Research article

Drug Testing and Analysis

Received: 7 December 2010 Revised: 13 March 2011 Accepted: 14 March 2011 Published online in Wiley Online Library: 3 May 2011

(www.drugtestinganalysis.com) DOI 10.1002/dta.287

Determination of pethidine hydrochloride using potentiometric coated graphite and carbon paste electrodes

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A new approach for lowering the detection limit of a pethidine ion-selective electrode is presented. A coated graphite (CGE) and carbon paste (CPE) electrodes for pethidine ions based on pethidine-phosphotungstate (PD-PT) as ion-pair complex are described. The sensors exhibit a Nernstian slope of 58.1 and 54.2 mVdecade^{-1} for pethidine ion over a wide concentration range from 2.6 × 10^{-7} to 1.0 × 10^{-2} M and 2.1 × 10^{-6} to 1.0 × 10^{-2} M with a detection limit of 1.8 × 10^{-7} M and 7.3 × 10^{-7} M for pethidine coated graphite (PD-CGE) and pethidine carbon paste electrode (PD-CPE), respectively. These sensors exhibited a fast response time (about 5–8 s) and good stability. The standard electrode potentials, E°, were determined at different temperatures and used to calculate the isothermal temperature coefficient (dE°/dT) of the PD-CGE and PD-CPE, which was 0.0062 and 0.0071 V/°C, respectively. Selectivity coefficients, determined by matched potential method (MPM) and separate solution method (SSM), showed high selectivity for pethidine hydrochloride (PDCl) over a large number of inorganic cations, organic cations, sugars, urine components, and some common drug excipients. The sensors were applied for determination of PDCl in ampoule and in spiked urine samples using potentiometric determination, standard addition and the calibration curve methods. The results obtained were satisfactory with excellent percentage recovery comparable and sometimes better than those obtained by other routine methods for the assay.

Keywords: potentiometry; carbon paste electrode; pethidine; analyzed sample; coated wire electrode

Introduction

Pethidine (meperidine hydrochloride) (ethyl, 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride) [50-13-5] (Figure 1) is a potent opiate analgesics, which has been employed in the treatment of a variety of medical conditions.[1] Pethidine hydrochloride (PDCl) is also used as an illicit drug and therefore it is placed on the schedule II controlled substances list (drugs that have acceptable medical use and have high potential for abuse) in the United States and many other countries. Pethidine is also prescribed as a substitute for heroin,[2] and often used medically as a postoperative analgesia. In sports, athletes often take far higher doses of drugs than have been given for therapeutic use or in clinical studies to excel in competition. They have been barred for use by the International Olympic Committee and other sports organizations.[3] Therefore, determination of pethidine has important practical meanings. Several sophisticated analytical methods were reported to determine the pethidine cation, such as high performance liquid chromatography (HPLC),[4,5] gas chromatography,[6] gas chromatography in combination with mass spectrometry (GC–MS),[7,8] and spectrophotometry.[9] The reported methods for the estimation of PDCl are mainly chromatographic or spectrophotometric. In spite of the high sensitivity of these methods, they are very expensive, involve the use of complex procedure with several sample manipulation, and require long analysis time. Besides, none of them are easy to automate.

Potentiometric methods with ion-selective electrodes (ISEs) have proved to be effective for the analysis of pharmaceutical formulations and biological samples, because these sensors offer the advantages of simple design, construction, and manipulation, reasonable selectivity, fast response time, applicability to coloured and turbid solutions and possible interfacing with automated and computerized systems.[10–13] With these properties in mind, it is suggested that ISEs be used as more desirable alternatives.

A number of ISEs based on PVC membrane[14–18] employing different ion-pairs, have been made for determination of pethidine ion. These PVC membranes are based on pethidine-phosphotungstate (PD-PT), phosphomolybdate, silicotungstate, tetraphenylborate and reineckate. The detection limits of these electrodes range from 8.2 × 10^{-7} to 1.0 × 10^{-5} M. The linear response covers the range 5.0 × 10^{-6} – 1.0 × 10^{-2} M to 1.0 × 10^{-5} – 1.0 × 10^{-3} M with a slope range from 51.8 to 56.7 mV per decade.

Studies have shown the flux of ions from the membrane, in contact with the inner electrolyte solution that contains a salt of the primary ion, towards the sample causes the concentration in the contacting aqueous layer to be ca. 10^{-6} M. Consequently, the lower detection limit was found to be around 10^{-6} M.[19–21] Despite some remedies, the internal solutions still pose a major hindrance in the miniaturization of the devices. Therefore, some

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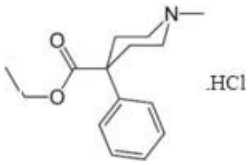

Figure 1. Chemical structure of pethidine hydrochloride.

new sensing systems, such as solid-contact (coated wire) and carbon paste electrodes (CPE) have been proposed.[22,23]

In a coated-wire electrode, the polymer membrane is directly cast on the solid surface, with no internal reference solution being interposed. This type of sensors eliminated the internal filling solution provides new advantages, for instance, good mechanical stability, simplicity, and possibility of miniaturization.[24]

CPE are mixtures prepared from graphite powder and various water-immiscible organic liquids of non-electrolytic character packed at the end of a teflon holder in contact with a copper wire thus eliminating internal solution. CPE have several advantages such as chemical inertness, robustness, renewability, stable response, low ohmic resistance and no need for internal solution.[23]

The advantages of coated wire and CPE have attracted the attention of researchers in recent years.[25–27]

To the best of our knowledge, no coated wire or CPE for the detection of pethidine ions have been reported to date.

In this work, coated graphite (CGE) and modified CPE based on PD-PT as ion-exchanger were prepared, optimized, and checked at different concentration ranges for pethidine ions. The results obtained using these electrodes surpass the published electrodes. The detection limit was lowered to 1.8×10^{-7} and 7.3×10^{-7} M, the concentration range $2.6\times10^{-7}-1.0\times10^{-2}$ and $2.1\times10^{-6}-1.0\times10^{-2}$ M, the slopes 58.1 and 54.2 for PD-CGE and PD-CPE, respectively. These electrodes were used successfully for determination of pethindine cation in ampoules and urine samples.

Experimental

Reagents and solutions

PDCl was obtained from General Administration of Pharmacy, Ministry of Health (Gaza, Palestine) as 100 mg/2-ml ampoule produced by Pharmazeutische Produkte Althofstrasse 12 5432 Neuenhof/AG (Switzerland) company. Graphite powder, 2-nitrophenyl octyl ether (2-NPOE), dioctyl phthalate (DOP), dibutyl phthalate (DBP), tris(2-ethylhexyl) phosphate (DOPh), as well as metal salts were purchased from Aldrich and used as received. Phosphotungstic acid (PTA) and Poly(vinylchloride) (PVC), sodium tetraphenyl borate (NaTPB), and tetrahydrofuran (THF) were purchased from Merck.

Apparatus

Potentiometric and pH measurements were made with a Pocket pH/mV Meters, pH315i (Wissenschaftlich-Technische Werkstatten GmbH (WTW), Weilheim, Germany). The saturated calomel electrode (SCE) was used as reference electrode for potential measurements and was obtained from Sigma-Aldrich Co. (St Louis, MO, USA). The emf measurements with the CGE and CPE were carried out with the following cell assemblies:

Hg, Hg_2Cl_2(s), KCl(sat.)||sample solution/membrane/graphite wire.

Hg, Hg_2Cl_2(s), KCl(sat.)||sample solution|carbon paste electrode.

Preparation of ion-exchanger complex

An ion-exchanger complex was made by mixing equal quantities of 1.0×10^{-2} M of PDCl and 3.3×10^{-3} M of phosphotungstic acid (PTA) or 1.0×10^{-2} M sodium tetraphenyl borate (Na-TPB) according to a previously reported method.[28] The product settled for 5 h and the precipitates formed were filtered off, washed thoroughly with distilled water, dried at room temperature, ground to fine powders and used as the active substances for preparing the sensors of PDCl.

Preparation of the electrodes

Preparation of graphite-coated electrode

A pure graphite rod of 1 mm diameter and 12 cm in length was insulated leaving 2 cm at one end for coating and 1 cm at the other end for connection. The coating solution was prepared by dissolving 0.5% PD-PT, 51.0% PVC, and 48.5% DOP in 5 ml THF. The polished surface of the graphite rod was coated with active membrane by dipping the exposed end into the coating solution and allowing the film to dry in air for about 1 min. The process was repeated until a plastic film of approximately 1 mm thickness was formed (about 10 times). The prepared electrode was preconditioned by soaking for 15 min in 10^{-3} M PDCl solution.

Preparation of carbon paste electrode

Modified CPE was prepared according to a previously reported method.[23,29] The paste was prepared by thoroughly mixing weighed amounts of 0.5% PD-PT, 49% high purity graphite, and 50.5% 2-NOPE (as shown in Table 2) in plastic Petri dishes until a uniformly wet paste was obtained which was used for sensor construction. Electrode bodies were made from 1-ml polypropylene syringes (3mmi.d.), the tips of which had been cut off with a cutter. The mixture was packed in the end of the syringe. Electrical contact to the carbon paste was made by a copper wire. A fresh electrode surface was obtained by squeezing out a small amount of paste and scraping off the excess against a conventional paper then polishing the electrode on a smooth paper to obtain a shiny appearance. The electrode was used directly for potentiometric measurements without pre-conditioning.

Selectivity of the sensor

Potentiometric selectivity factors of the electrodes were evaluated by applying the matched potential method (MPM)[30] and the separate solution method (SSM) According to the MPM, the activity of (PD) was increased from $a_A = 1.0\times10^{-5}$ M (reference solution) to $a_A^{\sim} = 5.0\times10^{-5}$ M, and the change in potential (ΔE) corresponding to this increase were measured. Next, a solution of an interfering ion of concentration a_B in the range $1.0\times10^{-1}-1.0\times10^{-2}$ M is added to new 1.0×10^{-5} M (reference solution) until the same potential change (ΔE) was recorded. The selectivity factor, $K_{A,B}^{MPM}$ for each interferent was calculated using the following equation:

$$K_{A,B}^{MPM} = \frac{a_A^{\sim} - a_A}{a_B} \quad (1)$$

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.

Table 1. Composition and Response Characteristics of PD-electrodes

Composition (%)								
Ion-exchanger		PVC	Plasticizer	Slope (mV/decade)	Linear Range (M)	Detection Limit(M)	R.S.D	$R_{(s)}$
Graphite electrode								
PD-PT			DOP					
1-	–	48.5	51.5	50.3	$8.6 \times 10^{-6} - 1.0 \times 10^{-2}$	6.5×10^{-6}	0.45	12–15
2-	0.5	48.5	51.0	58.1	$2.6 \times 10^{-7} - 1.0 \times 10^{-2}$	1.8×10^{-7}	0.32	8–10
3-	1.0	48.2	50.8	56.4	$8.3 \times 10^{-7} - 1.0 \times 10^{-2}$	6.2×10^{-7}	1.03	8–12
4-	2.0	47.8	50.2	51.2	$1.7 \times 10^{-6} - 1.0 \times 10^{-2}$	8.7×10^{-7}	1.25	10–12
PD-TPB								
5-	0.5	48.5	51.0	57.4	$4.6 \times 10^{-7} - 1.0 \times 10^{-2}$	3.1×10^{-7}	0.78	10–12
6-	1.0	48.2	50.8	56.5	$9.1 \times 10^{-7} - 1.0 \times 10^{-2}$	7.7×10^{-7}	1.18	10–15
7-	2.0	47.8	50.2	53.4	$2.1 \times 10^{-6} - 1.0 \times 10^{-2}$	9.1×10^{-7}	1.02	10–15
Carbon paste electrode								
Ion-exchanger	graphite	2-NPOE						
PD-PT								
8-	–	48.5	51.5	40.8	$1.7 \times 10^{-4} - 1.0 \times 10^{-2}$	8.3×10^{-5}	0.73	20–25
9-	0.5	48.5	51.0	54.2	$2.1 \times 10^{-6} - 1.0 \times 10^{-2}$	7.3×10^{-7}	1.09	5–8
10-	1.0	48.2	50.8	50.9	$5.3 \times 10^{-6} - 1.0 \times 10^{-2}$	3.0×10^{-6}	1.13	8–12
11-	2.0	47.8	50.2	48.2	$5.7 \times 10^{-6} - 1.0 \times 10^{-2}$	4.2×10^{-6}	1.25	10–12
PD-TPB								
12-	0.5	48.5	51.0	49.2	$2.6 \times 10^{-5} - 1.0 \times 10^{-2}$	1.3×10^{-5}	0.98	15–20
13-	1.0	48.2	50.8	47.1	$3.2 \times 10^{-5} - 1.0 \times 10^{-2}$	1.7×10^{5}	0.58	12–15
14-	2.0	47.8	50.2	47.7	$3.8 \times 10^{-5} - 1.0 \times 10^{-2}$	1.0×10^{-5}	1.18	15–18

$R_{(s)}$: response time(s), RSD: Relative standard deviation (five determinations).

These values were used to calculate the selectivity coefficient $K^{Pot}_{PD,J^{z+}}$ from the following equation:

$$K^{Pot}_{PD,J^{z+}} = \frac{E_2 - E_1}{S} + \log[PD] - \log[J^{z+}]^{\frac{1}{z}} \quad (2)$$

Determination of PDCl in ampoule sample

Potentiometric titration method

The potentiometric titration of different volumes of 1.0×10^{-3} M and 1.0×10^{-2} M PDCl solution: 5–10 ml equivalent to 1.42–28.4 mg, were transferred to a 25-ml beaker, and titrated with a standard solutions of Na-TPB and PTA using the prepared PD-sensors as indicator electrodes. The end points were determined from the S-shaped curve.

Calibration graph method

In the calibration graph method, different amounts of PDCl were added to 50 ml of water comprising a concentration range from 1.0×10^{-7} to 1.0×10^{-2} M and the measured potential was recorded using the present electrodes. Data were plotted as potential versus logarithm of the PD^+ activity and the resulting graph was used for subsequent determination of unknown drug concentration.[31]

Standard addition method

The standard addition method in which small increments (10–100 µl) of (0.1 M) PDCl solution were added to 50-ml aliquot-samples of various concentrations (5.0×10^{-6} to 1.0×10^{-5} M) PDCl was applied. The potential after each increment was recorded at 25 ± 0.1 °C and used to calculate the concentration of TDCl in the drug samples.

Analysis of spiked urine samples

The samples (5 ml of urine) were spiked with PDCl and left stirred for 5 min, transferred to a 25-ml volumetric flask and completed to the mark with distilled water to give 5.0×10^{-6} to 1.0×10^{-5} M PDCl. These solutions were subjected to the standard additions method or the calibration graph method for PDCl determination.

Result and discussion

Characteristics of the electrode

It is a well-known fact that sensitivity, detection limit, linear range, and selectivity coefficients of ion-selective electrodes depend significantly on the nature of the utilized electrode active substance, the other components of the electrode as well as the properties of the solvent mediators employed.

Effect of ion-exchanger

Ion-exchanger complexes used in ion-selective membrane sensors should have rapid exchange kinetics and adequate stability. In addition, they should have appreciable solubility in the membrane matrix and sufficient lipophilicity to prevent leaching from the membrane into the sample solution.[32] The ion-exchanger incorporated in each electrode was an ion-association complex of the drug cation with phosphotungstic acid $H_3PW_{12}O_{40}$ or sodium tetraphenyl borate $(C_6H_5)_4BNa$. These species have different lipophilicities and stabilities. They were used as electroactive materials in CGE and CMCPE. A few membranes or pastes with miscellaneous compositions were made and tested. The results are given in Table 1, from which it can be seen the electrodes

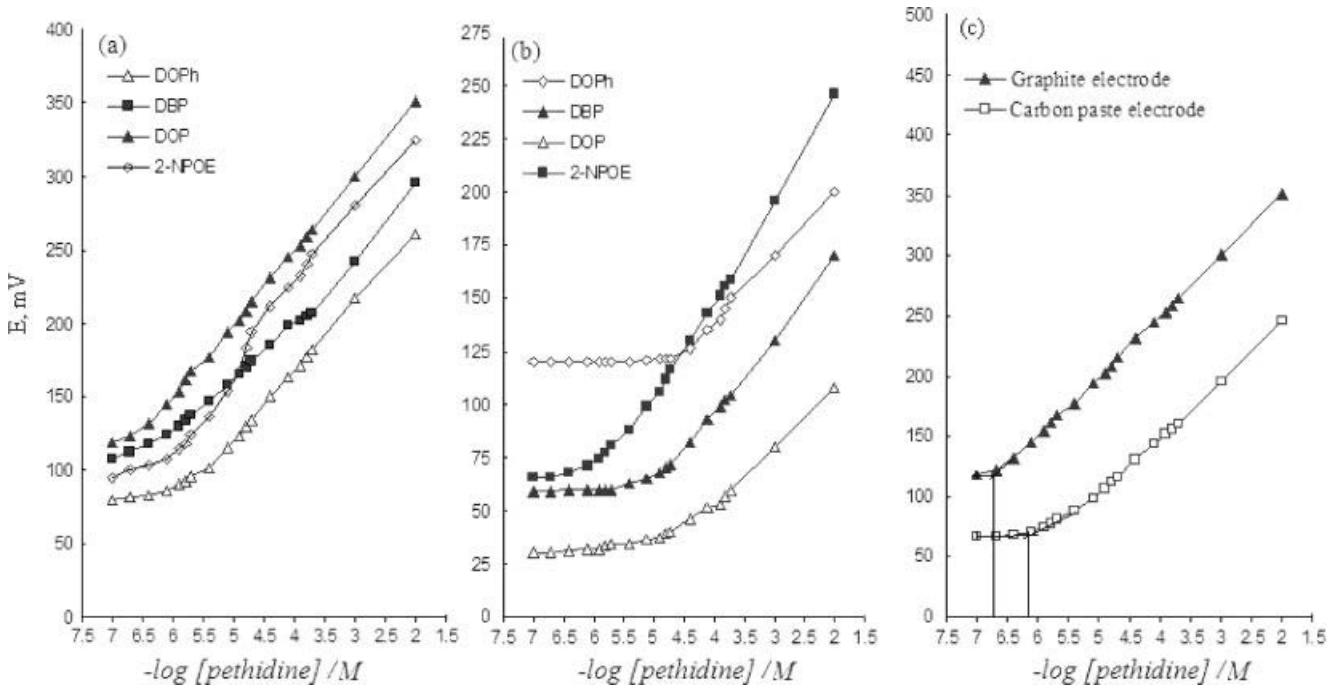

Figure 2. Effect of different plasticizers on the response of (a) PD-CGE, (b) PD-CPE, and (c) calibration graph and limit of detection of PD-CGE and PD-CPE.

containing zero percent of ion-exchanger complexes (sensor # 1 and 8) have lower sensitivity and selectivity with poor repeatability towards pethidine cations. However, in the presence of the ion-exchanger complexes the sensor displayed remarkable selectivity for pethidine cations. The lipophilicity of the first ion-association complex with the drug is more than that of the second complex as it is more bulky and has higher molecular weight. These properties are more similar to those of the drug and decrease leaching from the electrode. Therefore, the membrane or paste containing 0.5% of the PD-PT complex produced the best response (sensors # 2 and 9). Further addition of the ion-exchanger complexes (sensors # 3, 4, 10, and 11) resulted in a little decrease in the response of the electrode that is most probably due to some inhomogenieties and possible saturation of the paste.[33]

Effect of plasticizers

The nature of the plasticizer influences both dielectric constant of the membrane and the mobility of the ionophore.[34,35] The solvent mediator has a dual function, it acts as liquefying agent, enabling homogeneous solubilization and modifying the distribution constant of the ionophore used. For plasticizer to be adequate for use in sensors, it should gather certain properties and characteristics, such as having high lipophilicity, high molecular weight, low vapor pressure, and high capacity to dissolve the substrate and other additives present in the matrix.[36] In exploration for a suitable plasticizer for constructing this electrode, we used four plasticizers, with the values of dielectric constants (which is a measure of the molecular polarity),[34] lipophilicity and molecular weight respectively listed in parentheses, namely, 2-NPOE (ε_r = 23.6, P_{TLC} = 5.9, M.wt. = 251), DOP (ε_r = 5.1, P_{TLC} = 7.0, M.wt. = 391), DBP (ε_r = 6.4, P_{TLC} = 4.5, M.wt. = 278), DOPh (ε_r = 4.8, PTLC = 10.2, M.wt. = 434) in sample electrodes to figure out the plasticizer with the best response.[34,35,37] Pethidine carbon paste electrode (PD-CPE) with 2-NPOE as a solvent mediator produced the best response and DOP was suitable for PD-CGE, as shown in Figure 2. It is not clear why these mediators were the best among those used, but one can say that the outcome of their properties were the most effective on the electrode response. Among the different compositions studied, the electrode containing ion-exchanger complex 0.5 wt% PD-PT, 48.5 wt% graphite, 51.0 wt% 2-NPOE for PD-CPE and the other with 0.5 wt% PD-PT, 48.5 wt% PVC, 51.0 wt% DOP for PD-CGE exhibited the best response characteristics and the lowest detection limit. Therefore, these compositions were used to study various operation parameters of the electrodes. The electrochemical performance characteristics of these electrodes were systematically evaluated according to the International Union of Pure and Applied Chemistry (IUPAC) recommendations.[31]

Response time, reversibility and reproducibility of the electrodes

The response time[31] of the electrodes was obtained by measuring the time required to achieve a steady state potential (within ±2 mV) after successive immersion of the electrodes in a series of TDCl solutions, each having a 10-fold increase in concentration from 1.0×10^{-5} to 1.0×10^{-1} M. As shown in Figure 3, the electrodes yielded steady potentials within 5–8 s. The potential reading stays constant, to within ±1 mV, for at least 5 min.

On the other hand, in order to evaluate the reversibility of the proposed electrodes, the electrodes potentials of 10^{-3}M and 10^{-4}M pethidine solutions were measured alternately in the same solution after making the proper treatment. The results, shown in Figure 3, indicate that the potentiometric responses of the electrodes are reversible.

The repeatability of the potential reading for each electrode was examined by subsequent measurement in 1.0×10^{-3} M TDCl solution immediately after measuring the first set of solutions at 1.0×10^{-4} M TDCl. The electrode potential for five replicate measurements in 1.0×10^{-4} M solution of PD-CPE and PD-CGE are 145 and 250 mV with a standard deviation of 1.44 and 1.50

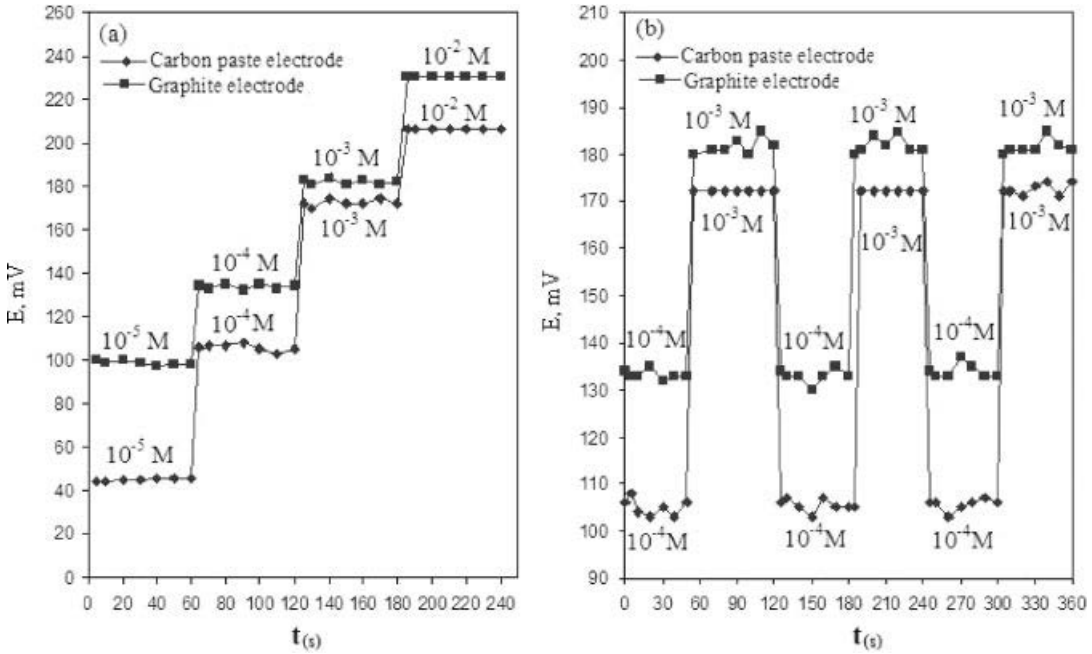

Figure 3. (a) Typical potential-time plot for response of PD-CGE and PD-CPE. (b) Dynamic response of the PD-CGE and PD-CPE for several high-to-low respective measurements.

respectively. The corresponding values in 1.0×10^{-3} M solution were 197 and 305 mV with standard deviation of 0.45 and 0.85. This indicates excellent repeatability of the potential response of the electrodes.

Homogeneity and surface-renewal of PD-CPE

To test paste homogeneity, the proposed electrodes were applied for pethidine determination in a 1.0×10^{-4} M PD(I) solution and the measurement was repeated ten times with a newly exposed surface of the electrode for each one. The average potentials was 54 mV/decade and the relative standard deviation (RSD) is 0.41. These results are reasonable considering the consistency observed in their determination. At a certain surface, the slopes of the calibration graphs were found to decrease slightly from 54.11 to 49.2 mV/decade after seven times of use. This decrease may be attributed to surface contamination and memory effect. Therefore, the electrode surface should be polished to expose a fresh layer for use. Accordingly, a paste of optimum composition and suitable weight (1.5 g) can be used for several months without any deterioration or change in the response of the electrode which is considered a characteristic property (surface renewal) of CPE.

Effect of diverse ions

The separate solution method (SSM) is recommended by IUPAC to determine the selectivity coefficient of the ISE.[30] 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 behaviour of interfering ions.[38] Therefore another method named the 'matched potential method (MPM)' was recommended[32] especially when the primary ion and/or the interfering ion dissatisfy with the Nernst response or when the involved ions have unequal charges.[39] The resulting values, presented in Table 2, show that the electrode display significantly high selectivity for pethidine over many common organic and inorganic compounds, sugars, amino acids and drugs that may taken during treatment with pethidine, except tramadol HCl and lidocaine which showed moderate interference that is likely due to having similar structure. Comparing the selectivity coefficients obtained for the investigated electrodes using SSM and MPM methods, collected in Table 2, makes obvious that there is a measurable difference between the values for each interfering ion obtained in both cases. The MPM produced more reliable values where the presence of the drug makes an interaction between the drug and the interfering ion likely which affects the amount of the free drug in solution.

In pharmaceutical analysis, it is important to test the selectivity towards the excipients such as such as lactose, glucose, sucrose, starch, stearic acid, magnesium stearate, and microcrystalline cellulose and the fillers added to the pharmaceutical preparations. 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 2. Furthermore, no interference was detected for other components of the urine such as urea, creatinine, and uric acids.

Effect of temperature

To study the thermal stability of the sensor, calibration graphs were constructed at different test solution temperatures 20, 30, 40, 50 and 60 °C. From these graphs the standard cell potentials (E^o_{cell}) at pPD = 0 were obtained and plotted versus (t−25), where t is the temperature of the experiment.

The isothermal temperature coefficient (dE^0/dT) of the cell can be calculated from the equation of Antropov:[40]

$$E^o_{cell} = E_{25} + (\frac{dE^o}{dT})(t - 25) \quad (3)$$

The value (dE^0/dT) of the PD-CGE and PD-CPE was found to be 0.0062 and 0.0071 V/°C, respectively. This indicates fairly

Table 2. Selectivity coefficients of various interfering ions for PD-sensors

	MPM		SSM	
Interfering ion	PD-CGE	PD-CPE	PD-CGE	PD-CPE
Na^{+}	4.11×10^{-3}	2.52×10^{-5}	3.72×10^{-5}	1.18×10^{-5}
K^{+}	8.88×10^{-3}	1.71×10^{-4}	1.52×10^{-5}	1.20×10^{-4}
NH^{+}	4.01×10^{-3}	1.41×10^{-4}	4.69×10^{-4}	8.41×10^{-5}
Li^{+}	1.13×10^{-3}	4.34×10^{-4}	1.55×10^{-4}	2.66×10^{-4}
Mg^{+2}	3.41×10^{-2}	1.94×10^{-4}	1.46×10^{-5}	7.81×10^{-6}
Ca^{+2}	7.28×10^{-3}	1.13×10^{-4}	1.28×10^{-5}	2.10×10^{-5}
Ba^{+2}	2.92×10^{-4}	8.02×10^{-4}	1.89×10^{-5}	2.02×10^{-5}
Zn^{+2}	2.81×10^{-3}	2.73×10^{-4}	3.19×10^{-5}	5.11×10^{-5}
Cd^{+2}	6.46×10^{-4}	5.69×10^{-4}	4.93×10^{-5}	8.34×10^{-6}
Co^{+2}	1.08×10^{-3}	1.19×10^{-4}	5.71×10^{-5}	3.85×10^{-5}
Al^{+3}	1.91×10^{-4}	6.98×10^{-4}	1.95×10^{-5}	7.73×10^{-5}
Ce^{+3}	1.24×10^{-3}	1.86×10^{-4}	7.74×10^{-5}	4.30×10^{-5}
Urea	6.24×10^{-4}	1.66×10^{-3}	1.74×10^{-3}	5.30×10^{-3}
Creatinine	2.12×10^{-3}	3.41×10^{-3}	3.24×10^{-3}	4.39×10^{-3}
Uric acid	3.72×10^{-3}	5.33×10^{-3}	3.96×10^{-3}	6.95×10^{-3}
Captopril	5.91×10^{-2}	6.76×10^{-2}	6.11×10^{-2}	2.45×10^{-2}
Tramadol HCL	9.23×10^{-2}	8.86×10^{-2}	8.08×10^{-2}	4.34×10^{-1}
Spectinomycine	4.21×10^{-2}	2.93×10^{-2}	7.22×10^{-2}	2.47×10^{-2}
Diclofine	9.13×10^{-1}	2.53×10^{-2}	5.37×10^{-2}	4.86×10^{-2}
Spiramycine	49.9×10^{-2}	3.41×10^{-2}	1.15×10^{-2}	4.86×10^{-2}
Ephidrine	3.02×10^{-1}	1.27×10^{-2}	3.15×10^{-2}	8.89×10^{-3}
Lidocaine	2.08×10^{-1}	1.27×10^{-1}	7.46×10^{-2}	4.86×10^{-2}
Maltose	–	–	8.37×10^{-7}	5.54×10^{-6}
Glucose	–	–	1.88×10^{-6}	2.47×10^{-6}
Glycine	–	–	5.19×10^{-6}	2.47×10^{-6}
D-Galactose	–	–	3.39×10^{-6}	1.35×10^{-6}
D-Fractose	–	–	6.44×10^{-7}	9.14×10^{-7}

high thermal stability of the electrode within the investigated temperature range and shows no deviation from the theoretical Nernstian behaviour.

Effect of pH

The pH dependence of the potentials of the proposed electrodes was tested over the pH range 2.0–10.0 for 1.0×10^{-4} M PDCl solutions. The acidity was adjusted by adding small volumes of (1.0 M HCl or NaOH) to the test solutions and the variation in potential was followed. As can be seen in Figure 4, the potential response remains almost constant over the pH range 2.5–7.5 and 2.7–6.8 for PD-CGE and PD-CPE, respectively which can be taken as the working pH range of the electrode. However, there is a slight deviation at pH values lower than 2.5 and 2.7 which may be due to H^{+} interference. On the other hand, the potential decreases gradually at pH values higher than 7.5 and 6.8. This drop may be attributed to formation of free pethidine base in the test solution.

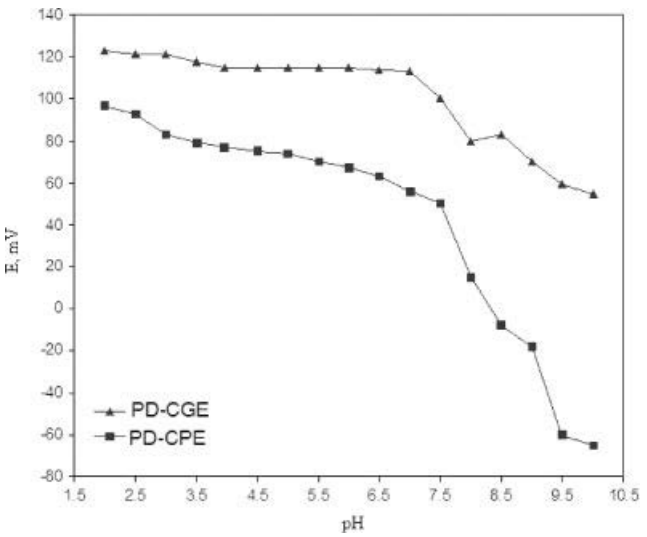

Figure 4. Influence of pH on the response of the PD-CGE and PD-CPE electrodes at 1.0×10^{-4} M.

Study of pethidine binding to bovine serum albumin

Serum albumin is a principal protein component of plasma and is remarkable for its power to bind a wide variety of molecules, including bilirubin, fatty acids, tryptophan, metal ions and numerous drugs.[41] Equilibrium dialysis techniques were used to investigate the interactions of the serum albumin and a number of drugs.[42] In the present work, the results obtained from potentiometric study of interaction of pethidine with bovine serum albumin (BSA) using the currently proposed electrodes are reported. The electrodes' responses in the presence and absence of BSA are shown in Figure 5. Deviation from the Nernst equation in the presence of BSA is due to pethidine-BSA interaction. At low

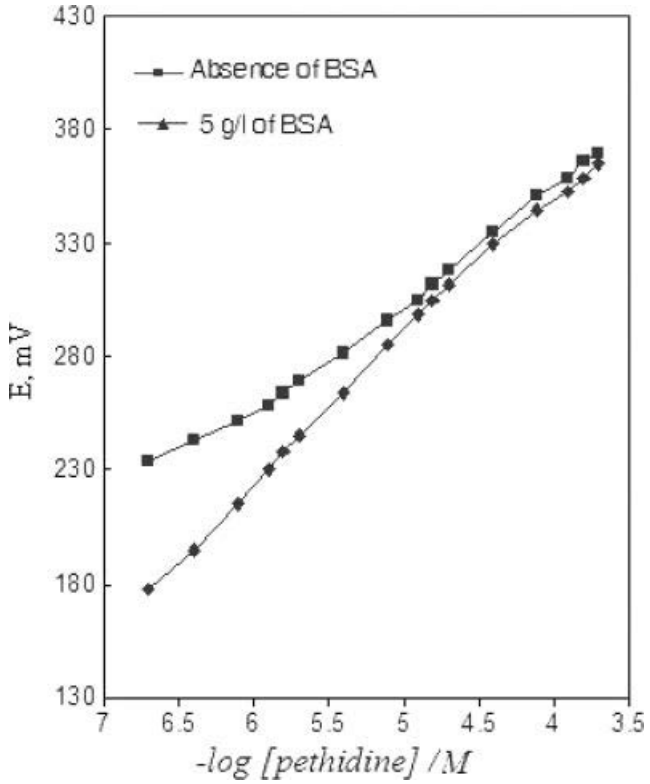

Figure 5. EMF response of PD-CGE in the absence and presence of BSA.

concentration of BSA, there was strong effect on the response of the electrodes which is believed to be due to binding of the drug to BSA and the behaviour is far from Nernstian. However, as more pethidine ions are added, the binding sites on BSA get saturated and the electrodes begin to develop Nernstian response.

Applications

Titration of pethidine solution with PTA and Na-TPB

The PD-CGE and PD-CPE were successfully used as indicator electrodes in the potentiometric titration of 5 ml of 0.01 M (14.2 mg) of PDCl with 0.01 M Na-TPB and 0.0033 M PTA. The method for pethidine ion (PD_+) titration is based on the decrease of (PD_+) concentration by precipitation with PTA and Na-TPB standard solution. As is obvious from Figure 6, the amount of pethidine can be accurately determined from the end point of the titration curve.

Determination of pethidine in ampoules

The proposed electrodes were used in the standard additions and calibration methods for determination of PDCl content in ampoule samples. As can be seen in Table 3, the recovery of PDCl is almost quantitative.

Recovery and determination of pethidine ions in urine

Clinical pharmacological studies indicate that meperidine is metabolized in the liver by hydrolysis to meperidinic acid followed by partial conjugation with glucuronic acid. Meperidine also undergoes N-demethylation to normeperidine, which then undergoes hydrolysis and partial conjugation. When urine pH is uncontrolled, 5–30% of the meperidine dose is excreted as normeperidine and approximately 5% is excreted unchanged.[43] Therefore, it is advisable to devise a method for fast, simple and accurate method to determine meperidine in the urine.

Recovery experiments were conducted by spiking urine samples with appropriate amounts of pethidine ions, and determined by these electrodes using the standard addition method and calibration curve. The results, shown in Table 3, indicate recoveries and RSD values range between 96.0% and 102.3% of pethidine, and 0.53 to 1.33 for the PD-CGE and PD-CPE. It is noted that the results are accurate and reproducible. Thus the sensors can be employed for quantification of pethidine in urine samples.

Statistical treatment of results

The results of applying the above methods are compared with the values obtained from the official method.[44] F test was used for comparing the precisions of the two methods and *t*-test for comparing the accuracy.[45] The calculated F and t-test Table 3 were less than the critical (tabulated) ones. Thus, there is no significant difference between the precisions or the accuracies of the methods at 95% confidence levels.

Comparison of the pethidine selective electrodes

The performance characteristics of the proposed electrodes and those of some reported electrodes are presented in Table 4 for comparison. It is clear that the proposed electrodes are comparable with most of the reported electrodes with regard to working concentration range, response time and low detection limit. Overall evaluation indicates these electrodes are more useful than the other electrodes in such applications.

Conclusions

The proposed coated wire and CPE based on pethidine phosphotungstate as an electroactive ion-exchanger complex might be a useful analytical tool and interesting alternative for the determination of PD ions in ampoules and urine samples. The electrodes show high sensitivity, reasonable selectivity, fast static response, long term stability and applicability over a wide concentration range with minimal sample pretreatment. The electrodes developed are superior as compared with the pethidine selective electrode described in the literature.[14–18]

Acknowledgements

The authors would like to thank professor Salman M. Saadeh (chemistry department, the Islamic university, Gaza, Palestine), Dr Muneer A. Alboursh and Dr Amal Zendah (general administration of pharmacy, Ministry of Health, Gaza- Palestine), Dr. Aleksandar Radu, Adaptive Sensors Group, National Centre for Sensor Research, School of Chemical Sciences, Dublin City University, Dublin 9, Ireland, Prof. Yousry M. Issa and Prof. Hosny Ibrahim (Cairo University -Egypt) for encouragement, support and providing facilities for research.

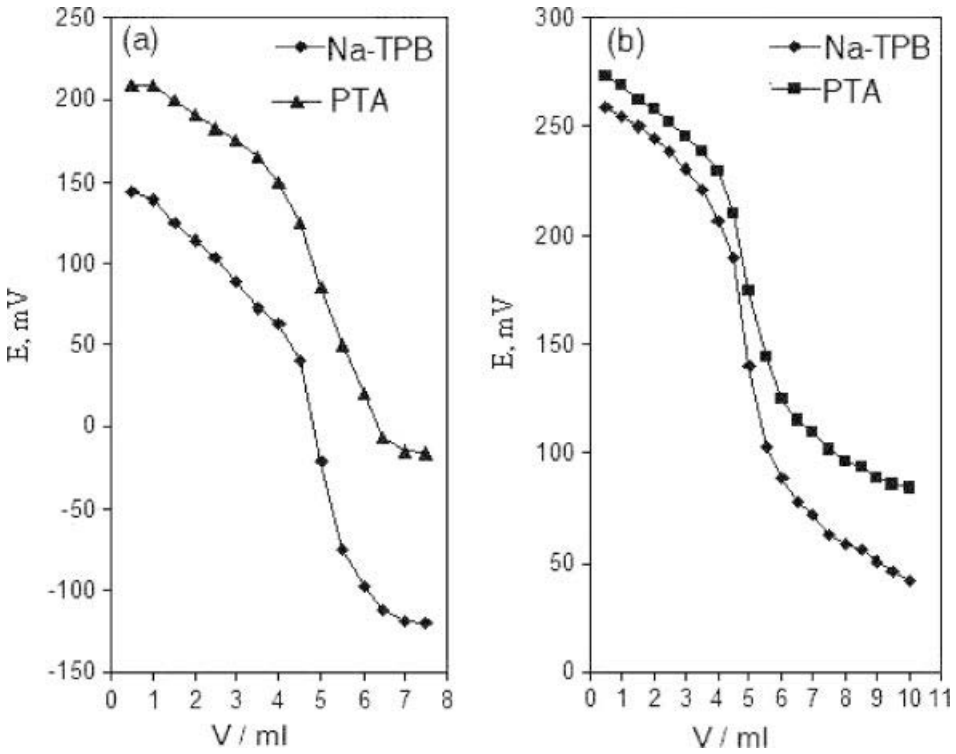

Figure 6. Potentiometric titration of 14.2 mg PDCl with Na-TPB and PTA as titrants using (a) PD-CGE and (b) PD-CPE.

Table 3. Results for determination of PDCl in ampoules and urine samples using PD-CGE and PD-CPE

Sample	PD/mg[a]	Recovery %	RSD[b] %	F-value	t-values
PD-CGE					
Ampoule					
SDM	0.144	98.8	0.53	4.09	2.33
	0.288	100.8	0.87	3.56	2.18
CCM	0.144	100.5	0.59	1.59	0.96
	0.288	97.6	0.96	1.12	0.84
Urine					
SDM	0.144	100.2	0.77	3.12	3.21
	0.288	97.9	1.15	2.96	2.96
CCM	0.144	100.8	0.99	3.32	2.78
	0.288	99.8	1.21	4.89	2.56
PD-CPE					
Ampoule					
SDM	0.248	97.2	0.72	1.85	1.02
	2.480	99.8	0.29	2.48	1.52
CCM	0.355	101.5	0.36	1.35	1.11
	3.550	100.8	0.44	1.28	0.98
Urine					
SDM	0.248	96.0	0.74	4.74	2.14
	2.480	97.8	1.02	3.02	3.25
CCM	0.355	102.3	1.33	4.14	2.85
	3.550	101.4	1.18	3.08	1.98

[a] Milligrams taken of PDCl in ampoules or spiked to urine samples.
[b] The number of replicate measurements = 4.
SDM: standard additions method, CCM: calibration curve method
RSD relative standard deviation,
The critical value of F = 9.28 and the critical value of t = 3.707.

Table 4. Comparison of the proposed pethidine electrodes with published sensors

Reference	S	C. R	LOD	$R_{(s)}$
[14]	55.3	$1.0 \times 10^{-5} - 1.0 \times 10^{-2}$	3.3×10^{-6}	10
[15]	53.7	$1.0 \times 10^{-5} - 1.0 \times 10^{-2}$	9.9×10^{-7}	<30
[16]	51.8	$1.0 \times 10^{-5} - 1.0 \times 10^{-2}$	2.2×10^{-6}	<30
[17]	56.7	$5.0 \times 10^{-6} - 1.0 \times 10^{-2}$	8.2×10^{-7}	<30
[18]	53.5	$1.0 \times 10^{-5} - 1.0 \times 10^{-3}$	4.4×10^{-6}	30
Present work				
PD-CGE	58.1	$2.6 \times 10^{-7} - 1.0 \times 10^{-2}$	1.8×10^{-7}	5–8
PD-CPE	54.2	$2.1 \times 10^{-6} - 1.0 \times 10^{-2}$	7.3×10^{-7}	5–8

C.R.: concentration range (M), LOD: limit of detection (M), S: slope (mV/decade), $R_{(s)}$: response time.

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