Haemostatic Agent as New Ionophore for Selective Determination of Copper in Environmental Samples and Pharmaceutical Formulations.

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ABSTRACT

The construction and electrochemical response characteristics of poly vinyl chloride (PVC) membrane sensors for the determination of copper were described. The sensors are based on using of ethamsylate as an ionophore and dioctylphethalate (DOP) as a plasticizer in the PVC matrix. Conventional and graphite membrane sensors were prepared and the performance characteristics are evaluated according to IUPAC recommendations, reveal fast, stable and linear response for copper over the concentration range 1×10^{-6}-1×10^{-2} M and 7×10^{-5} -1×10^{-2} M with cationic slopes of 29.5 and 27.8 mV per concentration decade at pH 5 for conventional and graphite membrane sensors respectively. The potentiometric selectivity data revealed no interference from common cations. The direct potentiometric determination of copper using the proposed sensors gave average recoveries of 99.89 ± 0.9 and 100.04 ± 1.1 for the conventional and graphite sensors, respectively. The sensors are used for direct measurement of copper content in industrial waste water, metal alloys samples from copper factories and pharmaceutical formulations. The developed method was found to be simple, accurate and precise when compared with a reported atomic absorption method.

INTRODUCTION

The introduction of new ion selective electrodes (ISEs) has promoted fundamental developments in potentiometry **(Jain, et. al, 1997)**. Copper is the third most abundant trace element for human, following iron and zinc. Copper has many applications in industry **(Greenwood and Earnshow, 1984)** biological and medical systems (**Marston, 1952; Dadfarnia, and M. Shamsipur; 1992)**. It has relatively non-toxic to mammals, but the intake of large quantities can be toxic. The toxicity is generally attributed to the formation of the aquo-complexes of copper ion (**Sadeghi, et. al, 2003)**. The sources of copper poisoning include beverages from vending machines, brass or copper vessels and sometimes water supplies (**Richter *et. al*., 2001)**. Thus the development of simple, reliable, and low cost techniques for copper determination is essential. Methods in current use for copper quantification in different matrixes include, voltammetry **(Janata and Růžička, 1982)**, spectrophotometry **(Asan, *et al* 2001; Ahmed , *et. al* 2002)**, inductively coupled plasma/mass spectrometry **(Jacintho, et.al, 1981; Zagatto, *et. al*, 1983)**, potentiometry **(Hu, et. al., 1982)**, atomic absorption spectrometry **(Hassan, 1984; Fang, *et. al*. 1984; Wolf and Stewart, 1979),** and stripping voltammetry (**Stankovic, et. al., 2011)**. The commercially used solid state copper electrode based on $CuS-Ag_2S$ has been used for the determination of copper ion although the Cd^{2+}, Fe^{3}, Hg^{2+}, Ag^{+}, S^{2-} and Cl^{-} ions seriously interfere.

Several ionophores have been suggested for the preparation of copper membrane selective sensors (Table 1), some of them including porphyrins **(Gupta, *et al*, 2006)**, ethambutol-copper (II) complex **(Gupta, *et al*, 2003)**, dithioacetal **(Abbaspour, and Kamyabi, 2002)** dithiocarbamate (**Kamata**, ***et al*, 1989)**, dithioaniline **(Gholivand, and Nozari, 2001)**, macrocyclic diamides (**Shamsipur, *et al*, 1999)**, thiohydrazone and thiosemicarbazone **(Gismera, *et al* 1999)**, thio- and dithiosalicylic acid **(Gismera, *et al* 2003)**, 1,10-phenanthroline **(Marzouk, *et al*, 2003)**, phenylglyoxal-alpha-monoxime **(Firooz, *et al*, 2002)**, Schiff's base **(Poursaberi, *et al*, 2001)** cyanocopolymers **(Gupta, and M. J. D'arc, 2000, 2001; Jain, *et al*, 2005)**, cyclic tetrapeptide derivatives **(Hassan, *et al*, 2005)**, thiacrown ethers (**Brzozka, 1988)**, pyrimidinethione derivatives **(Abbaspour and Moosavi, 2002)**, hydrotris(3-isopropyrazolyl)methane **(Yoshimoto *et al*, 2003)**, chelates of copper with acetylacetone, ethylacetoacetate and salicyldehyde **(Jain, *et al*, 2005)**, EDTA complex (**Reynold**, **1993**) and ion carrier **(Hassan, *et al*, 2003).**

Ethamsylate or cyclonamine (diethylammonium, 2,5-dihydroxybenzene-sulfonate) is a haemostatic agent commonly used in the prevention and control of haemorrhage from small blood vessels (Fig. 1) (**Reynold**, **1993**). Recently, some drugs are used as carriers for the determination of some cations (**(Hassan, *et al*, 2003; Rizk, *et al*, 2009)**. Because of the presences of some functional groups in the chemical structure of the drug which are valuable and attractive for the reaction with cations. In the present work, conventional and graphite membrane electrode for copper ion were constructed and the performance characteristics were studied. The sensors are based on using ethamsylate as neutral ionophore and dioctyl phethalate as a plasticizer in PVC matrix. The sensors possess the advantages of simple design, fast response time, near-Nernstian slop and high selectivity over many different metal cations

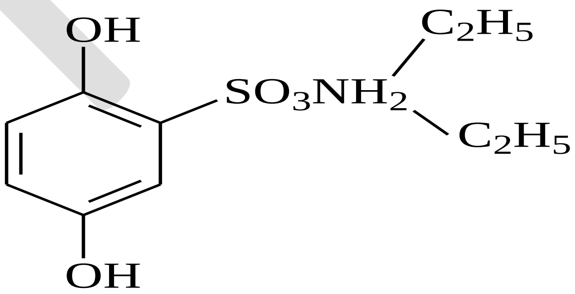


Fig. 1. Chemical structure of Ethamsylate.

Table 1 General performance characteristics of some potentiometric copper membrane sensors.

Ionophore	Linear Range (M)	Lower limit of detection (M)	Slope (mV/decad)	Interferent (M, Selectivity)	Ref
Dithiocarbamate	1×10^{-6} - 1×10^{-1}	4×10^{-7}	28-29	Cd^{2+} -2.1, Co^{2+} -1.9, Mn^{2+} -2.4, Mg^{2+} -2.8, Ag^{+} -0.6, Hg^{2+} -1.3	(Kamata, *et al*, 1989)
Dithioacetal	3×10^{-6} – 5×10^{-2}	1×10^{-6}	29±1	Ag^{+} -0.6, Hg^{2+} -1.3	(Abbaspour, and Kamyabi, 2002
Dithioaniline	7×10^{-7} – 5×10^{-2}	6×10^{-7}	30±1	Hg^{2+} -3.5, Ag^{+} -4.01, Fe^{2+} -3.27, Pb^{2+}-0.28.	(Gholivand, and Nozari, 2001)
Thia crowm ethers	1×10^{-5} - 1×10^{-1}	1.4×10^{-7}	22.3	Cd^{2+} -1.5, Co^{2+} -1.0, Ni^{2+}-1.4, Pb^{2+} +0.1	(**Brzozka, 1988)**
Ethambutol-copper(II) complex	$7.9.\times10^{-6}$ – 1×10^{-1}	7.0×10^{-6}	29.9	Hg^{2+} -0.1, Na^{+} -0.48, K^{+} -0.2, Co^{2+} -0.87, Pb^{2+}-0.81, Ni^{2+}-0.59, Al^{3+} -0.68	**(Gupta, *et al*, 2003)**
Macrocyclic diamides	3.2×10^{-5} - 1×10^{-1}	1. 2×10^{-5}	30	Na^{+} -0.48, K^{+} -0.88, Hg^{2+} -2.4, Cd^{2+} -1.58, Pb^{2+}-2.2, Ni^{2+}-2.01, Zn^{2+} -2.3, Sr^{2+} -1.03, CS^{+} -0.79, Ca^{2+}-1.63	(**Shamsipur, *et al*, 1999)**
Clycic tetrapeptide derivatives	1×10^{-6}- 1×10^{-2}	7.5×10^{-7}	30.3	Li^{+} -5.1, Na^{+} -5.15, K^{+} -5.1, CS^{+} -4.3, Ca^{2+} -3.4, Al^{3+} -4.06 , Mg^{2+} -3.22, Ag^{+} -3.09 , Sr^{2+} -2.82, Fe^{3+} -3.2, Fe^{2+} -2.84, Mn^{2+}-2.69, Ba^{2+} -3.00, Hg^{2+} -2.52, Co^{2+}-2.71, Ni^{2+}-2.52, Zn^{2+} -1.70, Cd^{2+} -2.39, Pb^{2+} -0.52.	**(Hassan, *et al*, 2005)**
	3.1×10^{-6} – 1×10^{-2}	2.1×10^{-6}	25.9	Li^{+} -5.51, Na^{+} -4.3, K^{+} -4.41, CS^{+} -4.42, Ca^{2+} -3.0, Al^{3+} -3.97, Mg^{2+} -2.85, Ag^{+} -2.6, Sr^{2+} -2.70, Fe^{3+} -3.06, Fe^{2+} -3.05, Mn^{2+}-2.82, Ba^{2+} -3.10, Hg^{2+} -2.39, Co^{2+}-2.60, Ni^{2+}-2.52, Zn^{2+} -1.52, Cd^{2+} -2.15, Pb^{2+} -0.39.	
	$10^{-7.6}$-$10^{-3.2}$	$10^{-7.9}$-$10^{-6.3}$	68.7	Pb^{2+} +0.61, Mg^{2+} +0.18, Cd^{2+} +0.03, Ca^{2+} -+0.29, Al^{3+} +0.32, Fe^{3+} -1.16.	
Ethamsylate, Conventional sensor	1×10^{-6} -1×10^{-2}	5×10^{-7}	29.5	Na^{+}-2.69, K^{+}-2.33, Ag^{+} -2.28, NH_4^{+}-2.46, CS^{+} -1.07 , Pb^{2+} -2.17, Mg^{2+} -3.33, Ca^{2+} -0.32, Co^{2+} -1.55, Cd^{2+} -1.25, Ni^{2} -1.04 , Fe^{2+} -1.37, Sr^{2+} -1.74, Zn^{2+} -1.49, Mn^{2+}-1.44, Ce^{3+} -1.56, Al^{3+}-2.85, Fe^{3+}-1.92 .	This work
Graphite sensor	7×10^{-5} -1×10^{-2}	1×10^{-6}	27.8	Na^{+}-1.49, K^{+}-1.32, Ag^{+} -1.14, NH_4^{+}-1.26, CS^{+} -1.88, Pb^{2+} -1.60, Mg^{2+} -2.88, Ca^{2+} -0.79, Co^{2+} -1.14, Cd^{2+} -1.17, Ni^{2+} -1.03 , Fe^{2+}-1.60 , Sr^{2+} -1.25, Zn^{2+} -1.25, Mn^{2+}-1.60, Ce^{3+} -1.36, Al^{3+}-1.03, Fe^{3+}- 1.23	This work

EXPERIMENTAL

Apparatus and reagents.

Potentiometric measurements at 25+1°C were made with an Orion digital ion-analyser (model, 420A) using conventional and coated graphite sensor with ethamesylate as ionophore dispersed in PVC matrix and plasticizer as solvent mediater. A copper membrane was used in conjunction with an Orion 90-02, Ag-AgCl double-junction reference electrode containing 10% (w/v) KNO_3 solution in the outer compartment. The cell assembly for the measurement of potential is Ag**/**AgCl**/**KCl(10^{-1}M), KNO_3 10^{-1} M**/**sample test solution**//**sensor membrane**//**internal filling solution **/**AgCl/Ag. Adjustment of the pH was made with an Orion 91-20 combination glass electrode. Atomic absorption spectrometric measurements of Cu^{2+} were made with Perkin-Elmer spectrometer (model 3100) using recommended optimum conditions (Hassan, 1984). Copper alloys samples were digested in a Microwave Sample preparation System (Type MDS-2000), CEM Cooperation.

All chemicals were of analytical-reagent grade, unless otherwise stated, and bidistilled deionized water was used throughout. Ethamesylate was obtained from Sigma Chem. Co. (St. Louis, MO., USA). Nitrophenyl octyl ether (*o*-NPOE), dioctylphethalate (DOP), dioctylsebacate (DOS), tetrahydrofuran (THF) were obtained from Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). Aqueous 10^{-2} –10^{-6} M copper solutions were freshly prepared by accurate dilutions of a standard 10^{-1} M stock drug solution by using 0.02 M borate buffer pH 5. Carbon rods (F-purity) were obtained from Ultra Carbon Co. (Bay City, MI, USA).

Preparation of conventional sensor

The cocktail was prepared by mixing 2 mg portion of ethamsylate ionophore mixed in a glass Petri dish (5 cm diameter) with 132 mg of dioctyl phthalate (DOP) and 66 mg of poly (vinyl chloride) (PVC) **(Hassan and Marzouk, 1994; Rizk, et al, 1994)**. The mixture was dissolved in a 5 ml of tetrahydrofuran (THF). The Petri dish was covered, and left to stand overnight to allow slow evaporation of the solvent at room temperature. A master PVC membrane (0.1 mm thickness) was obtained. The internal reference solution was prepared by mixing equal volumes of 1×10^{-2} M KCl and $CuCl_2$.

Preparation of graphite sensor

A rod of spectrographic graphite (5mm in diameter and 15 mm long) was inserted in a polyethylene sleeve, and about 3 mm of the other end of the protruded rod served as a measuring surface **(Rizk, and Othman, 2005).** This end of the rod was washed with acetone, dried in air for 3 h, and dipped rapidly into a homogeneous coating of the previous cocktail. The solvent was allowed to evaporate in air after each dipping, and the dipping process was repeated 6 - 8 times to supply for a uniform membrane on the surface of the graphite rod. Before use, the coated graphite rod was soaked for 2 h in a 1×10^{-2} M aqueous copper solution. One drop of mercury was added in the polyethylene sleeve to ensure electrical contact with the connection cable. The sensors were conditioned by soaking in a 1×10^{-2} M copper solution for 9 h, and stored in the same solution when not in use.

Calibration of copper membrane sensors

The membrane sensors were calibrated by immersion in a 1×10^{-6}-1×10^{-1} M copper chloride solution with 0.01 M acetate buffer, pH 5. A 1.0 ml aliquot of each solution was transferred into a 50 ml beaker containing 9 ml of a 00.01 M acetate buffer solution pH 5. Conventional and graphite copper sensors were immersed and allowed to equilibrate with constant stirring in conjunction with an Orion reference electrode. The sensors were washed with bidistilled deionized water between measurements. The electrode potential was recorded as a function of the copper concentration. The obtained calibration plot was used for subsequent measurements of unknown copper concentration under the same conditions.

Sensor Selectivity

The potentiometric selectivity coefficient ($K^{Pot}_{Cu(II),B}$ of the copper sensors was measured by the separate solutions method **(Rizk, *et al*, 2009; Umezawa, *et al*, 2000)**. In this method, the potentials of 10^{-3} M concentration of both copper and the interfering species in 0.02 M acetate buffer of pH 5 were determined. The selectivity coefficients were calculated using the following equation.

$$\log\ (K^{Pot}_{Cu(II),B})=(E_{Cu(II)}-E_B)/S-[1+Z_{Cu(II)}\ /Z_B]\ \log\ Cu(II)$$

Where E_{Cu} and E_B are the potential readings observed after 1 min of exposing the sensor to the same concentration of copper and interferents, respectively, in separate solutions and S is the slope of the copper calibration graph (mV/concentration decade).

Determination of copper in waste water

Six waste water samples were collected (Egyptian copper company). Each solution was mixed with nitric acid, then dilution by acetate buffer pH 5. Mixtures were transferred to a 100 ml volumetric flasks and diluted to the mark with 0.01 M acetate buffer of pH 5. The e.m.f of the sensors were measured as described above and compared with the calibration plot. Alternatively, the standard addition technique was used by monitoring the potential of 50 ml sample test solution before and after addition of 0.50 ml of standard 0.01 M copper chloride solution. The results obtained were compared with data obtained by atomic absorption method.

Determination of copper in alloys

Five alloy samples are collected (Egyptian copper company) and digested (using a Microwave Sample preparation System (Type MDS-2000)), (CEM Cooperation, with nitric acid. The samples were transferred to 50 ml to volumetric flasks and diluted to the mark with 0.01 M acetate buffer of pH 5. The potentional of the sensors were measured as described above and compared with the calibration plot. Alternatively, the standard addition technique was used by monitoring the potential of 20 ml sample test solution before and after addition of 0.50 ml of standard 0.01 M copper chloride solution. The results obtained were compared with data obtained by atomic absorption method.

Determination of copper in pharmaceutical formulations

A homogenized powder was prepared from 10 accurately weighed drug capsules containing copper. An appropriate amount of this powder (0.200 g) was transferred into a 100-mL volumetric flask. Dissolution of the drug was assisted by means of a magnetic stirrer. The solution was then diluted to the mark with water and the proposed electrode determined copper content by using the calibration method as mentioned before. The concentration of copper in samples were confirmed by applying atomic absorption method (**Hassan, et al, 1984)**.

RESULTS AND DISCUSSION

Composition of the electrodes

The capability of ethamsylate as a very suitable Cu^{2+} ion complexing agent is examined for the construction of a new copper (II) ion-selective electrode. The influence of the membrane composition on the potential response of the Cu^{2+} ion-selective electrode was investigated. The critical response characteristics of the electrodes were assessed according to IUPAC recommendations **(IUPAC, 1995)**.

From Table 2, five membrane compositions were investigated, the results showed that the electrodes made by membrane III with 3% ethamsylate as ionophore, exhibit the best performance characteristics (for conventional; slope 29.5 mV/decade, usable concentration range at 25°C 1×10^{-6}-1×10^{-2} M; for graphite; slope 29.5 mV/decade, usable concentration range at 25 °C 7×10^{-5}-1×10^{-2} M). Other membranes exhibit slopes ranging between 28.5-29.1 mV/decade and 25.8-27.1 mV/decade for conventional and graphite membrane electrodes. The optimum relative amounts of PVC, DOP and TPB-derivative (1-10 %) as an additives suitable for the construction of the copper ion-selective electrodes were investigated.

Table 2 Composition of conventional and graphite PVC copper membrane sensors.

Membrane	Electrode Composition (mg)				Conventional Electrode	Graphite Electrode
	Ionophore	PVC	DOP	Additive, %	Slope (mV/decade)	Slope (mV/decade)
I	0.0	65.0	132.0	0	0.0	0.0
II	1.0	65.7	131.5	2	28.5	25.8
III	3.0	66.0	132.0	5	29.5	27.8
IV	5.0	67.3	133.1	7	29.1	27.1
V	6.0	68.2	133.5	10	29.1	27.1

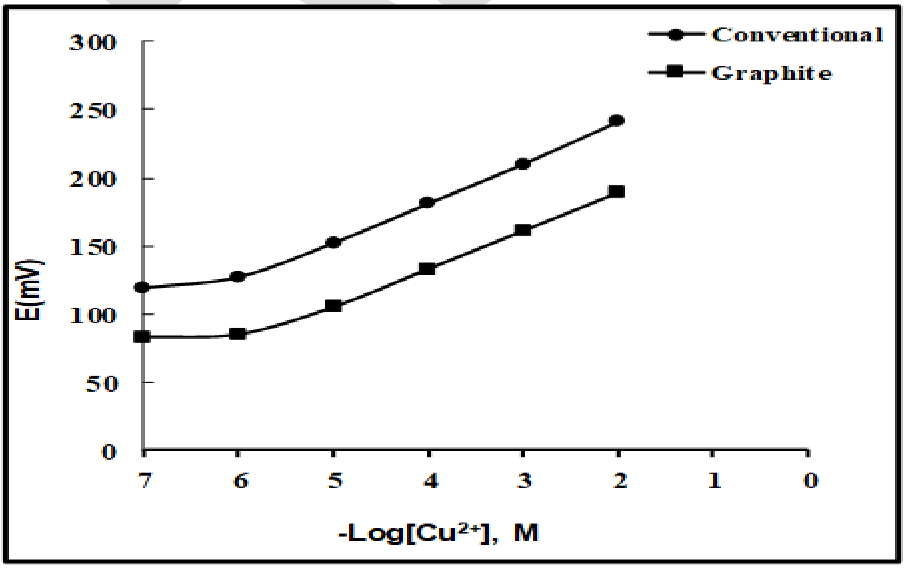


Fig. 2 Potentiometric response of copper PVC membrane sensors.

Tetraphenylborate was added to the membrane composition to see if it can improve the performance characteristics of the sensors or not. The results obtained indicated that there is an improvement in the electrodes characteristics, e.g., sensitivity (response time without additive, 30 s for conventional; 40 s and for graphite and response time with 5% additive, 10 s for conventional; 15 s and for graphite) and lifetime (without additive; 3 weeks for conventional; 2 weeks for graphite and lifetime with 5% additive; 4 weeks for conventional; 3 weeks for graphite) of the electrodes. The concentration of the internal solution $CuCl_2$ in the electrode was changed from 1×10^{-2} to 1×10^{-6} M and the potential response of the copper ion selective electrode was measured. It was found that variation of the concentration of the internal solution does not cause any significant difference in the potential response of the electrodes. A 1.0×10^{-3} M concentration of internal solution is quite appropriate for smooth functioning of the electrode.

The optimum equilibration time for the membrane electrode is 9 h. It generates stable potentials when placed in contact with Cu^{2+} solutions. The emf response of the membrane at varying concentrations of copper indicates a rectilinear range from 1×10^{-6} to 1×10^{-2} M as limit of detection which determined from the intersection of the two extrapolated segments of the calibration graph. All performance characteristics of the sensors are compiled in Table 3. Figure 2 represent the calibration curves of conventional and graphite electrodes.

The improvement in the performance characteristics of the sensors were attempted by the addition of different plasticizers to the membranes. The addition of plasticizers not only improves the workability of the membranes, but also contributes significantly towards the improvement in the working concentration range, stability and shelf life of the sensor. However, the selectivity remains usually unaffected and mainly depends on the metal–ionophore interaction. The plasticizer to be used in membranes should exhibit high lipophilicity, high molecular weight, low tendency for exudation from the polymer matrix, low vapor pressure and high capacity to dissolve the substrate and other additives present in the membrane. Additionally, its viscosity and dielectric constant should be adequate. Thus, three plasticizers namely, DOP, DBS, and *o*-NPOE were added in an attempt to improve the performance of the sensors. The performance characteristics of the membranes without ionophore were investigated and no potential was generated. The suggested mechanism for the proposed copper (II) ionophore is as follows: copper (II) forms sable complex with ethamsylate in a 1:2 copper (II) to drug ratio. The mechanism was proven by applying Job's method which is extremely versatile approach to the determination of reaction stoichiometries (**Taylor, 1987**).

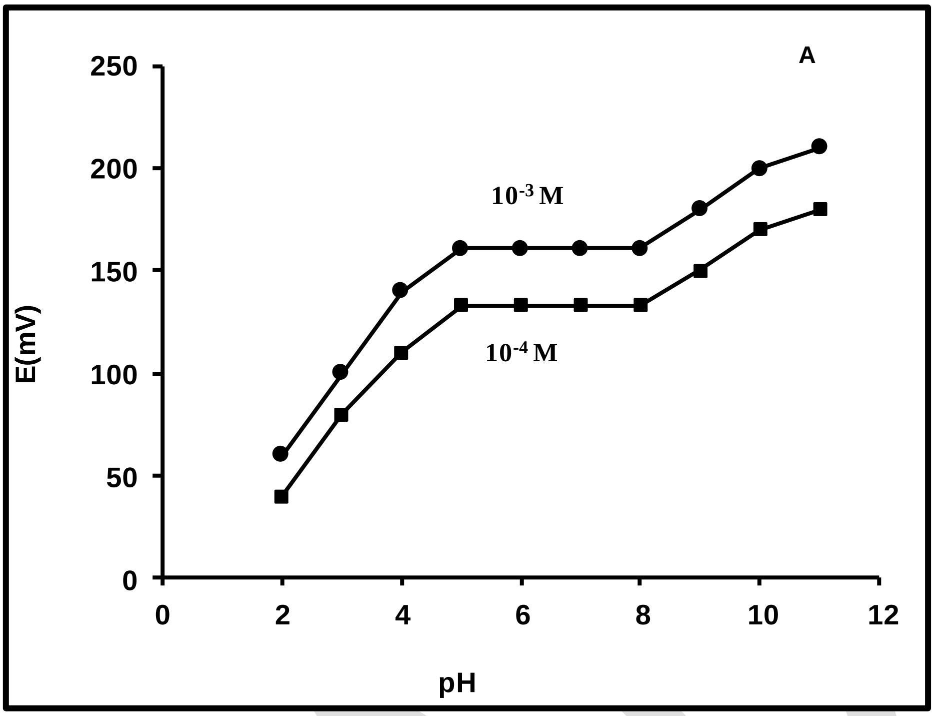
Response time and life time

The response time of the sensor was determined by measuring the time required to achieve a steady potential for plasticizer DOP improved the response time to the maximum extent. The response time of the two membranes of ethamsylate with plasticizer DOP and 3 % additive are found to be 10 and 15 s, for conventional and graphite sensors respectively. The main factor responsible for the limited lifetime of a sensor is believed to be the loss of one or more of its components while contacting with aqueous solutions. Among all the membranes prepared, the lifetime of the membrane sensors comprising DOP was maximum and found to be 4 and 3 weeks for conventional and graphite sensors respectively. During this lifetime of the sensors, no significant drift in potential was noticed. However, it is important to emphasize that the membranes were stored in a 0.01 M Cu^{2+} solution when not in use. As can be seen, over the whole concentration range the electrodes reach their equilibrium response in short time. This is most probably due to the fast exchange kinetics of complexation–decomplexation of the copper ion with the ionophore at the test solution-membrane interface.

Effect of pH and sensor selectivity

The pH dependence of response of the sensor has been tested in the range of 2–11 of two Cu^{2+} concentrations of 1.0×10^{-3} and 1.0×10^{-4} M Cu^{2+}. The pH was adjusted with dilute hydrochloric acid or sodium hydroxide solutions. The potential of the sensor was determined as a function of pH and the results are shown in Figure 3 for conventional and graphite electrodes respectively. The potential remains constant over the pH range of 4–7, which may be taken as the working pH range of the sensors assembly. The observed drift at higher pH values could be due to the formation of some hydroxyl complexes of Cu^{2+} ion in solution. At low pH, the H^+ ions interference and the membrane sensors responds to the hydrogen ions.

A number of mono, di- and trivalent cations have been tested using the separate solution method (SSM) using conventional and graphite electrodes. The results are given in Table 4. It is evident from the selectivity coefficient data that the sensors exhibit higher preference for copper (II) ion compared with alkali, alkaline earth, transition and heavy metal ions. The selectivity studies were carried out only for sensors, which exhibited the best performance characteristics in terms of working concentration range, slope, response time and life time. The results indicated that, both the electrodes are substantially selective to Cu^{2+} ions over all the interfering ions studied. It was found that, from Table 3, the conventional electrode exhibits better selectivity than the graphite electrode.



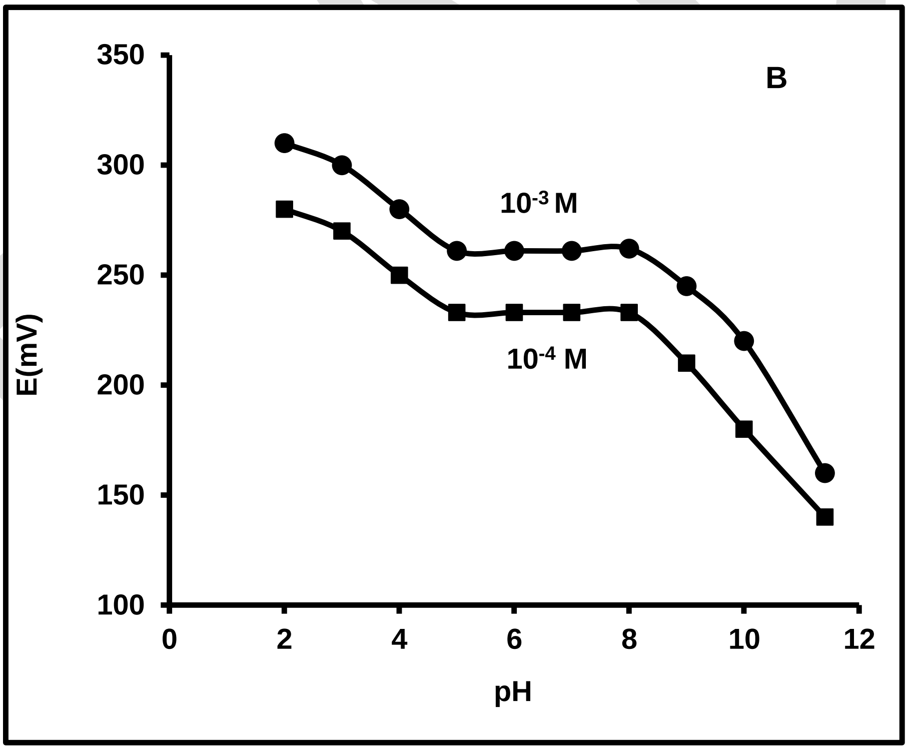


Fig. 3 Effect of pH on potential of copper (A) conventional; and (B) graphite PVC membrane sensor.

Table 2 Composition of conventional and graphite PVC copper membrane sensors.

Membrane	Electrode Composition (mg)				Conventional Electrode	Graphite Electrode
	Ionophore	**PVC**	**DOP**	**Additive, %**	**Slope (mV/decade)**	**Slope (mV/decade)**
I	0.0	65.0	132.0	0	0.0	0.0
II	1.0	65.7	131.5	2	28.5	25.8
III	3.0	66.0	132.0	5	29.5	27.8
IV	5.0	67.3	133.1	7	29.1	27.1
V	6.0	68.2	133.5	10	29.1	27.1

Table 3 Response characteristic of PVC copper membrane sensors.

Parameter [a]	Conventional sensor	Graphite sensor
Slope, mV/decade	29.5±0.3	27.8±0.8
Correlation coefficient, (r)	0.998	0.996
Lower limit of linear range, (M)	1×10^{-6}	7×10^{-5}
Lower limit of detection, (M)	5×10^{-7}	10^{-6}
Response time for 10^{-3} M, (s)	10	15
Recovery time for 10^{-3} M, (s)	25	30
Working range, pH	4-7	4-7
Life span, (week)	8	8
Accuracy (%)	99.89	100.04
Repeatability, CV_w (%)	0.7	0.9
Between day-variability, CV_b (%)	1.3	1.4
Standard deviation, σ (%)	0.9	1.1

[a] Average of five measurements

Table 4 Selectivity coefficients of PVC copper membrane sensors.

Interfering ion (B)	Selectivity coefficient ($K^{Pot}_{Cu(II),B}$)[a]	
	Conventional electrode	**Graphite electrode**
Na^+	2.0×10^{-3}	3.2×10^{-2}
K^+	4.6×10^{-3}	4.7×10^{-2}
Ag^+	5.2×10^{-3}	7.2×10^{-2}
NH_4^+	3.4×10^{-3}	5.4×10^{-2}
Cs^+	8.4×10^{-2}	1.3×10^{-2}
Pb^{2+}	6.7×10^{-3}	2.5×10^{-2}
Mg^{2+}	4.6×10^{-4}	1.3×10^{-3}
Ca^{2+}	4.7×10^{-1}	1.6×10^{-1}
Co^{2+}	2.8×10^{-2}	7.1×10^{-2}
Cd^{2+}	5.6×10^{-2}	6.7×10^{-2}
Ni^{2+}	9.1×10^{-2}	9.2×10^{-2}
Fe^{2+}	4.2×10^{-2}	2.5×10^{-2}
Sr^{2+}	1.8×10^{-2}	5.5×10^{-2}
Mn^{2+}	3.6×10^{-2}	2.6×10^{-2}
Zn^{2+}	3.2×10^{-2}	5.6×10^{-2}
Ce^{3+}	2.7×10^{-2}	4.3×10^{-2}
Al^{3+}	1.4×10^{-3}	9.2×10^{-2}
Fe^{3+}	$1.2\times10^{-}$	5.8×10^{-2}

[a] average of five measurements

Determination of Copper in waste water

Membrane (III) based conventional sensor was used for potentiometric determination of Cu^{2+} ions in some waste water samples obtained from Egyptian copper company. The samples were treated with nitric acid to dissociate the metal complexes. Data obtained (Table 5) using atomic absorption spectrometry is agree well with the data obtained by the proposed method.

Table 5 Determination of copper in mineral samples by conventional copper sensor and AAS spectrometry.

Samples	**Copper content, ^{a}**			
	Potentiometry		**AAS**	
	Waste Water, mg/l	**Metal Alloys, mg/g**	**Waste Water, mg/l**	**Metal Alloys, mg/g**
1	98.7±0.6	112.1±0.2	96.3±1.2	110.8±0.9
2	110.7±0.5	126.5±0.9	109.5±0.8	124.4±0.7
3	105.5±0.9	121.3±0.1	104.8±0.7	119.6±0.8
4	108.9±0.8	129.4±0.4	106.4±0.8	127.8±0.9
5	113.6±0.4	124.1±0.3	112.9±0.7	122.3±0.8
6	109.2±0.7	115.2±0.7	108.1±0.8	114.6±0.9

^{a} Average of five measurements

Determination of copper in alloys

The copper content of six metal alloys taken from Egyptian copper company were studied. The contents of copper were measured by direct potentiometry using conventional sensor based on membrane (III). The results obtained show an average Cu content ranging from 150-350 mg/g of alloys. Similar results are obtained using atomic absorption spectrometry (Table 5).

Determination of copper in pharmaceutical formulations

The validity of the proposed potentiometric methods for determining copper was assessed by measuring the range, lower limit of detection (LOD), accuracy (recovery), precision or repeatability (CV_w), between-day variability (CV_b), linearity (correlation coefficient) and sensitivity (slope). Data obtained on five batches (five determinations each) using the calibration graph method show results with average recoveries of 99.89 and 100.04 % and mean standard deviations of ±1.0 (Table 3). Copper was also determined in various dosage forms. The results obtained with conventional copper sensor, based membrane sensor for determination of copper amount in some pharmaceutical samples from local pharmacy are shown in Table 6. As it is seen, the results are in satisfactory agreement with the atomic absorption method and with the stated content on capsules.

Table 6 Determination of copper in some pharmaceutical preparations using conventional copper sensor and AAS spectrometry.

Trade name and source	**Nominal content (mg capsule $^{-1}$)**	**Copper content ^{a}**	
		Potentiometry	**AAS**
Enrich (Marc. Pharm. Ind., Egypt)	2.50	100.4 ± 0.5	98.1±0.4
Theragran Hematinic (Bristol-Myers Squibb, Egypt)	0.67	99.5 ± 0.7	98.5±0.3
Mamyvit (Multi- Apex Pharm)	4.00	100.2± 0.3	98.3±0.5

Comparison with Other Reported Copper Sensors

Table 1, shows a comparison of the performance characteristics of some previously reported Cu^{2+} membrane sensors with those described in this work.

Selectivity coefficients of the proposed sensors towards some potential interfering ions were in the order of 10^{-3} or smaller, indicating superior selectivity over other sensors (**Gupta, *et al*. 2003; Abbaspour, and Kamyabi, 2002; Kamata**, ***et al*. 1989**; **Gholivand, and Nozari, 2001**; **Shamsipur, *et al*. 1999**; **Gismera, *et al*. 2003; Brzozka, 1988)**. Wider working concentration range and lower detection limit are also offered by the proposed sensors compared with some of those previously suggested (**Abbaspour, and Kamyabi, 2002; Shamsipur, *et al*. 1999**; **Gismera, *et al*. 2003**)

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