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Coated Wire and Multiwalled Carbon Nanotube Composite Coated Wire Sensors for Determination of Chlorpromazine Hydrochloride in Pharmaceutical Preparations.

Riyadh M. Jihad* **Ismael K. Al-Hitti**** **Adawiya J. Hayder*****

* University of Anbar - Education College for Women
** University of Anbar - College of Science
*** University of Technology - Nanotechnology Center

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ABSTRACT

The fabrication and performance characteristics of novel potentiometric sensors for the determination of chlorpromazine hydrochloride are described. The proposed sensors include a coated copper wire sensor and a multiwalled carbon nanotube (MWCNT) composite coated copper wire sensor. The sensors are based on the chlorpromazine-phosphotungstate ion associate as electroactive material. The developed sensors exhibited near nernstian slopes of 53.69 and 57.31 mV concentration decade^{-1} at 25 °C, in the concentration range 5.0 x 10^{-5} – 1.0 x 10^{-2} mol L^{-1} chlorpromazine hydrochloride with limits of detection of 4.8 x 10^{-5} and 4.9 x 10^{-5} mol L^{-1} chlorpromazine hydrochloride for coated copper wire sensor and a (MWCNT) composite coated copper wire sensor, respectively. The proposed sensors exhibited good selectivity for chlorpromazine with respect to a large number of inorganic cations, amino acid and sugars. The developed sensor was successfully applied for the potentiometric determination of chlorpromazine hydrochloride in the pharmaceutical preparations and human urine samples.

Introduction

Chlorpromazine HCl is 10-(3-dimethyl-aminopropyl) - 2 - chlorophenothiazine hydrochloride (figure 1) [1], a dimethyl-amine derivative of phenothiazine. It is tranquilizer which antagonizes dopamine-2 receptors in the central nervous system [2]. It is readily absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism in the gut and the liver. Following oral administration, peak plasma levels are reached in 1-4 hours; following intramuscular injection, peak plasma levels usually occur in (15 - 30 minutes). Chlorpromazine is widely distributed to the body tissue [3].

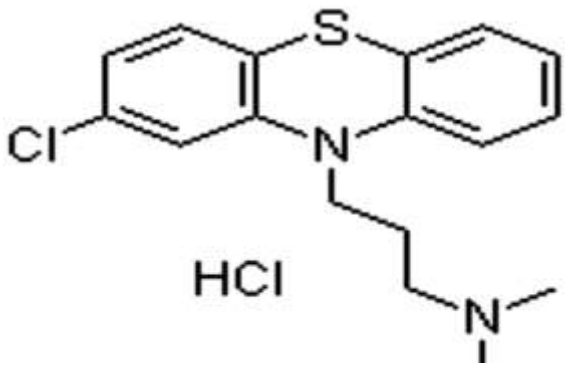

Figure (1): Chemical Structure of Chlorpromazine HCl.

The literature survey showed that Chlorpromazine HCl was determined by several analytical methods include high-performance liquid chromatography [4], liquid chromatography coupled with mass spectrometry [5-8], spectrophotometry [9,10], capillary

* Corresponding author at: University of Anbar - College of Science
Anbar, Iraq.E-mail address:

electrophoresis [11-13], flow injection analysis [14-16], and chemiluminescence [17].In the present study new selective electrode, coated wire sensor has been constructed for the determination of Chlorpromazine HCl in pure form, pharmaceutical preparations and urine samples.

Materials and methods

A. Apparatus

The electrochemical measurements were carried out with Mettler Toledo mV-pH meter (Switzerland) with an indicator electrode in conjunction with double junction Ag/AgCl electrode. An Ag/AgCl wire was used as the internal reference electrode. A combined glass electrode (Mettler Toledo) was used for pH adjustment.

B. Reagents and Materials

All chemicals used were of analytical grade, Distilled water was used throughout this work. Pure grade chlorpromazine HCl and the pharmaceutical formulations (largapromactil 50mg and 100mg) were supplied from SDI, Iraq. The pharmaceutical formulation, Largactil 25mg was supplied from Oubari Pharma, Syria and chlorpromazine Injection was supplied from Renaudin, France. Phosphotungstic acid (PTA) and polyvinyl chloride (PVC) of relatively high molecular weight were from Aldrich. Tetrahydrofuran (THF), dibutyl phthalate (DBPH) and dioctyl phthalate (DOPH) were from Merck, tributyl phosphate (TBP) and o-nitrophenyl phenyl ether (o-NPPE) from Fluka. MWCNT, purity more than 95%, were provided from Center of Nanotechnology, University of Technology, Baghdad, Iraq.

C. Standard drug solution

Stock chlorpromazine HCl solution 5.0x10-2 mol L-1 was prepared by dissolving 0.888g of a drug in distilled water and complete to 50 mL distilled water. Serial dilutions (1.0x10-6-1.0x10-2 mol L-1) were obtained using distilled water.

D. Preparation of ion-pair

The chlorpromazine-PT ion associate was prepared by mixing 150 mL 10-2 mol L-1 chlorpromazine HCl with 50 mL 10-2 mol L-1 PTA solutions. The obtained precipitate was filtered, washed thoroughly with distilled water and dried at room temperature. The composition of the ion associate was found to be 3:1 as confirmed by elemental analysis data obtained. The percentage values found are 15.90, 2.25 and 2.33 and the calculated values are 15.51, 1.82 and 2.13 for C, H and N, respectively.

E. Electrodes assembly

Preparation of plastic membrane electrodes

The membrane composition was studied by varying the percentage of the ion associate, PVC and DBPH, until the optimum composition that exhibits the best performance characteristics were obtained. The membranes were prepared by dissolving the required amount of the ion associate, PVC and DBPH in about 6 mL of THF. Three membrane compositions were prepared. This cocktail was poured into a glass rings struck onto a glass plate and left to dry in air. Disks of the membrane were used to assemble the electrodes by the general procedure [18].

Preparation of MWCNT composite coated copper wire electrode Pure copper wire of 2 mm diameter and of 12 cm in length was insulated by tight polyethylene tube leaving 2 cm at one end for coating and 1 cm at the other end for connection. The polished electrode surface was coated with the active membrane by quickly dipping the exposed end 8-10 times into the coating solution prepared by dissolving optimum ion associate

composition previously described under plastic membrane composition and allowing the film left on the wire to dry in air for about 1 min each time until a plastic film of approximately 0.2 mm thickness was formed. The prepared electrode was preconditioned by soaking for (3 hrs) in 1 × 10-3 mol L-1 drug solution. The electrochemical system of MWCNT composite coated copper wire electrode may be represented as follows: copper wire/ MWCNT composite membrane/ test solution // Ag /AgCl reference electrode.

F. Electrode selectivity

The selectivity coefficients (Kpot CPZ, Jz+) the electrode towards different cationic species (Jz+) were determined by a separate solution method [19]. The following equation was applied.

Log Kpot CPZ Jz+ = (E2-E1)/S + log [CPZ] – log [Jz+]1/z

Where E1and E2 are the electrode potentials in 1.0×10-3 mol L-3 chlorpromazine HCl and interfering ions (Jz+), respectively, and S is the slope in mV.

G. Effect of pH

The influence of the pH on the potential of chlorpromazine fabricated sensors was investigated. The potential was recorded for the standard cell and varying the pH over range from 1-10 by adding small volumes of (0.1-0.01 mol L-1) of each sodium hydroxide or hydrochloric acid separately.

H. Analytical application

1. Determination of chlorpromazine HCl in tablets The contents of ten (largactil 25, largapromactil 50 or largapromactil 100) tablets were accurately weighed and powdered in a morter. The required amounts of powdered tablets to prepare 1.0×10-3 mol L-1 chlorpromazine HCl solutions were dissolved in about 30 mL of distilled water and filtered in a 100 mL measuring flask. The residue was washed three times with distilled water and the volume was completed to the mark by the same solvent. The calibration method was applied for determination of chlorpromazine HCl content in tablets samples using the mentioned sensor.
2. Determination of chlorpromazine HCl in ampoules 710 µL of Chlorpromazine injection (25 mg / mL) was transferred to a (50 mL) volumetric flask and completed to the mark with distilled water. The calibration method was applied for determination of chlorpromazine HCl content in tablets samples using the mentioned sensor.
3. Determination of chlorpromazine HCl in spiked human urine samples The proposed sensors were used for determination of the drugs in urine. Spiking technique was used by adding a small volume of standard solution of drug to 5 mL of blank urine samples of two volunteers in 25 mL volumetric flasks and completed to the mark with distilled water. The drug selective and reference electrodes were immersed and the drug concentration was determined by direct potentiometry.

Results and Discussions

A. Optimization of the sensor

The potential response of a PVC sensor is related to its membrane composition [20-22]. Effect of membrane composition on the potential response of chlorpromazine sensor was investigated. For this purpose, different membrane compositions are tested which most important ones are shown in Table 1. As it can be seen from Table 1, the membrane with composition of 30% PVC, 7% chlorpromazine-PT ion associate and 63% DBPH (no. 3) showed the best potential response. The PVC acts as a regular support

matrix for the plastic membrane ion selective electrode, but its use requires a plasticizer which acts a fluidizer allowing homogeneous dissolution and diffusional mobility of the electroactive complex inside the membrane. Four plasticizers DBPH, DOPH, TBP and o-NPPE, were tested. The results indicated that o-NPPE is the best tested plasticizer. Poor sensitivities for electrodes plasticized by the other plasticizers are due to low distributions of the electroactive complex chlorpromazine-PT in these solvents.

Table 1. Optimization of membrane ingredients

Membrane no.	PVC (%wt.)	CPZ-PT (%wt.)	Plasticizer (%wt.)	Linear range (mol L-1)	Slope (mV decade-1)
1	30	3	DBPH,67	5.0x10-5-5.0x10-3	46.5
3	30	7	DBPH,63	5.0x10-3 5.0x10-5-5.0x10-3	49.5
5	30	7	TBP,63	5.0x10-5-5.0x10-3 5.0x10-5-1.0x10-2	53.5
2	30	5	DBPH,65	5.0x10-5-5.0x10-3	44.8
4	30	7	DOPH,63	5.0x10-3 5.0x10-5-5.0x10-3	50.8
6	30	7	o-NPPE,63	5.0x10-5-5.0x10-3 5.0x10-5-1.0x10-2	54.1

By using the optimum ion associate composition (7% CPZ-PT, with o-NPPE as a Plasticizer) described previously under plastic membrane composition, and using this composition for preparing copper coated wire electrodes, the performance characteristics of the prepared copper coated electrodes were slope 53.69 mV concentration decade-1 at 25 oC. By modifying the coating cocktail of the prepared copper coated electrodes by addition of 1% MWCNT, the composition of the prepared MWCNT composite coated copper wire electrode was 7% ion associate, 1% MWCNT, 30% PVC and 62% o-NPPE, it was found a significant improvement of the performance characteristics of the MWCNT composite coated copper electrodes. The characteristics are slope 57.31 mV concentration decade-1 at 25 oC.

B. Sensor properties

The properties of coated wire sensors are characterized by parameters like measuring range, detection limit, response time, selectivity and lifetime.

The measuring range of a coated wire sensor includes the linear part of the calibration graph as shown in (Fig. 2 and 3). The applicable measuring range of the proposed sensors is between 5.0 x 10-5 and 1.0 x 10-2 mol L-1. By extrapolating the linear parts of the ion-selective calibration curve, the detection limit of an ion-selective electrode can be calculated. In this work, the detection limits of the proposed sensors were 4.8 x 10-5 mol L-1 and 4.9 x 10-5 mol L-1 for coated wire sensor and MWCNT composite coated wire sensor, respectively.

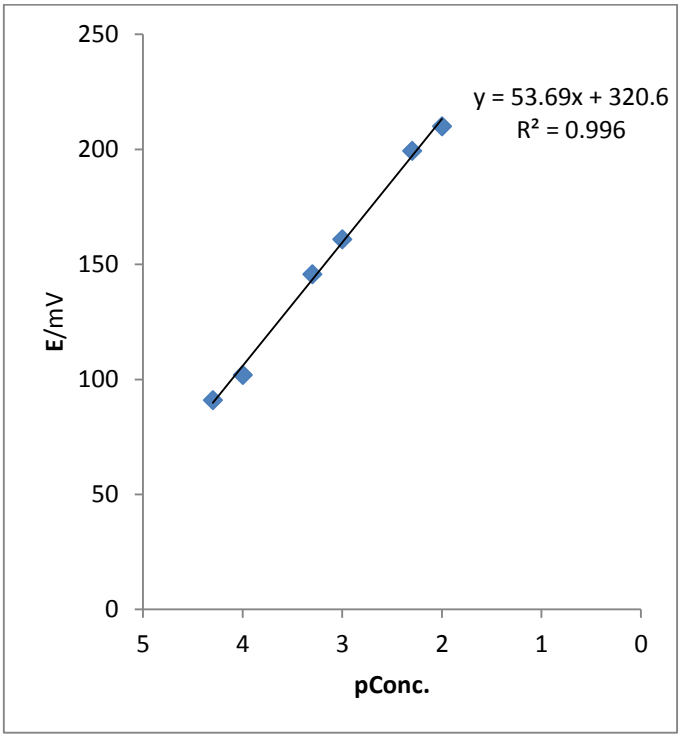

Figure 2. Calibration curve of chlorpromazine coated wire sensor.

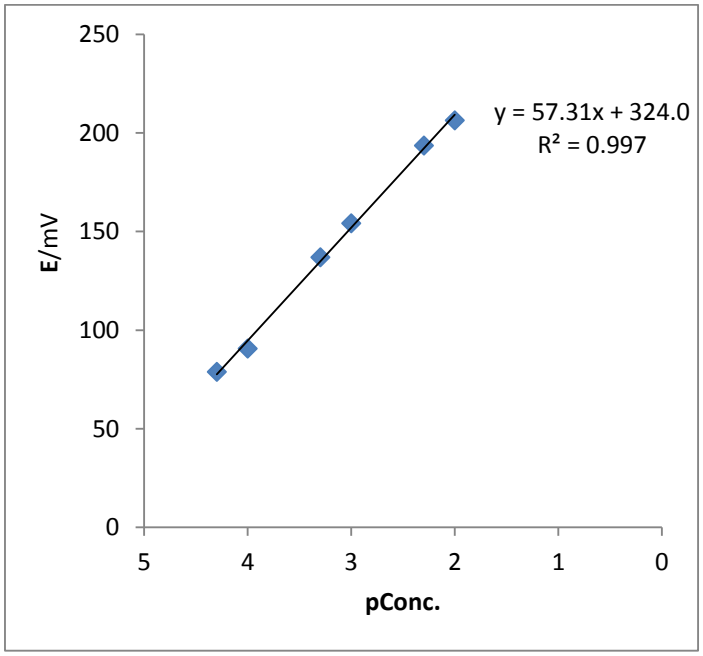

Figure 3. Calibration curve of chlorpromazine MWCNT composite coated wire sensor.

Response time and life time of the developed sensors were monitored. Response time of the CPZ coated wire sensor was less than 20 s and that in the case of MWCNT composite coated wire sensor was less than 18 s . The average response time is the time required for the sensor to reach a stable potential within ± 1 mV of the final equilibrium value. The life time of an electrode is limited by the diffusion of the membrane components from the membrane to the aqueous solution. A Nernstian slope was obtained for a period of seven weeks in the case of coated wire sensor and eight weeks for MWCNT composite coated wire sensor. During this period, the sensors showed no significant deviation in the optimized response characteristics.

C. Potentiometric Selectivity

The selectivity of the ion-pair associates based membrane electrode depends on the selectivity of the ion-exchange process at the membrane-test solution interface and the mobilities of the respective ions within the membrane, and on hydrophobic interactions between the primary ion and the organic membrane. The selectivity coefficients were determined by a separate solution method.

The resulting values, presented in Table 2, show that the sensor display significantly high selectivity for CPZ over many common organic and inorganic compounds. In pharmaceutical analysis, it is important to test the selectivity towards the excipients such as glucose and lactose.

Table 2. Selectivity coefficients of various interfering compounds for chlorpromazine sensors.

Foreign ion	CWS	NCCWS
	- log KpotA,B	
Na+	3.40	3.22
K+	3.42	3.35
NH4+	3.44	3.82
Mg2+	4.72	5.14
Co2+	4.14	4.60
Ni2+	4.37	5.00
Cu2+	3.76	3.95
Zn2+	4.17	4.65
Fe2+	4.33	4.47
Cr3+	4.21	4.33
Glycine	2.13	2.51
Glucose	2.62	2.86
Fructose	2.63	2.35
Maltose	2.43	2.33
Lactose	2.60	2.60

CWS: coated wire sensor.
NCCWS: nano composite coated wire sensor.

D. pH effect on the electrode response

The influence of pH on the potential response of CPZ coated wire and MWCNT composite coated wire sensors was investigated by recording the potential at concentration (1.0 x 10-3 M) of CPZ solution at different pH values. Figures 4 and 5 clearly depict the effect of pH of the test solution on the potential response of the developed sensors. The pH of the solution was varied from (1-10) by the addition of small volumes of HCl and NaOH (0.1- 0.01 M). The results indicate that the investigated sensors showed no pH response out the range (2–7) and (1-7) for the coated wire sensor and MWCNT composite coated wire sensor, respectively.

At higher pH values, the potential is decrease due to the gradual increase in the concentration of the unprotonated CPZ resulting in the precipitation of CPZ base. Accordingly, further studies were carried out at pH 5 by using 0.1 mol L-1 acetate buffer solutions.

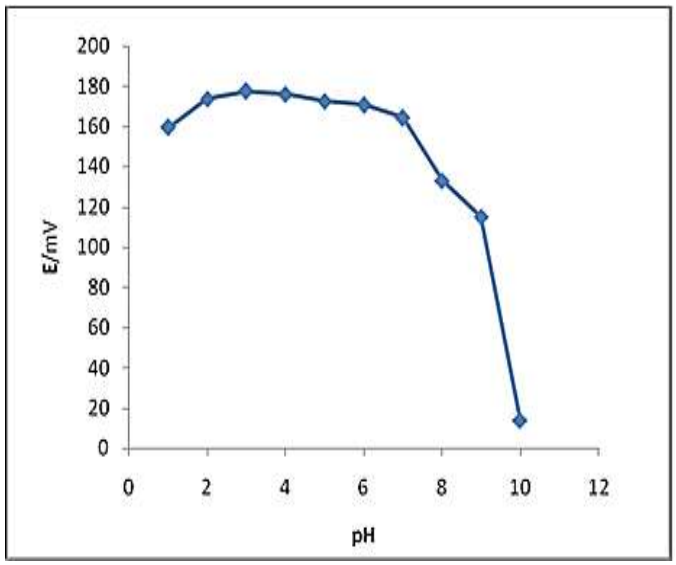

Figure (4) Effect of pH on the cell potential of CPZ coated wire sensor.

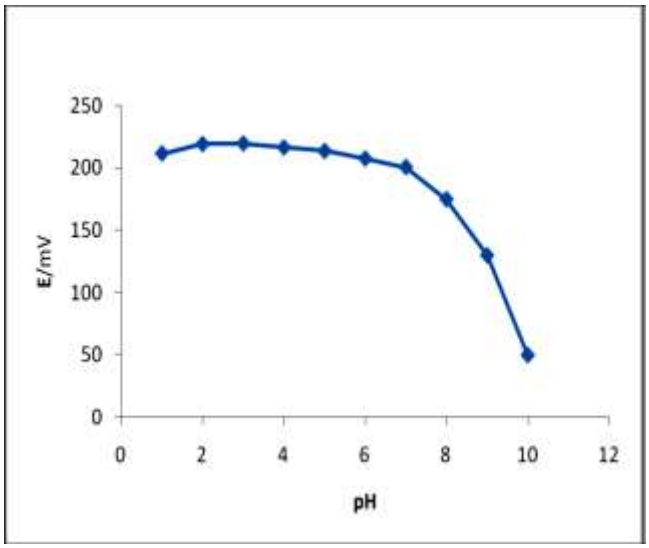

Figure (5) Effect of pH on the cell potential of CPZ-MWCNT composite coated wire sensor.

E. Analytical applications

The developed sensors were applied in the potentiometric determination of chlorpromazine HCl in pure form and the pharmaceutical preparations. The results were compared to those obtained from previously reported spectrophotometric method [23]. The results are illustrated in Table 3. The data indicate a satisfactory agreement between CPZ content determined by the developed sensors and the reference published method. Statistical comparison of the accuracy and precision of the developed method with the reference method was performed using student's t-test and F- ratio tests at a 95% confidence level. The t- and F- values did not exceed the theoretical values.

Table 3. Statistical treatment of the data obtained for the determination of CPZ in pure form by the developed sensors and reference method.

Parameter	CWS	NCCWS	Reference method
Taken	1.0 x 10-3	1.0 x 10-3	1.5 x 10-4
*Recovery/%	101.19	100.73	97
SD	1.157	0.689	1.41
RSD/%	1.143	0.685	1.45
SE/%	0.572	0.342	0.648
t-test (2.35)	2.06	2.12	
F-test (9.12)	1.49	4.19	

*Average of four replicates, SD: standard deviation.
RSD: relative standard deviation, SE: standard error.

The proposed chlorpromazine sensor was used for the determination of content uniformity assay of chlorpromazine HCl in tablets (25, 50, 100 mg/tablet) and injection (25 mg/ml). The content of tablets and injection was calculated from the regression equation for the proposed sensors. The results obtained in Table 4, as the mean % recoveries and relative standard deviations revealed that the described sensor gave good accuracy and high precision for routine quality control analysis.

The sensors proved useful for the determination of chlorpromazine content in biological samples such as spiked human urine. The mean recovery and relative standard deviations were calculated and summarized in Table 5.

Table 4. Determination of chlorpromazine HCl in its pharmaceutical formulations.

sample	CWS			NCCWS		
	Recovery%	RSD%	SE%	Recovery%	RSD%	SE%
Larga.25mg	97.12	0.249	0.124	97.15	0.518	0.259
Larga.50mg	92.25	0.554	0.277	92.76	0.865	0.432
Larga.100mg	95.68	1.107	0.553	95.41	0.866	0.433
Inj.25mg/mL	98.70	0.731	0.366	99.12	0.519	0.259

*Average of four replicates.

Table 5. Determination of chlorpromazine HCl in spiked urine samples.

Sensor	sample	Added	Recovery%	RSD%	SE%
CWS	Urine 1	1.0 x 10-3	94.86	0.924	0.462
	Urine2	1.0 x 10-3	94.66	0.247	0.123
NCCWS	Urine 1	1.0 x 10-3	95.22	0.518	0.259
	Urine 2	1.0 x 10-3	94.83	0.232	0.116

*Average of four replicates.

Conclusions

The proposed sensors based on chlorpromazine phosphotungstate as an electroactive ion exchanger complex might be a useful analytical tool and interesting alternative for the determination of chlorpromazine HCl in pharmaceutical preparations and urine samples. The multiwalled carbon nanotube composite coated copper wire sensor has high sensitivity than the coated wire sensor. The present sensors show high sensitivity, reasonable selectivity, fast static response and applicability over a wide pH range.

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