6}	103.0± 0.044	4.21	3.24
C	1.00 x10^{-4}	9.72 x 10^{-5}	97.2± 0.020	3.98	3.18
milk					
S	1.00 x10^{-5}	1.02 x 10^{-5}	102.0± 0.032	3.88	3.56
C	1.00x10^{-4}	9.62 x 10^{-5}	96.2± 0.039	4.12	3.22

P: potentiometric titration, C: calibration curve, S: standard addition method. The number of replicate measurements = 4. X±S.E.: recovery±standard error. R.S.D. relative, standard deviation. The critical value of F = 9.28 and the critical value of t = 3.707.

Table 4: Determination of TDCl in different samples.

However, the MPM gave more accurate ones as it is independent of the charge of the ion.

Effect of pH

Wide application of an ISE requires the knowledge of the pH range of the functioning of given electrode. The medium acidity may be affects the state of an ion associate and other membrane components [23]. In order to study the effect of pH on the performance of the sensor, the potentials were determined at two concentrations (1.0 × 10-3 and 1.0 × 10-2 M) of TD+ ions as a function of pH. The pH of the solution was varied by the addition of NaOH and HCl.

As can be seen from the results shown in Figure 5, the potential variation due to pH change is considered acceptable in the pH range 1.5–6.5. Nevertheless, at pH values higher than 6.1, the potential decreases gradually, which can be attributed to the formation of the free tramadol base in the test solution.

Analytical applications

The proposed sensor was employed for the assay of tramadol hydrochloride content in tablets, capsules, drops and ampoules by the standard additions, the calibration curve and potentiometric titration methods. The results are satisfactory considering the consistency and low standard deviation as shown in Table 4.

In pharmaceutical analysis, it is important to test the selectivity toward the excipients and the fillers added to the pharmaceutical preparations. Fortunately, such materials mostly do not interfere. This is clear from the results obtained for the pharmaceutical preparations (Table 4) that these excipients do not interfere.

The TD-PM was used as indicator electrode in the potentiometric titration of TDCl with NaTPB, and the resulting titration curve is shown in Figure 6. As seen, the amount of TD ion can be accurately determined with this electrode.

Tramadol is rapidly and almost completely absorbed after oral administration and has a bioavailability of 65–70% due to first-pass metabolism. Approximately 10–30% of the parent drug is excreted unmetabolised in the urine. In addition [24]. The possible risks to the neonates and infants should always be carefully considered, regardless of the fact that usually low drug concentrations may be found in the milk. It is estimated that 0.1% of the original dose of tramadol passes into milk [25]. Therefore, it is necessary to estimate

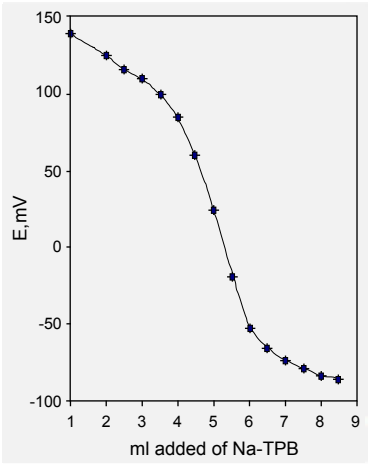

Figure 6: Titration of 5mL of a 0.001 M tramadol hydrochloride solution with a standard solution of 0.001 M Na-TPB.

tramadol in various samples such as urine, and humanized milk. Cosequently, a variety of these biological fluids were analyzed for tramadol using the standard addition method with the prepared TD-PM electrode.

In the present method TDCl was determined in urine and humanized cow milk samples spiked with known amounts of the drug applying the standard additions technique to overcome the matrix effects in these real samples.

The performance of the method was also assessed by calculation of the t- and F-values in comparison to the official method [26]. Mean values were obtained in a student's *t*- and *F*-test at 95% confidence limits for corresponding degrees of freedom [27], and the results showed in table 4 that the calculated *t*- and *F*-values did not exceed the critical values.

Conclusion

Tramadol hydrochloride was determined in pharmaceutical products as well as in biological fluids by using a new PVC-membrane electrode. The proposed PVC-electrode based on Dc-PM ion-exchangers as the electroactive compounds might be useful detectors and interesting alternatives for the determination of $[TD^+]$ in different real samples. The sensor displays a Nernstian response of 58 ± 0.3 mVdecade^{-1}, offers a wide linear response range (2.0×10^{-6} to 1.0×10^{-1} M), provides a low detection limit of 1.3×10^{-6} M, shows a fast response time (5 s), and exhibits excellent selectivities from several inorganic, organic ions, sugars and some common drug excipients.

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