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Self-assembled ruthenium decorated electrochemical platform for sensitive and selective determination of amisulpride in presence of co-administered drugs using safranin as a mediator

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Abstract

A wholly new electroanalytical protocol for the sensitive determination of Amisulpride (AMS) has been developed. AMS is an antipsychotic and antiemetic medicine that is prescribed at lower dosages intravenously to stop and cure vomiting and postoperative nausea; and at higher orally dosages and intramuscularly for treatment of schizophrenia and serious psychotic seizures. AMS detection is proposed here for the first-time using Ruthenium nanoparticles (Ru) and Safranin (Saf) as a modifier through carbon paste electrochemical sensor platform. The Ruthenium - Safranin sensor was found to possess good electrocatalytic activity and selectivity for simultaneous determination of AMS in the presence of co-administered drug citalopram (CIT). The Ru-Saf/CPE modified sensor exhibited a wide linear response range for electrochemical sensing of AMS (9.8×10^{-8} – 7.0×10^{-5} M) with LOD of 8.80×10^{-9} M.

Keywords

Amisulpride, Antipsychotic medications, Ruthinum nanoparticles, Safranin, modified electrochemical sensors, Real samples analysis

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Introduction

Depression is considered as a common mental disorder, which influences over 264 million people worldwide and becomes a critical health problem; approximately 800,000 persons have been died because of suicide every year [1]. Recently, the psychiatric consequences of the covid-19 infections to manifest are receiving high attention [2]. Historically, many of psychiatric situations have been described due to viral infections [2]. According to the recent studies [2], the epidemic covid-19 is likely to generate related or may be different psychiatric disorders. Therefore, more attention is directed to antipsychotic drugs due to the recent epidemic circumstances and the increase use of these kinds of drug. Serotonergic antidepressants are one of the first line agents for treatment of depression [3]. Amisulpride (AMS) is a substituted benzamide atypical antipsychotic that has high affinity for dopamine receptors toward management of psychoses such as schizophrenia [4, 5]. AMS obviously has the clinical profile of an atypical antipsychotic [6], known by its lower propensity to induce extrapyramidal side effects as well as its greater efficacy in treating negative symptoms compared to classical neuroleptics, particularly haloperidol which was used as comparative substance in most studies[6]. The mixture of an antidepressant with an antipsychotic agent has been proved to be effective for the treatment of psychotic depression [7]. Low-dose of AMS augmentation resulted in a significant clinical improvement along with serotonergic antidepressant Citalopram (CIT)[3].

AMS has IUPAC name; 4-amino-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(ethylsulfonyl)-2-methoxybenzamide. Citalopram (CIT), chemically 1-[3-(Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, belongs to selective serotonin reuptake inhibitors (SSRIs) family[5]. About 30%–40% of Alzheimer's disease patients have depressive and psychotic symptoms [8]. Patient with dementia described by Alzheimer had psychotic symptoms, including paranoid delusions and hallucinations. Consequently, the term “senile psychosis” was usually used to denote to psychosis in old patients with dementia [9], so there is a high need for sensitive selective determination of AMS alongside with administered Memantine hydrochloride (MEM). MEM is a 1-amino-3,5-dimethyladamantane derivative. MEM has low affinity, uncompetitive NMDA receptor antagonist used for the treatment of dementia. Lately, MEM was approved by FDA for the moderate treatment of serious Alzheimer's disease[10].

Various analytical methods have been described for the determination of AMS including spectrofluorimetric[11], spectrophotometric[12, 13], chromatographic [14-16], and electrochemical methods[17].

Electrochemical sensors, especially carbon paste electrode (CPE), is considered as a distinctive kind of heterogeneous carbonic electrochemical platforms including a mixture of graphitic carbon powder with a non-conductive and water immiscible binder[18, 19]. The easy functionalization, surface modification is the main feature of CPE, which makes them to offer higher electrocatalytic activity by increasing the electron transfer mechanism [18, 20-22].

Therefore, fabrication of CPE by employing appropriate mediators, and nanomaterials like carbon nanotubes [22], graphene derivatives[23, 24], metal and metal oxide nanoparticles[25], or their composites [24, 26], have attracted an increasing interest to be utilized in different electrochemical analyses.

Metal-oxide film based electrochemical platforms have been widely used for their high electrocatalytic activity and excellent perspective of different application as electrochemical sensors[27]. Metallic nanoparticles and metal oxide particles have received significant attention due to their unique properties such as conductivity and excellent electrocatalytic and electroanalytical properties due to their nano-size structures and effective surface area that in turns enhance the rate of electron exchange between the sensor surface and the different analytes [20, 28, 29]. Due to different oxidation states of ruthenium derivatives and their electrochemical reversibility makes them as excellent electron transfer mediators for modification of different electrochemical sensors surfaces [29, 30].

Safranin (SAF) is lipophilic electro active poly aromatic cationic dye[31], which is commonly used in cytology, histology and as a redox indicator in analytical chemistry [32].

In this work, we develop a self-assembled Ru decorated electrochemical sensing platform based on SPE, for sensitive and selective determination of AMS in the presence of co-administered drugs; MEM and CIT using SAF as a mediator. For additional enrichments on the sensor surface, Ru nanoparticles were integrated due to their reported excellent physicochemical characters like strong adsorptive ability, good biocompatibility, thermal stability, high surface area, and electrical/electrochemical properties[30]. To the best of our

knowledge, there is no work reported to date that employ Ru-SAF for the electrochemical determination of AMS. We therefore design the first ever example of using Ru-SAF/CPE sensor for bio monitoring of AMS in human urine and pharmaceutical products. The Ru-SAF/CPE constructed sensor offers a selective, simple and consistent electrochemical platform for simultaneous determination of AMS with a detection limit of 8.80×10^{-9} M and other common molecules like MEM and CIT.

Experimental

All details of the present experimental procedures, instrumentation and reagents are included in the Electronic Supplementary Information (ESI) part.

Results and discussion

Morphologic and Electrochemical characterization of the fabricated sensors

The scanning electron microscope (SEM) image of the bare unmodified sensor is shown in Fig. 1SA as the electrode surface was dominated by smooth and uniformly designed carbon flakes and divided sheets whereas, Figure 1SB clearly exhibited that the Saf particles were incorporated into the carbon paste and hence the captured image is relatively different. Next, Energy-dispersive X-ray (EDX) and SEM analysis are used to reveal the conformation of Ru nanoparticles formation on electrode surface. As illustrated in Figure 1A, the EDX analysis indicates the creation of Ru-nanoparticles over the sensor surface. As observed in the SEM images (Figure 1B), Ru nanoparticles are randomly distributed on the sensor surface, which increases the effective surface area and eventually improves the microscopic area of Ru-Saf/CPE surface and in turns increases the electrode response and sensitivity of voltammetric determination.

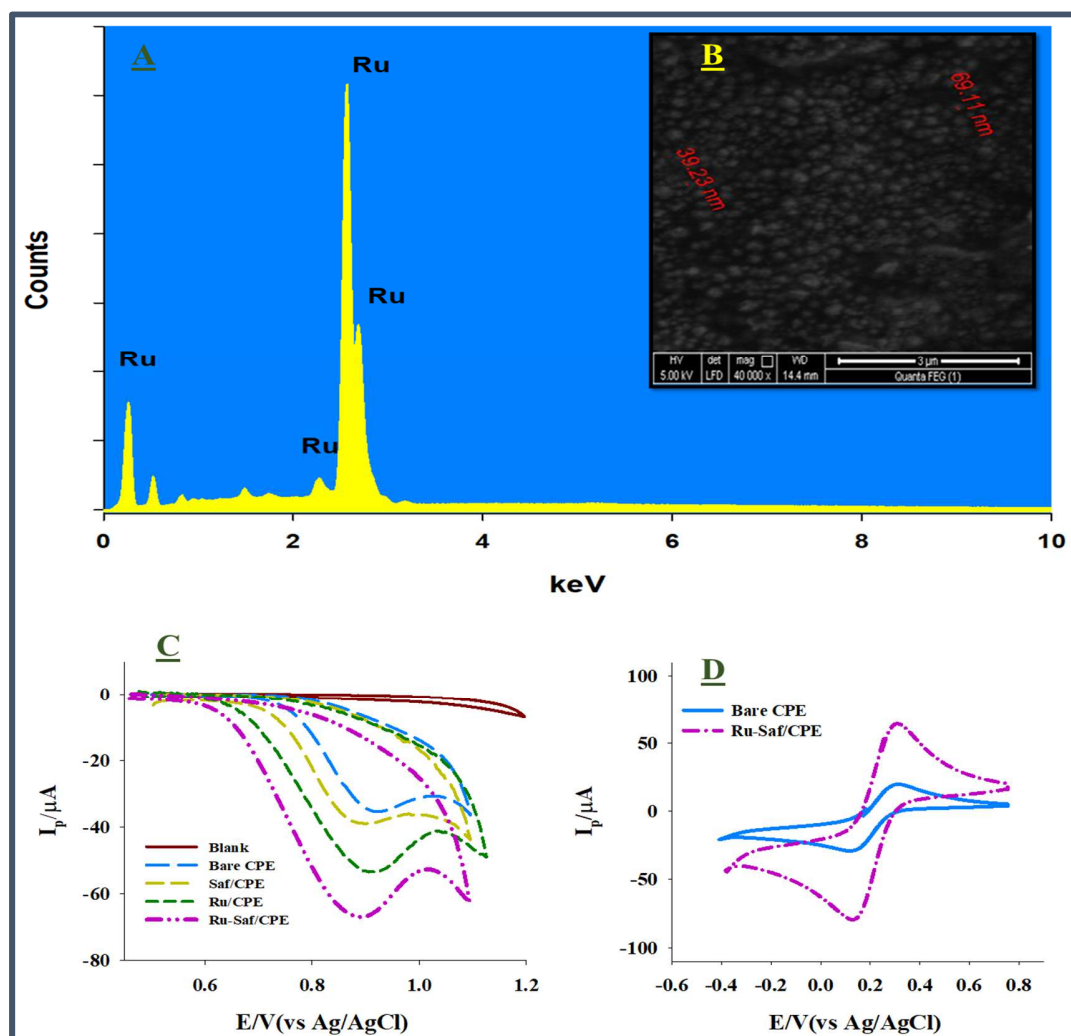


Figure 1. A) EDX of Ru-Saf/CPE; B) SEM of Ru-Saf/CPE; C) Cyclic voltammograms of different studied sensors recorded in 1.0×10^{-3} M AMS (pH 7.0; B–R buffer; Scan rate: 100 mV s^{-1}); D) CVs of CPE and Ru-Saf/CPE in a solution of $5.0 \text{ mM } [\text{Fe}(\text{CN})_6]^{3-/4-}$ and 0.1 M KCl with a scan rate of 100 mV s^{-1} .

Cyclic voltammograms (CVs) for the electrochemical oxidation of AMS (1.0×10^{-3} M) was performed using bare CPE, Saf/CPE, Ru/CPE and Ru-Saf/CPE sensors at a pH 7.0 using B-R buffer. The corresponding voltammograms are illustrated in figure 1C. Figure 1C shows the typical cyclic voltammograms for all the fabricated sensors. At the CPE unmodified sensor, the obtained anodic peak current (I_p) with a value of $35.0 \mu\text{A}$ at 0.915 V coincide with the electrochemical oxidation of AMS. As Saf is considered as a powerful redox material with high electrochemical activity, it is predictable to assist and improve the AMS electrochemical

oxidation at the Saf/CPE sensor surface. The anodic peak current I_p value for the oxidation of AMS was elevated to 39.0 μA and moved to a less positive potential (0.907 V). Next, upon the deposition of Ru nanoparticles at fixed potential (Ru/CPE; exhibited in Figure 1C), anodic current I_p is further increased. The anodic peak appears at 0.988 mV with a current value of 52.0 μA , which is attributed to the high conductivity and greater surface area of Ru nanoparticles that can act as a promoter for the electron transfer process that facilitates the AMS oxidation at the fabricated electrochemical platform. Surprisingly, accompanying the deposited Ru nanoparticles with the Saf material inside the sensor composite resulted in more enrichment to the AMS anodic current (e.g. I_p is raised up to 67.0 μA at 0.980 V). Because of the incorporation of Ru nanoparticles with Saf, anodic peak current I_p much enhanced comparing to other sensors that may be attributed to the enhancement of electrochemical properties, ease of electrons transfer and surface area.

Based on the above discussion, CV was exploited to detect the electrochemical behavior of different bare and Ru-Saf/CPE using the redox couple of $[\text{Fe}(\text{CN})_6]^{3-/4-}$ in f 5.0 mM $[\text{Fe}(\text{CN})_6]^{3-/4-}$ and 0.1 M KCl solution. Figure 1d shows a CV response of bare CPE along with Ru-Saf/CPE in a 5.0 mM $[\text{Fe}(\text{CN})_6]^{3-/4-}$ and 0.1 M KCl solution with a scan rate of 100 mV s⁻¹. The AMS voltammetric behavior was scanned in the range between +0.4 to +1.2 V. The electroactive area was calculated from the slope of the plot of I_p versus $v^{1/2}$ and the calculated areas were found to correspond to 0.054 and 0.173 cm² for CPE, Ru-Saf/CPE, respectively.

Fig. 1D shows the comparatively weak redox current of CPE. Upon modifying the CPE with Ru-Saf, the redox current significantly increased to ~ 2.6 times as against of the CPE. This indicates that the synergetic effect of involving both Ru nanoparticles and Saf in the sensor composite might offer the essential conduction pathway for the electrocatalytic mechanism.

Optimization of the experimental parameters

The electrochemical behavior of AMS is dependent on the pH of buffer. In the pH investigation, cyclic voltammetry is done on the Ru-Saf/CPE using 1.0 x10⁻³ M of AMS in different pH values (3.0 - 9.0 of 0.04 M B-R buffer; SR=100 mVs⁻¹). This this scan rate was selected due to the high sensitivity with well-shaped voltammograms and a relatively narrow peak width at this value. Fig 2. A, signifies the performance of AMS due to changing the pH as the peak potentials (E_p) are moved to a lower positive potential upon rising the pH value. The highest anodic peak

current (I_p) was showed at pH 7.0 and chosen as an optimal pH for further studies and drug determination. Figure 2B displays the response of 1.0 mM AMS over a range of pH values using Ru-Saf/CPE sensing platforms. A linear relationship between the pH values and peak potential (E_p) was depicted as the following mathematical equation:

$$E_p(V) = 1.209 - 0.0521 \text{ pH}; R^2 = 0.998$$

The obtained slope from this equation is 52.1 mV/pH that follows Nernst equation with electrochemical oxidation process that include the same number of electron and protons. The proposed mechanism of the electrochemical oxidation is depicted in Figure 2C.

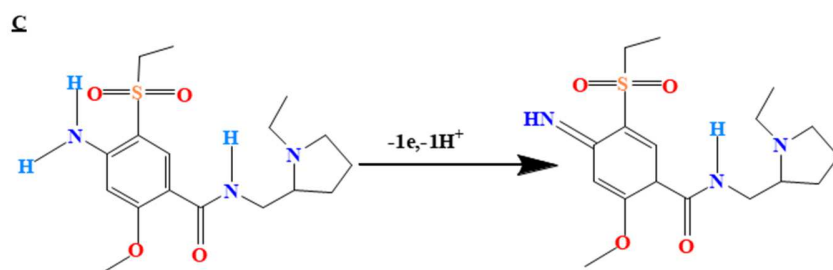
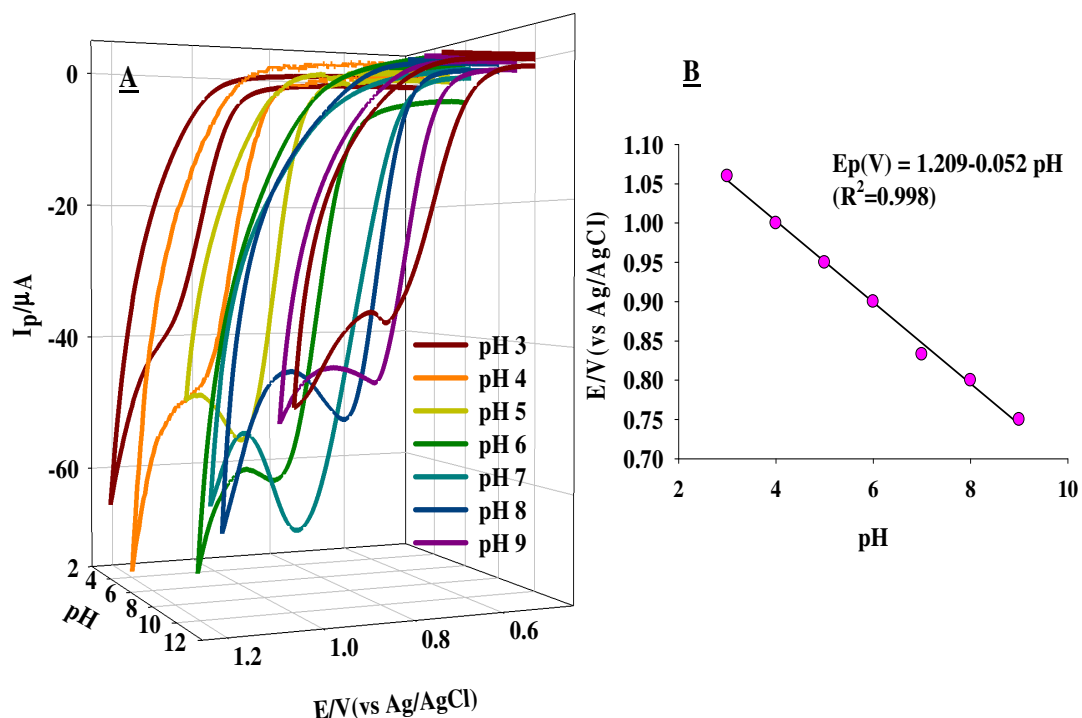


Figure 2. A) Voltammetric responses of 1.0 mM AMS over a range of pH values using Ru-Saf/CPE sensing platforms. Scan rate: 0.1 V s⁻¹. B) The oxidation peak current and peak potential AMS as a function of pH variations. C) Suggested electrochemical oxidation of AMS.

By the inspection of the suggested oxidation mechanism, AMS oxidation is may be due the amino group oxidation that exists in primary amine group on the *m*-anisidine ring [17, 33].

Next, the mechanism of the electrochemical reaction can be assessed through the investigation of the influence of scan rate (ν) of the oxidation peak signal by Ru-Saf/CPE in 1.0×10⁻³ M AMS in B-R buffer (pH 7.0). The result is demonstrated in **Figure S2**. Upon increasing the potential scan rate in the 20-100 mV s⁻¹ range, the current value increased, and the peak potential shifted to more positive values with no noticeable reverse reduction peak, suggesting that the oxidation of AMS is an irreversible process. By plotting the peak current (I_{pa}) against the square root of the scan rate ($\nu^{1/2}$), a linear straight line was obtained (**Figure S2**, inset A), indicating that the reaction is controlled by diffusion, according to:

$$I_p (\mu A) = 8.176\sqrt{\nu} - 16.45; R^2 = 0.9982.$$

Direct relation was acquired between log I_p and log ν in the 20 - 100 mVs⁻¹ range as the following:

$$\log I(\mu A) = 0.314 + 0.7317 \log \nu; R^2 = 0.9956.$$

By changing the scan rate (ν), electron-transmission kinetic parameters of AMS at Ru-Saf/CPE sensor can be determined. Applying log ν and anodic peak potential (E_p), a linear performance was detected (Fig. S2) and can be described by the following equation:

$$E/mV = 0.633 + 0.1252 \log \nu (V/s) (R^2 = 0.9781)$$

Furthermore, kinetic parameters were calculated for the electrochemical process on Ru-Saf/CPE using the theory of Laviron for irreversible reactions[34]. For a totally irreversible reaction, α (electron transfer coefficient) was assumed as 0.5, then n (the number of electrons transferred) was determined to be 0.944, suggesting that one electron was involved in the oxidation of AMS. Applying Laviron equation, k^0 (the standard heterogeneous rate constant of the surface reaction) was found to be 1.177 s⁻¹.

Last, the influence of the amount of Saf, Ru deposition potential and time used in the construction of the Ru-Saf/CPE based on the value of the voltammetric response / peak

sharpness are tested. The I_p for AMS was tested towards varying the amount of Saf over the range 3.0 mg to 25.0 mg.

10.0 mg of Saf was found to be the most appropriate amount as any addition cause a background augmentation with poor AMS detection repeatability.

Different deposition potentials are studied in the range -0.1 to -0.4 V. Upon the highest anodic peak current and stability, -0.4 V is chosen. The Ru electrodeposition at -0.4 V offers the development of Ru dense film that displays great electrocatalytic activity and enhances the AMS oxidation [35]. Furthermore, the deposition time is depicted at different time intervals (from 10 sec to 50 sec) and 40 sec was chosen due to the highest current response.

Optimization of developed electrochemical platform

The procedures delivered by the International Conference on Harmonization (ICH) for methods validation were followed for the validation of our developed protocol [36]. The SWV experiments were performed using Ru-Saf/CPE in B-R buffer at pH 7.0 solution containing different concentrations of AMS. The calibration curve was drawn based on the necessary practical consideration, to offer accurate, precise and linear results. Figure S3 illustrates the SWV of AMS at Ru-Saf/CPE in B-R buffer at pH 7.0 containing different concentrations, for each at scan rate: 0.1 V s^{-1} , $P_H= 0.25 \text{ V}$, $P_W=0.50 \text{ V}$, $S_H=0.02 \text{ V}$. Insets: the plot of the peak current as a function of AMS in concentration range $9.5 \times 10^{-8} - 7.0 \times 10^{-5} \text{ M}$. The plot of the peak current vs. AMS concentration showed wide linear for AMS concentrations: for $9.8 \times 10^{-8} - 7.0 \times 10^{-5} \text{ M}$, the regression equation was $I(\mu\text{A})=0.385 C + 0.13$ ($R^2=0.9992$). Lower limit of detection (LOD) and lower limit of quantification (LOQ) for linear calibration curve were calculated and found to be 8.80×10^{-9} and 2.93×10^{-8} , respectively. In addition, the repeatability and intermediate precisions were calculated and found to be 0.78 - 0.92%, respectively. Moreover, stability factor was tested for Ru-Saf/CPE sensor, where the anodic peak current (I_p) was not found to vary upon the storage in air at room temperature for 7 days. The modified sensor reserved 97.90 - 98.87% of its initial response.

Comparing to the previously published electrochemical determination of AMS, Ozkan et al[17] reported a bare unmodified stationary glassy carbon electrode with a linearity range $4.0 \times 10^{-6} - 6.0 \times 10^{-4} \text{ M}$ and detection limit of $1.9 \times 10^{-7} \text{ M}$. While the present protocol offers wider linearity range and lower detection limits.

Determination of AMS in the presence of co-administered drugs

To check the selectivity of Ru-Saf/CPE based sensing platform for AMS detection, other co-existing significant analytes or frequently co-formulated drugs CIT and MEM were tested in the presence of AMS. So, simultaneously varying drugs concentrations with recording the voltammetric responses at the fabricated electrochemical platform. Referring to Fig. 3, it is clear the presence of well sharp separated anodic peaks at potentials of +1.117 and +0.830 V (*vs.* Ag/AgCl), corresponding to the oxidation of CIT and AMS, respectively. This clarifies the high accuracy and precision of the developed sensor for the simultaneous determination of CIT and AMS. Figure 3B displays the current response obtained upon the oxidation of the molecules based on their respective concentrations. The plot of the peak current (I_p) as a function of AMS and CIT concentrations was demonstrated, Figure 3. The calibration plots are linearly for AMS and CIT over the range 3.0×10^{-7} to 2.4×10^{-5} M for both the drugs. The regression equations were: $I_p(\mu\text{A}) = 0.38C(\mu\text{M}) + 0.39$, $R^2 = 0.9990$; and $I_p(\mu\text{A}) = 0.481C(\mu\text{M}) + 0.913$, $R^2 = 0.9987$; for AMS and CIT, respectively. The analytical sensitivity of the AMS at Ru-Saf/CPE sensor is found to be $0.38 \mu\text{A}/\mu\text{M}$ that is very close to the obtained value in the absence of interfering AMS ($0.385 \mu\text{A}/\mu\text{M}$), signifying that the oxidation processes of both drugs at Ru-Saf/CPE are independent and consequently, the determination AMS of the mixture with CIT is promising without major interference.

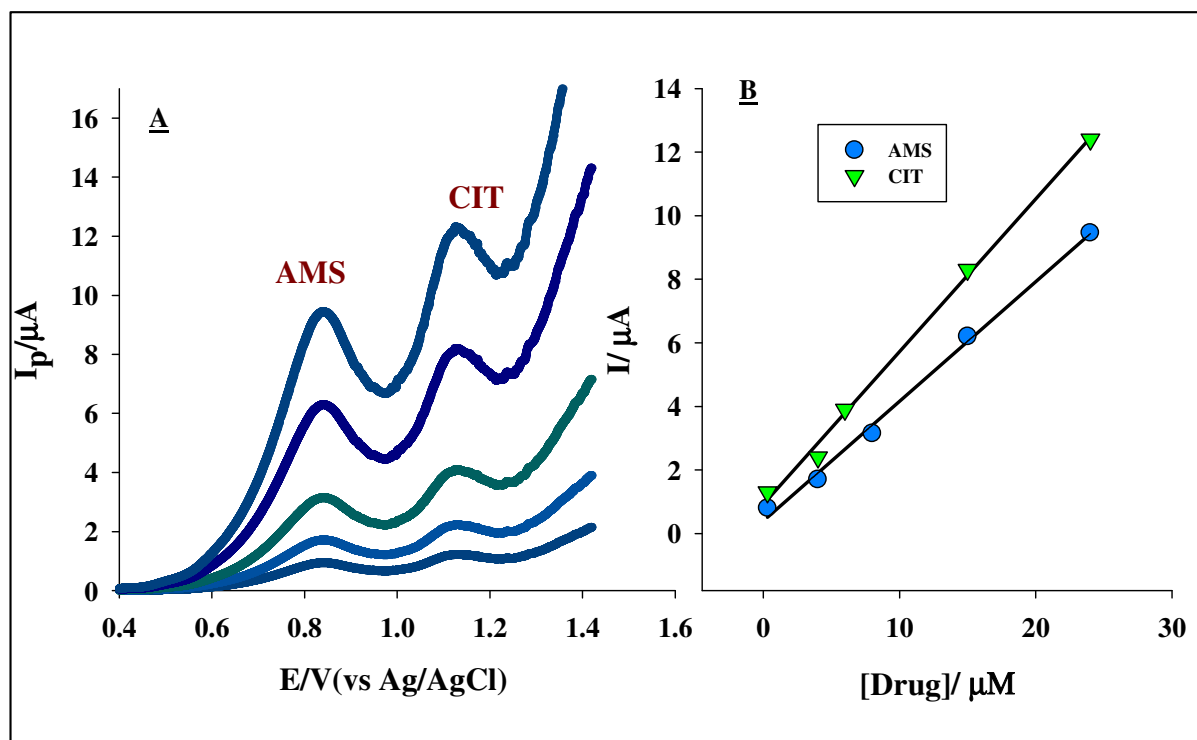


Figure 3. Electrochemical determination of AMS and CIT. (A) Square wave voltammograms using a Ru-Saf/CPE sensing platform in a pH 7.0 B-R buffer containing different concentrations of AMS and CIT correspond to 3.0×10^{-7} to 2.9×10^{-5} M, for each at scan rate: 0.1 V s^{-1} , $P_H=0.25 \text{ V}$, $P_W=0.50 \text{ V}$, $S_H=0.02 \text{ V}$. (B) Corresponding current response of AMS and CIT oxidation (analytical curves). Inset B: plots of I_p versus AMS and CIT concentrations.

The co-administered drug MEM displayed no electrochemical activity at the suggested electrochemical platform Ru-Saf/CPE under the optimized experimental conditions. Paracetamol (PAR ; acetaminophen) is one of the most common pharmaceutical medication used as painkiller globally due to its safety and efficiency [37]. PAR can be prescribed as analgesic co-administered medication with AMS. Furthermore, inflammation is accompanying with psychological distress and depression, so nonsteroidal anti-inflammatory drugs like PAR might be prescribed as associate therapy with antidepressants[38]. The SWVs of both AMS, PAR, ascorbic acid (ASA) and Caffeine (CAF) were performed under the optimized experimental conditions showing an excellent peak separation that allows the precise selective determination of AMS, Figure 4A and B.

Levodopa (LEV) is a catecholamine class pharmaceutical, precursor of dopamine and is used in the treatment of Parkinson's disease [39] was also checked with AMS at Ru-Saf/CPE. High resolution was observed along with good sharpness were achieved. The oxidation signal of LEV was recorded at 0.4 V while the anodic peak of AMS was achieved at 0.83 V, Figure 4C.

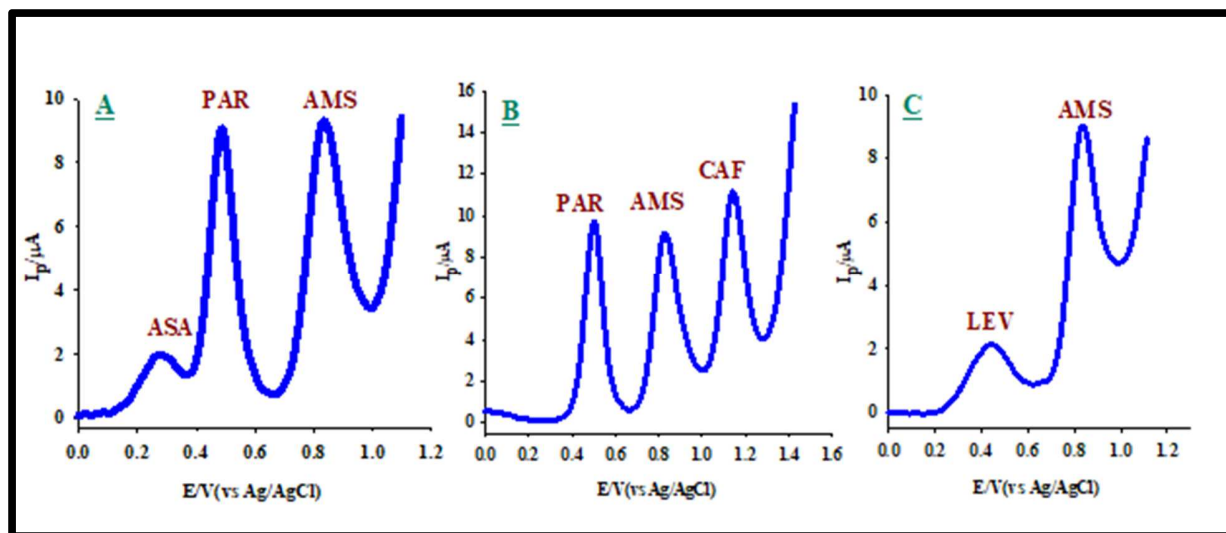


Fig. 4. Square wave voltammograms using a Ru-Saf/CPE sensing platform in a pH 7.0 B-R buffer containing 3.5×10^{-6} M AMS, 1.0×10^{-3} M ASA, 1.0×10^{-4} M PAR and CAF, and 1.0×10^{-4} M LEV, for each at scan rate: 0.1 V s^{-1} , $P_H = 0.25 \text{ V}$, $P_W = 0.50 \text{ V}$, $S_H = 0.02 \text{ V}$.

Reproducibility study and stability of developed electrochemical sensor

The electrochemical responses of 1.0 mM AMS at Ru-Saf/CPE at the optimum conditions for five consecutive measurements were measured to test the reproducibility factor. The relative standard deviation (RSD) for the I_p of AMS in five consecutive experiments was calculated and found to be 1.12 %. Furthermore, the fabrication protocol reproducibility was tested by preparing independently three modified sensors with the same way. The RSD was found to be 1.15%. In addition, inter-day precision was also calculated using different drug concentrations over a period of three days. Intra-day and inter-day precision were examined as relative standard deviation (RSD %) and presented in Table S1. The %RSD of all tested concentration levels was below 1.64% which confirms a good precision.

Analysis of AMS in real samples

The feasibility of Ru-Saf/CPE for analysis of AMS in real human fluids like human plasma, urine and evaluation of dosage form were examined using SWV. The standard addition methods were applied to assess the sensor performance for AMS analysis and compared the obtained data with the calibration plot, Table 1. The values of the recovery display a high accuracy of the developed electrochemical platform. Referring to the experiments outcomes, it is evident that this sensor has extreme potential for the determination of trace amounts of these compounds in biological fluids. Moreover, the dosage form was analyzed by keeping the similar parameters of SWV experiment applied before. The recovery experiment was presented in Table 1, which confirm that, the Ru-Saf/CPE is very sensible for the determination of low and high concentrations of AMS in different real samples.

Table 1. Determination of AMS in human urine and synthetic tablets using the proposed sensing protocol Ru-Saf/CPE

Sample	Amount added standard (μM)	Amount found (μM)	Apparent recovery%
Urine	0.50	0.48	96.00
	10.00	9.80	98.00
	40.00	39.29	98.22
	70.00	69.62	99.45
	100.00	98.98	98.98
Recovery% \pm R.S.D			98.13 \pm 1.30
Plasma	0.50	0.49	98.00
	10.00	9.78	97.80
	40.00	39.36	98.40
	70.00	69.51	99.30
	100.00	99.70	99.70
Recovery% \pm R.S.D			98.80 \pm 0.76
Amipride[®] Tablets	10.00	9.84	98.37

40.00	39.36	98.41
70.00	69.38	99.12
100.00	98.10	98.10
Recovery%±R.S.D		98.50±0.44

Interference studies

Under optimized conditions, the interference from selected metal ions and organic compounds on the determination of 1.0×10^{-5} M AMS was evaluated. Numerous potential interferents were chosen, which are commonly present in the pharmaceutical dosage forms (cations, anions and organic compounds). As can be seen in Table S2, the attained RSD values were low in all cases, indicating the Ru-Saf/CPE can be successfully used for the selective determination of AMS in pharmaceutical, environmental and biologic samples.

4. Conclusion

This study shows the fabrication of a chemically modified carbon paste electrode (CPE) by the combination of Ru nanoparticles and Saf. Through the cooperation of the proposed modifiers, excellent electrocatalytic activity and voltammetric behavior are achieved for sensing of AMS. The electrochemical oxidation behavior of AMS on the new electrochemical platform was depicted. The established sensor showed high selectivity, reproducibility, and sensitivity with other advantages like time simplicity, saving and cost-effectiveness. Additionally, the proposed electrochemical sensor was utilized for the quantitative detection of AMS in tablets, urine and plasma.

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