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Metal ion sensors for trace determination of metals in drugs and pharmaceuticals

Abstract: The new specific metal sensors for copper, zinc, nickel, cobalt, iron, arsenic, antimony, bismuth, vanadium, molybdenum, selenium, and lead were synthesized by using *N*-phenyl[1,2 methano fullerene C60]C61 complexes. The metal sensors were characterized by pH range, electrode response, response time, and associated metals. The limit of detection of the sensors was found to range between 3×10^{-7} and 5×10^{-7} , with lifetime between 6 and 8 months. These metal sensors were used for the detection and quantitative determination of trace metal impurities in drugs and pharmaceuticals.

Keywords: drugs; metal sensors; trace metals.

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Introduction

Some of the trace metals are essential for human health; however, when their concentration exceeds the limit, they become toxic (Oehme 1978). In literature, atomic absorption spectrometry and inductively coupled plasma are the most common techniques reported for the determination of trace metals. These are costly, and prior separation is required (Lobinski and Maczenko 1997, Hill 1999). The trace metals impurity occurs in drugs and pharmaceuticals through the bulk drugs (Ahuja and Alsanite 2004, Smith and Webb 2007). In view of this, it is desirable to develop suitable sensitive metal sensors for the quantitative estimates of trace metals in particular drugs and pharmaceuticals. Hydroxamic acids have a remarkable applicability

for metal ions (Agrawal 1979, 1980, Agrawal and Patel 1980, Agrawal and Sharma 2005, Agrawal and Vyas 2009). Fullerene hydroxamic acids are more selective and sensitive reagents for metal ions (Agrawal 2003, 2004). In the present investigation, the *N*-phenyl [1,2 methano fullerene C60]C61-formohydroxamic acid (PMFHA) metal sensors are reported for the direct determination of trace metals in pharmaceuticals.

Experimental

All the chemicals used were of analytical reagent (AR) or guaranteed reagent (GR) grades of E. Merck (Mumbai, Maharashtra, India) unless otherwise specified. Ion-free distilled water was used throughout the experiments.

Reagents

PMFHA was synthesized as described elsewhere (Agrawal 1997).

The drugs samples were obtained from Torrent Pharmaceuticals (Ahmedabad, India).

Apparatus

A Philips DC microvolt meter (model PP9004) (London, UK) with a saturated calomel electrode as a reference was used for potential measurements. A Systronics (Ahmedabad, Gujarat, India) μ c-based 361 pH system was used for pH measurements. The conductance was measured on a Systronics μ c-based conductivity meter 306.

Plasma scan model 710 sequential inductively coupled plasma-atomic emission spectrophotometer (ICP-AES) with plasma scan multitasking computer and peristaltic pump was used.

The following operating conditions were set for ICP-AES: radiofrequency, 27.12 MHz; incident power, 2000 W; GMK nebulizer; sample concentration, 1 ng ml⁻¹; radiofrequency power, 5 W; observation height, 14 mm; argon coolant flow rate, 10 l min⁻¹; argon carrier flow rate,

1 l min⁻¹; intergraph period, 10 s; resolution, 0.004 mm; and peristaltic pump flow rate, 1 ml min⁻¹.

Water content

The conditioned membranes were first soaked in water to elute diffusible salt, blotted quickly with Whatman filter paper to remove surface moisture, and immediately weighed. These were further dried to a constant weight in a vacuum over P₂O₅ for 24 h. The water content (% of total weight) was calculated as follows:

$$\frac{W_w - W_d}{W_w} \times 100$$

where W_w and W_d are the weight of the wet and dry membranes, respectively.

Thickness and swelling

The thickness of the membrane was measured by using a coordinate microscope.

Swelling was measured as the difference between the average thicknesses of the membrane equilibrated with 1 M NaCl for 24 h and dry membrane.

Electrolyte absorption

The membranes were immersed in 1 M of NaCl solution until equilibrium was attained. The electrolyte absorption was made by immersing the membrane in 1 M NaCl until the equilibrium was attained. It was taken out afterward, wiped to free it of the adhering electrolyte, and dipped into 25 ml of conductivity water for 3 to 4 h with intermittent shaking. The solution was transferred into a 100-ml measuring flask, and the process was repeated three times. The entire solution was collected in a measuring flask diluted to the mark with conductivity water, and its conductivity was measured.

Specific conductance

For electrical conductance measurements, the membranes were cemented between two half cells with 0.1 M NaCl. After equilibration, NaCl was replaced by mercury that had been equilibrated previously with the NaCl solution. The conductance was measured by connecting the platinum electrodes dipped in mercury to the conductivity bridge.

Metal sensors

The electroactive material required for the preparation of membrane metal ion sensors was of corresponding metal hydroxamate complexes of PMFHA. The material (250 mg) was mixed with polyvinyl chloride (125 mg) in 8 ml of tetrahydrofuran and finally mixed with 0.5 ml of dioctylphthalate used as a plasticizer (Cragg et al. 1974). The resulting solution was cast carefully on a glass plate and kept for slow evaporation to obtain a thin membrane.

Characterization of sensors

The physicochemical properties of membrane thickness, water content, and exchange capacity were determined as described elsewhere (Gregor et al. 1957, Srivastava et al. 1978) after conditioning the membrane. The membranes were conditioned by equilibrating with 1 M NaCl at pH 4.5–6.5 for 24 h.

Fabrication of membrane

The membrane metal sensors were fabricated as per the procedure of Cragg et al. (1974). Membranes of appropriate size were cut from the master membrane and moved at the lower end of the glass tube. A 0.1 M metal solution was used as internal reference.

Porosity

Porosity (E) was determined as the volume of water incorporated in the cavities per unit membrane volume from the water content data.

$$E = \frac{W_w - W_d}{AL\rho_w}$$

where W_w and W_d are the weight of wet and dry membranes, respectively; A and L are the area and thickness of the membrane, respectively; and ρ_w is the density of water.

Results and discussion

The properties of the fullerenes hydroxamate metal complexes are given in Table 1. The membrane properties such as porosity, water content, swelling, electrolyte absorption, and specific conductance are given in Table 2.

Metal	Metal complex	ν (cm ⁻¹)	Metal (%)		n (%)	
			Calculated	Found	Calculated	Found
Fe(II)	[C ₁₃₆ H ₁₂ N ₂ O ₄]Fe	1604	3.12	3.10	1.61	1.58
Co(II)	[C ₁₃₆ H ₁₂ N ₂ O ₄]Co	1599	3.28	3.24	1.56	1.54
Ni(II)	[C ₁₃₆ H ₁₂ N ₂ O ₄]Ni	1610	3.27	3.22	1.56	1.50
Cu(II)	[C ₁₃₆ H ₁₂ N ₂ O ₄]Cu	1615	3.53	3.49	1.55	1.52
Zn(II)	[C ₁₃₆ H ₁₂ N ₂ O ₄]Zn	1608	3.63	3.60	1.55	1.58
Cd(II)	[C ₁₃₆ H ₁₂ N ₂ O ₄]Cd	1610	6.08	6.01	1.51	1.47
Hg(II)	[C ₁₃₆ H ₁₂ N ₂ O ₄]Hg	1605	10.34	10.36	1.44	1.40
Pb(II)	[C ₁₃₆ H ₁₂ N ₂ O ₄]Pb	1618	10.65	10.59	1.44	1.39
As(III)	[C ₁₃₆ H ₁₃ N ₂ O ₅]As	1620	4.13	4.15	1.54	1.49
Sb(III)	[C ₁₃₆ H ₁₃ N ₂ O ₅]Sb	1605	6.54	6.58	1.51	1.47
Bi(III)	[C ₁₃₆ H ₁₂ N ₃ O ₇]Bi	1610	12.03	12.08	1.44	1.40
Se(IV)	[C ₁₃₆ H ₁₂ N ₂ O ₅]Se	1605	4.34	4.30	1.54	1.49

Table 1 Characteristics of metal hydroxamates.

The metal sensors of Fe(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Hg(II), Pb(II), As(III), Sb(III), Bi(III) and Se(IV) were prepared and characterized by studying the electrode response, response time, pH range, and selectivity factor. The data are given in Table 3. Characterization of the metal sensors is essential to correlate the movement of ions in the membrane with the potential generating across it. The physical characteristics of polyvinyl chloride matrix membranes based on PMFHA were analyzed to correlate with the movement of the ions in the membrane phase, potential generated across it, and the selectivity of the ions of interest. It was observed that the membranes were of less porosity and swelling (Table 2). The data given in Table 2 show that as swelling decreases the thickness increases. The water content and porosity of the membranes are of the same order. The electrolyte absorption reveals that the diffusion will take place only through the exchange sites

present in the membrane phase. Such membranes are expected to be selective in their response to a particular ion, hence leading to high selectivity of the membrane sensors. Generally, an ideal membrane should have less thickness; moderate swelling porosity and water content capacity as in the case of present membranes have better prospects for the selective determination of metals on the basis of their physical properties. The membranes were further characterized by response time, pH, and selectivity factor.

Effect of pH

The series of solutions with pH ranging from 1 to 13 was prepared (Jeffery et al. 1996), with the metal ion concentration constant. The pH studies were also performed

Hydroxamate membrane	Thickness (mm)	Water contents as % weight of wet membrane	Porosity	Swelling % of wet membrane	Electrolyte absorption (NaCl g ⁻¹) of wet membrane (μ g)	Specific conductivity (Ω^{-1} cm ⁻¹)
Fe(II)	0.65	18.5	0.095	0.250	25	1.31
Co(II)	0.83	20.2	0.102	0.185	28	1.22
Ni(II)	0.58	16.5	0.108	0.165	26	0.89
Cu(II)	0.90	19.0	0.099	0.215	29	0.95
Zn(II)	0.85	22.5	0.112	0.265	30	1.15
Cd(II)	0.75	25.0	0.115	0.285	24	1.62
Hg(II)	0.69	26.2	0.181	0.265	22	1.45
Pb(II)	0.98	23.0	0.187	0.198	28	2.00
As(III)	0.79	21.0	0.201	0.210	20	1.95
Sb(III)	0.52	19.8	0.212	0.185	21	2.10
Bi(III)	0.60	18.6	0.199	0.221	23	2.20
Se(IV)	1.10	27.8	0.089	0.188	29	2.40

Table 2 Characteristics of the membrane.

Electrode	Response time (s)	pH range	Slope (mV decade ⁻¹)		Detection range (M)	Detection limit (10 ⁻⁷ M)	Lifetime (month)	Correlation coefficient
			Graphical	Least square				
Fe(II)	25	2–6	40	39.8	10 ⁻¹ –10 ⁻⁷	3	7	0.999
Co(II)	30	1–6	38	38.5	10 ⁻¹ –10 ⁻⁷	3	6	0.999
Ni(II)	35	2–6	45	45.3	10 ⁻¹ –10 ⁻⁷	3	8	0.998
Cu(II)	20	2–5	35	34.9	10 ⁻¹ –10 ⁻⁷	3	8	0.999
Zn(II)	28	2–8	42	41.85	10 ⁻¹ –10 ⁻⁶	4	8	0.998
Cd(II)	35	2–9	40	40.56	10 ⁻¹ –10 ⁻⁶	4	8	0.998
Hg(II)	22	2–9	50	51.08	10 ⁻¹ –10 ⁻⁷	3	6	0.997
Pb(II)	26	2–9	48	47.52	10 ⁻¹ –10 ⁻⁷	3	7	0.996
As(III)	38	3–9	42	42.05	10 ⁻¹ –10 ⁻⁶	5	6	0.998
Sb(III)	20	4–9	46	45.68	10 ⁻¹ –10 ⁻⁶	5	6	0.997
Bi(III)	25	4–9	39	39.01	10 ⁻¹ –10 ⁻⁶	4	6	0.996
Se(IV)	35	2–10	44	44.18	10 ⁻¹ –10 ⁻⁷	3	7	0.999

Table 3 Characterization of the sensors.

at the various metal ions concentration (10⁻¹–10⁻⁴ M). The results shown in Table 3 indicate that metal sensors have a wide range of working pH (1–10).

Response time

The metal sensors' response time was studied for all the metal ion sensors. The response time was measured by recording the electromotive force of sensors as a function of time when it is immersed in the solution to be studied.

The electrode was first dipped in a 0.01 M solution of the desired ion, and immediately the potential was noted (reading at 0 s). Then, immediately the sensor was shifted to another solution of 0.1 M (concentration 10-fold higher) and the potential was noted at intervals of 5 s. The potential was then plotted against time. The time taken by sensors to obtain a steady potential is the response time of the electrode (Table 3).

Sensors' response

The sensors' response of the membrane ion-selective sensors was determined by measuring the potential at varying concentrations ranging from 1×10⁻¹ to 1×10⁻⁷ M.

It was observed that the response curve is linear up to the optimum concentration after which the curve tends to become parallel to the x-axis. Suitable concentrations were chosen corresponding to the sloping portion of the linear curve for the measurement of the potential (Figures 1 and 2). The sensors have a lifetime of between 6 and 8 months (Table 3).

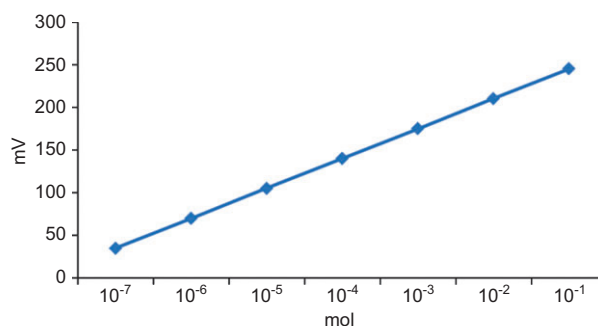


Figure 1 Copper metal sensors' response.

All the sensors of divalent and trivalent metals have a prompt response. The slope derived from the calibration curve is given in Table 3. A statistical *evaluation* of the linear sensors response was carried out by regression analysis and was compared with those computed graphically. It was found that both are in good agreement (Table 3).

International Conference on Harmonization (2005a,b) guidelines for method of validation and limit of detection

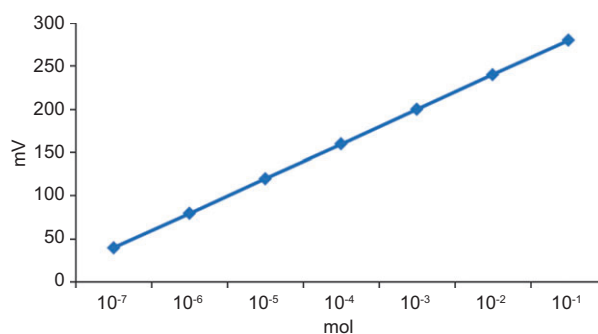


Figure 2 Cadmium metal sensors' response.

Membrane sensors	0.01 M solution of interfering ions											
	Fe(II)	Co(II)	Ni(II)	Cu(II)	Zn(II)	Cd(II)	Hg(II)	Pb(II)	As(III)	Sb(III)	Bi(III)	Se(IV)
Fe(II)	3.50	0.001	0.005	0.008	0.000	0.065	0.008	0.100	0.150	0.165	0.156	0.080
Co(II)	0.058	2.90	0.118	0.115	0.058	0.100	0.950	0.152	0.118	0.702	0.152	0.110
Ni(II)	0.118	0.115	2.50	0.210	0.003	0.008	0.115	0.079	0.002	0.111	0.080	0.005
Cu(II)	0.158	0.075	0.182	3.20	0.119	0.210	0.095	0.121	0.132	0.160	0.210	0.118
Zn(II)	0.008	0.004	0.075	0.032	4.01	0.175	0.632	0.008	0.213	0.222	0.180	0.005
Cd(II)	0.055	0.115	0.095	0.225	0.156	1.95	0.555	0.116	0.118	0.095	0.112	0.111
Hg(II)	0.118	0.210	0.115	0.310	0.225	0.009	1.08	0.095	0.118	0.115	0.000	0.116
Pb(II)	0.225	0.114	0.095	0.085	0.099	0.116	0.121	2.30	0.212	0.310	0.320	0.018
As(III)	0.000	0.095	0.110	0.065	0.210	0.205	0.115	0.333	1.85	0.485	0.502	0.010
Sb(III)	0.000	0.065	0.119	0.100	0.119	0.221	0.113	0.310	0.421	1.65	0.495	0.118
Bi(III)	0.000	0.55	0.092	0.880	0.185	0.196	0.111	0.229	0.520	0.444	1.50	0.225
Se(IV)	0.915	0.084	0.087	0.019	0.190	0.206	0.121	0.232	0.010	0.115	0.115	4.50

Table 4 Selectivity coefficient $K_{A,B}$ for metal sensors.

were followed. The concentration range (linearity) was estimated on the basis of the registration curve and the correlation coefficient (r) obtained from the standard solutions of the metal (Figures 1 and 2; Table 3). To study and check the accuracy of the proposed metal sensors, the experiments were carried out by the addition of standard metal ions into the drug solution of three different concentration levels. The results of the recovery studies were found to be satisfactory (Tables 4 and 5).

The limit of detections were calculated on the basis of the standard deviation of the response and the slope of the calibration curve according to the following formula: Limit of detection = $3.3(\text{standard deviation/slope})$. The values are given in Table 3.

Selectivity coefficient

The selectivity coefficient was calculated by measuring the potential of a cell comprising a metal sensor and a

reference electrode with a solution of 10^{-2} M interference ions (a_B) and varying the activity of the primary ion (a_A). The potential values obtained were plotted against the activity of the primary ion, and the selectivity coefficient (Bailey 1976) $K_{A,B}^{\text{POT}}$ was calculated from the following equation:

$$K_{A,B}^{\text{POT}} = \left(\frac{a_A}{a_B} \right)^{\frac{z_A}{z_B}}$$

In most of the cases, fixed concentrations of interfering ions (10^{-2} and 10^{-4} mol) were used against the varying concentration of the primary ion. The selectivity coefficients calculated are given in Table 4.

Selenium metal sensors have the maximum selectivity compared with the 13 other metal sensors and a negligible interference from other ions (Table 5). However, the high concentration of lead interferes with nickel metal sensors. Similarly, cobalt has a selectivity of 2.90 but shows interference with copper, which has a selectivity of 3.20. However, a concentration of $<10^{-2}$ M can easily be

Metals	Metal added (ppm)	Metal found		Metal found in ibuprofen (ppm)	
		Metal sensors	ICP-AES	Metal sensors	ICP-AES
Fe	10	9.98±0.05	9.99±0.04	0.115±0.003	0.113±0.002
Co	10	10.05±0.08	9.97±0.05	0.003±0.001	0.004±0.001
Ni	10	10.03±0.06	10.05±0.08	0.005±0.001	0.007±0.002
Cu	15	14.95±0.06	14.98±0.05	0.109±0.002	0.100±0.003
Zn	15	14.98±0.05	14.94±0.08	0.001±0.001	0.001±0.001
As	15	15.02±0.05	15.05±0.05	0.004±0.001	0.005±0.001
Sb	15	15.04±0.05	15.06±0.08	ND	0.001±0.001
Bi	15	14.97±0.05	14.98±0.05	0.003±0.001	0.005±0.002

Table 5 Analytical data for sensors.

Average of 10 determinations. ICP-AES, inductively coupled plasma-atomic emission spectrophotometer; ND, not determined.

Drugs/pharmaceuticals	Metals (ppm)											
	Fe	Co	Ni	Cu	Zn	Cd	Hg	Pb	As	Sb	Bi	Se
Serteraline	0.058	0.005	0.005	0.085	0.002	0.050	ND	0.002	0.005	ND	0.004	0.001
Fluoxetine	0.075	0.004	0.003	0.115	0.003	0.095	0.001	0.002	0.003	ND	0.005	0.001
Nimesulide	0.105	0.006	0.004	0.120	0.002	0.09	0.002	0.002	0.002	ND	0.003	0.002
Ibuprofen	0.115	0.003	0.005	0.109	0.001	ND	0.001	0.002	0.004	ND	0.003	0.001
Citalopram	0.045	0.004	0.002	0.113	0.003	ND	0.001	0.001	0.005	ND	0.003	0.005
Venlafaxin	0.055	0.005	0.004	0.265	0.002	ND	0.001	0.001	0.003	ND	0.002	0.002
Diclofenal	0.095	0.006	0.003	0.098	0.002	ND	ND	0.001	0.003	ND	0.001	0.001
Paroxetine	0.113	0.002	0.005	0.995	0.002	ND	ND	0.001	0.002	ND	0.002	0.002

Table 6 Determination of trace metal in drugs/pharmaceuticals. ND, not determined.

tolerated. Most of the other ions do not show any interference. Table 4 shows that these metal sensors can be used for the determinations of trace metals.

Determination of trace metal impurities in drug

The weight quantity of the drug was digested with concentrated HClO_4 and HNO_3 (1:0.1) and diluted to 100 ml with distilled water. The appropriate aliquot was transferred and further diluted with distilled water. The selective metal sensors and calomel reference electrode were

immersed and the potentials were noted. The metal ion concentration was calculated from the calibration curve.

The accuracy, selectivity, and validity of the sensors were checked by determining the standard metal solutions by using the metal sensors and ICP-AES. They were also validated by adding the standard metal solution into the drug solutions and determining the metals with both metal sensors and ICP-AES. The data given in Table 5 are in good agreement with the values obtained by using metal sensors and ICP-AES. The trace metal impurities in the drugs are given in Table 6.

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