Int. J. Electrochem. Sci., 15 **(2020)** 9223 – 9232, doi: 10.20964/2020.09.39

International Journal of
ELECTROCHEMICAL
SCIENCE
www.electrochemsci.org

Ion-selective Membrane Sensor for Magnesium Determination in Pharmaceutical Formulations

Sabry Khalil[1,2,*] *and Salman S. Alharthi*[3]

[1] Food Nutrition Science Department, Faculty of Science, Taif University, Taif 21974, P. O. Box 888, KSA.
[2] Chemistry Department, Faculty of Science, Fayoum University, Fayoum, Egypt.
[3] Chemistry Department, Faculty of Science, Taif University, Taif 21944, P. O. Box 7685, KSA.
[*]E-mail: S_Khalil_99@Yahoo.co.uk

Received: 22 May 2020 / *Accepted:* 3 July 2020 / *Published:* 10 August 2020

An optimal composition for magnesium liquid membrane sensor based on the reaction of magnesium ions with the macro cyclic reagent 1,4,7 - triazacyclononane - 1,4,7 - tris - methylene methylphosphinic acid. The characteristics slope (30.5 mV), the limit of detection (6.2 x 10^{-7} M), the coefficient of selectivity toward some metal ions, response time (15 s), lifetime (180 days),the effect of pH on the sensor potential and the basic analytical parameters were studied. The sensor was used to estimate the concentration magnesium ions concentration in pharmaceutical preparations. The obtained results by the developed sensor were statistically analyzed and compared with those of other different reported methods.

Keywords: A triazacyclo complex, Membrane sensor, magnesium estimation, pharmaceutical analysis.

1. INTRODUCTION

The very important role of magnesium in human body including many functions helping with muscle and nervous system, it binds in reactions of over than 300 enzyme, supporting the immune system and regulating blood pressure. Doctors relate its deficiency with a wide range of health complications. Therefore, people should aim to take their daily recommended amounts of magnesium [1-3]. It is one of seven essential macro minerals that people need to consume at least 100 milligrams per day. Getting enough amount of magnesium can help in treatment many chronic diseases, such as type- 2 diabetes, migraine, cardiovascular and diseases.

The methods for the trace amounts of magnesium ions determination are atomic absorption spectrophotometry, (AAS) [4, 5], inductively coupled plasma mass spectrometry (ICP-MS) [6], inductively coupled plasma atomic emission spectrometry, ICP-AES [7], liquid

chromatography/inductively coupled plasma atomic emission spectrometry, (LC/ICP-AES) [8], mass spectrometry, MS [9], isotope dilution mass spectrometry [10], X-ray fluorescence spectrometry [11]. There were many kinds of magnesium determination in the literature including selective membrane sensors[12-31]. However, most of the developed sensors have a very narrow working concentration range and suffer from calcium interference.

A number of new specific ligands related to heterodiazo dyes which form stable chelating complexes with many active metal ions were prepared to estimate them in pharmaceutical preparations by new, selective and very sensitive spectrophotometric estimation [32-33].

The reagent 1,4,7-triazacyclononane-1,4,7-tris-methylene methylphosphinic acid., CNTMMP which forms the relatively most stable complex with magnesium. has not only good sensitivity but also a very good selectivity coefficient. So, without frequency we took our decition to use its analytical usefulness in the construction of a magnesium membrane sensor. It has proven to be the best using ligand for magnesium ions estimation [34].

2. EXPERIMENTAL

2.1. Materials and Reagents

Sulphates of magnesium, zinc and nickel , chlorides of cobalt, cadmium, sodium and calcium, hydrogen peroxide, ammonium and sodium hydroxide. PVC and TEHP [tri - (2 - ethylhexyl) phosphate] were Aldrich products. Sulfuric , hydrochloric acids and TBP (tributylphosphate) from Merck [Germany]. Pharmaceutical formulations containing magnesium; Vita Force 21-Plus, Magnesium Gluconate, Magnesium Aspartate, Magnesium Citrate, Magnesium with B6 and Magnesium Orotate were obtained from local markets in Egypt and Saudia Arabia.

2.2. Stock Solutions Preparation

Sulphate stock solutions of magnesium, nickel and zinc and chloride stock of cobalt, cadmium, calcium and sodium of 10^{-1} molar solutions were prepared by dissolving the required weighed quantities of each salt in bidistilled water. Solutions of 10^{-6} - 10^{-1} molar concentration were prepared by dilution.

Magnesium sulphate standard solutions used in estimation of magnesium in pharmaceutical formulations were prepared by dissolving a calculated quantity of the salt in 5 x 10^{-2} molar sodium chloride and dilution.

2.3. Mineralization of the Pharmaceutical Preparations

The required solutions for potentiometric measurements were prepared as follow: a content of pharmaceutical formulations (Vita Force 21-Plus, magnesium gluconate, magnesium aspartate, magnesium citrate, magnesium with vitamin B6 and magnesium orotate) was transferred into a

conical flask, adding 10 ml 30 % H_2O_2 and left to stand till dissolving. Then, adding 1 ml of concentrated H_2SO_4 , heating until H_2O_2 analized. This step was repeated six times. After mineralization adding 25 ml water and 10 ml ammonia solution , left to stand for on hour. After that filter the solution quantitatively and diluted with bidistilled water.

2.4. Construction of the Sensor

The construction of the sensor membrane was introduced as described previously [35]. The sensor includes a teflon exchangable coloumn electrode and a body full of a membrane liquid phase + an internal reference Ag/Ag Cl electrode.

2.5. The Liquid-Membrane Layer Active component

The reagent 1,4,7-triazacyclononane-1,4,7-tris-methylene methylphosphinic acid., CNTMMP is a white powder active membrane component. It dissolved completly in 10 % alkaline solutions; the stablility constant of its magnesium complex (log K = 12.5).

2.6. The Potential Layer Preparation

An accurate weight mixture of 0.01g active component [Mg (CNTMMP)$_2$], , 0.45g TEHP, 0.08g PVC and 0.45g TBP and perform the sensor's layer membrane. A sensor teflon with an electrode of Ag/AgCl was filled with the freshly prepared mixture, then transforming to gel by heating at 375 K of temperature for 20 minute. After cooling, the electrode was soaked for 30 minutes in 0.001 M magnesium ions solution.

2.7. Measurements of the EM F

The measurements of the EMF of magnesium sensor system an Orion 90-02 reference electrode was used with a mechanical stirrer to give an accuracy of 0.1 mV at room temperature. An Orion 90-00-01 solution containing 1.5 M potassium nitrate, 0.55 M potassium chloridel,0.05 M sodium chloride and 40 % formaldhyde 1 ml was used to fill the stable reference electrode's bridge.

3. RESULTS AND DISCUSSION

The basic analytical parameters of the constructed magnesium sensor were studied to detect its importance applications in analytical estimation.The selectivity, dependence of pH on the sensor's potential, response time, detection limit and the characteristics slope were reported.

3.1. Calibration curves

Fig.1 shown the magnesium sensor's calibration curves estimated in magnesium and its interfering ions of 10^{-6}-10^{-1} molar solutions.

The magnesium sensor's characteristics slope is 30.5 mV ,the detection limit is 6.2 x 10^{-7} molar and the measuring range is 10^{-6} – 10^{-1} M. Table 1 presented the analytical characteristic parameters of the proposed magnesium sensor.

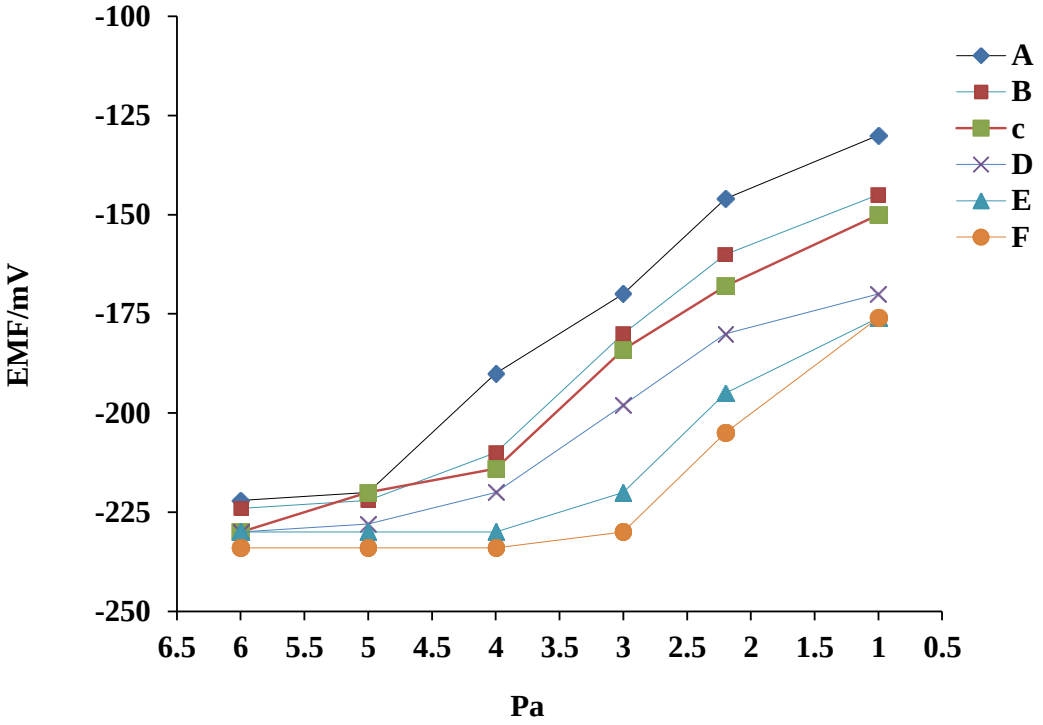

Figure 1. Calibration curves of magnesium sensor, (A) Mg, (B) Cu, (C) Cd, (D) Ni, (E) Co and (F) Ca cations estimated in magnesium and its interfering ions of 10^{-6}-10^{-1} molar solutions

Table 1. Analytical characteristics parameters of the magnesium sensor matrix (reference electrode Ag/AgCl) membrane sensor preparation.

Slope of the characteristics / mV	30.5 + 0.1
Intercept / mV	- 68.7 + 0.4
Limit of detection / mol dm^{-3}	6.2 x 10^{-7}
Measuring range / mol dm^{-3}	1 x 10^{-6} - 7.3 x 10^{-1}
Response time / s	15
Lifetime / d	180
pH range	5.5 – 8.2

3.2. Selectivity Coefficients Sensor's Measurements

The selectivity coefficients of the magnesium sensor with reference to interfering ions were estimated by the separate solution or by the MP, (matched potential) methods described by Gadzekpo and Christian [36] using the equations:

$$\log k_{ij}^{pot} = \frac{E_2 - E_1}{S} - (\frac{z_i}{z_j} - 1)\log a_i, \qquad K^{pot}_{Mg/M} = \frac{ai}{ai^{\frac{zi}{zj}}}$$

By using the separate solution method, at the value of EMF with magnesium ions concentration 0.001 M and, the potential –160 mV. For the MPM method, the equation is:

$$K^{pot}_{Mg/M} = \frac{ai}{ai\frac{zi}{zj}}$$

The obtained data are shown in Table 2.

Table 2. Selectivity coefficients (K) of the magnesium sensor matrix (reference electrode Ag/AgCl) membrane sensor preparation.

Separate solution method			
K	$E_i = E_j$	$a_i = a_j$	MPM
$MgCl_2$	0.315 + 0.021	0.376 + 0.01	0.343 + 0.03
$NiCl_2$	0.234 + 0.006	0.311 + 0.02	0.274 + 0.012
$CoCl_2$	0.074 + 0.002	0.132 + 0.004	0.263 + 0.015
$ZnCl_2$	0.012 + 0.0005	0.032 + 0.005	0.005 + 0.0003
$CdCl_2$	0.253 + 0.007	0.326 + 0.02	0.286 + 0.009
$CaCl_2$	0.013 + 0.0006	0.048 + 0.003	0.014 + 0.0005

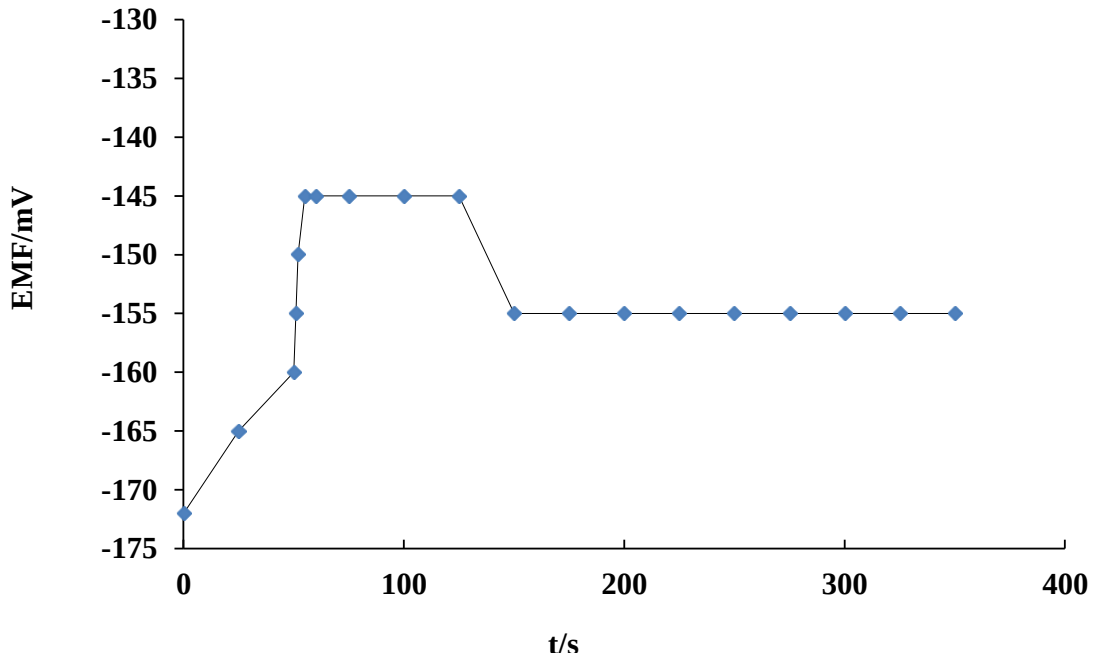

Figure 2. The response time of the sensor in magnesium ions concentration [10^{-6} - 10^{-1} M].

3.3. Response Time

For analytical applications, the response time of a fabricated sensor is of critical importance. The average time required for the electrode to reach a steady potential response within ±1 mV of the final equilibrium value after successive injection of a series of magnesium ion solutions, each having a 10-fold difference in concentration. After injecting the standard concentrated solution, adding water (1:1) for dilution. Solutions used for evaluation of the investigated sensor response time has these conditions: c1 : c2 = 1:100, v1 : v2 = 1: 20, where c1 is the sample concentration, c2

, the standard concentration, v1 is the sample volume and v2 is the standard volume. The results obtained are introduced in Fig. 2. The response of the sensor is stabilized after 15 second of the mercury addition. The timer is started at the instant of injection of the concentrated sample, this fast and stable potential reading is reflected on the time needed for complete titration process.

3.4. Effect of pH on EMF

The effect of potential of the sensor on pH was studied according to the chemical character of magnesium salts. Hydrochloric acid or drops of sodium hydroxide were added to the 0.001 M magnesium ions concentration sample under investigation. After each addition of the acid or base the pH was measured, the ratio of the EMF of the magnesium sensor systemn / reference electrode was read after the sensor's response stabilised. The effect of pH on the EMF is introduced in Fig.3. Below and above this range of pH (5.5 – 8.2) the clear decreasing in potentials may be attributed to the hydrolysis or non-complete complex formation or magnesium ions.

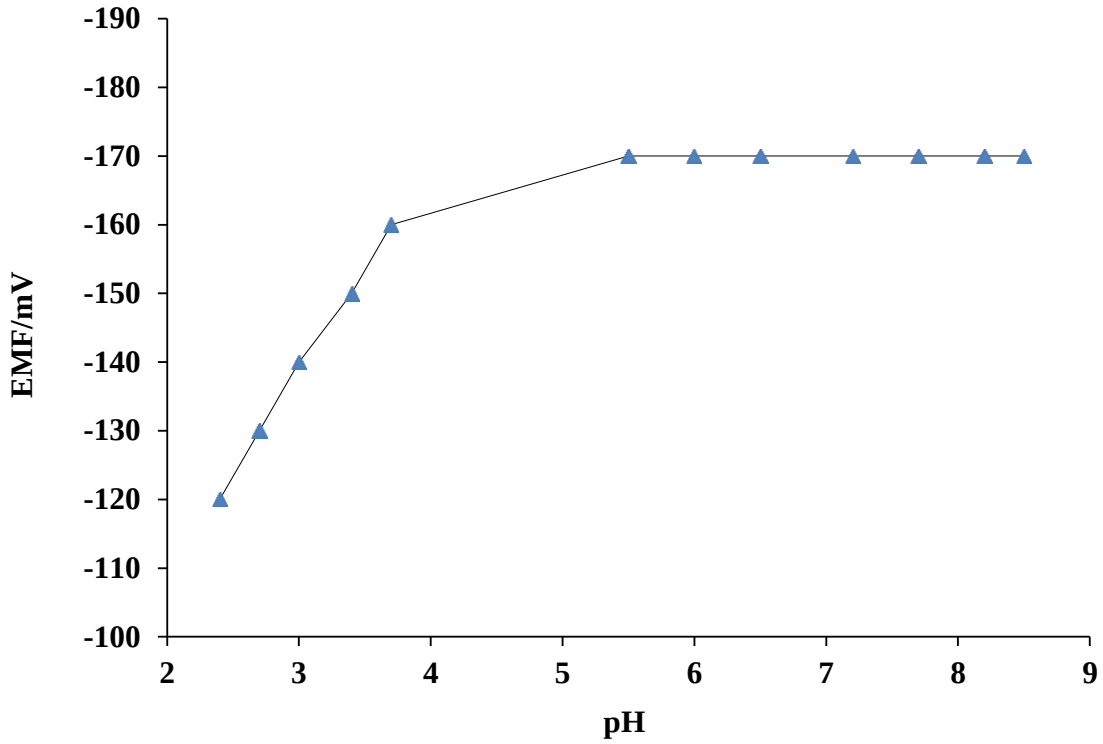

Figure 3. pH dependence of the sensor response in magnesium ions concentration [10^{-6} - 10^{-1} M].

3.5. Lifetime of the Sensor

The lifetime of the sensor under investigation was tested by measuring the characteristics slopes of the sensor stored in drying air. The regular examinations were carried out in a systematic way once a week, in freshly prepared solutions. According to the basis of the obtained data, the lifetime of the sensor is aproximatly six months.

3.6. Magnesium Estimation in Pharmaceutical Products

Estimation of magnesium in pharmaceutical preparations was carried out by using the prepared sensor to test its analytical usefulness. The standard additions and the calibration curve methods of the sample were used. The estimated data and their statistical treatment are shown in Table 3.

Table 3. Magnesium estimation results in pharmaceutical formulations using matrix (reference electrode Ag/AgCl) membrane sensor preparation.

Product (Active principal)	Calibration Curve Method				Standard addition in the sample with dilution			
	Product Data mg	Mg^{+2} Found mg	Relative Error %	V %	Product Data mg	Mg^{+2} Found mg	Relative Error %	V %
Vita Force 21-Plus	20	20.08	0.4	0.16	20	20.25	1.25	0.20
Magnesium Gluconate	341	341.04	0.01	0.35	341	341.36	0.11	0.34
Magnesium Aspartate	50	50.06	0.12	1.30	50	50.65	1.30	1.75
Magnesium Citrate	75	75.12	0.16	1.54	75	75.56	0.74	1.12
Magnesium with B6	100	100.06	0.06	1.56	100	100.42	0.42	1.14.
Magnesium Orotate	25	25.05	0.20	1.75	25	25.34	1.36	2.44

- The averages of 5 estimations.
- $V = \frac{\delta n - 1}{x} \times 100\ \%$.

3.7. Comparison with the literature

Table 4. Comparison of analytical parameters of different methods for magnesium estimation.

Method	Slope (mV)	Linear Range (M)	Lifetime	Detection Limit (M)	Ref.
Present Method " this work data "	30.5 ± 0.1	1×10^{-6}-7.3×10^{-1}	Six months	6.2×10^{-7}	--
Mg - Spectrophotometry	---------	$0.0 - 2.0 \times 10^{-2}$		2.4×10^{-4}	11
Mg - Spectrophotometry	---------	0.5×10^{-4}- 1.2×10^{-3}		1.2×10^{-5}	12
Mg - Ion-Sel. Electrode	28.4	1.0×10^{-6} - 1.0×10^{-3}	Eight months	1.7×10^{-6}	13
Mg - Ion-Sel. Electrode	29 ± 0.2	1.9×10^{-6} - 1.0×10^{-1}	Three months	5.0×10^{-5}	14
Mg - Ion-Sel. Electrode	31 ± 1	1.0×10^{-5}- 1.0×10^{-1}	Four months	2.3×10^{-4}	17
Mg - Ion-Sel. Electrode	28.6± 0.4	6.0×10^{-4} - 1.8×10^{-3}	One week	$0{,}1 \times 10^{-5}$	18
Mg - Ion-Sel. Electrode	30	3.2×10^{-5} - 1.0×10^{-1}	One month	-----	22
Mg - Spectrophotometry	----------	0.038×10^{-6} - 0.204×10^{-6}		------	23
Mg - Ion-Sel. Electrode	29.2 ± 0.4	9.4×10^{-6} - 1.0×10^{-1}	Five months	-------	24
Mg - Spectrophotometry	----------	2.0×10^{-5} - 1.4×10^{-4}		1.25×10^{-6}	25
Mg - HPLC	----------	4.0×10^{-5} - 4.2×10^{-4}		2.80×10^{-5}	26
Mg - Spectrophotometry	----------	5.0×10^{-5} - 5.0×10^{-4}		1.66×10^{-5}	27
Mg - Spectrophotometry	---------	2.91×10^{-6} - 1.25×10^{-3}		2.41×10^{-6}	28
Mg - Spectrophotometry	---------	3.0×10^{-5} - 1.79×10^{-5}		3.12×10^{-6}	29
Mg - Sequential Injection	---------	4.16×10^{-5} - 2.00×10^{-4}		----------	30
Mg - ICP- OES	---------	8.30×10^{-2}		----------	31

The obtained results by the developed sensor method were statistically analyzed and compared with those obtained by other different reported methods. Table 4 shows a comparison between some characteristics of the quantitative estimation of magnesium ions using different methods cited in the literature which applied the ISE's, and other methods. This comparison was made to establish, whether the proposed sensor gives reliable results and be accepted for magnesium ions analysis in pharmaceutical preparations. It can be observed from Table 4 that The proposed sensor exhibits comparable linear range (1×10^{-6} - 7.3×10^{-1} M) which is superior to the methods reported for magnesium ion- selective electrodes [13, 14, 17, 18, 22 and 24] , to the spectrophotometric methods reported for determinaation of magnesium [11, 12, 23, 25 and 27-29], HPLC- method [26] and those other methods for magnesium determination sequintial injection and ICP-OES [30-31]. It has a long shelf life, (six months) compared to the other reported sensors, [14]; (Three months), [17]; (Four months), [18]; (One week), [22]; (One month) and [24]; (Five months), all methods reach low detection limits although the lowest of them all corresponds to that reported in this work (6.2×10^{-7}). Further, the sensor proposed has advantages as compared with others in that it is easy to construct, it is plainly affordable. Therefore, it can be safely stated that the sensor proposed is comparable in all senses with other sensors and methods to determine magnesium.

No interference was presented from the excipients found in the pharmaceutical preparations. The calibration curves recovered a good linear responses on a wide suitable range. Most of the methods show an excellent recovery with respect to the known values and there is no significant differences for either accuracy or precision were observed.

4. CONCLUSION

An optimal composition of the magnesium sensor was introduced. The proposed sensor is characterized by excellent analytical characteristics: for the Nernstian slope, short response time and relatively long lifetime. The analytical properties of the investigated sensor are shown in Tables 1 and 2.

The sensor was used for magnesium ions estimation in six different pharmaceutical preparations used in common. The calibration curve and the standard additions methods were employed. The analysis of the results of magnesium estimation in pharmaceutical sample products shows that the method of calibration curve is recommended in magnesium estimation while the method of standard additions is less reliable. Therefore, the error is no bigger than 2 % due to the obtained reproducible results. The developed sensors method was found as precise and accurate as compared to other reported techniques which is widely used in their estimation in pharmaceutical formulation Table 4.

Generally, the quality of the obtained data was extremly satisfied confirming the excellent of the analytical applications using the proposed sensor. It can be used in common both in research and in pharmaceutical industry laboratories. The consuming time needed for analyses is decreased without any effect on the accuracy, precision and reproducibility of the results.

ACKNOWLEDGEMENTS
Many thanks to Professor M. M. Omar, College of Sciences, University of Cairo, Egypt for his kind interest helping this work. The Authors also wish to thank of Faculty of Science - Taif University, KSA for their invaluable assistance in the use of equipments available in the chemistry laboratories

References

1. R. K. Rude , P. M. Coates, J. M. Betz, M. R. Blackman, G. M. Cragg, M. Levine, J. Moss and J. D. White, eds. Encyclopedia of Dietary Supplements. 2nd ed. New York, *Informa Healthcare*, (2010), 527.
2. R. K. Rude , A. C. Ross, B. Caballero, R. J. Cousins, K. L. Tucker and T. R. Ziegler, Modern Nutrition in Health and Disease. 11th ed. Baltimore, Mass: Lippincott Williams & Wilkins, (2012) 159.
3. A. Abarca, E. Canfranc, I. Sierra and M. L. Marina, *J. Pharm. Biomed. Anal*., 5-6 (2001)941.
4. B. Ftima, *Food Chem.*, 116 (2009)580.
5. Y. Sahan, F. Basoglu and S. Gucer, *Food Chem*., 105 (2007) 395.
6. A. Krejcova, T. Cernohorsky and E. Curdova, *J. Anal. At. Spectrom*., 16 (2001) 1002.
7. B. Bocca, A. Alimonti, E. Coni, M. Di Pasquale, L. Giglio, A. P. Bocca and S. Caroli,*Talanta*, 2 (2000) 295.
8. A. J. Walder, I. Platzner and P. A. Freedman, *J Anal. At. Spectrom*., 8 (1993) 19.
9. H. L. Yuan, S. Gao, C. L. Zong and M. N. Dai, *Spectrochimica Acta Part B: Atomic Spectroscopy*, 64 (2009) 1228.
10. G. N. Eby, *Irish J. Agr. and Food Res*, 56 (2017)1.
11. S. F. D'Souza, *Microbial biosensors*, *Biosensors and Bioelectronics*, 16 (2001) 337.
12. M. Shamsipur, A. Soleymanpour, M. Akhond, H. Sharghi and A. R. Massah, *Talanta*, 58 (2002) 237.
13. Z. R. Zhang and R. Q. Yu, *Talanta*, 41 (1994) 327.
14. A. K. Singh, P. Saxena, S. Mehtab, and B. Gupta, *Talanta*, 69 (2006) 521.
15. M. Maj-Zurawska, M. Rouilly, W. E. Morf and W. Simon,*Analytica Chimica Acta*, 218 (1989) 47.
16. V. K. Gupta, S. Chandra and R. Mangla, *Sensors and Actuators* B, 86 (2002) 235.
17. X. Zhang, A. Fakler and U. E. Spichiger, *Electroanalysis*, 10 (1998)1174.
18. W. Zhang, L. Jenny and U. E. Spichiger, *Analytical Sciences*, 16 (2000) 11.
19. M. Urbanowicz, D. G. Pijanowska, A. Jasiński, M. Ekman and M. K. Bocheńska, *J. Solid State Electrochemistry*, 23(2019) 3299.
20. S. Chandra, K. Sharma and A. Kumar, *J. of Chemistry,* 1(2013) 1.
21. H. Gohari, *Open J. of Anal. and Bioanal.Chem*., 1(2017) 1.
22. A. K. Singh, A. Panwar, S. Kumar and S. Baniwal, *The Analyst*, 124 (1999) 521.
23. S.Mandal, A. Alispahic,A.Dedic and H. Dzudzevic - Cancar, *Kem. Ind.*,68(2019)197.
24. V. K. Gupta, R. P. Prasad and A. Kumar, *Talanta,* 63(2004)1027.
25. M. Benamor and N. Aguerssif, *Spectrochimica Acta part A*, 69(2008)676.
26. A. Vawaresou, E. Tsirivas, K. Lakovou, E. Gikas and L. Panderi, *Analytica Chimica Acta*,573-574(2006)284.
27. A. Y. Shishov, L. S. Nikolaeva, L. N. Moskvin and A. V. Bulatov, *Talanta*, 135(2015)133.
28. A. Shokrollahi, K. Hemmatidoust and F. Zarghampour, *J. of Taibah Univ, for Sci.*,10(2016)161.
29. K. A. Idriss, . Sedaira and H. M. Ahmed, Talanta, 54(2001)369.
30. A. Machado,R. Maneiras, A. A. Bordalo and R. B. R. Mesquita, *Talanta*, 186(2018)192.
31. J. C. Farinas, I. Rucandio, M. S. Pomares-Alfonso, M. E. Villanueva and T. Larrea, Talanta,154(2016)53.
32. E. A. Gautier, R. T. Gettar and R. E. Servant, *Anal. Chim. Acta*, 283(1993) 350.

33. P. Janos and M. Broul, *Chem. Listy*, 86 (1992) 139.
34. J. Huskens and A.D. Sherry, *J. Am. Chem. Soc*., 118(1996) 4396.
35. R. Dumkiewicz, *Analyst*,(1989), 114, 21.
36. V. P. Y. Gadzekpo and G. D. Christian, *Anal. Chim. Acta*, 164(1984) 279.

© 2020 The Authors. Published by ESG (www.electrochemsci.org). This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/4.0/).