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Copper Oxide Based Disposable Sensors for Sensitive Voltammetric Assay of Sumatriptan

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Sumatriptan (SUM) is a member of the triptan family that is widely applied for the treatment of cluster headache attacks and migraines. Herein, novel disposable screen-printed sensors (SPS) were incorporated in situ with copper oxide nanoparticles (CuO) and utilized for differential pulse voltammetric determination of the submicromolar concentration of sumatriptan in pharmaceutical formulations and biological fluids. Modification with copper oxide nanoparticles enhanced both the peak height and electroactive surface area which in turn improved the sensitivity towards SUM compared with the blank electrode. At the optimum measuring parameters, the peak heights were linearly proportional to the SUM concentration ranged from 0.33 to 3.54 µmol L^{-1} (I_P=0.067+0.132 SUM [µmol L^{-1}], r=0.9996) with a detection limit (3.3 σ/S) 0.066 µmol L^{-1}. The fabricated sensor showed high sensitivity, fabrication reproducibility and prolonged operational lifetime. The CuO/SPE exhibits improved resolution effect between the sumatriptan voltammetric peaks and those for uric acid, ascorbic acid and paracetamol offering a simple simultaneous determination of sumatriptan in the clinical and pharmaceutical formulations in presence interferents. The applicability of the fabricated modified electrodes was demonstrated by assaying of sumatriptan with sensitivity and selectivity in agreement with the pharmacopial methods. The oxidation of sumatriptan on the electrode surface was studied electrometrically and the proposed mechanism was illustrated with the aid of molecular orbital calculations.

Keywords: Sumatriptan; Disposable screen printed sensors; Copper oxide nanoparticles; Differential pulse voltammetry; Molecular orbital calculations.

1. INTRODUCTION

Sumatriptan (1-[3-[2-(dimethylamino) ethyl]-1*H*-indol-5-yl]-*N*-methyl methane sulfonamide, $C_{14}H_{21}N_3O_2S$), a sulfonamide derivative of triptan, was medically administrated for treatment of migraines and cluster headache attacks [1-3]. It selectively binds the activate serotonin (5-HT1D) receptors which results in the constriction of cerebral blood vessels and leads to a relief in pain from vascular headaches. Moreover, sumatriptan may mitigate vascular headaches via diminishing the release of vasoactive neuropeptides during a migraine in addition to decreasing the releasing of other mediators of inflammation from the trigeminal nerve [4-6].

Saka reported a comprehensive review for determination of triptans including chromatographic, electrochemteric, spectrometric, and capillary electrophoretic methods [7]. UV spectrometric method by following the sumatriptan absorbance at 227 nm was early reported [8]. A validated UV first order derivative method for the simultaneous assaying of sumatriptan and naproxen in pharmaceutical formulations was reported [9]. A blue colored complex with maximum absorption at 760 nm was formed through the reaction of SUM with Folin-Ciocaltaeu reagent allowing sensitive determination of SUM [10]. Charge transfer complexation reactions between sumatriptan and different σ- and π-acceptor were suggested for colorimetric assaying of the target analyte in different pharmaceutical formulations [11-13]. Extractive spectrophotometric analysis protocols were reported for SUM determination through the formation of colored extractable ion-association complexes between different acidic dyes and SUM [14-16]. The formation of the formation of a binary complex between Eosin Y with sumatriptan resulted in quenching of the florescence of Eosin E for sensitive spectrofluorimetric determination of SUM in the linear range from 0.2 to 1.0 µg/mL [17].

Chromatographic protocols including reversed-phase (RPHPLC) [18-20], HPLC [21, 22], liquid chromatographic tandem mass spectrometric [23-25] thin-layer chromatographic [26, 27], gas chromatography [28] and capillary electrophoretic approaches have been applied for SUM determination [29]. Even though the spectrophotometric and chromatographic protocols showed high sensitivities, the expensive required instrumentations, tedious sample preparations, and time-consumption with the exposure of organic solvents, are critical obstacles to the application of these analyses protocols.

Contrary, electrochemical techniques enable screening more than one electroactive species in a single test applying simple instrumentation with improved accuracy and sensitivity. Electroanalytical approaches were widely suggested for assaying of many pharmaceutical species [30-33]. Carbon paste and glassy carbon electrodes combined with different nano structure composites were empolyed for sensitive and selective volatmmetric assay of sumatriptan [35-43].

For biomedical monitoring and routine analysis of large number of samples, the bulky glassy carbon and carbon paste electrodes are unfavorable due to the necessity for sterilization and regeneration with memory effect oppose the commercialization of these sensors. Thus, the introduction of the disposable electrochemical sensors with their requirements of a decentralized assay is welcomed [44-48]. Modification with nanostructured materials with their high specific surface area showed excellent conductivity and catalytic activity which improve both sensitivity and response of the sensor [49-54].

The present work described differential pulse voltammetric (DPV) assay employing home-made disposable printed electrodes modified with copper oxide nanoparticles for fast and sensitive determination of sumatriptan

2. EXPERIMENTAL

2.1. Reagents and chemicals

Traditional synthetic graphite powder (1-2µm, Aldrich) and cellulose triacetate (CTA, Fluka) were used for preparation of the printing carbon ink. Copper (II) oxide nanopowder (Alfa Aesar, 30-50 nm) was applied as electrode modifier. Universal Britton–Robinson buffer (4.0×10^{-2} mol L^{-1}) was prepared and the desired pH value was adjusted using 2.0×10^{-2} mol L^{-1} NaOH.

2.2. Sumatriptan working solution

The stock SUM fresh solution was prepared by dissolving the appropriate amount of sumatriptan succinate ($C_{14}H_{21}N_3O_2S.C_4H_6O_4$, purity of 99.0±1.5%, obtained from Standard Laboratory, National Organization for Drug Control and Research, Egypt) in water and kept at 4^{o}C.

2.3. Sample analysis

Four sumatriptan tablets (Sumigran, SIGMA Pharmaceutical Industries, Egypt, assigned to 25 mg SUM) were weighed and ground. Amount equivalent to one tablet was dissolved water and filtered. The SUM content was assayed by spiking the sample solution with different SUM standard solution.

Fresh serum samples were treated with acetonitrile (2:1) for denaturation and precipitation of serum protein. After dilution with water, samples were vortexed, centrifuged and a protein free human serum was obtained using a Milli-pore filter.

For urine samples, aliquots of standard SUM solution were added followed by 0.2 mL of methanol for protein removal. After centrifugation, the clear upper layer was transferred to measuring cell containing the universal buffer at the optimum pH value.

2.4. Apparatus and sensor fabrication

Voltammetric measurements were performed using 797 VA Metrohm voltammetric analyzer (Metrohm, Switzerland). The measuring cell composed of the Ag/AgCl/KCl double-junction reference electrode, platinum as an auxiliary electrode. The working screen-printed carbon electrode were printed on a PVC sheet applying homemade carbon printing ink prepared as described in details elsewhere [55, 56] by mixing of 5.0 g CTA solution (8 % CTA in acetone-cyclohexanon mixture) and 3.0 g carbon

powder. After curing, the printed sensors were modified imply by soaking in 5% copper oxide suspension (5% in DMF) for 2 h.

2.5. Analytical procedures

Aliquots SUM stock solution were added to the measuring cell at pH 7.0 and the DP voltammograms were monitored at scan rate value of 40 mV s^{-1}, pulse time 40 ms, pulse width 100 ms, and pulse height +50 mV. The peak currents were plotted against the SUM concentration in µmol L^{-1} scale to illustrate the calibration graph

2.6. Computation

Molecular orbital studies were proceeded to sustain the proposed electrochemical oxidation mechanism at electrode surface applying Gaussian 09 suite programs [57].

3. RESULTS AND DISCUSSION

3.1. Oxidation of SUM on CuO/SPE surface

Sumatriptan showed cyclic voltammograms of on copper oxide modified electrode surface showed a well-defined anodic wave with the enhancement of the peak height (about 7 fold) relative to the blank electrodes (Fig. 1a). No cathodic peaks were recorded assuming a totally irreversible oxidation process. Moreover, modification with CuO resulted in shifting of the oxidation peak by more than 0.055 V. This noticeable enhancement of current with the shifting of the peak potential can be explained on the basis of the increased active surface area and electrocatalytic effect of CuO.

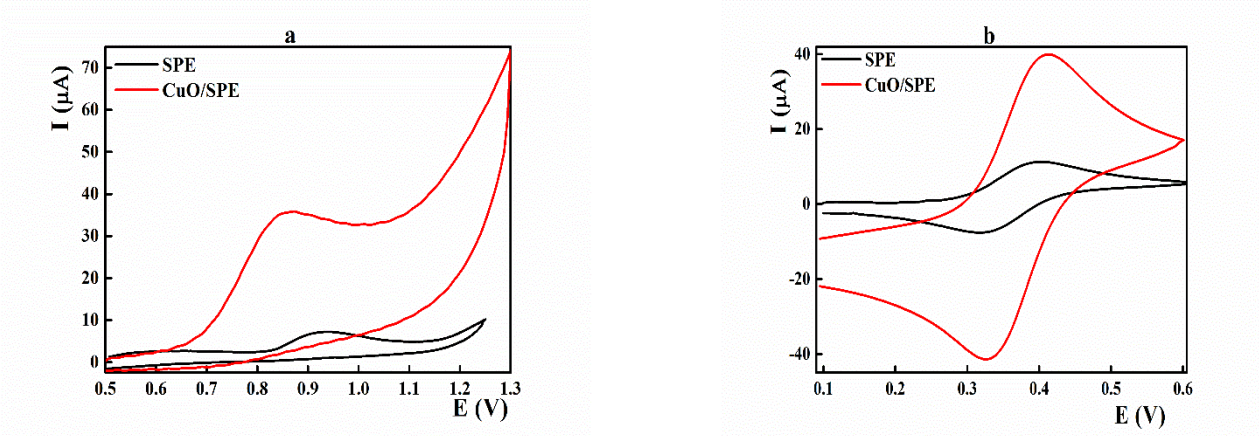


Figure 1. Voltammetric behavior of a) 1.6 µmol SUM at pH 7.0 buffer solution, b) 3.0×10^{-5} mol L^{-1} $[Fe(CN)6]^{3-/4-}$ on CuO screen printed sensors with scan rate 50 mV s^{-1}

Cyclic voltammograms performed on CuO-modified sensors in ferricyanide solution produced well-defined redox peaks of $[Fe(CN)_6]^{3-/4-}$species with the oblivious enhancement of the peak current

(about 4 fold) compared with the blank carbon screen-printed electrode (Fig. 1b). Redox peak current ratio (Ipc/Ipa) of SPE and CuO/SPE was found to be 0.67 and 0.968 which can be attributed to the acceleration of electron transfer at the copper oxide nanoparticles modified electrode surfaces

Following, the proper modifier content was studied by varying the copper oxide concentration in the soaking solution was varied from 0 to 10%, and 5% was the most promising (Fig.2a, b).

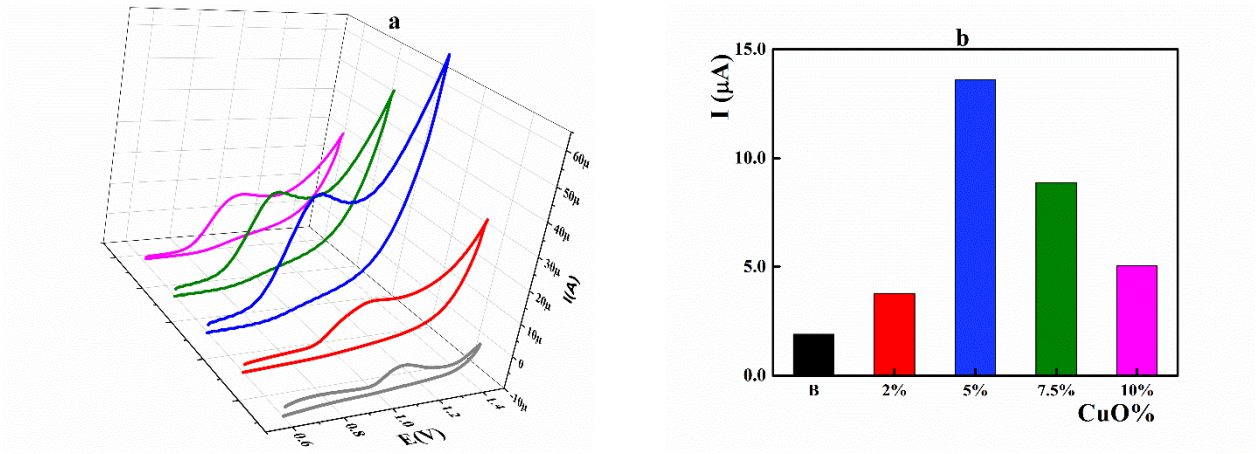


Figure 2. Voltammetric behavior of 1.6 µmol SUM at pH 7.0 buffer solution using screen printed sensors modified with different CuO contents, scan rate value was 0.05 V s^{-1}.

The electroactive surface areas of the blank and copper oxide sensors explored according to the Randles-Sevik equation were found to be 0.219967 and 0.6654 cm^2, respectively [58]. It can be obviously noticed that modification with CuO nanoparticles improved the surface area of the blank electrodes (about 3 folds) which was reflected in the electrode response towards sumatriptan and ferricyanide.

3.2. Optimization of measuring parameters for SUM determination

3.2.1. Working pH range

It was reported that sumatriptan possesses four pKa values of 9.63 and 12.0 for the tertiary amine and sulfonamide groups, and 4.21 and 5.67 for the succinic acid part, respectively [35], therefore the pH value of the supporting electrolyte showed crucial rule on the electrochemical behavior of SUM. Below the pH 9.63, SUM present in the protonated form which is suitable for determination.

Herein, the electrochemical behavior of sumatriptan on CuO/SPE sensor was tested at different pH values ranged from 3.0 to 8.0 (Fig. 3). The peak height increases to reach its maximum value at pH 7.0. Contrary, the peak potential ($E_{(V)}$) was shifted linearly towards the negative direction with pH value [$E_{(V)}$ = 1.1146 – 0.0558 [pH], r = 0.9977]. The slope value was close to the theoretical Nernstian compliance sustaining the participation of an equal number of protons and electrons in the oxidation reaction.

Next, from different buffer systems at pH 7.0 (universal Britton–Robinson, acetate, phosphate, Tris or HEPES buffer), Britton–Robinson buffer was the most appropriate.

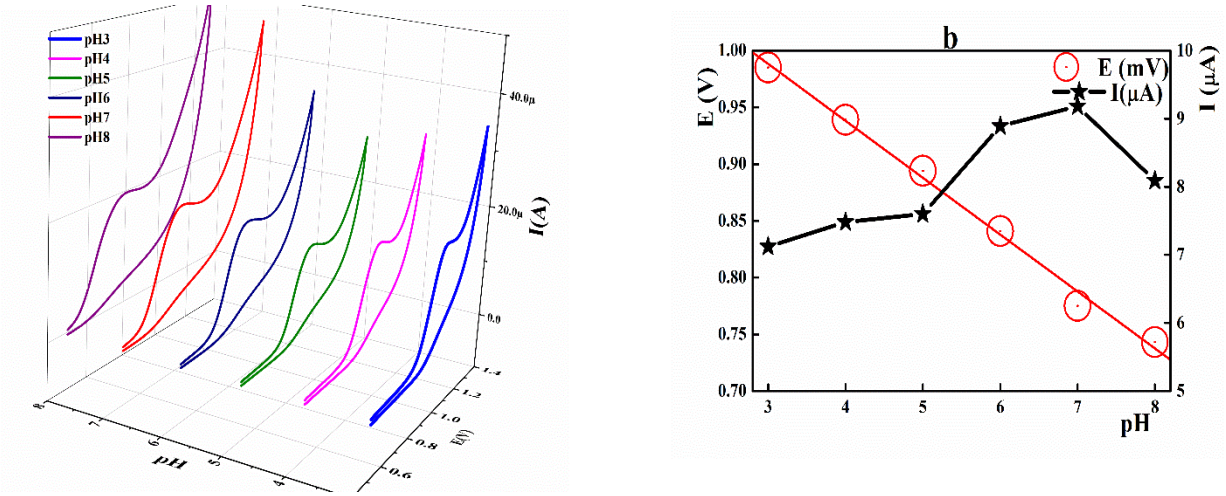


Figure 3. (a) Cyclic voltammograms for 1.6 µmol SUM at 5.0 % CuO/SPE at different pH values; (b) peak heights and peak potentials at pH values. The experiments were conducted at 0.050 V s^{-1}.

3.2.2. Effect of the scan rate

A more detailed explanation of the electrochemical oxidation mechanism of sumatriptan on the electrode surface may be investigated by performing the cyclic voltammetric measurements at different potential sweep rates (Fig. 4a). The SUM peak current increases linearly against the square root of the scan rate (Fig.4 b), with high correlation coefficients (r=0.9999), suggesting the diffusion-controlled mechanism. Potting the log values of peak current (log I) against the log value of the scan rate (log υ) showed a linear relationship with a slope value of about 0.5606 sustaining diffusion-controlled electrode mechanism (Fig. 4 c).

Moreover, the peak potential was shifted to the more positive potential with scan rate (Fig. 4d), due to the irreversibility of the SUM oxidation process on the electrode surface [59, 60]. In the scan rate ranging from 0.2 to 0.18 Vs^{-1}, a linear relationship was achieved ($E_{(V)}$ = 0.8833 + 0.05824 [log υ]; r=0.9799). Applying Laviron equation, the calculated number of electrons involved in the VPZ electro oxidation process was 1.97 [62].

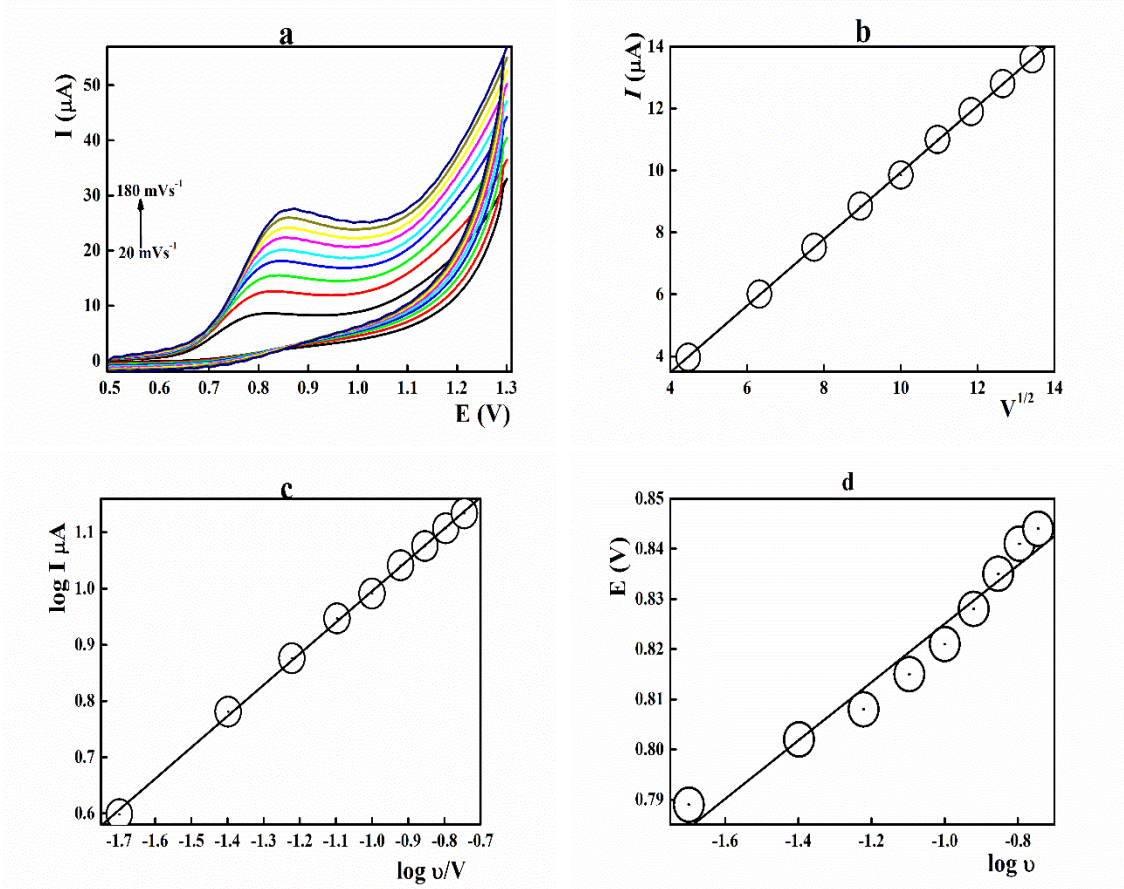
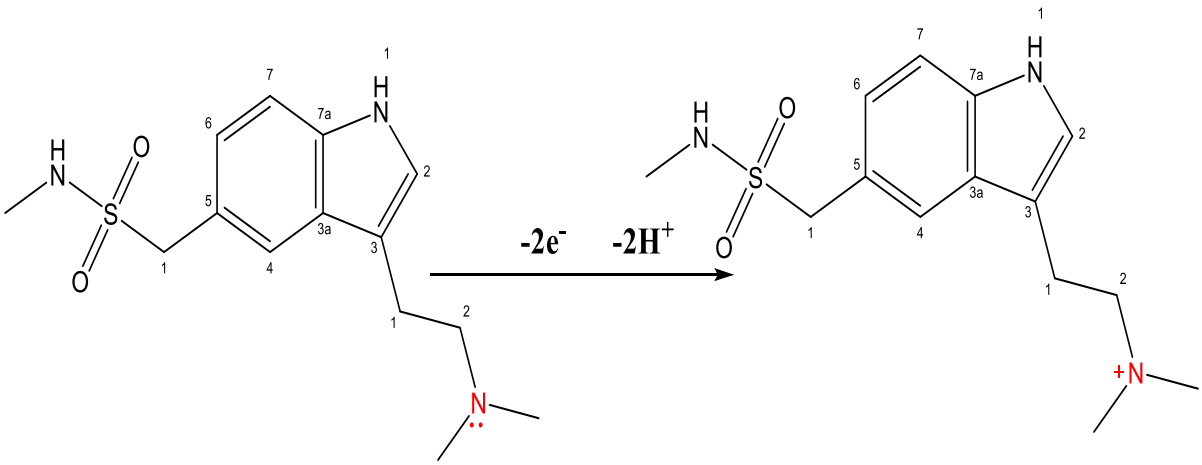


Figure 4. voltammetric behavior of 1.6 µmol L^{-1} SUM using 5.0 % CuO /SPE sensors at pH 7.0



Scheme 1. Computed electron and proton transfer involved in the electrochemical redox reaction of SUM at CuO/SPE surface

Molecular orbital calculations were performed to explain the proposed oxidation mechanism (scheme 1). The irreversible electrochemical oxidation process takes place through oxidation of the terminal amino group with transferring of 2 electrons and two protons as obtained with the effect of the pH (sec 3.2). This suggested mechanism disagrees with those postulated in references [35, 40 and 41].

3.3. Analytical characterizations

Table 1. Regression and statistical parameters for differential pulse voltammetric determination sumatriptan on CuO/ screen printed electrodes at pH 7.0

Parameters	
LR (µmol)	0.33 - 3.54
Slope (a) (μAcm^{-2})	0.132
s_a (μAcm^{-2})	0.001
Intercept (b) ($\mu A\ mL\ \mu mol^{-1}$)	0.067
s_b ($\mu A\ mL\ \mu mol^{-1}$)	0.003
$S_{y/x}$ ($\mu A\ cm^{-2}\ mL\ \mu mol$)	0.004
Correlation coefficient (r)	0.9996
r^2	0.9992
LOD (µ mol)	0.066
LOQ (µ mol)	0.201
RSD %	0.821
N	11

At the optimum measuring conditions described above, 11-successive additions of sumatriptan stock solution were added to the measuring cell covering the concentration range from 0.33 to 3.54 µmol L^{-1} and the differential pulse voltammograms were recorded. The obtained peak currents were plotted against the corresponding SUM concentration (Fig. 5). Calibration graphs showed high correlation with the low standard deviations verifying the linearity and the applicability of the method over the tested sumatriptan concentration range (Table 1).

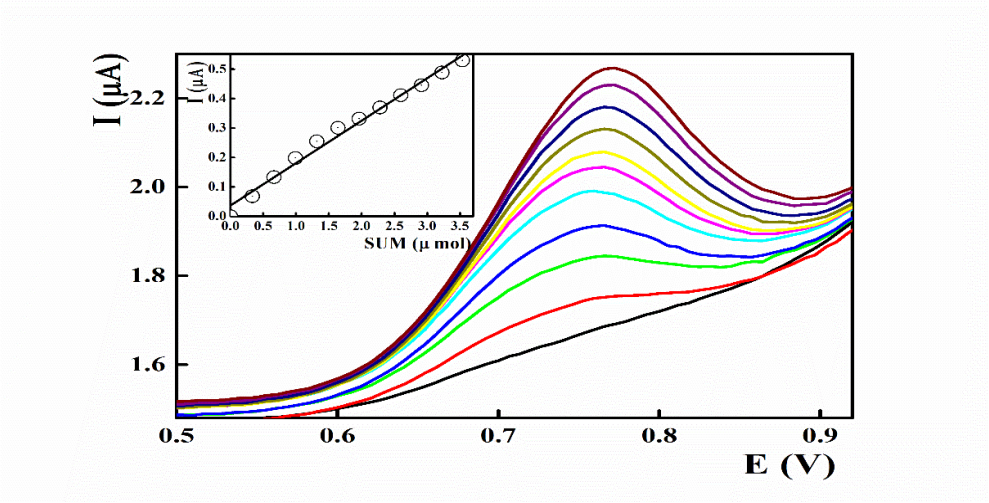


Figure 5. Differential pulse voltammetric determination of nadifloxacin using 5.0% CuO/SPE at pH7.0, the scan rate value was 0.05 Vs^{-1}.

The analytical features of the proposed sensors compared to the previously reported methods were tabulated in Table 2. The present work exhibits acceptable sensitivity for assaying of SUM near the physiological conditions (pH 7.4). Application of disposable homemade screen printed sensors with

the simple modification protocols, high measuring repeatability and fabrication reproducibility with long operational lifetime and the possibility of miniaturization and commercialization can be considered as valuable advantages of the presented sensor.

Table 2. Comparison of analytical futures of the proposed sumatriptan sensor with those reported in literature

Modified electrode	Method applied	Linear working range (LWR) (µM)	Limit of detection (LOD) (µM)	Ref.
GCE	DPV	1.0-8.0	0.5	35
MWCNT/AgNP/Pyrolytic graphite electrode	CV	0.08- 100	0.04	36
MWCNT and polypyrrole doped with new coccine/GCE	LSV	0.02- 10.0	0.006	37
MWCNT/cobalt-Schiff base/CPE	DPV	1.0-1000	0.3	38
CMK-3/GCE		1.5-120	0.8	39
Graphene/AuNP/Nafion/GCE	AdSDPV	0.00214- 1.0, 1.0- 41.2	0.0007	40
Pt-ZrO_2/CPE	Amperometry	0.01- 55	0.003	41
Cu NPs/poly-melamine/GCE	DPV	0.58–6.5	0.025	42
MXene/MWCNT/Chit/GCE	AdSDPV	0.0033- 61	0.00042	43
CuO/SPE	DPV	0.33 to 3.54	0.066	Present

Abbreviations: DPASV: Differential pulse anodic stripping voltammetry; SWV: Square wave voltammetry; AdSSWV: Adsorptive stripping square wave voltammetry; CV: Cyclic voltammetry; LSV: Linear sweep voltammetry; rGO: Reduced graphene oxide; PtNP: Platinum nanoparticles; AuNP: Gold nanoparticles; AgNP: Silver nanoparticles

3.4. Reproducibility and life time

The stability of the fabricated CuO based disposable sensor was performed through recording of the differential pulse voltammograms for 1.6 µmol L^{-1} SUM periodically. Reproducible oxidation peak were observed during the first 30 days, however, the peak current started to deteriorate slowly (about 4%) in the next period followed with 7% decrease for the rest 30 days. The repeatability of the measuring was tested by measuring the corresponding peak currents of 10 replicate successive DPV for 1.6 µmol L^{-1} SUM; the standard deviations did not exceed 2.62%.

The fabrication reproducibility was investigated by recording the DPV response for 10 different CuO/SPE sensors within the same batch. The obtained results showed acceptable RSD of 3.1% was achieved indicating the high fabrication reproducibility

3.5. Interference studies

Pharmaceutical formulations and biological samples usually contain a variety of contaminates and excipients giving a false indication of the target analyte, therefore, the interference study is quite important. The response of CuO/SPE was recorded toward sumatriptan in presence of excipients, biomolecules, some metal ions and chemically related drugs. The voltammetric peaks for 2.0 µmol L^{-1}

SUM was recorded in the presence of paracetamol, biomolecules (ascorbic or uric acid) and common excipients usually present in pharmaceutical formulations (including glucose, starch, citric acid, propylene glycol dicaprylate) in addition to metal ions. The tolerance limit is the maximum interferent concentration which resulted in ±5% error in recovery. The obtained voltammograms clearly suggested the high selectivity of CuO/SPE toward SUM with no significant interference of the cited species.

Figure 6 represent the voltammograms of a measuring solution containing ascorbic acid, SUM and paracetamol at pH 7. The working sensors showed well defined peaks for the cited species with obvious high resolution allowing smiltaneous measurement of these compounds. Linear relation with high correlation coefficients were achieved as following: I_p (µA)=0.52+0.13 SUM [µ mol], R=0.9986 for sumatriptan and I_p (µA)=11.81+1.26 PAC [µ mol], R=0.9997.

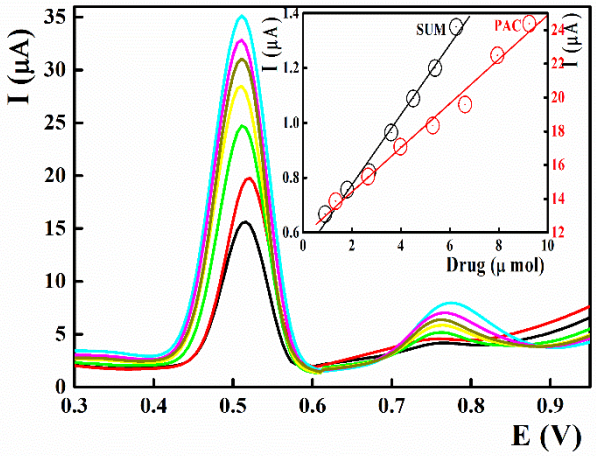


Figure 6. Simultaneous voltammetric determination of sumatriptan and paracetamol at 5.0 %CuO/SPE at pH 7.0, the scan rate value was 0.05 V s^{-1}.

Furthermore, the sensor response towards molecules with similar active group of SUM including 5-hydroxyindole-3-acetic acid, indole-3-acetic acid, indole-3-lactic acid and indole-3-pyruvic acid was investigated. At the optimum pH value for sumatriptan, these compounds did not show any significant interference as their pKa values ranged between 3.0 and 4.7 [63, 64].

3.6. Sample analysis

To examine the practical applicability of the proposed sensor, the sumatriptan content was assayed in different pharmaceutical and biological samples. Preliminary investigation showed no distinct signal for SUM in healthy human urine and serum samples. Sumatriptan is predominantly metabolized by monoamine oxidase producing indole acetic acid and indole acetic acid glucuronide as major products. Other metabolites including glucuronide ester of the indole acetic acid derivative and indole ethyl alcohol derivatives did not show a noticeable interference with sumatriptan [65].

Known SUM increments were spiked to the samples solution and the differential pulse voltammograms were recorded applying the optimum measuring condition using the CuO/SPE. The mean value for five replicates was considered for calculation of the average recovery against the official

method. The results have been tabulated in Table 3 showing percentage recoveries ranged from 99.93±0.07 to 100.065±0.04suggesting the disposable CuO/SPE as an accurate, selective, reproducible, rapid responses highly promising approach for quality control for sumatriptan in pharmaceutical dosage forms and assaying in biological fluids**.**

Table 3. Voltammetric determination of sumatriptan in pharmaceutical formulations and biological samples

Sample	Sumigran ® Labeled (25mg/tab.)			Spiked plasma			Spiked urine		
Analysis protocol	Added (µg/ml)	Founded (µg/ml)	Recovery	Added (µg/ml)	Founded (µg/ml)	Recovery	Added (µg/ml)	Founded (µg/ml)	Recovery
% Found	1.50	1.49	99.33	0.69	0.689	99.85	0.69	0.69	100.15
	2.00	2.003	100.15	0.82	0.821	100.16	0.82	0.82	99.56
	2.50	2.490	99.60	1.10	1.099	99.95	1.10	1.10	99.94
	3.00	2.990	99.66	2.00	2.060	100.30	2.00	2.00	100.05
Mean±S.D.		99.68±0.01			100.06±0.04			99.93 ±0.07	
t-test			0.38					0.98	
t-Critical			2.35						
F-test			4.1					6.62	
F- Critical			9.27						

* Each result is the average of five different separate determinations. Figures in parentheses are the tabulated t and F values respectively at P= (0.05).

4. CONCLUSION

Herein, novel disposable screen printed carbon sensors incorporated with copper oxide nanoparticles were employed as an efficient analysis protocol for sub micromolar voltammetric determination of sumatriptan. Application of copper oxide nanoparticles as electrode modifier offered electrocatalytic activity towards the electrochemical oxidation of sumatriptan with significant enhancement of the peak current. In addition, the fabricated sensors were successfully applied for simultaneous detection of sumatriptan and paracetamol and free from the interference from ascorbic acid, uric acid, common excipients usually present in pharmaceutical formulations. The proposed analysis protocol was employed for assaying of sumatriptan with high accuracy and recoveries comparable with pharmacopial method which contribute a great help to the drug quality control and biomedical analysis.

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