



An electrochemical platform of tannic acid and carbon nanotubes for the sensitive determination of the antipsychotic medication clozapine in pharmaceutical and biological samples

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ABSTRACT

The combination (TA/MWCNTs) of tannic acid decorated with carbon nanotubes was prepared to build a new electrochemical sensor to detect the clozapine (Clp). Scanning electron microscopy (SEM) and cyclic voltammetry (CV) techniques were used to characterize the morphological and electrochemical changes of the platform (TA/MWCNTs/GCE) obtained by modifying the glassy carbon electrode with the TA/MWCNTs combination. The active surface areas of the bare GCE and TA/MWCNTs/GCE were found to be 0.124 cm² and 0.340 cm², respectively. TA/MWCNTs/GCE surface exhibited a well-defined redox couple for Clp at 0.42 V and 0.36 V in pH 8.0, phosphate buffer solution. Under optimum conditions, the peak currents of square wave voltammograms of Clp with a detection limit of 0.55 nM and a quantification limit of 1.67 nM showed a linear increase at the 0.05 μM ~ 0.375 μM interval. The proposed TA/MWCNTs/GCE platform exhibited good repeatability, high sensitivity and excellent accuracy for Clp. The proposed platform was successfully applied for the quantification of Clp in pharmaceutical, serum and urine samples. Such precise quantification of Clp makes it important and interesting for monitoring the therapeutic use of the proposed platform.

1. Introduction

Clp (8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine), an atypical antipsychotic drug, is an effective drug in acute exacerbation and maintenance treatment of a schizoaffective disorder, especially schizophrenia, effective in a manic episode of bipolar disorder, in the treatment of acute maintenance and psychotic symptoms in dementia, and post-traumatic stress disorder [1]. Clp reaches steady-state plasma concentration after 7–10 days [2]. The antipsychotic effect can take weeks to be seen, and it may take months for the maximum effect to be seen [3]. The use of antipsychotic drugs provides a significant advantage in the treatment of schizophrenia patients, decreases the incidence of side effects of the drugs, shortens hospitalization times, and affects the course of the disease positively [4]. However, there are also research findings that the use of antipsychotic drugs have various risks in terms of the interaction of bioactive that act as a causative agent, increases morbidity and mortality rates and health expenditures in schizophrenia patients, imposes heavy burdens both for the patient and for the country's economy, reduces compliance with the drug, and can cause direct harm to the patient or the

environment in terms of pharmacological concerns [5,6]. Potential side effects such as convulsive seizures, myocarditis, cardiomyopathy, ischemic colitis, and paralytic ileus that may pose a serious threat to the health of the patient may occur when an overdose is taken or the required dose cannot be increased to the effective dose in plasma [7]. The more common and less serious side effects are sedation, hypersalivation, tachycardia, hypotension, hypertension, constipation [8–10]. It is very important for both the patient and the reliability and ethics of the drugs to be used that these indications can be determined by safe and high precision detection methods before the treatment phase is initiated and even during antipsychotic drug production and clinical laboratory studies. With the increasing interest in studies on the determination of antipsychotic drugs in recent years, the interest in the development of analytical methods has also increased at this point [11].

Electrochemical sensors are analytical systems with unique binding properties against target analytes [12,13]. Many conventional analytical methods are used for this purpose, including HPLC, flow injection technique, UV spectrophotometry, fluorimetry, and spectroelectrochemistry. However, electrochemical methods with simple equipment,

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sensitivity, high selectivity, and rapidity are more attractive because the low selectivity, cost, and time-consuming steps make some of these methods unsuitable for the analysis of samples [14–17]. These systems and methods can be widely used in clinical pharmacy R&D, pharmaceutical industry, drug delivery, medical diagnosis and health, analytical chemistry, food analysis tests, environmental monitoring, and military applications [18–24]. Electrochemical sensors have many advantages in terms of very high sensitivity, low cost, fast and real-time sampling capability, and low detection limit. In recent years, scientists have stepped up surface modification efforts to give new properties to a limited number of electrode materials [12]. As immobilization support for diagnostic molecules in electrochemical sensors, gold nanoparticles, metal oxide nanoparticles, carbon nanotubes, and quantum dots, etc. nanomaterials are used [25]. Compared to other nanomaterials, carbon nanotubes (CNTs) have been recognized as one of the most important materials for electrochemical transduction in electrochemical sensors due to their many superior properties such as rapid electron transfer, capabilities, small dimensions, cylindrical shapes, wide surface/volume ratio, high conductivity, and biocompatibility, helping to increase signal sensitivity during detection, high chemical stability, high surface area for signal amplification [26–28]. Having unique structures, they have different electronic properties and are extremely advantageous for the transmission of electrical signals produced upon the recognition of the target [29]. Besides these advantages, CNTs can also interact strongly with chemical species thanks to their mechanical, thermal, and electronic properties [30].

Tannic acid (TA) are polymers that are naturally present in plants. In the center, they contain groups of carbohydrates (usually D-glucose) and hydroxyl groups that are esterified with phenolic groups. TA, a water-soluble polyphenol compound, has been used for the treatment of many diseases for years [31,32]. A study with lymphocytes found that TA reduces DNA damage in oxidative DNA stress-induced with H₂O₂ [33]. It has been suggested that TA prevents oxidative damage by binding to iron ions (chelation) to prevent the formation of hydroxyl radicals [34]. The integration of TA into analysis systems is very important because there is a wide range of studies such as environment, medicine, food, and water analysis. TA is used as an immobilized biopolymer substance in the fields of medicine, clinical pharmacy, and pharmaceutical technology due to its antimicrobial, anticarcinogenic, and antimutagenic potentials as well as its use as a sweetener and food additive [35–37]. Moreover, TA is important for the dispersion stabilization of carbon nanostructures as it does not require surface modification or the addition of extra surfactants [38]. In addition, the TA molecule contains a large number of active phenolic groups and is easily converted into composites that can adhere to various molecules via covalent and/or non-covalent bonds [39,40]. Therefore, it is of great interest as a surface modification material in electrochemical sensor applications due to its good adhesion, excellent biocompatibility, biodegradability, antimicrobial and antioxidant effects [41,42]. In the other words, TA is a compatible polymer for the sensor interface, so when integrated with carbon-based nanostructures or nanoparticles, it can trigger accurate enzymatic reactions, significantly increasing the detection capability of the modified electron. Thus, it provides the potential to provide fast, simple, durable, and accurate, high-precision measurements in the development of electrochemical sensor systems [43–45].

In this paper, a simple nanocomposite (TA/MWCNTs) was prepared by integrating functionalized multi-wall carbon nanotubes (MWCNTs) with tannic acid and used in the modification of the surface of glassy carbon electrodes as a new type of modifier. The combination of MWCNTs with large surface area, high electrical conductivity, and functional groups in its structure with polyphenolic tannic acid make this nanocomposite a promising candidate as a sensing platform for Clp. Here, the proposed electrochemical sensor (TA/MWCNTs/GCE) has been proven to have a promising electrocatalytic effect for the

Clp and increase active surface area. In addition, TA/MWCNTs improved performance characteristics such as well-defined voltammetric peak current, low detection limit, fast response time, high precision for nanocomposite Clp, enabling the application of the proposed electrochemical sensor to real samples. Thus, it was shown that the proposed electrochemical sensor can be successfully applied for the quantification of Clp in pharmaceutical, serum, and urine samples.

2. Experimental

2.1. Materials, reagents and apparatus

Tannic acid (TA), KH₂PO₄ was purchased from Merck company; NaOH, Na₂HPO₄, ascorbic acid, dopamine, uric acid from Sigma-Aldrich company; chloroform and acetonitrile from VWR company; Clp, haloperidol, risperidone TCI-America company; glycine, sucrose from Amresco company; and 110–170 nm diameter MWCNTs from Sigma company. All solutions and samples were prepared with ultrapure water and stored in the refrigerator at + 4 °C for their stability. The electrochemical cell was deoxygenated by being treated with 99% pure nitrogen gas before each measurement.

A Gamry Interface 1000B Potentiostat/Galvanostat/Zra analyser with a three-electrode system was used to examine the electrochemical behaviour of Clp at room temperature (25 ± 1 °C). For the three-electrode system, TA/MWCNTs/GCE working electrode, platinum wire (Pt wire) counter electrode, Ag/AgCl/KCl_(doy) (BASi model MF-2052) were used as the reference electrode. Thermo orion 4-star pH meter was used for pH measurements.

2.2. Preparation of standard, supporting electrolyte and real samples

Standard solutions of 0.1 mM Clp were prepared quantitatively in 0.1 M HNO₃ by weighing the equivalent amount in a 10.0 mL volumetric flask. 0.1 M phosphate buffer solution (PBS) was prepared by dissolving equivalent amounts of sodium monohydrogen phosphate and potassium dihydrogen ortho phosphate in 250 mL ultrapure water. Optimum pH 8.0 was obtained by the quantitative additions of 0.1 M NaOH/HCl. Standards and supporting electrolytes were stored at + 4 °C. Clp tablet, human blood serum and urine samples were used as real samples. Clp tablets (4 pieces) were prepared by sonicating in 25 mL water and were adjusted to the appropriate condition with pH 8.0. The urine samples collected were cooled in the refrigerator and then centrifuged at 2500 rpm for 15 min. The supernatant was filtered on 47 mm Whatman paper, 2 mL of which was taken and completed to 15 mL with pH 8.0 PBS. Human blood serum was commercially obtained (Seronom Human, high (serum control for clinical chemistry), SERO203005-10x5mL). Without further processing, 2 mL of commercial blood serum was taken and completed to 10 mL with pH 8.0 PBS. No Clp was detected in serum and urine samples. Therefore, various concentrations of Clp were added to these samples before dilution for recovery tests, and square wave voltammograms were recorded.

2.3. Preparation of TA/MWCNTs combination and TA/MWCNTs/GCE

Prior to the modification, GCEs were cleaned and activated according to a procedure we previously reported [46]. MWCNTs were sonicated and functioned for 5 h in concentrated HClO₄ + HNO₃ (3:7, v: v) in an ultrasonic bath to increase surface conductivity and sensitivity and then filtered, washed to neutrality with ultrapure water and dried at room temperature. A combination suspension of TA/MWCNTs was prepared by sonicating 1.0 mg of TA and 0.1 mg of functionalized MWCNTs in 5 mL chloroform for 40 min. 5 µL of TA/MWCNTs suspension solution was dropped onto the GCE surface and the chloroform was evaporated (at 25 °C). The obtained TA/MWCNTs/GCE was reac-

tivated by cyclic voltammetry in the range of -1.0 to $+1.0$ V in 0.1 M PBS after extensive washing with ultrapure water.

2.4. Optimization of TA/MWCNTs combination for Clp detection

TA and MWCNTs were mixed at the rates of $0.5:0.5$ mg; $1.0:0.5$ mg; $0.5:0.1$ mg, respectively and the electrochemical responses for Clp were compared and evaluated. In addition, the TA/MWCNTs combination suspension was modified by being dropped at the rates of 1.0 , 3.0 , 5.0 and 7.5 μL onto the GCE surface, and its electrochemical sensitivity for Clp was examined by CV. When the mixing ratio of the combination suspension TA/MWCNTs modified to the GCE surface became $1.0:0.1$ mg and the amount of suspension dropped became 5.0 μL , a well-defined higher current voltammetric peak for Clp was revealed.

3. Result and discussion

3.1. Characterization of electrode layers

The surface morphology of the prepared modified electrodes plays an important role in the selective and sensitive detection of the target analyte [47]. Therefore, MWCNTs and TA/MWCNTs modifiers dispersed in chloroform were immobilized on the GCE electrode surfaces and then characterized by SEM. Fig. 1A presents that the characteristic structure MWCNTs were homogeneously dispersed on the GCE surface, without surface agglomeration. Fig. 1B presents that TA with multi-arm polyphenol structure was homogeneously distributed in the structure of MWCNTs and exhibited a graft structure. This showed

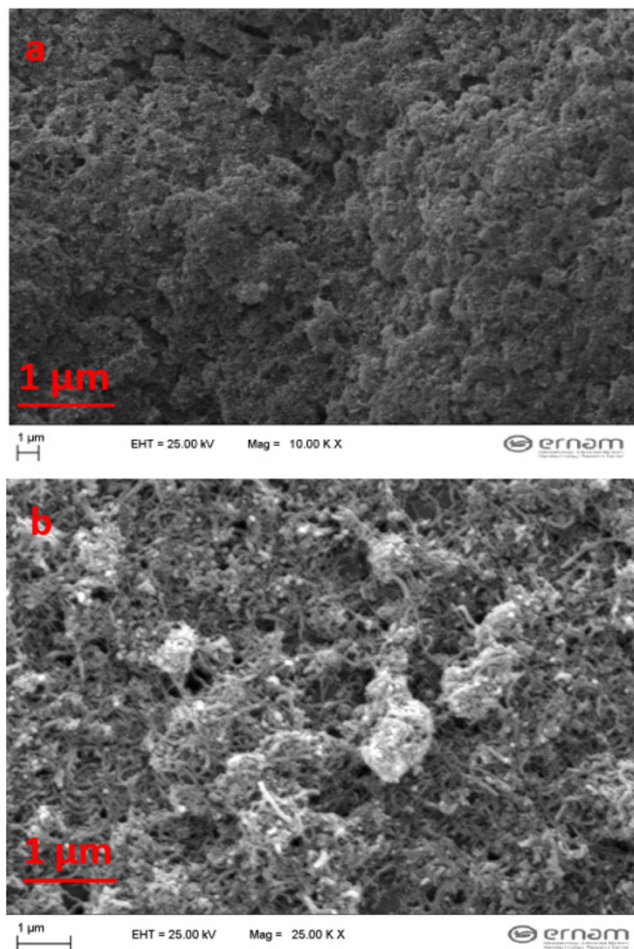


Fig. 1. SEM images of A) MWCNTs/GCE, B) TA/MWCNTs/GCE.

that GCE was successfully modified by TA/MWCNTs. Also, Fig. 2 presents a typical SEM-EDX analysis of TA/MWCNTs/GCE. As expected, EDX results showed that the main elements C, O, and N in the structure of the composite were on the surface.

3.2. The electrochemical performance of the bare GCE and TA/MWCNTs/GCE

The active surface area was compared between the bare GCE and TA/MWCNTs/GCE using CV. For this purpose, 1.0 mM $\text{K}_3[\text{Fe}(\text{CN})_6]$ solution dissolved in 0.1 M KCl was used as a probe. To determine the active surface area of the electrodes using the Randles-Sevcik equation, cyclic voltammograms of the bare GCE and TA/MWCNTs/GCE in this probe at scan rates ranging from 25 to 700 mV/s were used. As is known, the Randles-Sevcik equation ($I_{pa} = 2.69 \times 10^5 n^{3/2} A C_0 D^{1/2} \nu^{1/2}$) ($n^{3/2} A C_0 D^{1/2} \nu^{1/2}$) (at 25 °C) is used to determine the active surface area in reversible processes. All parameters such as electron transfer number ($n = 1$), diffusion coefficient ($D = 7.6 \times 10^{-6}$ $\text{cm}^2 \text{s}^{-1}$) and $\text{K}_3[\text{Fe}(\text{CN})_6]$ ($C_0 = 1 \times 10^{-3}$ molL^{-1}) used for the $\text{K}_3[\text{Fe}(\text{CN})_6]$ probe concentration are constant. Therefore, the slope of the plot of the square root of the scan rate ($\nu^{1/2}$) against the anodic peak current (I_{pa}) is proportional to the active surface area of the modified electrode [48]. Fig. 3A and Fig. 3B present the cyclic voltammograms of a 1.0 mM $\text{K}_3[\text{Fe}(\text{CN})_6]$ probe at different scan rates using the bare GCE and TA/MWCNTs/GCE. An active surface area calculated from I_{pa} vs $\nu^{1/2}$ slopes (Fig. 3C and Fig. 3D) was found to be 0.124 cm^2 and 0.340 cm^2 for bare GCE and TA/MWCNTs/GCE, respectively. Comparison of the two slopes revealed that the GCE modified with the TA/MWCNTs combination was 2.74 times bigger than the modified GCE. This can be attributed to the excellent interaction of TA [49] with a five polyphenol arm structure in combination with the functionalized MWCNTs, with the possible effect of MWCNTs with large specific surface area [50].

3.3. Electrochemical behaviour of Clp on electrodes

Fig. 4A. shows the cyclic voltammogram of TA/MWCNTs/GCE in 0.1 M PBS at pH 8.0 in the absence of Clp no peak current of Clp was observed. Fig. 4B. presents cyclic voltammetric responses of 100.0 μM Clp in pH 8.0 PBS with a scan rate of 100 mV/s on surfaces of the bare GCE, MWCNTs/GCE, TA/GCE, TA/MWCNTs/GCE. Weak cathodic peak currents of Clp and small anodic peak currents at 0.41 V, 0.39 V and 0.46 V were observed on the bare GCE, MWCNTs/GCE and TA/GCE surfaces, respectively. However, the TA/MWCNTs/GCE surface showed a weak cathodic peak current in reverse scan and a highly developed and well-defined anodic peak cur-

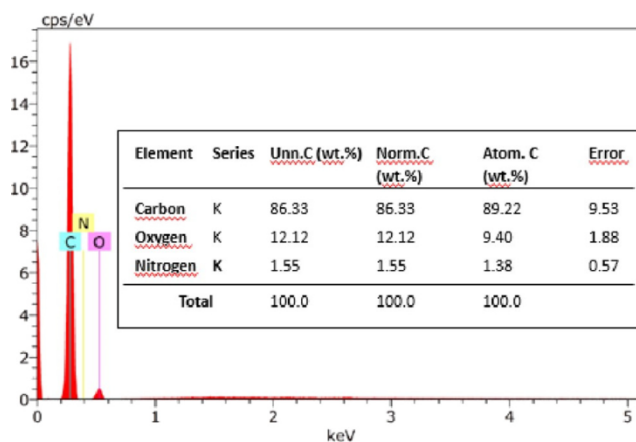


Fig. 2. EDX analysis of TA/MWCNTs/GCE.

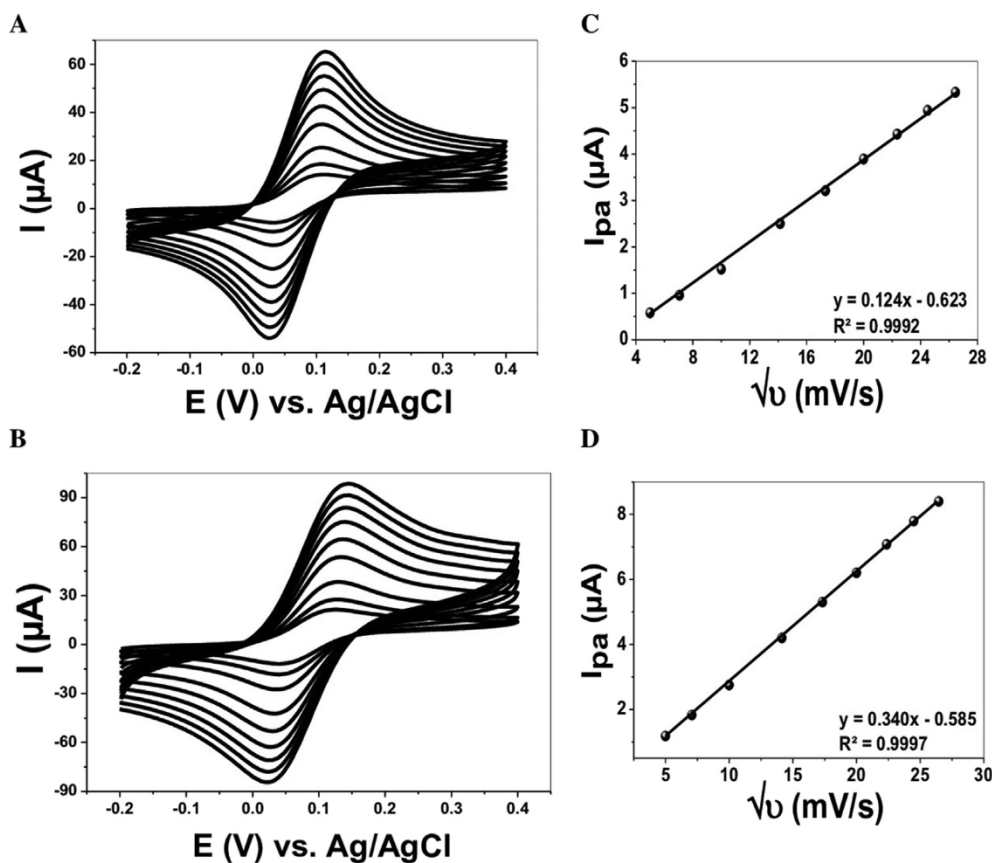


Fig. 3. Cyclic voltammograms of 1.0 mM $K_3[Fe(CN)_6]$ in 0.1 M KCl at 25; 50; 100; 200; 300; 400; 500; 600; 700 scan rates using bare GCE; (A), TA/MWCNTs/GCE (B). A plot of anodic peak currents versus square root scan rates (C) of voltammograms in A, (D) of voltammograms in B.

rent of Clp at 0.42 V. Therefore, the reduction process is partially reversible [51]. The good voltammetric behaviour of the electrode prepared with TA/MWCNTs combination can be attributed to the excellent properties of MWCNTs with high specific surface area, electronic properties, strong adsorption ability and functional groups, as reported by the previous findings in the literature [52-56]. In addition, the decoration of TA, which has a five polyphenol arm structure, with MWCNTs increased the adsorptive sites, resulted in a significant increase in the oxidation current [57]. The fact that the electrode obtained with this combination (TA/MWCNTs/GCE) increased approximately 3 times compared to other electrodes stemmed from the large active surface area.

3.4. Effect of pH and scan rate on the peak potentials and peak currents

The effect of pH ranging from 3.0 to 9.0 on the peak potentials and peak currents of Clp was investigated using the CV method in a 0.1 M PBS solution containing 50.0 μM Clp. Fig. 5A. presents the electrochemical behaviour of Clp on TA/MWCNTs/GCE electrodes at different pHs. It was observed that well-defined anodic peak currents and weak cathodic peak currents of Clp shifted linearly to more negative with increasing pH. The peak currents of Clp increased up to pH 8.0 due to the deprotonation and then decreased. This suggests that the peak potential and pattern of Clp oxidation depend on the pH of the solution. In general, when the pH of the solution is much lower than the pK_a , oxidation may be difficult due to strong protonation and the analytical signal will be lower. If solution pH exceeds the pK_a , it may lead to a decrease in the solubility of Clp, and precipitation to decrease the peak currents [58,59]. For this reason, higher pH values were not used and pH 8.0, where the best analytical signal was

obtained, was accepted as optimum. Fig. 5B. shows the relationship of anodic peak potentials (E_{pa}) and peak currents of Clp versus the solution pH. The linear equation for the anodic peaks was calculated as $E_{pa}(V) = -0.055pH + 0.817$ ($R^2 = 0.973$), and a slope of -55.2 mV/pH was obtained. The calculated slope being approximately equal to the theoretical value (59 mV) indicated that the ratio of electrons and protons of the proposed electrode in the Clp oxidation reaction mechanism, as presented in Scheme 1 [60 48].

The impact of the scan rate study plays an important role in understanding the reaction mechanism on the electrode surface and the associated sensor process [61]. Therefore, cyclic voltammograms of 50.0 μM Clp at pH 8.0 PBS at varying scan rates (25 ~ 250 mVs^{-1}) were recorded on the TA/MWCNTs/GCE surface (Fig. 6A.). It was proved that the anodic peak current (I_{pa}) and cathodic peak current (I_{pc}) increased linearly when the scan rate (v) increased (Fig. 6B.). Since the reduction process is partially reversible [51], while Clp has sharper and higher current oxidation peaks on the TA/MWCNTs/GCE surface the anodic peak currents against the square root of the scan rate were evaluated. Thus, in Fig. 6C. $I_{pa} (\mu A) = 2.007\sqrt{v} - 6.817$ equation with a regression coefficient of $R^2 = 0.9898$ was obtained. The linear correlation between $\sqrt{v} - I_{pa}$ was not close to the theoretical value of 1.0, indicating that Clp oxidation on the electrode surface could be achieved by an adsorption-controlled process [48,52]. In addition, a $\log v - \log I_{pc}$ plot was formed with increasing scan rate values and a linear line with the equation $I_{pa} (\mu A) = 0.721 \log v - 0.332$ was obtained (Fig. 6D.). The fact that the slope value of 0.721 corresponding to this equation was greater than the theoretical value of 0.5 proved that the electrochemical reaction took place with an adsorption-controlled process [61].

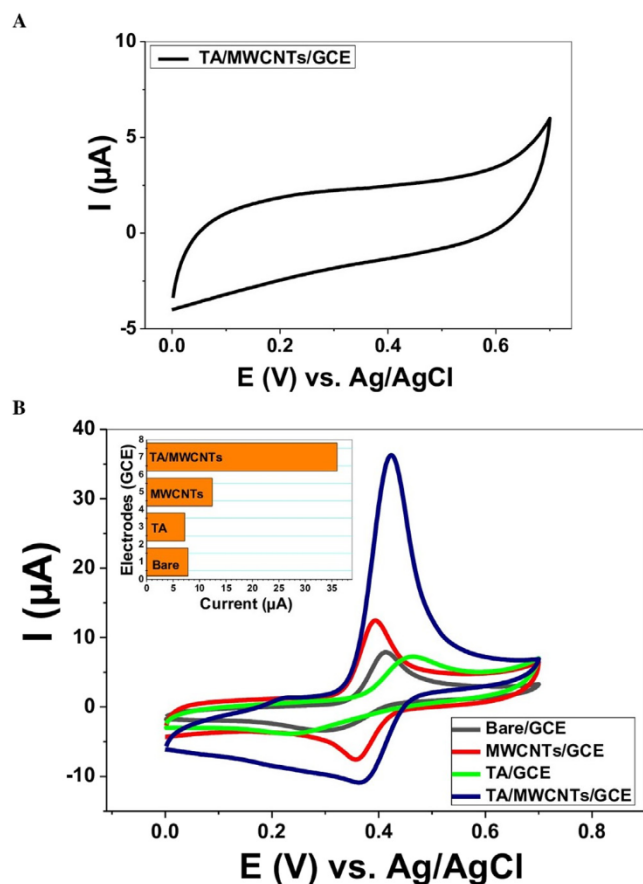


Fig. 4. A) Cyclic voltammograms of TA/MWCNTs/GCE in the absence of Clp in 0.1 M PBS at pH 8.0. Scan rate: 100 mV/s B) Cyclic voltammograms of 100.0 μM Clp at bare GCE, MWCNTs/GCE, TA/GCE, TA/MWCNTs/GCE in 0.1 M PBS at pH 8.0. Scan rate: 50 mV s^{-1} .

3.5. Electrochemical determination of the Clp

Electrochemical determination of Clp on TA/MWCNTs/GCE surface was performed by SWV technique to avoid large capacitive current and improve resolution and sensitivity. For this purpose, square wave voltammograms and calibration curves of Clp obtained in the concentration range of 50 ~ 375 nM are presented in Fig. 7. At the TA/MWCNTs/GCE surface, the plot of peak currents versus Clp concentration showed a linearity in the range of 0.05 μM to 0.375 μM with the equation $I_{pa}(\mu\text{A}) = 6.061C(\text{nM}) + 0.191$ and a correlation coefficient of 0.9958. LOD of 0.55 nM and LOQ of 1.67 nM were obtained from the calculations using the equations of $3.3(S_b/m)$ and $10(S_b/m)$ (S_b : blank standard deviation, M : slope). The obtained results showed that the proposed platform responded with a much higher sensitivity for the determination and quantification of Clp compared to the platforms reported in the literature with similar techniques (Table 1.). This can be attributed to create a good electrocatalytic effect on TA/MWCNTs/GCE surface thanks to the interaction of -OH groups on tannic acid [62] with functional carbon nanotubes. Thus, it is suggested that the proposed electrochemical sensor (TA/MWCNTs/GCE) for the very low detection limit of Clp is promising.

3.6. Reproducibility and stability

The reproducibility and stability of the newly fabricated sensor (TA/MWCNTs/GCE) were tested to evaluate practical use and electrochemical investigation. For this purpose, 4 different electrodes were prepared under the same conditions for reproducibility, and voltam-

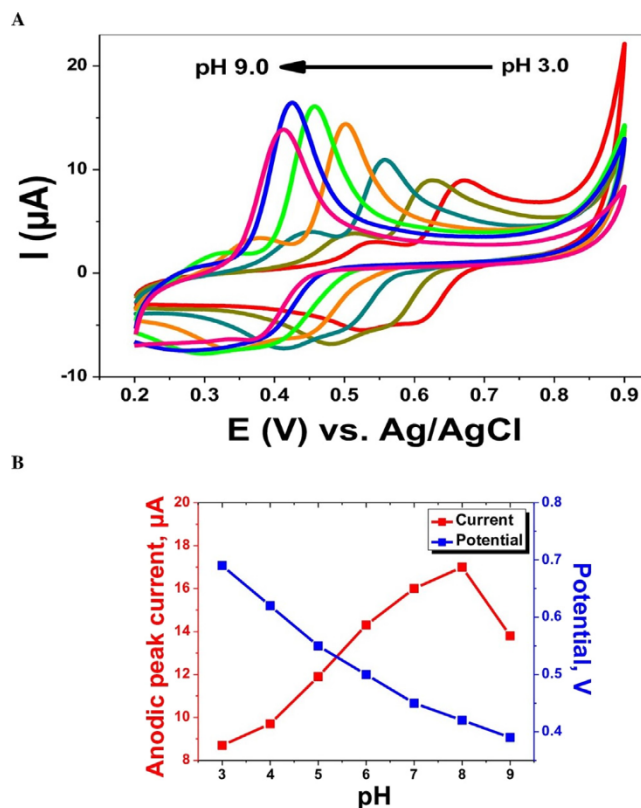
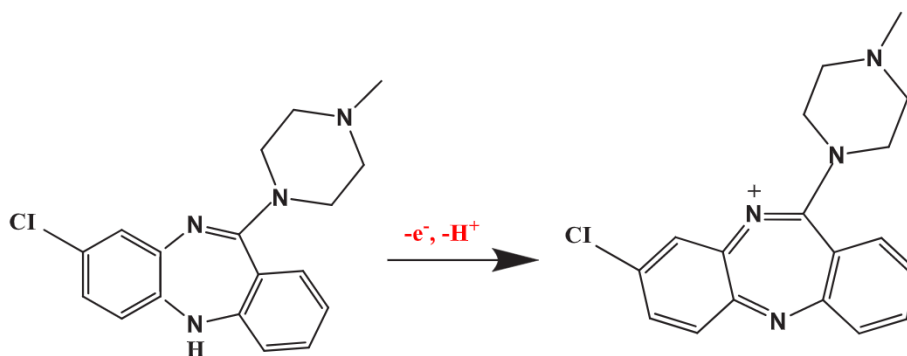


Fig. 5. A) Cyclic voltammograms of 50.0 μM Clp at TA/MWCNTs/GCE in 0.1 MPBS with pH 3.0; 4.0; 5.0; 6.0; 7.0; 8.0; 9.0 values. Scan rate: 50 mVs^{-1} . B) Variations of peak potential and peak current with pH.

mograms were recorded in pH 8.0 PBS containing 10.0 μM Clp at a scan rate of 50 mV. An RSD (relative standard deviation) of 2.7 was calculated for electrodes fabricated by the same procedure independently of each other (average of three determinations on each electrode). These results confirmed that the Clp sensitive TA/MWCNTs/GCE sensor has good reproducibility in the preparation process and electrochemical determinations. However, for repeatability, an electrode was prepared 4 times with the same procedure, and voltammograms were recorded at a scan rate of 50 mV in pH 8.0 PBS containing 10.0 μM Clp. An RSD of 1.8 was calculated with the electrochemical responses of this electrode, which was prepared with the same procedure each time. These results showed that the Clp sensitive TA/MWCNTs/GCE sensor also had good repeatability. In addition, TA/MWCNTs/GCE was incubated in pH 8.0 PBS and cyclic voltammograms of 10.0 μM Clp were recorded at certain periods for 1 month. Compared to pre-incubation voltammograms, only a 5.81% reduction in peak currents of Clp was observed. This overall slight decrease in peak currents of Clp after 1 month indicated the long-term stability of the combination formed on the electrode surface. In addition, the sensor did not show a clear decrease in peak currents after 20 times of use, indicating that it has a long usage time and good stability.

3.7. Interference studies

Since selectivity is an important factor in assessing applicability in real sample analysis, it was investigated how the proposed TA/MWCNTs/GCE sensor affects Clp analysis results in the presence of various species. For this purpose, solutions of some general biological compounds (lactose, tartaric acid, uric acid, ascorbic acid, dopamine, glycine, citric acid, sucrose, urea, haloperidol, risperidone) that are often found together with Clp in clinical and real samples with a con-



Scheme 1. The electrode reaction of Clp at TA/MWCNTs/GCE.

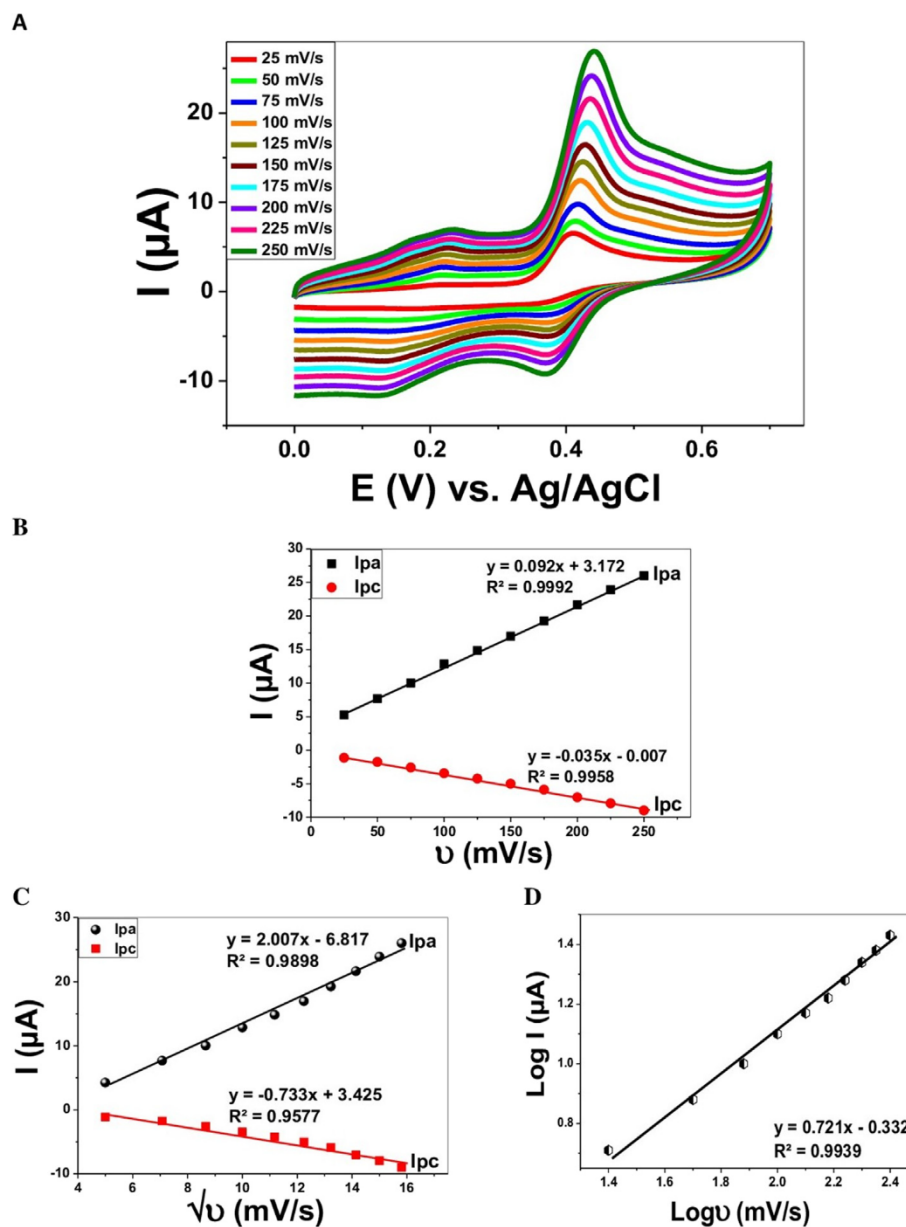


Fig. 6. A) Cyclic voltammograms of 50.0 μM Clp in pH 8.0 PBS at TA/MWCNTs/GCE with scan rate of: 25 mVs^{-1} ; 50 mVs^{-1} ; 75 mVs^{-1} ; 100 mVs^{-1} ; 125 mVs^{-1} ; 150 mVs^{-1} ; 175 mVs^{-1} ; 200 mVs^{-1} ; 250 mVs^{-1} . A plot of B) peak current versus scan rate C) peak current versus square root scan rate, D) anodic peak potentials of Clp versus logarithm of scan rates.

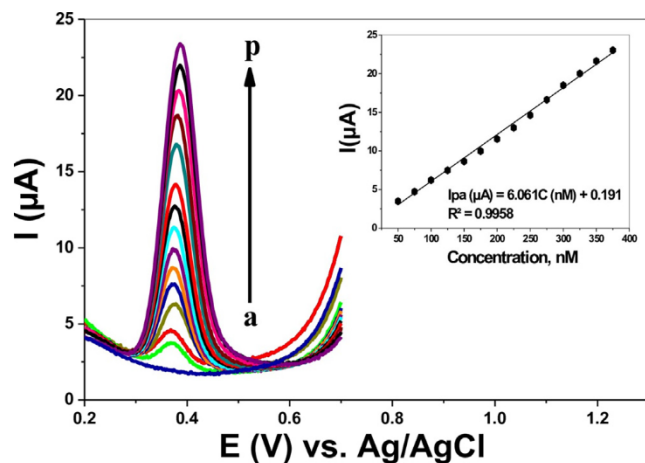


Fig. 7. SWVs with increasing concentrations of Clp in pH 8.0 PBS at TA/MWCNTs/GCE Frequency: 22 Hz. Step potential: 100 mV/s. Amplitude: 50 mV/s. a) 0.0 nM; b) 50 nM; c) 75 nM; d) 100 nM; e) 125 nM, f) 150 nM; g) 175 nM h) 200 nM; i) 225 nM; k) 250 nM l) 275 nM; m) 300 nM; n) 325 nM o) 350 nM; p)375 nM. Inset: A plot of peak currents versus the concentrations of Clp.

centration 100 times higher than Clp were prepared. This is because usually our body environment contains natural compounds in high concentrations compared to the analyte concentration [65]. The effect of each component on the voltammetric signals of Clz under optimum conditions was examined one by one. It was clearly seen that the interference species did not cause a significant effect on CV responses for Clp (Fig. 8A.). In addition, voltammograms of 50.0 µM Clp solutions of the proposed sensor with and without lactose, tartaric acid, uric acid, ascorbic acid, dopamine, glycine, citric acid, sucrose, urea, haloperidol, risperidone species, which have a 100-times higher concentration in pH 8.0 PBS were compared (Fig. 8B.). The results showed that the peak potential of Clp shifted very slightly but there was almost no change in the peak current. This indicates that Clp reactions in the detection sensitivity of the sensor are not affected by any species in the environment. Therefore, the proposed sensor can be used successfully as it shows good selectivity in detecting Clp.

3.8. Real sample analysis

To further confirm the reliability of the practical use of TA/MWCNTs/GCE, the detection of Clp in human blood serum, urine

Table 1

Comparison of the analytical performance of the proposed sensor for Clp detection with various working electrodes from the literature.

Electrode configuration	Method	Linear range/µM	Detection limit/µM	Ref.
RuTiO ₂ -CPE ^a	SWV	0.9–40	0.43	[63]
GPE ^b	DPV ^g	0.0095–1.5	2.86	[64]
WO ₃ -TRP-GCE ^c	SWV	2.0–150	0.03	[48]
EPGCE ^d	DPV	0.1–1.0	8.0	[59]
RuTiO ₂ /MWCNTs-CPE ^e	SWV	0.01–0.07	0.057	[65]
TiO ₂ NP/CuO/CPE ^f	DPV	1.0×10^{-3} – 1.0×10^{-4}	0.015	[61]
MWCNT/CPE ^h	CV ⁱ	1.0×10^3 – 3.5×10^3	950	[66]
TA/MWCNTs/GCE	SWV	0.05 – 0.375	5.5×10^{-4}	This work

^a Ruthenium doped TiO₂ nanoparticles modified carbon paste electrode

^b Graphite pencil electrode

^c WO₃ nanoparticles and α-t erpineol hybride modified glassy carbon electrode

^d Electrochemically pretreated glassy carbon electrode

^e Ru doped TiO₂ nanoparticles and multiwall carbon nanotubes hybride modified carbon paste electrode

^f titania nanoparticles and copper oxide modified carbon paste electrode

^g Differential pulse voltammetry

^h Multiwall nanotube modified carbon paste electrode

ⁱ Cyclic voltammetry.

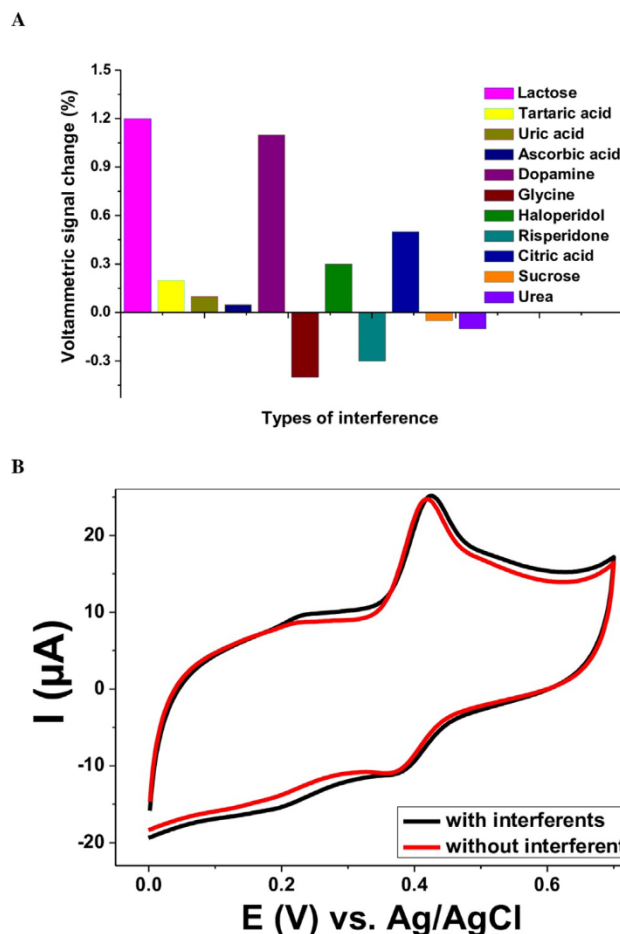


Fig. 8. A) The effect of possible interference on the voltammetric response of the Clp. B) CVs of 50.0 µM Clp with interference species and without species in pH 8.0 PBS of proposed electrode.

and tablets was tested by the SWV technique. Since Clp was not detected in blood serum and urine samples, different concentrations of Clp were added to these samples using the standard addition method and square wave voltammograms were recorded. Recovery values were calculated by comparing the determined concentrations with the added concentrations. RSD and recovery results were obtained based on five replications and are presented in Table 2.

Table 2
Recovery studies and determination of the Clp in real samples by the TA/MWCNTs/GCE.

Samples	Added(nM)	Found (nM)	RSD (%)	Recovery(%)	Error (%)
Serum	0	Not detected	–	–	–
	1	0.92	2.27	92.97	–7.02
	2	2.08	1.32	104.21	+4.21
	4	4.00	0.80	100.13	+0.13
	6	5.97	0.46	99.65	–0.34
Urine	0	Not detected	–	–	–
	1	0.91	2.62	91.46	–8.53
	2	2.06	1.97	103.11	3.11
	4	4.08	1.08	102.15	2.15
	6	5.93	0.65	98.91	–1.08
Tablet	1	1.02	0.84	101.79	+1.70
	2	2.05	1.89	102.57	+2.57
	4	3.96	2.18	99.05	–0.94
	6	5.86	2.74	97.68	–2.31
	8	8.10	1.96	101.35	+1.35

n = 5

RSD (%) = (Standard deviation / The average of the data obtained by repeating 5 times.) × 100.

Error (%) = [(found value - added value)/added value] × 100.

The results presented in Table 2 showed that TA/MWCNTs/GCE yielded satisfactory results with good accuracy for Clp determination in these samples. Satisfactory recovery percentages between 91.46% and 104.21% showed that real samples had no interference interaction effect on Clp detection even though they had complex matrices. This shows that the proposed sensor and method have good sensitivity and accuracy in detecting Clp, suggesting its successful applicability for clinical applications.

4. Conclusions

The nanocombination obtained by decorating tannic acid with MWCNTs exhibited excellent electrochemical sensing capabilities without further surface treatment. It has been shown that the electrode modified with this combination can be used as a sensor for the electrochemical detection of Clp with high sensitivity. As can be seen from the data, the proposed sensor performed very well in detecting the trace amount of Clp in solutions. In addition, the proposed electrode showed good properties such as high selectivity, repeatability and long life. The TA/MWCNTs nanocombination for Clp determination is very impressive due to its sensitivity, selectivity and low LOD value compared to the modifiers presented in previous reports. Therefore, thanks to the fast, practical and economical features of the TA/MWCNTs/GCE sensor, it can be profitable to detect and quantify Clp in clinical dosage forms, human blood serum and urine samples.

CRedit authorship contribution statement

Rumeysa Saylakci: Resources, Visualization, Writing - review & editing. **Hilal Incebay:** Methodology, Validation, Formal analysis, Resources, Visualization, Investigation, Supervision, Writing- Reviewing and Editing, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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