Anodic Stripping Voltammetric Determination of Copper in Multivitamin-Mineral Formulations using Iodine-Coated Platinum Electrode

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Recieved: March 02, 2021; Accepted: March 25, 2021
DOI: 10.17721/moca.2021.48-56
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In this work, the utilization of the modified iodine-coated polycrystalline platinum electrode as a voltammetric sensor for copper determination in pharmaceutical formulations was reported. The optimized experimental parameters for the determination of copper were using 0.1M KCl as a supporting electrolyte with a scan rate of 50 mV/s, deposition potential of -0.2 V, and a deposition time of 2 minutes. The anodic peak related to Copper oxidation is centered at about +0.05 V. The extended detected linear range for the developed method was between 1 ppm and 100 ppm. The anodic current showed excellent linearity with $R^2 = 0.9986$. The limit of detection (LOD) and limit of quantitation (LOQ) were 0.115 ppm and 0.346 ppm, respectively, which attests to the sensitivity of the method. The investigation for the effect of potential interferences from multivitamins tablet ingredients indicated a specific selectivity toward copper and the absence of any electrochemical response toward these components. The developed method was successfully applied to analyze copper and the obtained results were in good agreement with the labeled values, besides that, the statistical tests indicated no significant difference at p = 0.05 with 95% confidence level.

Keywords: copper, pharmaceutical formulation, vitamins-minerals, anodic stripping voltammetry, iodine-coated platinum electrode

Determination of trace copper in pharmaceutical formulations is of great importance. Copper element considers one of the important trace minerals for human health. It is cannot be formed by the human body. For that, it must be ingested from dietary sources every day [1]. It is found in all human body tissues. Together with iron, copper enables the body to produce red blood cells [2]. Cu is largely present in biological systems as a cupric form (Cu^{2+}) [3]. It helps maintain the health of bones, blood vessels, nerves, and immune function [4]. Also, it is an essential component in several proteins indispensable for life [5]. Whereas, copper deficiency has been correlated with bone distortion during development and as a contributory factor to osteoporosis in adults and also associated with other malfunction in human body [6]. Multivitamin-minerals tablets are popular and widely used in our country and abroad. These tablets contain, in general, essential vitamins (vitamin B-complex, vitamin C, and vitamin E) and some other trace elements. As medicines, these considered as a good alternative resource for natural vitamins and minerals. Copper is both vital and toxic for human health. Thus, the determination of trace amounts of copper is becoming increasingly important. Frequently used methods for the determination of copper are atomic absorption spectrometry [7-9], spectrophotometry [10], flow injection [11], and ICP-MS [12], where all these applied methods are expensive and need special instrumentation, skilled person, and environmentally unfriendly reagents.

The approaches of electroanalysis are innovative and active for analytical practices that have a clear impact on the health of humans and the environment by analyzing an extended range of various samples. Electrochemical methods are pointedly recognized due to their great properties of low cost, ease of preparations, and short time of analysis time with a distinguishable analytical performance [13-18]. Pencil graphite electrode is a recognized multipurpose tool for electroanalysis of bioactive molecules because of carbon atom hybridization (sp^2) which has several characteristics such as little background current, easy exterior modification, excellent electrical conductivity, adsorption, and mechanical stability [19, 20]. Also, carbon nanotubes (CNTs) became widely utilizes in electrochemical sensor fabrications because of their great electronic properties, extensive potential ranges, rapid renewal, and less residual noise with extreme stability [21-23]. Surfactants and nanomaterials can also change and control the characteristics of electrode surface, which alter the reaction rates and pathways. Surfactant-modified electrodes have extended applications in the electroanalysis of organic molecules

which including medicinal, nutritional, and bio-samples assessment [24-27].

A few methods have been reported for the use of voltammetric sensors for copper determination in pharmaceutical formulations [28, 29].

Modification of solid electrode surfaces improving the electrochemical methodology. The adsorbed iodine at platinum electrode surface enhances the reproducibility of voltammetry and simplify the background behavior [30]. Also coating of solid electrodes surface alter the kinetics and mechanisms of reactions run at electrode surface. Iodine is one the anions simply adsorbed to electrode surface. The chemisorptions process achieved by two ways; from solution or from vacuum to form stable chemisorbed mono layers even the iodine coated electrode would be rinsed or evacuated [31]. The iodine is adsorbed at potential 0.2 V vs. Ag/AgCl or SCE reference electrodes [32] which is the double layer potential. At the surface of polycrystalline platinum electrode an oxidation reaction of iodine anions from solution leads to spontaneous chemisorption of iodine anion to form stable neutral iodine atoms at the electrode surface accompanied by hydrogen gas evolution. The adsorbed iodine is less reactive toward electrochemical oxidation compared with the free iodine anion in solution [33]. The adsorbed iodine depends on the electrode potential [34]. The chemisorbed iodine can be desorbed from platinum electrode surface if the potential scanned lower than -0.2 V which lead to reduction of hydrogen ions and generation hydrogen gas [33]. Also the rate of iodine desorption from electrode surface increase as the potential become more negative [34]. At the positive direction, the chemisorbed iodine begins to be desorbed at potential 1.0 [32]. Carbon monoxide is completely desorbed iodine from platinum electrode surface at potential lower than 0.35 V while at higher potential incomplete desorption is occurred [35].

Iodine-coated platinum electrode has been applied for the electrochemical determination of organic and non-organic species in many works [36-44]. Iodine-coated platinum electrode is characterized by the simplicity in preparation, application, and the absence of the need for environmentally unfriendly chemical reagents. The simplicity of the instrumentations all stimulated the implementation of the present work. This work was undertaken with the aim of extending the use of anodic stripping voltammetry at iodine-coated platinum electrode for analyzing copper in pharmaceutical formulations.

Experimental part

Materials and apparatus. A potentiostat (PAR Model 362, EG & G) interfaced to a computer via GPIB interface (IEEE) equipped with a locally modified Labview® (IEEE) software was used for data acquisition and experimental control. A one-compartment electrochemical cell with an inlet/outlet system for deoxygenation and blanketing with highly pure nitrogen gas was used. A 0.5 mm polycrystalline platinum wire purchased from Aldrich (99.99 % minimum purity certified reagent) was used as a working electrode. The immersed part of the platinum electrode was curved at the end to make a mark for a consistent surface area of the immersed part of the electrode. A silver/silver chloride was used as a quasi-reference electrode (QRE). A 0.5 mm polycrystalline platinum wire (Aldrich, certified 99.99 % minimum purity) was used as auxiliary electrode. All reagents were of analytical grade and were used as received from the suppliers without further purification. Sulfuric acid (95-97 %) was supplied from Merck, copper sulfate pentahydrate was purchased from Scharlau, potassium iodide and potassium chloride were purchased from Sigma-Aldrich. Ultra-pure water, Millipore-MilliQ system was used for the preparations of all solutions. The nitrogen gas was a five grade, 99.999 % minimum purity supplied from International Jordanian Gases Company (Amman, Jordan).

Preparation of iodine-coated platinum electrode. Preparation of iodine-coated platinum electrode was described in one of our previous publications [36], These preparation steps include a cyclization of a platinum electrode placed in of 0.5 M H_2SO_4 between -0.25 V and 1.3 V until getting a reproducible cyclic voltammogram of polycrystalline platinum electrode with the well-known oxygen and hydrogen adsorption/desorption features, which is indicative of the cleanliness of the electrode surface and electrochemical cell contents (Fig.1).

Thereafter, the clean electrode was immersed in 0.5 M H_2SO_4+10^{-2} M KI solution for five minutes under closed-circuit potentiostatic conditions in the double layer region (~0.2 V) to accomplish dosing of the platinum electrode surface with iodine. After that the electrode was subjected to multiple rinses with water and 0.5 M H_2SO_4 solution, and then the electrode potential was cycled in supporting electrolyte solution between -0.2 V and +0.8 V at 50 mV/s to confirm the completeness of the coating process (Fig.1). The absence of oxygen and hydrogen adsorption/desorption peaks from the recorded cyclic voltammogram of an iodine-coated platinum electrode provides a conclusive evidence for the complete coverage of platinum electrode surface with a monolayer of iodine.

Sample preparation. The multivitamins-multi-minerals samples (FertiFi M, USA), (Vitro+, Switzerland), and (Valupak, UK) were purchased from Jordanian local pharmacies in the form of tablets. The selected samples were analyzed for their copper (II) content. The tablet of each brand was powdered using porcelain mortar and dissolved in 25.0 mL of 0.1 M KCl supporting electrolyte. The solution was heated for 10 minutes at a temperature of 80 ºC and sonicated for 10 minutes to ensure complete dissolution of samples and left to equilibrate for 10 minutes. Then, the solution

was filtrated and transferred to a 50 mL volumetric flask and diluted to the mark. An aliquot of this solution was diluted to 10.00 mL with 0.1 M KCl to be within the established calibration curve concentrations' range and placed in the electrochemical cell. The solution was bubbled with nitrogen gas and kept under a nitrogen gas atmosphere during conducting the voltammetric measurements.

Optimized voltammetric conditions. Voltammetric analysis was conducted for determination of copper (II) content in pharmaceutical tablets at the iodine-coated electrode within a potential window -0.2 V and +0.8 V where the adsorbed iodine is stable within this potential range of the scan. 0.1M KCl was used as a supporting electrolyte. The deposition potential was -0.2 V. The deposition time was two minutes including one minute for purging and one minute for solution equilibrium. The potential was then scanned in a positive direction with a scan rate of 50 mV/s.

Results and discussions

The electrochemical response of platinum electrode in 0.1 M KCl to ward Cu(II) was investigated. Figure 1 presents the cyclic voltammograms of platinum electrode in 0.1 M KCl and in 500 ppm Cu(II) + 0.1M KCl solutions. A clear electrochemical response for Cu(II) at platinum electrode surface. Platinum electrode surface adsorbs a wide range of organic and inorganic species which affect the reactivity of the surface of platinum electrodes [45]. The adsorbed iodine at platinum electrode surface enhances the reproducibility of voltammetry and simplify the background behavior.

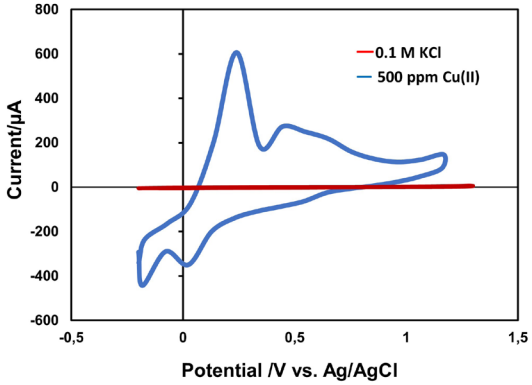

Fig. 1. Cyclic voltammogram curves of (a) poly-crystalline platinum electrode in 0.1M KCl and (b) 500 ppm Cu(II) in 0.1 M KCl. Scan rate 50 mV/s.

A reproducible cyclic voltammogram for polycrystalline platinum electrode which indicates to the cleanness of electrochemical system was obtained (Fig. 2a), which leads to the successful coating process, the cyclic voltammogram of iodine-coated platinum electrode between potential limits of -0.2 V and 0.8V was displayed (Fig. 2b), where the adsorbed iodine is stable within this potential range. The complete absence of $H_2$and O_2 oxidation-reduction features is the main indicator for a successful coated step.

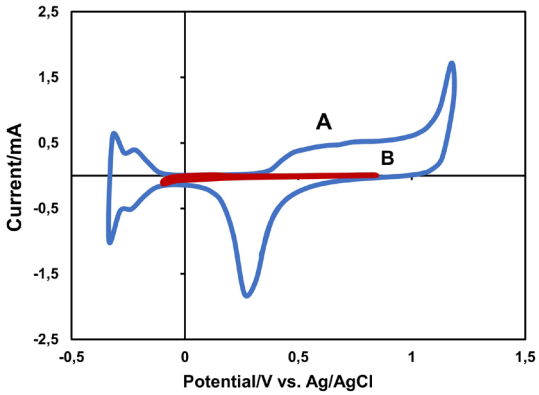

Fig. 2. Cyclic voltammogram curves of (a) poly-crystalline platinum electrode in 0.5 M H_2SO_4 and (b) iodine-coated platinum electrode in 0.1 M KCl.

The effect of the pH in the acidic range was investigated by following the effect of pH change on the peak current for copper (II) oxidation. Three representative pH values; 7, 3.5 and 0.3 were selected to demonstrate the effect of solution acidity on the analytical signal (peak current). Copper (II) standard solution was analyzed in 0.5M H_2SO_4 (pH=0.3), phosphate buffer (pH=3.5), and 0.1M KCl (pH=7) media. Figure 3 shows the effect of pH on the copper (II) oxidation current peak. As displayed in Figure 3, the value of the oxidation peak current of copper (II) increases with increasing pH. In 0.1M KCl supporting electrolyte, the highest value of current for the same concentration of copper (II) was obtained. Subsequently, it was considered as a convenient supporting electrolyte for determination of copper (II) for the following study. Two observed oxidation peaks for the adsorbed copper in 0.1 M KCl. The first peak is a sharp peak while the second peak is a broad peak.

The first feature for the stripping of adsorbed copper from the iodine layer (Eq.1) shows a sharpness peak compatible with a simple stripping process. This peak is followed by a broader peak.

$$PtI\,(ads) + Cu^{2+} \rightarrow PtI\,Cu\,(ads) \qquad (1)$$

The electrodepostion of copper is clearly affected by interactions between the surface of platinum electrode and the solution brought about by changes in electrode surface roughness accompanying with the film deposition. This process has been manifested through a comparison of copper and silver electrodeposition onto both platinum and iodine-coated platinum electrodes. Regarding to silver, the obtained cyclic voltammogram of the iodine-coated platinum electrode in supporting electrolyte is simple, displaying one deposition and one stripping process in the negative and positive-going scans, respectively. As for copper, the presence of a layer of iodine mediates interactions between the analyte and the electrolyte to a lesser extent because of the interaction between

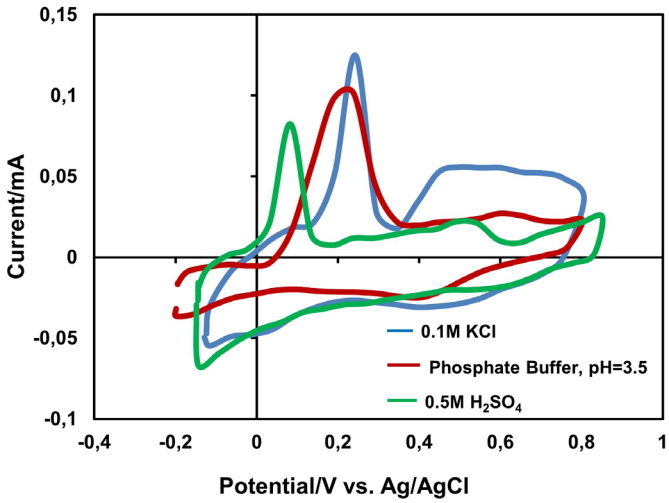

Fig. 3. Effect of type of supporting electrolyte on the electrochemical signal of copper (II) at iodine-coated platinum electrode, copper; 50 ppm, H_2SO_4; 0.5 M, phosphate buffer; pH=3.5; KCl, 0.1 M; n = 3. Scan rate 50 mV/s.

the copper and the halogen film and the formation of copper islands on the electrode surface [46].

The effect of scan rate on the obtained anodic peak current of copper was studied. As presented in Fig. 4, there is a linear relationship between the square root of scan rate and oxidation peak current of copper (first peak, $Cu^0 \rightarrow Cu(I)$) over the range of 1-100 mV/s, which suggested a diffusion-controlled irreversible oxidation process of copper at iodine-coated platinum electrode.

The recorded cyclic voltammograms for iodine-coated platinum electrode in a series of copper (II) standard solutions show that the oxidation current for the first peak increased linearly with the increase of copper (II) concentration (Fig. 5). Three voltammograms were recorded for each standard solution. The anodic peak current was extracted for each cyclic voltammogram.

Plotting the anodic peak current variation against copper (II) concentration gave a straight and extended dynamic range with a concentrations ranging from 1 ppm to 100 ppm. The calibration curve shows the relationship between copper(II) concentration in ppm and the oxidation peak current measured from cyclic voltammograms for copper(II) in 0.1 M KCl at iodine-coated platinum electrode (scan rate 50 mV/s) is given by equation:

$$I(\mu A) = 6.0103\ C_{Copper} - 11.964;\ R^2 = 0.9986,$$

where i represents the anodic peak current which attributed to the copper (Cu^0 to Cu(I)) oxidation.

The second peak which is attributed to the oxidation of Cu(I) to Cu(II) shows a linear relationship between Cu(II) concentrations and the extracted current values but with a lower coefficient of determination, $R^2 = 0.9567$. For this reason, the first peak anodic determination current was taken as the analytical signal for Cu(II).

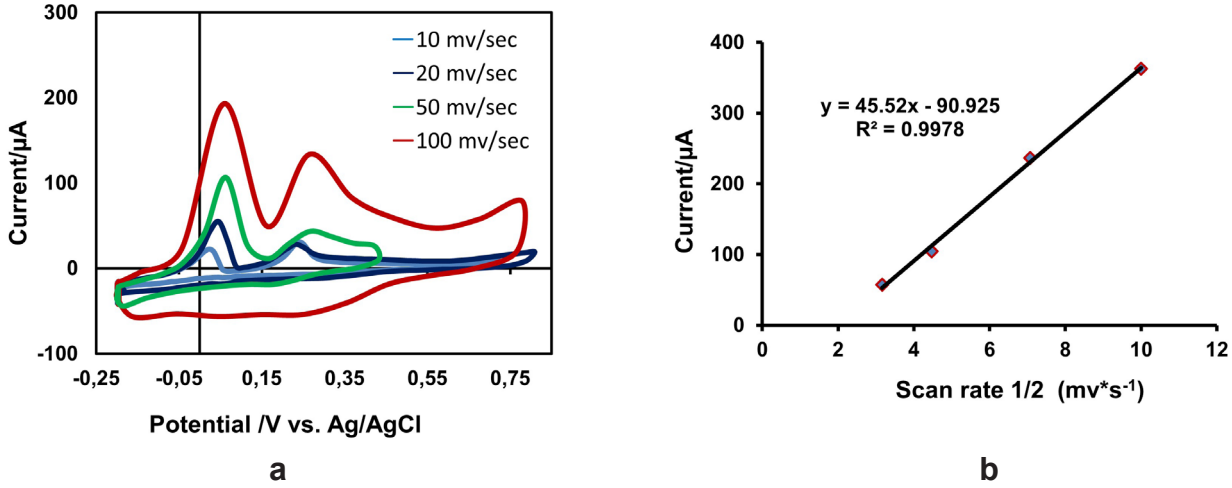

Fig. 4. a) Cyclic voltammograms of iodine-coated platinum electrode in 0.1 M KCl and 50 ppm of copper recorded at 10, 20, 50, and 100 mV/s. b) The least square line for the copper oxidation peak current vs. the square root of scan rate.

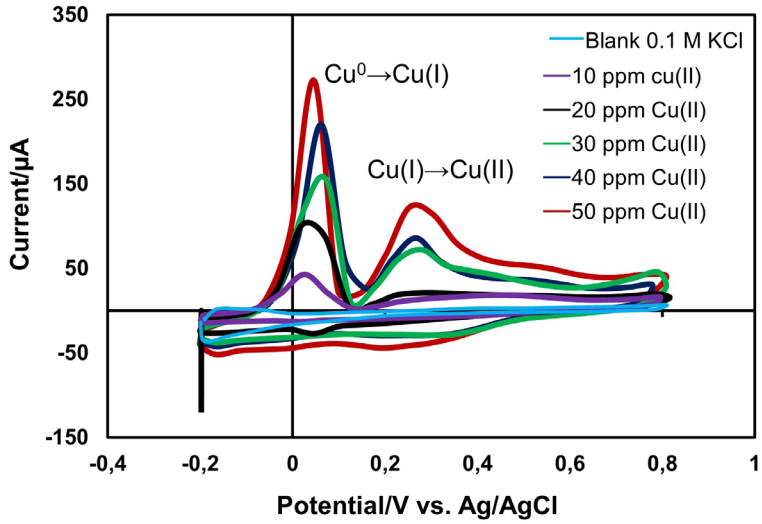

Fig. 5. Cyclic voltammograms of iodine-coated platinum electrode in 0.1 M KCl solution containing 50,100, 200, and 300 ppm of copper(II). All the scans were recorded at a scan rate of 50 mV/s.

The precision (repeatability) of the method was assessed by extracting the anodic peak current of recorded cyclic voltammograms for a solution containing 20 ppm copper (II). The achieved standard deviation and coefficient of variation for 10 successive measurements was 3.81 and 3.76 % which indicates the high precision of the developed method.

The limit of detection based on the formula LOD=3.3б/S, and the limit of quantitation based on the formula LOQ=10б/S, where б represents the blank signal (background current) and S represents the sensitivity of calibration curve was calculated. The estimated limits were 0.115 ppm and 0.346 ppm respectively.

Potential interference

In order to verify the existence of matrix effects of multivitamins-multiminerals tablets on copper (II) determination anodic stripping voltammetry. The influence of (vitamins B1, B2, B6, B12, D3,E, K1, C, Biotin, Niacin, Pantothenic acid, and folic acid), as well as the influence of the elements (Ca, Mg, P, Fe, I, K, Mn, Cr, Mo, Se, and Zn), were investigated. The recorded cyclic voltammograms for each of these vitamins and elements show the absence of any electrochemical response of iodine-coated platinum electrode toward these compounds except Fe and ascorbic acid (vitamin C). Where iron (Fe) does not respond to iodine-coated electrode in a neutral medium (0.1 M KCl) because it is insoluble in neutral and basic media. Regarding ascorbic acid (vitamin C), the recorded cyclic voltammogram for copper (II) with a concentration of 20 ppm with various concentrations of ascorbic acid up to 5-folds of copper(II) concentration shows that the anodic peak current of ascorbic acid overlaps completely with the second peak of copper oxidation (Cu(I)→ Cu(II) without any interference with the first oxidation peak (Fig. 6) which is the considered peak for copper determination in this work.

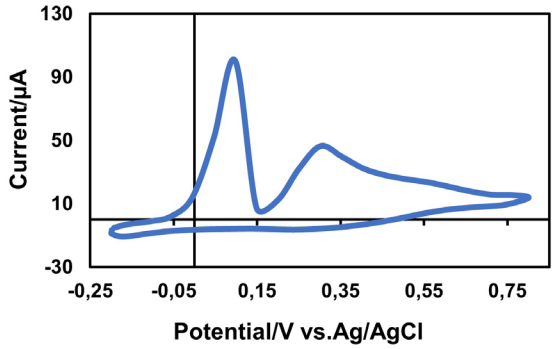

Fig. 6. Cyclic voltammograms of iodine-coated platinum electrode in 0.1 M KCl solution containing 20 ppm of copper (II) and 100 ppm of ascorbic acid (vitamin C). Scan rate 50 mV/s.

Also, Figure 7 shows that the spiking of a diluted solution of multivitamins-multiminerals sample with a various concentrations of copper(II), show a linear response between copper(II) concentration and recorded cyclic voltammogram without any interference with complex contents of the sample.

Recovery of the developed method

Recovery data of the developed method on multivitamin-mineral formulations, Valupak, FirtiFit, and Vitro+ were found by adding a known amount of Cu(II) standard solutions, i.e 5, 10, and 15 ppm, respectively, to a diluted solution, resulting from the extraction of powdered tablets of each preparation to avoid, in general, matrix effect and the interference of ascorbic acid in case high concentration. As listed in Table 1, the recovery values were found to be in the range of 96.91-104.59 %, 98.14-101.04 %, and 91.04-97.93 % with standard deviations values lower than 3.77, 2.16, and 4.45 in Valupak, FertiFit, and Vitro+ respectively.

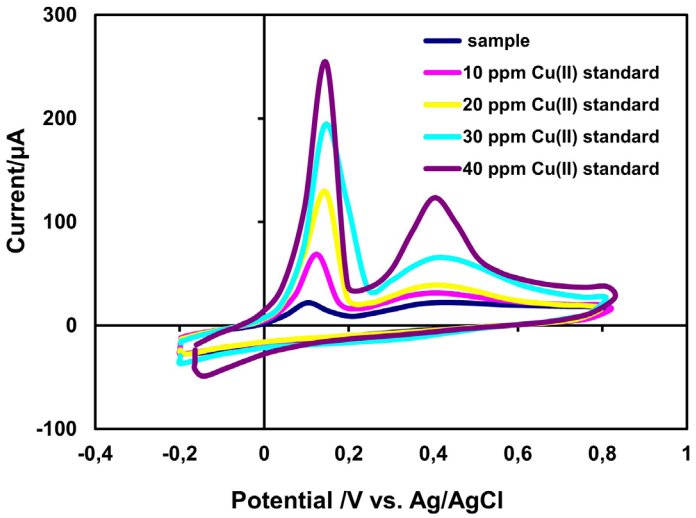

Fig.7. Cyclic voltammograms of iodine-coated platinum electrode in diluted multivitamins-minerals sample spiked with 10, 20, 30, and 40 ppm of copper(II) solution. Scan rate 50 mV/s.

Table 1. Recoveries of Cu(II) from spiked multivitamin-mineral formulations obtained by the developed method.

Formulation	Added (ppm)	Detected (ppm)	Recovery (%)[a]
Valupak®	0	4.60	-
	5	9.83	105±1
	10	14.97	104±4
	15	19.14	96±3
FertiFit®	0	4.60	-
	5	9.58	100±2
	10	14.70	101±3
	15	19.32	98±2
Vitro+®	0	4.6	-
	5	9.40	96±2
	10	13.70	91±4
	15	19.29	98±4

[a] average of three determinations

Pharmaceutical preparation analysis

The developed voltammetric method was applied for the analysis of copper in three brands of pharmaceutical multivitamin-mineral formulations. The standard addition method was applied to a diluted real samples analysis to avoid the matrix effect. The evaluation copper concentration was found to be more suitable with the aid of a calibration graph. The results for the analysis of these multivitamin-multimineral formulations with the developed voltammetric method were mentioned in Table 2.

Table 2. Copper content in a multivitamin-mineral formulations collected from the Jordanian local pharmacies as determined by cyclic voltammetry at iodine-coated platinum electrode.

Pharmaceutical preparation	Nominal mass (mg) of copper/ tablet	Average of determined mass (mg) of copper / tablet (n=3)	Standard deviation	95% confidence limits	95% confidence interval	Relative error	Coefficient of variation
FirtiFit®	0.9	0.886	0.028	0.89± 0.070	0.82—0.96	-0.016	3.16%
Valupak®	0.9	0.92	0.021	0.92± 0.052	0.87—0.97	+0.022	2.28%
Vitro+®	0.9	0.884	0.026	0.88± 0.06	0.82—1.04	+0.018	2.94%

The modified and optimized voltammetric method was applied for the determination of copper content in multivitamin-mineral formulations samples. The results obtained by applying an anodic stripping voltammetry at iodine-coated platinum electrode were compared with the labeled values claimed by manufacturers. The data displayed in Table 2 shows that all nominal values are within a confidence interval of 95% which confirms the clear absence of errors in the results. The relative errors for the analysis of the three types of pharmaceutical formulations were lower than 5%, which confirms the accuracy of the developed voltammetric method. The values of the measured coefficient of variation, (0.55-2.19%), are considered obvious evidence of the precision of the developed method. The paired t-test was used to inspect the significant difference at 95% confidence level between the labeled values and the obtained results determined by the developed method. The comparison of the calculated t value which is -0.026 with the critical t value which is 4.30 at p=0.05 [47] shows that this result consolidate the null hypothesis and indicates there is no significant difference between the values obtained by the voltammetric method and the nominal value obtained by manufacturers.

A comparison between the developed voltammetric method and some of the common analytical and voltammetric methods for copper determination in terms of limit of detection and linear range was presented in Table 3. As shown, the iodine-coated platinum electrode exhibited lower detection limit than that of differential pulse voltammetry method [49] and a detection limit value very closed to the value obtained by square–wave voltammetry method [50]. Whereas, the obtained linear range was convenient and extended compared by other voltammetric method.

Table 3. A comparison of analytical performance of the developed voltammetric method using iodine-coated platinum electrode with other analytical methods that reported in literature.

Method	Linear range	Detection Limit	Reference
Spectrophotometry	0.63-5.04μg/mL	0.007μg/mL	[10]
Atomic absorption spectrometry	1.0-5.0 μg/mL	-	[7]
ICP-MS	-	0.3 μg /L	[48]
Differential pulse voltammetry	1-9mg/L	0.16-0.37mg/L	[49]
Square-wave voltammetry	31.78-635.46mg/L	31.78mg/L	[50]
Anodic stripping voltammetry	1-100mg/L	0.18mg/L	This work

Conclusion

The method presented in this study represents a successive using of iodine-coated platinum electrode for determination of copper was achieved. The developed method does not include any sophisticated procedures. On the contrary, It is considered a green method for the simplicity of analysis procedures. The reported extended dynamic range (1-100) ppm of copper support the applicability of the voltammetric method for copper determination in pharmaceutical formulations. The absence of any interference from the other ingredients of pharmaceutical formulations except ascorbic acid (vitamin C) at very high concentrations considered an evident indicator for selectivity of the developed method. The statistical analysis of the results showed no significant difference between the values obtained by the developed voltammetric method and the labeled valued claimed by the manufacturers. Therefore, with this simple sample preparation and analysis, it is recommended to introduce this method for the routine determination of copper in multivitamin-mineral formulations.

References

1. Soetan, K.O.; Olaiya, C.O.; Oyewole, O.E. The importance of mineral elements for humans, domestic animals and plants: A review. *African Journal of Food Science*. **2010**, 4(5), 200-222.

2. Amal, A.H.; Manal, M. Z.; Manal, A. A E.; Amal, A.M.; Raya, A. S. Relation between anemia and blood level copper, zinc and iron among children. BMC Research Notes, **2010**, 3, 133-142. https://doi.org/10.1186/1756-0500-3-133.

3. Richard, A.F.; Dennis, J.T. Copper: an Essential Metal in Biology. *Curr Biol*. **2011**, 8(21), 877-883. doi: 10.1016/j.cub.2011.09.040

4. Preeti, T.B.; Satya, R. M.; Mohsina, H. Nutritional Aspects of Essential Trace Elements in Oral Health and Disease: An Extensive Review. *Scientifica (Cairo)*. **2016**, 5, 1-12. doi: 10.1155/2016/5464373.

5. Lisa, M. G.; Hannah, S. C-J.; Ching K, C. Copper: Toxicological relevance and mechanisms. *Arch Toxicol*. **2014**, 88(11), 1929-1938. doi: 10.1007/

s00204-014-1355-y.

6. Araya, M.; Pizarro, F.; Olivares, M.; Arredondo, M.; Gonzalez, M.; Mendez, M. Understanding copper homostasis in humans and copper effects on health. *Biol Res*. **2006**, 39(1), 183-189. doi: 10.4067/s0716-97602006000100020.

7. Mihaela, S.; Ion, G. T.; Serban, F.; Vasile, M.; Andrei, A.B.; Hassan, Y. A-E. Flame atomic absorption spectrometry assay for copper determination in pharmaceutical products for veterinary use. *Analytical Letter*. **2007**, 40, 2097-2104. https://doi.org/10.1080/00032710701566693.

8. Young, S, C.; James, P. V.; William, H. S. Determination of copper and manganese in vitamin-mineral tablets by atomic absorption spectroscopy. *Journal of Pharmaceutical sciences*. **1973**, 62, 1838-1840. https://doi.org/10.1002/jps.2600621123.

9. Silvio, S.; Annibal, D.; Pereira, N.; & Ricardo, J.C. Determination of Cu, Fe, Mn and Zn by flame atomic absorption spectrometry in multivitamin/multimineral dosage forms or tablets after an acidic extraction. *Journal of Pharmacutical and Biomedical Analysis*. **2007**, 43(1), 304-310. doi: 10.1016/j.jpba.2006.06.009.

10. Hashem, E.Y., Seleim, M.M.; El-Zohry, A.M. Spectrophotometric determination of copper (II) in pharmaceutical, biological and water samples by 4-(**2′**-benzothiazolylazo)-salicylic acid. J*ournal of Applied Spectroscopy,* **2011,** 78, 586-593. https://doi.org/10.1007/s10812-011-9502-1.

11. Ferando, C. V.; Willian, T. S.; Eder, T.G.C.; Orlando, F-F. Flow-injection spectrophotometric determination of captopril in pharmaceutical formulations using a new solid-phase reactor containing AgSCN immobilized in a polyurethane resin. *Brazilian Journal of Pharmaceutical Sciences*. **2012**, 48,325-333. https://doi.org/10.1590/S1984-82502012000200016.

12. Lewen, N.; Mathew, S.; Schenkenberger, M.; Raglione, T. A rapid ICP-MS screen for heavy metals in pharmaceutical compounds. J*ournal of Pharmaceutical and Biomedical Analysis*. **2004**, 35 (4), 739–752. doi:10.1016/j.jpba.2004.02.023.

13. Beitollahi, H.; Taher, M. A.; Ahmadipour, M.; Hosseinzadeh, R. Electrocatalytic determination of captopril using a modified carbon nanotube paste electrode: Application to determination of captopril in pharmaceutical and biological samples. *Measurement*. **2014**, 47, 770–776. doi:10.1016/j.measurement.2013.10.001.

14. Beitollahi, H.; Mostafavi, M. Nanostructured Base Electrochemical Sensor for Simultaneous Quantification and Voltammetric Studies of Levodopa and Carbidopa in Pharmaceutical Products and Biological Samples. *Electroanalysis*, **2014**, 26(5), 1090–1098. doi:10.1002/elan.201400074.

15. Mohammadi, S. Z.; Beitollahi, H.; Bani Asadi, E. Electrochemical determination of hydrazine using a ZrO2 nanoparticles-modified carbon paste electrode. *Environmental Monitoring and Assessment*, **2015**, 187(3). doi:10.1007/s10661-015-4309-9.

16. Uslu, B.; Ozkan, S. A. Electroanalytical Methods for the Determination of Pharmaceuticals: A Review of Recent Trends and Developments. *Analytical Letters.* **2011**, 44(16), 2644–2702. doi:10.1080/00032719.2011.553010.

17. Labib, M.; Sargent, E. H.; Kelley, S. O. Electrochemical Methods for the Analysis of Clinically Relevant Biomolecules. *Chemical Reviews*. **2016**, 116 (16), 9001–9090. doi:10.1021/acs.chemrev.6b00220

18. Rajendrachari, S. Effect of Sintering Temperature on the Pitting Corrosion of Ball Milled Duplex Stainless Steel by using Linear Sweep Voltammetry. *Analytical and Bioanalytical Electrochemistry.* **2018**, 10(3), 349-361.

19. David, I. G.; Popa, D.-E.; & Buleandra, M. Pencil Graphite Electrodes: A Versatile Tool in Electroanalysis. J*ournal of Analytical Methods in Chemistry.* **2017**, 2017, 1–22. doi:10.1155/2017/1905968.

20. Torrinha, Á.; Amorim, C. G.; Montenegro, M. C. B. S. M.; Araújo, A. N. Biosensing based on pencil graphite electrodes. *Talanta*. **2018**, 190, 235–247. doi:10.1016/j.talanta.2018.07.086.

21. Punbusayakul, N. Carbon nanotubes architectures in electroanalysis. *Procedia Engineering,* **2012**, 32, 683–689. doi:10.1016/j.proeng.2012.01.1327

22. Manjuntha, J.; and Jayaprakash, G. K. Electrooxidation and Determination of Estriol Using a Surfactant Modified Nanotube Paste Electrode. *Eurasian Journal of Analytical Chemistry*. **2019**, 14(1), em20190001. https://doi.org/10.29333/ejac/20190101

23. Manjunatha, J. G. Surfactant modified carbon nanotube past electrode for the sensitive determination of mitoxantone anticancer drug. *Electrochem.Sci. Eng.* **2017**, 739-49.

24. Atta, N.; Darwish, S.; Khalil, S.; Galal, A. Effect of surfactants on the voltammetric response and determination of an antihypertensive drug. *Talanta*. **2007**, 72(4), 1438–1445. doi:10.1016/j.talanta.2007.01.053.

25. Vittal, R.; Gomathi, H.; Kim, K.-J. Beneficial role of surfactants in electrochemistry and in the modification of electrodes. *Advances in Colloid and Interface Science*, **2006**; 119 (1), 55–68. doi:10.1016/j.cis.2005.09.004.

26. Tigari, G.; Manjunatha, J. G.; Raril, C.; Hareesha, N. Determination of Riboflavin at Carbon Nanotube Paste Electrodes Modified with an Anionic Surfactant. *Chemistry Select*. **2019**;4(7), 2168–2173. doi:10.1002/slct.201803191.

27. Gamboa, S.M.; Rojas, E.R.; Martínez, V.V.; Vega-Baudrit, J. Synthesis and characterization of silver nanoparticles and their application as an antibacterial agent. I*nt J Biosen Bioelectron*. **2019**; 5(5), 166-173.

28. Economou, A.; Fielden, P.R. Determination of Copper (II) by Anodic Stripping Voltammetry Using a Flow-through System. *Analyst.* **1996**, 121, 1903-1906.

29. Lutka, A.; Bukowska, H. Honorata, B. Voltammetric determination of zinc in compound pharmaceutical preparations-validation method. *Acta Poloniae*

Pharmaceutica-Drug Research. **2009**, 66,471-475.

30. Cox, J.A.; Kulesza, P. J. Oxidation and Determination of Nitrite at Modified Electrodes. *J.Electroanal. Chem.* 1984, 175(1-2), 105-118. https://doi.org/10.1016/S0022-0728(84)80349-6.

31. Felter, T. E.; Hubbard, A. T. L.E.E.D. and Electrochemistry of Iodine on Pt (100) and Pt (111) Single-Crystal Surfaces. *J. Electroanal. Chem*. **1979**, 100, 473-491.

32. Shu, Z. X.; Bruckenstein, S. Iodine Adsorption Studies at Platinum. *J. Electroanal. Chem*. **1991**, 317, 263-277.

33. Mebrahtu, T.; Rodriguez, J. F.; Bravo, B. G.; Soriaga, M.P. Hydrogenative/Cathodic Stripping of Iodine Chemisorbed on Smooth Polycrystalline Platinum Electrode. *J. Electroanal. Chem.* **1987**, 219, 327-333.

34. Thomas, A. E.; Wieckowski, A. Surface Diffusion Limited Desorption of Iodine on a Platinum Electrode?. *Journal of Electroanalytical Chemistry*. **1995**, 399, 207-212.

35. Podlovchenko, B. I.; and Kolyadko, E. A. Adsorption of Carbon Monoxide on Platinized Platinum Electrode with Preadsorbed Iodine and Iodide Anions. *Russian Journal of Electrochemistry*. **2003**, 39, 823-827.

36. Mohammed, K. H. Determination of Silver (I) by Cyclic Voltammetry at Iodine-Coated Electrodes. *Analyst*. **1994**, 119, 1975-1978.

37. Ross, F. L.; Arthur, T.H.; Ken, F.; Robert, J.B. Brain catecholamines: detection in vivo by means of differential pulse voltammetry at surface-modified platinum electrodes. *Brain Research*. **1976**, 114(2),346-352. https://doi.org/10.1016/0006-8993(76)90678-8

38. Hourani, M.; Jarar, M.; Arar, S. Atmospheric SO_2 Determination by Voltammetric Analysis at an Iodine-Coated Platinum Electrode. *Electroanalysis*. **1999**, 9, 637-640. https://doi.org/10.1002/(SICI)1521-4109(199907)11:9<637::AID-ELAN637>3.0.CO;2-R.

39. Hourani, M.K.; Esaifan, M. Indirect Voltammetric Method for Determination of Nitrogen Dioxide in the Ambient Atmosphere. *Jordan journal of Chemistry*. **2009**, 4, 367-375.

40. Hourani, M. K.; Hijaz, b. Voltammetric Analysis of Hydroquinone and Catechol at Iodine-Coated Polycrystalline Platinum Electrode. J*ournal of Natural and engineering Science*. **2014**, 8(2), 25-29.

41. Mohammad, A.; Mohammed, K.H. Determination of Iron in Dietary Supplements by Voltammetric Analysis at an Iodine-Coated Polycrystalline Platinum Electrode. *Int.J. Electrochem. Sci*. **2018**, 13, 975-983. doi: 10.20964/2018.01.81

42. Mohammad, A.; Mohammed, H. Direct Determination of Hemoglobin in Blood Using Iodine-Coated Platinum polycrystalline electrode. *Analytical and Bioanalytical Chemistry Research*. **2019**, 6, 59-68. 10.22036/ABCR.2018.125953.1198

43. Mohammed, K. H.; Mohammad, A.; Wafa, H. A Voltammetric Sensor Based on Iodine-Coated Platinum Electrode for Determination of Iron in Blood Serum. *Anal.Bioanal.Electrochem.* **2018**, 10, 1620-1628.

44. Mohammad, A.; & Mohammed, H. Determination of Iron in Spinach Using Sweep Voltammetry at Iodine-Coated Platinum rotating Disk Electrode. *Journal of AOAC International.* **2019**,102 (2), 666-668. https://doi.org/10.5740/jaoacint.18-0267.

45. Chikasou, M.; Hirarayashi, T.; Nakamura, T.; and Hinoue, T. Activation Effects of a Platinum Electrode by Laser Pulse Irradiation on the Electro-Oxidation of Glucose in Alkaline Solution. *Analytical Sciences*. **2004**, 20, 1171-1177.

46. Jeffrey, C. A.; Storr, W. M.; Harrington, D. A. Electrochemical quartz-crystal microbalance study of silver and copper electrodeposition on bare and iodine-covered platinum electrodes. J*ournal of Electroanalytical Chemistry.* **2004**, 569(1), 61–70. doi:10.1016/j.jelechem.2004.02.014.

47. Miller, J.N.; Miller, J.C. Statistics and Chemometrics for Analytical Chemistry, Pearson, England, **2010**.

48. Scott, P. D.; Stephen, G.C. Multi-element Analysis of Food by Microwave Digestion and Inductively Coupled Plasma-Atomic Emission Spectroscopy. *Journal of Food Composition and Analysis*. **2002**, 15 (2),593-615. https://doi.org/10.1006/jfca.2002.1064.

49. Lutka, A.; Maruszewska, M.; Voltammetric determination of copper in selected pharmaceutical preparations--validation of the method. *Acta Pol Pharm.* **2011**, 68(2), 179-84.

50. Shi, C.; Xie, S.; Jia, J. The study of a new method to determine copper ion by square-wave voltammetry-extraction iodometry at the liquid/liquid interfaces. *J Autom Methods Manag Chem.* **2008**, 2008:453429. doi: 10.1155/2008/453429.