Research Article

Ketoifen drug and its use as a modern and accurate sensor respective for trace quantities of Cupper(II)

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Abstract

The proposed sensor is composed of in curporated **of Ketoifen** as an electro active material in PVC matrix membrane and dioctyl phthalate or dioctylesepacate as solvent mediators. The sensor exhibited fast and stable near Nernstian cationic response of 29.3 $\pm 0.1 \text{ mV}$ concentration decade of Cupper(II) in the concentration range of $1.0 \times 10^{-6} - 1.0 \times 10^{-1}$ M. The lower limit of detection was $1.5 \times 10^{-7} \pm 0.2$. It is to be noted that the sensor based on Ketotifen was used throughout this investigation in the pH range 4- 8.5. The sensor displayed a good selectivity for Cupper with respect to a number of common foreign inorganic and organic species. The sensor was also successfully applied for the determination of Cupper (II) in drink water and in waste water.

Keywords: Ketoifen, PVC matrix membrane etc.

1. Introduction

Cupper is an essential element that's also toxic at low levels Concentration. The toxicity is generally attributed to the aquo-Complexed "free" Cupper (II) ion rather than its organic or inorganic Complex(De MarCo., *et al.*,1997,Jain.,*et al* 1994 and Kouljenovic., *et al.*, 1990). Cupper deficiency results in anemia while its accumulation resulting in Wilson diseasealso the excessive dosage and long term exposure may cause irritation of the nose, mouth and eyes and it causes headache, stomach ache, dizziness, vomiting and diarrhea (Yoshimoto.S *et al*,2003,Gismera. *et al* .,2003 and Gupta. *et al* .,2003).

Cupper ions are found in the active sites of a large number of metalloproteins involved in important biological electron-transfer reactions, as well as in redux processing of molecular oxygen (Holm *et al.*, 1996 and Karlin *et al.*, 1993). The former Comprises "blue" Cupper sites in electron transfer proteins or multi Cupper oxidases (Holm *et al.*, 1996, MesSchmidt.,*et al.*, 1993 and Chapman., *et al.*, 1991) while the latter includes hemocyanins (arthropodal and molluscan blood O_2 carrier protein),(Solomon., *et al.*, 1996 and Cuff., *et al.*, 1998)Oxygenases inserting O atoms, ion substrates (Solomon., *et al.*, 1996, Docker., *et al.*, 2000) and oxidases Couplings substrate additions to Cupper mediated dioxygen peroxide or water (Masserchindt., *et al.*, 1993, Solomon., *et al.*, 1996 and Klinman., *et al.*, 1996) Close environment about the metal ion provided by the protein amino acids (i.e., the first and/or second metal Coordination shell) (Kartin., *et al.*, 1997 and Kathin,., *et al.*, 1998) it is therefore of interest to employ model Cumpound investigations (Spodine., *et al.*, 1992 and Blackman ., *et al.*, 2000) to understand how a ligand environment (as determined by the identify of its donor atoms and their arrangement) modulates details of structure, Cu(II)/Cu(I) redox properties Cu(I)/O₂ reactivity and Cu(I) or Cu(II) spectroscopic properties.

Ketoprofen is generally prescribed for arthritis-related inflammatory pains or severe toothaches that result in the inflammation of the gums[Hamilton., *et al*2015, Mazières.,*et al*2005]

Ketoprofen topical patches are being used for treatment of musculoskeletal pain.[a b Sekiya.,et al 2010]Ketoprofen can also be used for treatment of some pain, especially nerve pain such as sciatica, postherpetic neuralgia and referred pain for radiculopathy, in the form of a cream, ointment, liquid, spray, or gel, which may also contain ketamine and lidocaine, along with other agents which may be useful, suchas cyclobenzaprine, amitriptyline, acyclovir, gabapent in, orphenadrine and other drugs used as NSAIDs or adjuvant, atypical or potentiators for pain treatment

A systematic review indicated "The efficacy of orally administered ketoprofen in relieving moderate-severe pain and improving functional status and general condition was significantly better than that of ibuprofen and/or diclofenac."[Sarzi-Puttini.,*et al* 2013]

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A Cochrane systematic review investigating ketoprofen as a single-dose by mouth in acute, moderate-to-severe postoperative pain concluded that its efficacy is equivalent to drugs such as ibuprofen and diclofenac [Gaskell, Helen *et al* 2017].

There is evidence for topic ketoprofen for osteoarthritis but not other chronic musculoskeletal pain [Derry.,*et al*, 2016].

Ketoprofen should not be used in combination with other NSAIDs or corticosteroids, as this increases the risk of gastrointestinal (GI) ulceration. It should also be used with caution with other anticoagulants. It is commonly used with omeprazole, sucralfate, and cimetidine to help protect the GI tract.

The patches have been shown to provide rapid and sustained delivery to underlying tissues without significantly increasing levels of drug concentration in the blood when compared to the traditional oral administrationz [Ketoprofen.,2010]

Ketoprofen undergoes metabolism in the liver via conjugation with glucuronic acid, CYP3A4 and CYP2C9 hydroxylation of the benzoyl ring, and reduction of its keto function.Ketoprofen is used for its antipyretic, analgesic, and anti-inflammatory properties by inhibiting cyclooxygenase-1 and -2 (COX-1 and COX-2) enzymes reversibly, which decreases production of proinflammatory prostaglandin precursors.[Lemke TL.,*et a*/2008]

2.Experimental

2.1. Reagents and materials.

All chemicals were of analytical reagent grade. Dioctyl phthalate (DOP), dioctylsebacate (DOS), dibutylsebacate (DBS) and orthonitrophenyloctyl ether (o-NPOE) were purchased from FlukaChemika-Biochemika (Ronkonkoma, NY). High molecular weight poly (vinyl chloride) powder (PVC) of molecular mass 100,000, tetrahydrofuran (THF), and high relative molecular weight PVC were purchased from Aldrich chemical Company, and the other chemicals used are from Merck. They were of the highest purity available and used without any further purification expect for vacuum drying over P2O5. Doubly distilled water was used throughout this work. The stock solution $(10^{-1}M)$ cadmium chloride, sodium chloride and Cupper nitrate (Milwaukee, WI, Darmstadt, Germany) were prepared. Also, the working solutions $(1.0 \times 10^{-2} - 1.0 \times 10^{-6} \text{ M})$ were prepared by successive dilution with water and the pH was adjusted using 0.01 M HCl or NaOH according to the pH required.

2.2. Apparatus

Potentiometric measurements were performed at $25 \pm 10C$ with an Orion digital pH/mV meter (Model SA720) using the PVC membrane sensors in Conjunction with an Orion Ag/AgCl double junction reference electrode

(Model 90-02) filled with 10% (w/v) KNO3. A Combination Ross glass-pH electrode (Orion 81-02) was used for pH measurements. The cell used for EMF measurements is of the type: Ag/AgCl/ KCl (0.1 M)/sample test solution //sensor membrane //internal filling solution /AgCl/Ag. The potential readings of stirred 10-2 M - 10-6 M working solutions were measured, recorded after stabilization to ± 0.5 mV and a calibration graph was Constructed.

2.3. Instrumental Measurements

2.3.1. Spectrophotometric measurements.

a- Infrared spectra: IR spectra was measured by a Perkin-Elmer instrument using potassium bromide disc technique, at the analytical laboratory, chemistry department, faculty of science, king kaled Universitysudia Arabia.

b- Ultra Violet spectra: The ultraviolet spectra was measured at room temperature in the UV range, (200-800 nm) using Perkin Elmer Lambda 20 spectrophotometer at king kalid UniversitySaudiArabia

c- Atomic absorption: All the Complexes formed are identified by measuring it's atomic absorption spectra (using GBI 932AA) at the micro analytical laboratory, Cairo University and (Variozise 600) at king kalid University

2.3.2. pH measurement.

A Ross glass-pH electrode (Orion model 81-02) used for all pH measurements and Orion digital pH/mV model(90-02) meter Ag/AgCl double junction reference electrode was used for potentiometric measurements.

2.4. Sensor of Cupper(II)

2.4.1. Membrane preparation and sensor Construction cupper responsive membrane sensor was prepared as described previously (Hassan et al., 2003) by mixing 0.01 gmionophore (ketofain drug, Fig 2.5), 0.35gm DOS plasticizer and 0.19 gm PVC .The mixture was dissolved in 0.35 ml THF in a glass Petri dish (~3 cm diameter), Covered with a filter paper and left to stand overnight to allow slow evaporation of the solvent at room temperature. Disks (0.7 mm diameter) were cut out from the parent membrane and mounted in the PVC electrode body (0.6 mm diameter) using THF. A mixed solution Consisting of equal volumes of 10-3 M Cupper nitrate and 10-3 M KCl was used as an internal reference solution and Ag/AgClCoated wire (3 mm diameter) was employed as an internal reference electrode. The sensor was conditioned by soaking overnight in a solution of 10⁻² M Cupper nitrate and stored in the same solution when not in use.

2.4.2. Sensor calibration

The sensors were calibrated by transferring 10 ml aliquots of 10^{-2} M to 10^{-6} M aqueous CU²⁺solution to the 50 ml double walled-glass cell. The potential readings were reCorded after stabilization (to ± 0.2 mV) and plotted as a function of logarithmic Concentration of CU²⁺. The calibration graphs were used for subsequent determination of unknown Cupper Concentration.

2.4.3. Effect of plasticizers

Two different membrane sensors were prepared using DOP and DOS as plasticizers, then calibration experiments were carried out using these Cupper sensors. The results were tabulated and compared.

2.4.4. Effect of pH

The dependence of sensor's potential response on the pH has been tested by changing the pH of 10-2, 10-3 and 10^{-4} M CU²⁺solution. The pH of the solutions was changed from 2 to 10, and the operational range was studied by varying the pH with Concentrated and diluted HNO3 and NaOH solution. The Corresponding mV reading was recorded after each addition.

2.4.5. The response time.

The response time of sensor was determined by measuring the potential response as a function of time for various Concentration of Cu2+ ions $(10^{-2} - 10^{-6} \text{ M})$, and the results were plotted.

2.4.6. Analytical Applications.

2.4.6.1. Determination of cupper in beer

Salts of Cupper are added to beer to improve foam and to prevent gushing. As a Consequence, Commercial beer normally Contains a minute Concentration of Cupper, usually a few hundredths of a part per million. Experiments were performed to measure Cu2+ in beer samples.. So there is a need to develop an accurate method to check whether a beer sample does or does not Contain added Cupper. An amount of 1ml of 18N H2SO4 was added to 50 ml of degassed beer. The beer was evaporated to dryness and 10 ml of distilled water were added. The pH was adjusted to 5.5 using either 0.1N HCl or 0.1 N NaOH. The solution was filtered and finally diluted up to 50 ml with water. Aliquots of Cupper solution were added to 50ml samples of this beer, to give known Concentration of added Cupper ranging from about 0.5–1.2 ppm. The Concentration of added Cupper was then determined for each sample using the ionselective electrode Constructed and the results are tabulated. The method detecting such additions is therefore, of interest to brewers.

2.4.6.2. Determination of cupper in waste water

20 ml aliquot of waste water sample Containing cupper ions obtained from electroplating factories were treated with 20 ml of 0.1 normal nitric acid. The solution was shaken well and heated to boiling on a hot plate for 15 min to decompose the metal completely. The solution was quantitatively transferred to 100 ml measuring flask and Completed to the mark with acetate buffer of pH 5.5. The Cupper sensor (II) and the double junction Ag/ AgCl reference electrode were immersed in 10 ml of the sample and the emf was recorded. The Concentration of CU^{2+} ions was determined by constructing calibration curve for the sensor. The samples were also determined by using atomic absorption spectrometry (AAS) and the results obtained by the proposed and standard method were compared.

2.6.6.3. Use of the proposed Cupper sensor as a successful indicator electrode in potentiometric titration

The proposed Cupper ion-selective electrode was successfully applied as an indicator electrode in potentiometric titration of Cu2+ solutions with EDTA. A 1.0×10^{-2} M CU²⁺solution of 10 ml was titrated with a 1.0×10^{-2} M solution of EDTA at pH 6 using the proposed sensor as an indicator electrode. The resulting titration curve was plotted.

3. Result and Discussion for Cupper sensor

3.1. Characteristics of the Cupper sensor

The most important characteristics of any ion-sensitive sensor are its response to the primary ion (Cupper ions) in the presence of other ions in the solution. This is expressed in terms of the potentiometric selectivity Coefficient.

In this work, the ligand (ketofan) used as an ionophore in the CU (II) ion-selective electrode should fulfil certain Conditions. It should be selective for CU²⁺ion over other metal cations, and it should have rapid exchange kinetics and be sufficiently lipophilic to prevent leaching of the ligand into the aqueous solution surrounding the membrane electrode (Gupta, *et al.*, 2000, and 2001). this ligand was expected to act as a suitable ion carrier in the PVC membrane sensors. Thus, ketofan was used, in the primarily experiments, as a neutral carrier to prepare polymeric membrane electrodes for a variety of Cupper ions>



Fig.3.1: Chemical formula of Ketofan





Fig.3.2: Potentimetric response curves of the proposed sensor with different plasticizers

The effect of different plasticizers DOS and DOP on CU^{2+} membrane electrodes based on Ketofan is represented in Fig. (3.28). It is noteworthy that the lipophilicity of the plasticizer influences both the dielectric Constant of the polymeric membranes and the mobility of the ionophore. It is clear from Fig. (3.31) that DOS is a more effective plasticizer than DOP.

Table 3.1: Response c	haracteristics	of the	ketofan	PVC
Cu	upper sensor			

Daramatar	Value		
Parameter	DOS	DOP	
Slope (mv, decade)	29.7	29.4	
Linear range (M)	1.00 x 10 ⁻⁷ - 1.00 x10 ⁻²	1.5 x 10 ⁻⁶ - 1.00 x10 ⁻²	
Detection limit (M)	1.5 x 10 ⁻⁷	1.2 x 10 ⁻⁶	
Intercept (mv)	511	491	
pH range	4-8.6	4-8	
Response time (sec)	21≥	35≥	
Accuracy (%)	98	97	
Standard deviation (%)	±0.3	±0.4	
CorrelationCoefficient (T)	0.999	0.999	

3.3. Potentiometric selectivity

The selectivity is the most important characteristic of any sensor, which defines the extent to which it may be used to selectively estimate a particular ionic species likely to be present in actual samples along with other species to be determined. The potentiometric selectivity Coefficients were experimentally determined in which the cell potential was measured for the same Concentration (ai =aj = 1.0×10^{-3} M) of the primary ion solution and the interfering ion solution separately. The obtained cell potential for interfering ions and the analyte ions (\square Ej and \square Ei, respectively) are inserted into the following equation to calculate the selectivity Coefficient, log Ki,jpot (Goilbault *et al.*, 1976).

$$\log K_{ij}^{\text{pot}} = \frac{(\Delta E_j - \Delta E_i)Z_iF}{2.303\text{RT}}$$

Where Zi: charge of the primary ion, R: Molar gas Constant,

T: absolute temperature and

F: Faraday's Cunstant (96487 cal mole-1).

The results obtained are summarized in Table (3.10) it Could be shown that the selectivity of the proposed sensor towards Cupper is more than a large number of Inorganic cations, such as Na^+ , K^+ , Ca^{2+} , Mg^{2+} , CU^{2+} , etc. Also Comparing the selectivity Coefficient of the Considered sensor with of different electrodes shows that the proposed sensor has a good response to Cupper ions over a number of other electrodes as given in Table (3.2).

Table 3.2: Potentiometric selectivity Coefficients of ketofan membrane sensor

Interfering Ion	$Log K^{POT}_{Co++,B}$
Cu2+	-4.59
Cu2+	-3.24
AI3+	-3.10
K+	-2.90
Ag+	-2.73
Na+	-2.69
NH4+	-2.49
Ba2+	-3.16
Fe3+	-2.18
Mg2+	-2.28
Sr2+	-2.15
Cd2+	-1.53
Hg2+	-1.46
Ni2+	-1.33

3.4. Effect of pH

The pH dependence of the electrode potential is plotted over the pH range of 2–10 for $1.0\times10-2$ and $1.0\times10-3$ M Cu (II) ions solutions in Fig. (3.30). the pH of the solutions was adjusted by the addition of small drops of HNO3 (0.1 M) and NaOH (0.1 M). It is clear from the figure that the useful range is 4–8.5 because the potential remains Constant at this range. The sharp change in potential at higher pH values may be due to the formation of some hydroxyl Complexes of CU²⁺, while at lower pH values H₃O⁺ ions may start to Contribute to the charge transport process by the membrane, thereby causing interference.

The performance characteristics of the sensor were evaluated under many different variables such as

plasticizers, and the influence of pH. The results obtained are summarized in Table (3.1). The data show that the proposed sensor is highly selective and sensitive with respect to CU^{2+} ions, and this is appeared in the values, of the slope (which obeys Nernst equation), the lower limit of detection and the wide linear range.



Fig.3.3: Effect of pH on the potential response of the proposed sensor

3.5. Response time

The optimum response time for the membrane electrode in $1.0 \times 10-1$ M Cu²⁺ solution was found to be after 4 times when its starts generating stable potential. The response time of the electrode was determined by measuring the time required to achieve 90% of the steady potential. The static response time thus obtained was 18-20 sec over the entire Concentration range Fig. (3.3).



Fig.3.3: Dynamic response time of ketofanmembrane sensor

3.6. Direct potentiometric determination of ${\rm CU}^{2*}$ ionand the life time of the sensor

The potentiometric determination of CU^{2+} ions using a membrane based on Ketofan, DOS and DOP as a

plasticizers , PVC the sensor exhibits best results is the best one the sensor exhibits the best sensitivity to Cu^{2^+} over the widest working Concentration range of 1.0×10^{-7} to 1.0×10^{-2} M with a Nernstian slope of 29.5 ± 0.2 mV per decade of activity. The detection limit as determined from the intersection of the two extrapolated segment of the calibration graph Fig (3.2) is 1.5×10^{-7} M. The life time of the proposed electrode was determined by performing periodic calibrations with a standard solution and calculating the response and slope over the range of 1.0×10^{-7} to 1.0×10^{-2} M Cu²⁺ solution. It was found that the electrode worked well over a period of more than 5 months without showing any significant divergence in the Concentration range, slope and response time.

3.7. Applications

3.7.1. Determination of cupper in some waste water samples potentiometrically using the proposed sensor and a standard method (AAS)

The electrode was also applied to the direct determination of Cupper in different waste water samples obtained from some electroplating factories. It is found that the Cupper contents obtained from triplicate measurements using potentiometric measurement are in a satisfactory agreement with those obtained by using the AAS method. Thus, the electrode provides a good alternative procedure for the determination of CU^{2+} in real samples. The results are given in Table (3.13).

Table 3.4: Determination of Cupper (II) in some industrial
waste water samples with the sensor based on Ketofan,
and the AAS method

Sample	Potentiometrically (mg1-1)	AAS (mg 1-1)
1	9.2 ± 0.2	9.0 ± 0.5
2	11.5 ± 0.3	11.2 ± 0 .2
3	10.2 ±.0 2	9.8 ±0.2
4	8.9 ±0.4	8.7 ± 0.4

3.7.2. Titration of Cupper with EDTA

The proposed Cupper ion-selective electrode was applied as an indicator electrode in the potentiometric titration of CU^{2+} solutions with EDTA. 10 ml of 1.0×10^{-2} M CU^{2+} solution were titrated with 1.0×10^{-2} M solution of EDTA at pH = 6 using the proposed Cupper sensor. The resulting titration curve is shown in Fig. (3.32) .The observation of an unsymmetrical titration curve is due to the fact that, before the end point, the potential showed a usual logarithmic change with the volume of the titerant added, while the potential response after the end point remained almost Constant due to the low Concentration of the free Cu²⁺ in solution (Jain et al., 1997)



Fig.3.5: Potentiometric titration curve of 10 ml 10^{-2} M Cu (II) with EDTA solution (10^{-2} M) using the proposed electrode at pH

Conclusion

The proposed sensor is Composed of incorporated Ketofan as an electro active material in PVC matrix membrane and dioctyl phthalate or dioctylesepacate as solvent mediators. The sensor exhibited fast and stable near Nernstian cationic response of 29.7 ±0.1 mV Concentration decade of Cupper in the Concentration range of 1.0×10^{-6} -1.0 × 10^{-1} M. The lower limit of detection was $1.5 \times 10^{-7} \pm 0.2$. It is to be noted that the sensor based on Ketofan was used throughout this investigation in the pH range 4-8.5. The sensor displayed a good selectivity for Cupper with respect to a number of Common foreign inorganic and organic species. The was also successfully applied for sensor the determination of Cupper in waste water and in beer. It is also used as indicator electrode in the titration of Cupper with EDTA.

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