J. Electrochem. Sci. Eng. **16** (2026) 3459; https://doi.org/10.5599/jese.3459

Open Access : : ISSN 1847-9286
https://pub.iapchem.org/ojs/index.php/JESE

Original scientific paper

Tadalafil electrooxidation on gold and MWCNT-based nanocomposites modified carbon paste electrodes: comparative study and analytical application

Jasmina Anojčić[1,✉], Sanja Mutić[1], Sanja Stevanović[2], Nebojša D. Nikolić[2], Dušan Mijin[3], Slobodan Petrović[3], Zoltán Kónya[4,5] and Milka Avramov Ivić[2]

[1]*University of Novi Sad, Faculty of Sciences, Department of Chemistry, Biochemistry, and Environmental Protection, Trg Dositeja Obradovića 3, 21000 Novi Sad, Serbia*
[2]*University of Belgrade-Institute of Chemistry, Technology and Metallurgy, Department of Electrochemistry, Njegoševa 12, 11000 Belgrade, Serbia*
[3]*University of Belgrade, Faculty of Technology and Metallurgy, Karnegijeva 4, 11000 Belgrade, Serbia*
[4]*Department of Applied and Environmental Chemistry, University of Szeged, Rerrich Béla tér 1, 6720 Szeged, Hungary*
[5]*MTA-SZTE Reaction Kinetics and Surface Chemistry Research Group, Rerrich Béla tér 1, 6720 Szeged, Hungary*

Corresponding Author: ✉jasmina.anojcic@dh.uns.ac.rs

Received: May 22, 2026; Accepted: June 27, 2026; Published: July 7, 2026

Abstract

The electrochemical behaviour of tadalafil (TAD) was investigated using a solid gold electrode and carbon paste electrodes (CPE) modified with multiwalled carbon nanotubes (MWCNT) or their nanocomposites with noble metal particles (Ag-MWCNT and Au-MWCNT). Cyclic voltammetric study revealed that the oxidation of TAD is irreversible and that adsorption plays a significant role in the oxidation mechanism. Among the investigated electrodes, the Au-MWCNT/CPE exhibited the best electroanalytical performance and was used to develop a sensitive and reliable square-wave adsorptive stripping voltammetric method for TAD determination in Britton-Robinson buffer solution as supporting electrolyte. The optimal pH was 4.0, with target analyte accumulation being most pronounced at E_{acc} = 0.6 V and t_{acc} = 10 s. Linearity was obtained in the TAD concentration range of 0.10 to 1.96 µg mL^{-1}, with calculated limit of detection of 0.03 µg mL^{-1}. The constructed sensor showed excellent repeatability and reproducibility, as well as anti-interference ability, making it highly suitable for analytical applications, such as the quantification of TAD in the pharmaceutical formulation Cialis® and in human blood serum sample.

Keywords

Pharmaceuticals; electroanalysis; electrochemical sensors; voltammetry; pharmaceutical formulation; human blood serum sample

Introduction

Tadalafil (TAD, IUPAC Name: (6R,12aR)-6-(1,3-benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydro-pyrazino [1',2':1,6] pyrido[3,4-b] indole-1,4-dione) is a drug with a wide range of applications in men's health and cardiovascular medicine. It is a phosphodiesterase type 5 (PDE-5) inhibitor primarily used for the treatment of adult men with erectile dysfunction, the symptoms of benign prostatic hyperplasia, and pulmonary hypertension [1,2]. Additionally, TAD offers cardiovascular benefits due to vasodilatory effects, with lower mortality, cardiovascular disease, and dementia risks compared to sildenafil [3]. It is commonly sold under the commercial name Cialis®. Among PDE-5 inhibitors, TAD has significant differences, including a longer half-life, resulting in a longer period of responsiveness (up to 36 h). It also features higher selectivity for PDE-6, responsible for visual disturbance, and generally minimal side effects, making it a patient-preferred drug [4]. Given the widespread use of TAD, determining its precise concentration and purity is critical to ensuring pharmaceutical quality, patient safety, and clinical efficacy.

Numerous analytical methods have been proposed for the determination of TAD in pharmaceutical formulations and biological samples for quality control or pharmacokinetic studies. Commonly employed techniques include high-performance liquid chromatography with UV [5-7], diode array and/or mass spectrometry detection [8,9], as well as gas chromatography with mass spectrometry [10,11]. Spectrophotometry is also a viable option, involving either direct TAD detection [12] or the formation of ion-pair complexes with bromocresol purple and methyl orange [13]. Furthermore, derivative UV spectrophotometric methods have been developed [14]. Thermal behaviour of TAD was investigated in detail, focusing on decomposition and kinetic studies by thermoanalytical techniques [15].

Considering the chemical structure of TAD (Figure 1), it is possible to develop electroanalytical methods for its determination, which provide additional advantages in terms of simpler sample preparation, reduced reagent consumption and portability compared to conventional analytical methods [4]. Recent innovations in pharmaceutical electroanalysis utilize advanced nanomaterials like graphene, carbon nanotubes (CNTs), metal nanoparticles, and quantum dots to significantly enhance sensor sensitivity and selectivity. By creating hybrid composites, for example by incorporating metal nanoparticles into carbon-based materials, a synergistic effect can be achieved, resulting in improved catalytic activity and signal-to-noise ratios for the detection of drugs in complex sample matrices [16]. CNTs are superior materials characterized by a high surface-to-volume ratio and outstanding electrical conductivity [17].

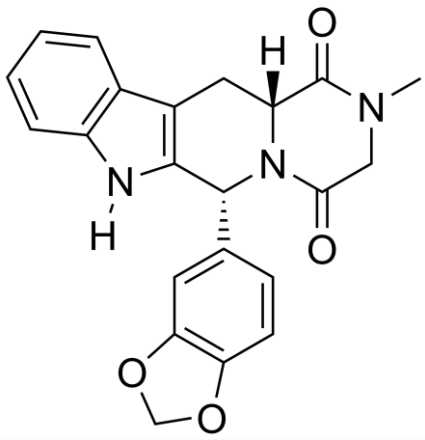

Figure 1. *Chemical structure of TAD*

Consequently, decorating CNT surfaces with metal nanoparticles, including gold, silver, platinum, and palladium, has been widely employed. These metal nanoparticles act as catalytic centres,

improving analyte adsorption, electron transfer kinetics, and the sensitivity of electrochemical sensors, in addition to the potential biocompatibility of their nanocomposites [18,19].

Several voltammetric methods have been developed for the sensitive quantification of TAD, employing working electrodes made of carbonaceous materials. A cathodically pretreated boron-doped diamond electrode was successfully applied for TAD determination in pharmaceutical formulations, without requiring modification of the working electrode [20]. On the other hand, composite electrodes and their modifications have also been proposed to enhance sensitivity. By utilizing multiwalled carbon nanotube (MWCNT) paste electrode and modified TiO_2-MWCNT paste electrode [21], as well as MWCNT modified glassy carbon electrode (GCE) [22] or vertically oriented MWCNT on a copper plate [23], it was demonstrated that CNTs are very versatile materials for TAD electrochemical sensor design. Electrochemical detection of TAD at a GCE modified with a ruthenium(II) complex is an interesting example of application of metal complexes in the electroanalysis of different analytes, including TAD [24]. More complex electrode materials and modifications have further lowered the limits of detection for TAD as a target analyte. A voltammetric sensor based on a montmorillonite clay-CeO_2 nanoparticle-modified composite pencil graphite paste electrode was constructed for the trace determination of TAD [25]. A study employed carboxymethyl-β-cyclodextrin and thiol-β-cyclodextrin functionalized gold nanoparticles-silicon carbide (Au@SiC) film modified GCE showed that TAD electrochemical signal could be significantly amplified by introducing a certain amount of acetonitrile in buffer medium and further enhanced by the host-guest molecular recognition capacity of β-cyclodextrin [26].

The aim of this work was to investigate the electrochemical behaviour of TAD at different electrode surfaces: a solid gold electrode and carbon paste electrodes (CPE) modified with MWCNT nanocomposites. To the best of our knowledge, MWCNTs in combination with noble metal particles *i.e.* Ag-MWCNT and Au-MWCNT, have not been utilized for TAD electrochemical sensor design. The objective was to expand the application of Ag-MWCNT and Au-MWCNT in the electroanalysis of pharmaceuticals, building on the excellent performance of these nanocomposites in the amperometric determination of H_2O_2, as demonstrated in a previously published study [27]. In this study, TAD exhibited more favourable interactions with the Au-MWCNT/CPE surface, a characteristic exploited to develop a novel, simple, and sensitive voltammetric method for its determination in pharmaceutical formulation and human serum samples.

Experimental

Chemicals and solutions

A stock solution of TAD at a concentration of 100.0 μg mL^{-1} was prepared by dissolving the analytical grade chemical standard (kindly provided by Hemofarm Stada A.D., Vršac, Serbia) in high-purity methanol. This stock solution was stored in the dark and in the refrigerator to maintain its stability, and was diluted daily with a supporting electrolyte to obtain working solutions of lower concentrations. The supporting electrolyte used was a Britton-Robinson (B-R) buffer solution of different pHs from 2.0 to 12.0, which was prepared from phosphoric acid, acetic acid, and boric acid (0.04 mol L^{-1}), whereby the desired pH values were adjusted by adding sodium hydroxide solution (0.2 mol L^{-1}). For the interference study, analytical reagent-grade potassium nitrate (KNO_3), sodium hydrogen carbonate ($NaHCO_3$), magnesium sulphate heptahydrate ($MgSO_4 \times 7H_2O$), calcium chloride ($CaCl_2$), ascorbic acid (AA), dopamine hydrochloride (DA), uric acid (UA) and glucose (Glu) were used.

Graphite powder (particle size <20 μm, synthetic, Sigma-Aldrich) and paraffin oil (Kemika, Croatia) were utilized for the preparation of CPE. MWCNT and their nanocomposites (Ag-MWCNT

and Au-MWCNT) were modifiers of CPE. Details of nanomaterial synthesis procedure, along with physical characterization (SEM-EDS and X-ray diffraction measurements), are provided in previously published work [27].

Apparatus

Electrochemical measurements were performed using an AUTOLAB PGSTAT 12 potentiostat/ /galvanostat (Ecochemie, The Netherlands) controlled by GPES 4.9 software. In a conventional three-electrode cell, the working electrode was a solid gold electrode (Gamry, 3 mm diameter), CPE (2 mm diameter), or nanocomposite-modified CPE; the reference electrode was a saturated calomel electrode (SCE) and the counter electrode was gold or platinum wire.

The morphological aspects of TAD were studied using an optical microscope (OM), model Olympus CX41, connected to a computer.

UV spectrophotometric measurements were performed using a T 80+ ultraviolet-visible (UV/Vis) spectrometer (PG Instruments Ltd., UK).

All pH values of the supporting electrolyte were precisely measured using a pH meter (inoLab® Multi 9620 IDS, Germany) equipped with a combined glass electrode (SenTix® 980 IDS, Germany).

Procedures

Pretreatment of the solid gold electrode

The solid gold electrode underwent a cleaning procedure to ensure a reproducible, uncontaminated surface. It was mechanically polished on a soft polishing cloth using diamond paste, chemically treated in concentrated sulfuric acid, and washed with double-distilled water.

Preparation of carbon paste electrodes and its modification

The unmodified CPE was prepared manually by mixing graphite powder and paraffin oil at a weight ratio of 70:30 using porcelain mortar and pestle. The mixture was homogenized for at least 30 min until a uniform, paste-like consistency was obtained, afterwards a proportion of prepared carbon paste was packed into the cavity of a Teflon electrode body (2 mm inner diameter) introduced by *Švancara et al.* [28]. The prepared CPE was stored at room temperature. The freshly generated electrode surface was obtained mechanically by squeezing a small amount of paste from the electrode holder and then wiping the excess onto a piece of clean, smooth paper.

The modified CPEs were prepared using the drop-casting method. Suspensions of MWCNT, Ag-MWCNT and Au-MWCNT were prepared by dispersing the corresponding nanomaterial in absolute ethanol (1.5 mg mL^{-1}) followed by ultrasonication for 15 min [27]. 3.0 µL of such prepared suspensions was carefully dropped onto the freshly renewed CPE surface and allowed to dry at room temperature for about 10 min. The modified electrodes are designated as MWCNT/CPE, Ag-MWCNT/CPE and Au-MWCNT/CPE.

Voltammetric measurements of tadalafil

Cyclic voltammetric (CV) measurements were performed with different working electrodes in B-R buffer solution at pH 4.0, over the potential range of 0.0-1.2 V, at a scan rate (v) of 50 mV s^{-1}, and a TAD concentration of 9.09 µg mL^{-1}. The Au-MWCNT/CPE was found to be the most appropriate working electrode for TAD electroanalysis, so further optimization of the voltammetric method was carried out using this electrode. The effect of v was also investigated under the same CV experimental conditions by a solid gold electrode and Au-MWCNT/CPE but varying the v from 20 to 140 mV s^{-1}.

The effect of pH on the oxidation signal of TAD (4.76 μg mL^{-1}) was studied by Au-MWCNT/CPE and SWV using the following operational parameters: potential step 5 mV, frequency 50 Hz, amplitude 25 mV. The adsorption parameters, including accumulation potential (E_{acc}) and accumulation time (t_{acc}), were optimized with an equilibration time (t_{eq}) of 5 s. Square-wave adsorptive stripping voltammograms (SW-AdSVs) (E_{acc}=0.6 V, t_{acc}=10 s) for increasing TAD concentrations from 0.10 to 1.96 μg mL^{-1} were recorded to construct a calibration curve. The limit of detection (LOD) and the limit of quantitation (LOQ) were evaluated based on signal-to-baseline noise ratios of three and ten, respectively [29]. For the interference study, the TAD (1.78 μmol L^{-1}) oxidation signal was recorded using the optimized SW-AdSV method in the presence of 100 times higher molar concentrations of KNO_3, $NaHCO_3$, $MgSO_4$, $CaCl_2$ and 10 times higher molar concentrations of AA, DA, UA and glucose. The mixture of 5.0 mL of B-R buffer solution (of the appropriate pH) and 5.0 mL of double-distilled water served as a blank solution for baseline recording in all voltammetric experiments.

The intensity of TAD signals was evaluated using the integration procedure available in the GPES 4.9 software. In this procedure, the baseline is determined using the tangent-fit method, in which a tangent is drawn from the left to the right side of a peak.

Real sample analysis

Pharmaceutical formulation. Two tablets with TAD as active ingredient named Cialis® (20 mg film-coated tablets, Eli Lilly (Suisse) SA, Belgrade, Serbia) were crushed in a mortar with a pestle. 0.0452 g of the obtained powder was dissolved in 25.0 mL of methanol and analysed by SW-AdSV, while filtration was required prior to spectrophotometric measurements. SW-AdSV measurements (E_{acc}=0.6 V, t_{acc}=10 s, t_{eq}=5 s) of TAD in Cialis® tablets were conducted using Au-MWCNT/CPE with the aid of the standard addition method. In 10.0 mL of B-R supporting electrolyte pH 4.0, 60.0 μL of the as-prepared sample of the pharmaceutical formulation was added, followed by three standard additions of TAD (0.198, 0.396 and 0.593 μg mL^{-1}). Voltammograms for the sample and each standard addition were recorded and the corresponding analytical curve was constructed. The linear regression line was extrapolated to the *x*-intercept (*y*= 0), where the absolute value of the *x*-intercept equals the concentration of TAD in the sample solution. The dilution factor was considered and the final amount of TAD in the sample was expressed as mg TAD/tablet. Comparative UV spectrophotometric measurements were also performed. The prepared and filtered Cialis® tablet sample was diluted 10-fold with methanol. The absorbance was read at 284 nm, with methanol serving as a blank [12]. The concentration of TAD was calculated using the calibration curve equation over the TAD concentration range of 1.0 to 20.0 μg mL^{-1}. All measurements were performed in triplicate.

Blood serum sample. Informed consent was obtained from the human subject before collecting the blood sample. Blood was sampled from a healthy male volunteer and centrifuged to separate the serum in a certified laboratory (Novi Sad, Serbia). The serum sample was analysed by Au-MWCNT/CPE under previously optimized conditions (pH 4.0, E_{acc} = 0.6 V, t_{acc} = 10 s, t_{eq} = 5 s). The 20.0 μL of untreated serum sample was introduced into 10.0 mL of supporting electrolyte and spiked with TAD (0.398 μg mL^{-1}). The standard addition method was used to assess method reliability and calculate recovery. All measurements were performed in triplicate.

Results and discussion

Morphological aspects of tadalafil

To characterize TAD from a morphological point of view, a few drops of solution prepared by dissolution of TAD standard in methanol were placed onto an atomically flat mica surface. The TAD

standard crystals obtained after drying in the air are shown in Figure 2. It can be seen from Figure 2 that very small 2D (two-dimensional) crystals, with a size that can be estimated at several micrometres and less, were obtained. The 2D crystals are crystallized individually or grouped in agglomerates of various sizes.

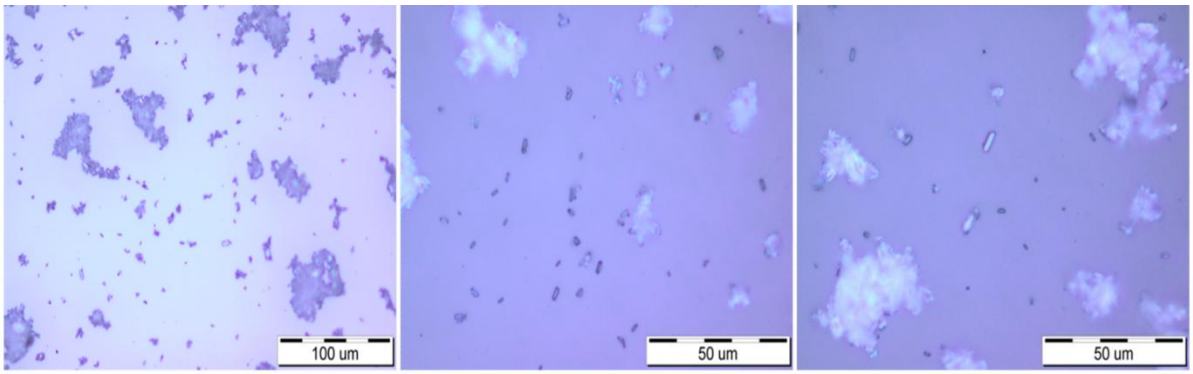

Figure 2. *Morphology of TAD standard crystals obtained after air drying at different optical microscope magnifications*

Electrochemical oxidation of tadalafil on gold electrode

CV study of TAD electrooxidation on a solid gold electrode at pH 4.0 is presented in Figure 3A. In the absence of the target analyte, a typical voltammogram was observed with a notable current increase beginning from 0.9 V related to the formation of a gold oxide layer at the electrode surface. In the reverse scan, a well-defined peak corresponding to the reduction of gold oxides can be seen at 0.6 V.

With the addition of TAD, a new peak appears at around 0.75 V in positive ongoing potential direction, at the potentials before the oxide formation; also, the current intensity resulting from oxide formation increases, suggesting TAD electrooxidation at the Au electrode surface. The oxides reduction decreases as a consequence of the reduction of TAD products formed at anodic potentials. It is important to note that during consecutive sweeps (n = 5), TAD oxidation currents decrease slightly and stabilize by the fifth sweep; the currents obtained at the first sweep are shown in Figure 3A.

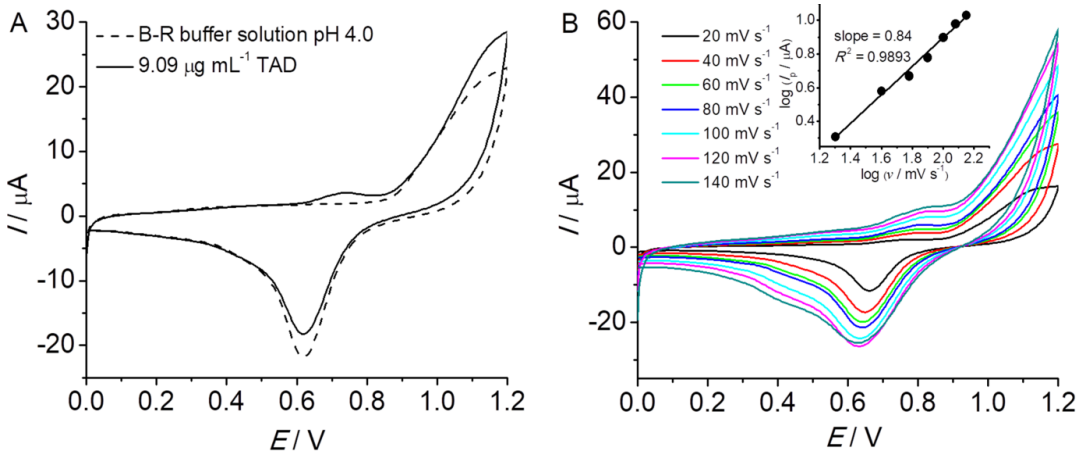

Figure 3. *(A) CVs recorded with gold electrode in B-R buffer solution pH 4.0 in the absence (dashed line) and in the presence of TAD (9.09 μg mL^{-1}, first sweep, full line),* ν *= 50 mV s^{-1}. (B) The effect of scan rate together with log* I_p *vs. log* ν *correlation (inset)*

More detailed insight into the electrochemical behaviour of TAD at the Au surface was achieved by studying the effect of scan rate (Figure 3B; the first sweep is presented). By varying the v, the irreversible nature of the electrochemical process was observed, since the oxidation peak potential (0.75 V) shifts toward more positive values as the v increases. The peak current intensity (I_p) increases

linearly with *v*, and plotting log I_p against log *v* yields a straight line with a slope of 0.84 (inset, Figure 3B), indicating that the electrochemical process is "mixed" diffusion-adsorption controlled [30].

Electrochemical oxidation of TAD on MWCNT-based nanocomposites modified CPEs

The oxidation reaction of TAD was also investigated on heterogeneous carbon electrodes, to compare the behaviour with a gold electrode, but also to overcome cost and manipulation issues. MWCNTs in their native form, when decorated with noble metal nanoparticles, can enhance the performance of a traditional CPE and address the problem of TAD current decrease during sweeping on a solid gold electrode. Under the same experimental conditions, the CV responses in the presence of target analyte were evaluated for unmodified CPE, as well as CPEs modified with 3.0 µL of nanomaterial suspensions (1.5 mg mL^{-1}) *i.e.* MWCNT/CPE, Ag-MWCNT/CPE and Au-MWCNT/CPE (Figure 4A and Figure S1, Supplementary material). In all cases, a single oxidation signal of TAD can be identified with a peak potential (E_p) of 0.87 V for unmodified CPE, while E_p was slightly shifted for nanomaterial-modified CPEs, reflecting an enhancement in electron-transfer kinetics. The I_p of TAD increased in order CPE < MWCNT/CPE < Ag-MWCNT/CPE < Au-MWCNT/CPE. Introducing MWCNT into electrochemical sensor modification enhances performance by increasing electrode conductivity, surface area, and electrocatalytic activity [31]. Additionally, combining Ag or especially Au nanoparticles with MWCNT yielded a more pronounced TAD signal improvement, arising from the synergistic effect of the nanocomposite constituents. Notably, the modification of the CPE with nanocomposite materials led to an increase in the background current. This phenomenon could be primarily attributed to the expanded electroactive surface area and confirms the successful integration of the nanomaterials onto the electrode surface. Among the investigated electrodes, the Au-MWCNT/CPE gave around 1.8 times higher signal of TAD compared to CPE and is preferred for routine sensing and analytical application due to its cost-effectiveness, ease of bare electrode modification, and higher sensitivity. Therefore, the Au-MWCNT/CPE was used for further experimental work.

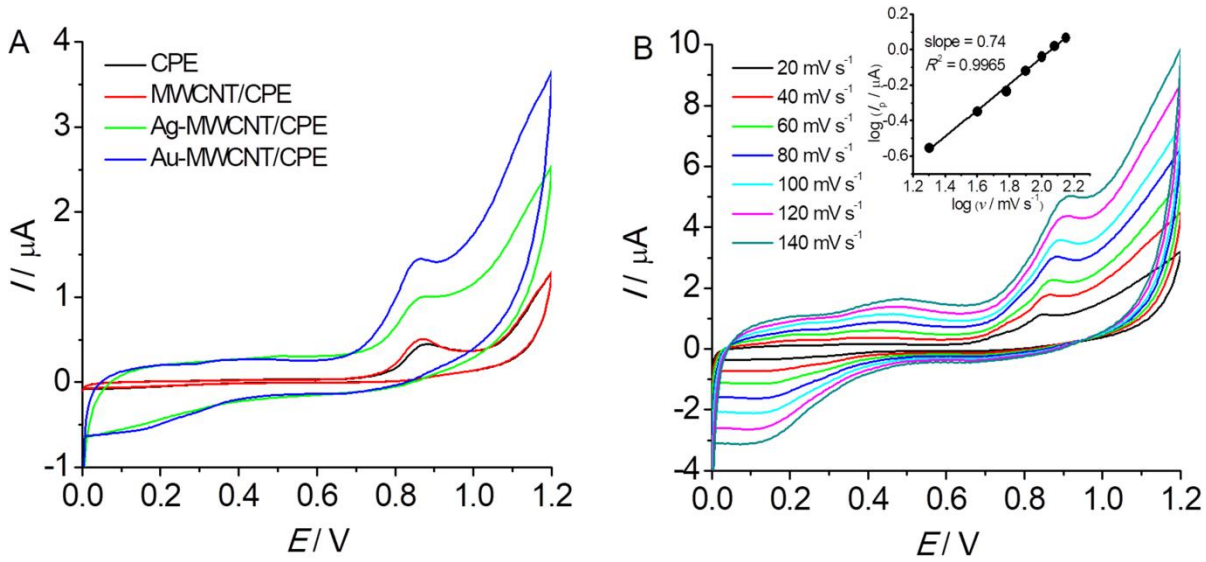

Figure 4. *(A) CVs of TAD (9.09 µg mL^{-1}) recorded with CPE, MWCNT/CPE, Ag-MWCNT/CPE and Au-MWCNT/CPE in B-R buffer solution pH 4.0,* v *= 50 mV s^{-1}. (B) The effect of scan rate together with log* I_p *vs. log* v *correlation (inset) obtained using Au-MWCNT/CPE, with 4.0 µL of nanocomposite loading amount*

The amount of Au-MWCNT suspension dropped onto the CPE surface was optimized by CV to ensure maximal electrochemical response and optimal electrode performance for TAD (Figure S2). Different volumes of a nanocomposite suspension (1.5 mg mL^{-1}), ranging from 2.0 to 5.0 µL, were applied to the CPE surface, and the TAD oxidation signal increased up to 4.0 µL. Since no further significant

enhancement was observed at 5.0 µL and to minimize nanomaterial consumption, 4.0 µL was chosen as the optimal volume of suspension for CPE modification. Excessive modifier loadings usually result in the formation of a thicker and denser film on the electrode surface that leads to an increase in capacitive background current and limits both mass transport and interfacial electron transfer [32].

To investigate the reaction kinetics of TAD oxidation, CV measurements were performed using the Au-MWCNT/CPE at different *v*, following the same experimental protocol employed for the solid gold electrode (Figure 4B). Similarly, the TAD oxidation signal increased proportionally with *v*, while E_p shifted toward more positive potential values, indicating an irreversible electrode reaction. A strong correlation with *v* was obtained, along with a slope of 0.74 for log I_p *vs.* log *v* dependence, indicating a "mixed" process - diffusion-controlled with notable adsorption contribution. MWCNTs and their composites have shown remarkable adsorption potential for capturing various compounds from aqueous media due to their hollow structures, numerous internal and external active sites, and high affinity toward target analytes [33]. The adsorption of TAD on Au-MWCNT/CPE is a process probably driven by a combination of non-covalent interactions such as *π*-*π* and hydrophobic interactions, alongside the unique electrocatalytic properties of the nanocomposite. Moreover, according to the literature, the p*K*a of the TAD molecule is around 3.5 [24,34], so at pH 4.0, the predominance of the neutral form [35] of TAD facilitates interactions with the hydrophobic MWCNT surface.

Effect of pH

While CV is usually used for electrochemical characterization of pharmaceutical compounds, square wave voltammetry (SWV) is one of the most reported techniques for their quantification. SWV is generally more sensitive than CV because the contribution of non-faradaic current in the voltammogram is minimized, making it better for detecting low concentrations of analytes [36,37]. So, the next steps in the development and optimization of an analytical method for TAD determination are performed using SWV with an Au-MWCNT/CPE as the working electrode. The influence of the pH of the B-R buffer solution on the TAD signal shape, intensity and peak potential was systematically investigated in a wide range from pH 2.0 to 12.0. Some illustrative voltammograms obtained at selected pHs are presented in Figure 5A, while a detailed evaluation of the dependence of I_p and E_p on pH is shown in Figure 5B.

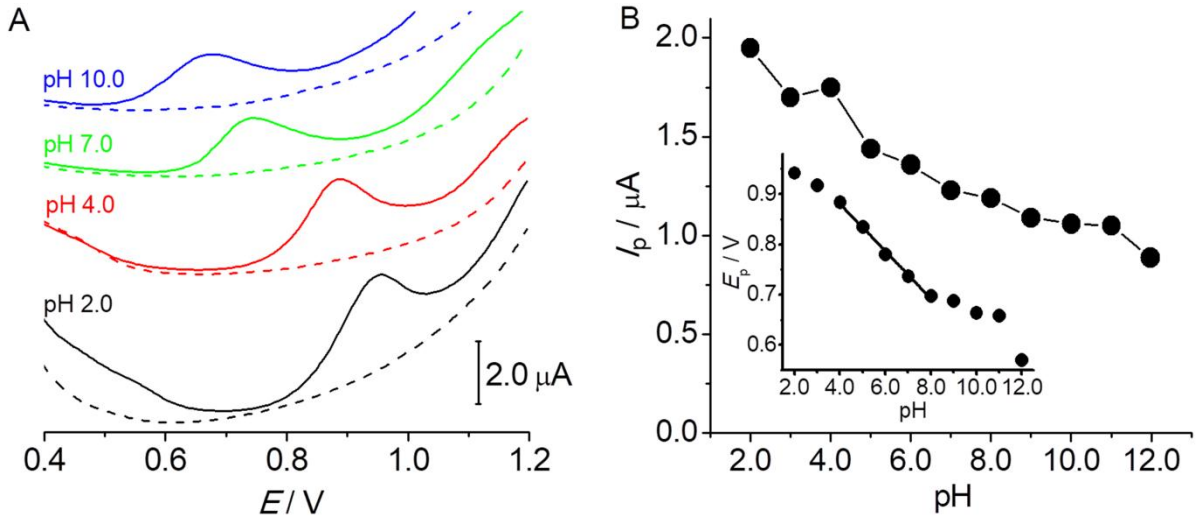

Figure 5. *(A) SWVs of TAD (4.76 µg mL^{-1}) recorded using Au-MWCNT/CPE at different pHs of B-R buffer solution. (B) Dependencies of* I_p vs. *pH and* E_p vs. *pH (inset).*

As can be seen, an acidic environment is more favourable for TAD oxidation, particularly in the range from pH 2.0 to 4.0. Although the most intensive signal of TAD was observed at pH 2.0, pH 4.0

was selected as optimal considering the shape and symmetry of the peak. Beyond pH 4.0 the I_p gradually decreases, although the changes in current intensity are not very pronounced. Therefore, Au-MWCNT/CPE could be employed to determine TAD at different pH values depending on the analysis requirements, but to ensure maximum sensitivity and repeatability, it is recommended to use B-R buffer solution pH 4.0.

The E_p of TAD oxidation signal shifted toward more negative values as the pH increased (inset, Figure 5B). The dependence of E_p on pH showed linearity within the range of 4.0 to 8.0, following the equation: E_p = −0.047 pH + 1.07, R^2 = 0.9952. The obtained slope of -0.047 V pH^{-1} is close to the Nernstian value, suggesting that an approximately equal number of electrons and protons are involved in the electrochemical oxidation of TAD. The first change in slope is consistent with the p*K*a of TAD (3.5), and after pH 8.0, another change in slope occurs, indicating that the oxidation process becomes largely independent of proton concentration.

The oxidation mechanism of TAD is a complex and pH-dependent process. Demir *et al.* suggested that the electroactive centre responsible for the TAD anodic peak formation was the nitrogen atom on the indole ring, whose oxidative process finally leads to hydroxylation of the benzene ring. TAD is irreversibly oxidized with two electrons and one proton at electrodes [21]. On the other hand, the same number of electrons and protons in the oxidation of TAD has also been reported. *Sartori et al.* suggested that one electron and one proton participate in the oxidation of the TAD molecule using a cathodically pretreated boron-doped diamond electrode in B-R buffer solution at pH 4.0, probably occurring on the secondary amine group of the molecule [20]. The oxidation peak of TAD can be attributed to the production of two protons and two electrons during oxidation [24,25]. However, most studies have shown that TAD oxidation is due to the indole moiety.

Square-wave adsorptive stripping voltammetry for tadalafil determination

Based on the CV measurement results, adsorption appears to play a significant role in the oxidation mechanism of TAD. Therefore, the main adsorption parameters of TAD at the Au-MWCNT/CPE surface, including E_{acc} and t_{acc}, were optimized in B-R buffer solution at pH 4.0 to further improve the method's sensitivity. The results of E_{acc} optimization (Figure 6A and Figure S3A) led to the conclusion that E_{acc} more negative than -0.4 V deteriorated signal intensity and was not appropriate for accumulation of the target analyte across the electrode surface. With the other E_{acc} tested, TAD oxidation signal was enhanced, and although the I_p remained very similar in the E_{acc} range of -0.4 V to 0.6 V, E_{acc} = 0.6 V was chosen as optimal because it gave the largest increase in TAD oxidation current. From the t_{acc} optimization (inset in Figure 6A and Figure S3B), it was clear that TAD could be readily adsorbed onto the Au-MWCNT/CPE surface. The t_{acc} of only 10 s TAC was sufficient to increase the TAD oxidation signal by about 2-fold compared to the direct SWV method, offering a significant advantage in analysis time. At longer t_{acc}, a plateau was reached due to saturation of the electrode surface with the analyte.

The linear concentration range of the SW-AdSV method was investigated by recording voltammograms of various TAD concentrations (Figure 6B). The preconcentration step (E_{acc} = 0.6 V, t_{acc} = 10 s, t_{eq} = 5 s) in a stirred solution provided high sensitivity and thus the suitability of the Au-MWCNT/CPE sensor for practical application. The I_p was evaluated for each signal obtained at 0.86 V and plotted versus TAD concentration (inset, Figure 6B). After a linear fit, an excellent correlation was achieved with R^2=0.9992 demonstrating a wide linear dynamic range from 0.10 to 1.96 μg mL^{-1} of TAD. The obtained LOD and LOQ were 0.03 and 0.10 μg mL^{-1}, respectively. To evaluate repeatability, multiple measurements (n=6) of a fixed TAD concentration (0.99 μg mL^{-1}) were

performed on the same Au-MWCNT/CPE surface, yielding a calculated RSD of 3.4 %, indicating good precision and reliability of the sensor (Figure S4A). Under the same experimental conditions, the reproducibility of the sensor fabrication was investigated by recording the oxidation signals of TAD using three independently prepared Au-MWCNT/CPEs (Figure S4B). The calculated RSD of 1.0 % confirmed that the electrode modification procedure is highly reproducible and robust.

The developed method was compared to previously reported ones for TAD determination. As shown in Table 1, the sensitivity regarding the LOD is comparable to that reported for other chemically modified electrodes, indicating that the Au-MWCNT/CPE surface exhibits highly competitive electrocatalytic activity for trace analysis [20,21,23-25]. Regarding the MWCNT-based sensors, the analytical performance of Au-MWCNT/CPE is very similar to that of TiO_2-MWCNTPE or vertically oriented MWCNT (voMWCNT), but the present work employs a CPE surface modification, which reduces nanomaterial consumption and makes sensor preparation more economical. While more complex nanocomposites and sensors lead to improved sensitivity of the method, the Au-MWCNT/CPE prioritizes analytical simplicity and ease of handling.

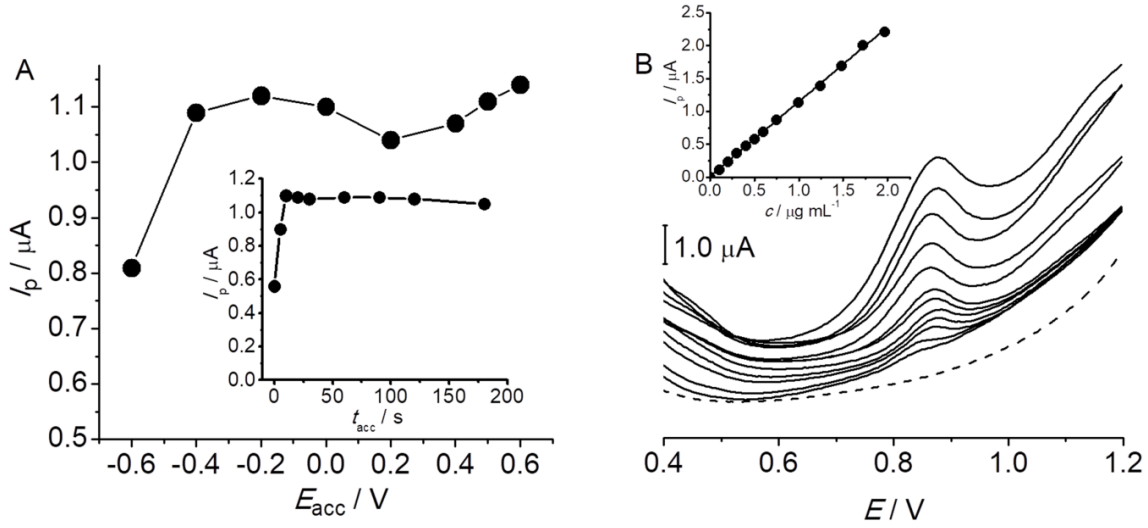

Figure 6. *(A) Optimization of* E_{acc} (t_{acc} *= 30 s) and* t_{acc} (E_{acc} *= 0.6 V) (inset) for TAD (0.99 μg mL^{-1}) accumulation onto Au-MWCNT/CPE surface. (B) SW-AdSV signals (*E_{acc} *= 0.6 V,* t_{acc} *= 10 s) of various TAD concentrations along with the corresponding calibration curve (inset). Supporting electrolyte: B-R buffer solution pH 4.0*

Table 1. *Comparison of electrochemical performance for TAD determination*

Working electrode	Method	Linear range, μg mL^{-1}	LOD, μg mL^{-1}	Ref.
[a]TiO_2-MWCNTPE	SW-AdSV	0.11 to 5.92	0.03	[21]
[b]voMWCNT	[c]LSV	0.33 to 3.47	0.03	[23]
[d]MMT-CeO_2NPs/CPG-PE	SW-AdSV	0.002 to 0.039 and 0.039 to 3.86	0.00008	[25]
[e]CP-BDDE	SWV	0.058 to 0.50	0.008	[20]
[f]Ru(II)/GCE	[g]DPV	11.68 to 31.15	1.5	[24]
Au-MWCNT/CPE	SW-AdSV	0.10 to 1.96	0.03	This work

[a]TiO_2-MWCNTPE - TiO_2-multiwalled carbon nanotube paste electrode; [b]voMWCNT - vertically oriented carbon nanotubes; [c]LSV - linear sweep voltammetry; [d]MMT-CeO_2NPs/CPG-PE - montmorillonite clay - CeO_2 nanoparticles modified composite pencil graphite paste electrode; [e]CP-BDDE - cathodically pretreated boron-doped diamond electrode; [f]Ru(II)/GCE - dichlorobis[8-(diphenyl-phosphino)quinoline]ruthenium(II) modified glassy carbon electrode; [g]DPV - differential pulse voltammetry

Selectivity is an important parameter that needs to be examined during method development and is often achieved through electrode modification and precise control of the electrochemical environment. The SW-AdSV signals of TAD (0.70 μg mL^{-1} *i.e.* 1.78 μmol L^{-1}) were recorded under optimized conditions using an Au-MWCNT/CPE at pH 4.0, in the presence of common interfering ions/substances (such as K^+, Na^+, Ca^{2+}, Mg^{2+}, Cl^-, HCO_3^-, SO_4^{2-}, NO_3^-, AA, DA, UA and Glu) at molar ratios

of 1:100 for inorganic ions, and 1:10 for organic substances (Figure S5 and Table S1). The addition of these investigated interferents did not affect the TAD peak current ($\Delta I_p \leq 1\%$) as they do not undergo redox reactions in the high positive potential range where TAD is oxidized. Among the investigated interferences, only oxidation signals of DA at 0.35 V and UA at 0.50 V were recognized on the recorded voltammograms. However, their E_p were significantly lower (more negative) than that of TAD. The Au-MWCNT/CPE exhibited excellent selectivity for TAD determination, confirming the method's suitability for complex matrices and therefore for real sample analysis.

Analytical application

The analytical application of the developed SW-AdSV method was tested by analysing two different samples: pharmaceutical formulation Cialis® and human blood serum. For both sample types, the standard addition method was used as described in the Experimental section. Illustrative voltammograms are presented in Figure 7, and for better visibility of the increase in TAD peak intensity, the same voltammograms obtained by baseline correction (linear baseline) are presented in Figure S6.

TAD was determined as the active ingredient in Cialis® tablets using both voltammetric and spectrophotometric approaches for comparison. Based on SW-AdSV results and corresponding analytical curves, evaluated values of TAD concentration in the tablet sample were 0.607; 0.606 (Figure 7A) and 0.585 μg mL^{-1}. When these concentrations were converted to the total TAD content per Cialis® tablet, the average value from triplicate measurements was 20.08 mg TAD per tablet with an RSD of 2.1%. These findings confirmed that the proposed SW-AdSV method is highly accurate and precise for pharmaceutical quality control, showing a negligible deviation from the manufacturer's declaration (20 mg TAD per tablet). To verify the results obtained using the SW-AdSV method, the property of TAD to exhibit an absorption maximum in the UV region at 284 nm in methanol was considered. The spectra were recorded in the TAD concentration range from 1.0 to 20.0 μg mL^{-1} (Figure S7A), and the constructed calibration curve (inset, Figure S6A) can be described by the equation: $A = 0.004 + 0.033\ c$ (μg mL^{-1}), $R^2 = 0.9978$. Spectra of the Cialis® sample were recorded (Figure S7B), and the concentration of TAD in the sample was calculated based on the given equation. The average value was 20.10 mg TAD per tablet with an RSD of 1.2% (n=3). Therefore, an excellent agreement between the results obtained by the proposed SW-AdSV method and the comparative spectrophotometric method was achieved.

The practical applicability of Au-MWCNT/CPE was also demonstrated in complex matrices like human blood serum. Human serum contains numerous redox-active and surface-active species, and its voltammetric analysis is significantly influenced by the type of working electrode, the pH of the buffer, the accumulation time, the potential applied prior to the voltammetric scan, and the type of voltammetric technique [38]. Some illustrative voltammograms obtained for human serum sample analysis under optimized conditions are presented in Figure 7B. After introducing the sample into a B-R buffer solution pH 4.0, no TAD peak was observed. Subsequently, the voltammogram of the spiked serum (0.398 μg mL^{-1} of TAD in the voltammetric vessel) was recorded, followed by three standard additions of TAD. A matrix influence was noted, characterized by the suppression of TAD signal intensity, shift of peak potential and TAD peak broadening. However, it was possible to reliably read the peak intensities and construct analytical curves. The average value (n=3) of TAD concentration in the spiked serum sample was 0.405 μg mL^{-1}, with RSD = 3.5%. The recovery was also calculated, and for three measurements, the average value was 101.8%. The results showed that despite the matrix effects typical of complex biological fluids, the Au-MWCNT/CPE remains highly reliable, precise, and sensitive enough for TAD determination.

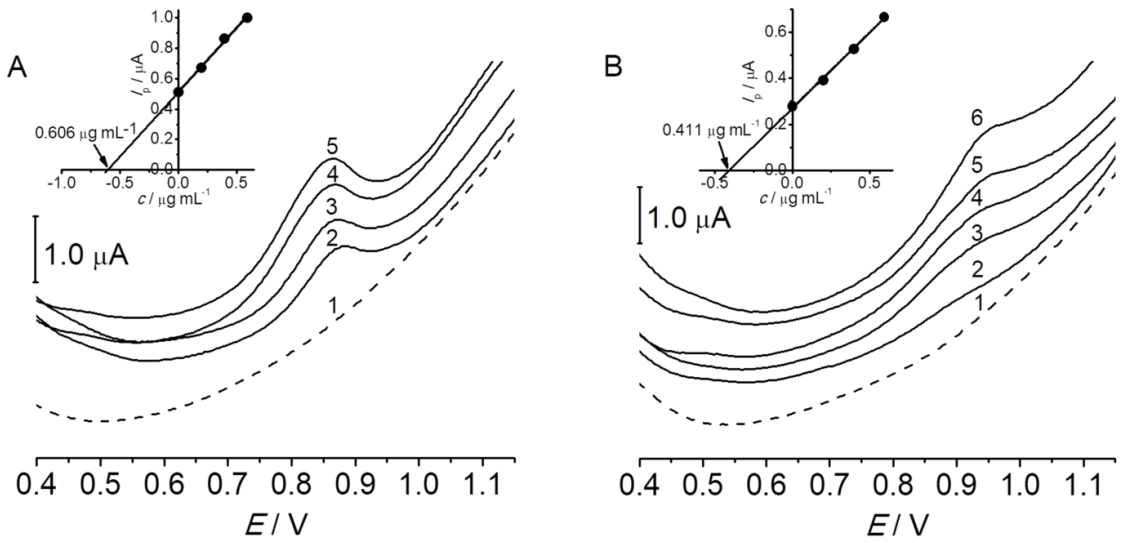

Figure 7. *SW-AdSVs of TAD determination in (A) pharmaceutical formulation and (B) human blood serum sample using the standard addition method and Au-MWCNT/CPE as working electrode. The curves, (A): baseline (1), pharmaceutical formulation sample (2) and three standard additions of TAD (3 to 5); (B): baseline (1), serum sample (2), spiked serum sample (3) and three standard additions of TAD (4 to 6). The insets present the appropriate analytical curves. Supporting electrolyte: B-R buffer solution pH 4.0*

Conclusions

A novel voltammetric approach for the determination of TAD was developed. The study of TAD electrochemical oxidation indicated a superior performance of the Au-MWCNT/CPE over a solid gold electrode, MWCNT/CPE and Ag-MWCNT/CPE. The sensor fabrication is both simple and cost-effective, since it involves only drop-coating a nanomaterial suspension onto the CPE surface. The Au-MWCNT/CPE showed high sensitivity for TAD determination with a LOD of 0.03 µg mL^{-1}, which enabled reliable and precise analysis of pharmaceutical formulation and human blood serum samples. It should be noted that the developed SW-AdSV method doesn't require sample pretreatment and sophisticated instrumentation, significantly reducing analysis time. Therefore, it could serve as a good alternative to traditional techniques for routine analysis of drugs in biological samples, and for rapid quality control of pharmaceutical formulations. Future research will focus on sensor miniaturization, making it much more convenient for small sample amount analysis and in-field measurements.

Supplementary material

Additional data are available at https://pub.iapchem.org/ojs/index.php/JESE/article/view/3459, or from the corresponding author on request.

Acknowledgements: *The authors gratefully acknowledge the financial support of the Ministry of Science, Technological Development and Innovation of the Republic of Serbia (Grants No. 451-03-33/2026-03/200125, 451-03-34/2026-03/200125, 451-03-33/2026-03/200026 and 451-03-34/2026-03/ 200135) and CEEPUSIV (CZ-0212-19-2526) network.*

References

[1] N. A. Bhale, S. Shah, A. S. Jahnavi, A. Vishwakarma, T. S. Thakur, S. P. Thomas, S. Srivastava, A. G. Dikundwar, Three strikingly different crystal habits of tadalafil: Design, characterization, pharmaceutical performance, and computational studies, *Molecular Pharmaceutics* **21** (2024) 6234-6244. https://doi.org/10.1021/acs.molpharmaceut.4c00601

[2] T.-Y. Lan, C.-H. Chiang, J.-W. Chen, T.-T. Chang, Potential beneficial impacts of tadalafil on cardiovascular diseases, *Journal of the Chinese Medical Association* **88** (2025) 267-272. https://doi.org/10.1097/jcma.0000000000001205

[3] D.V.H. Jehle, R. Sunesra, H. Uddin, K.K. Paul, A.A. Joglar, O. D. Michler, T.A. Blackwell, D. Gaalema, S. Hayek, H. Jneid, Benefits of tadalafil and sildenafil on mortality, cardiovascular disease, and dementia, *The American Journal of Medicine* **138** (2025) 441-448.e3 https://doi.org/10.1016/j.amjmed.2024.10.039
[4] B. Bozal-Palabiyik, C. Erkmen, E. Demir, B. Uslu, *Reviewing analytical methods for detection and determination of tadalafil*, in *Advances in Health and Disease*, L.T. Duncan, Ed., Nova Science Publishers, New York, **18**, 2020, pp 53-106. ISBN: 978-1-68507-820-1
[5] C.-L. Cheng, C.-H. Chou, Determination of tadalafil in small volumes of plasma by high-performance liquid chromatography with UV detection, *Journal of Chromatography B* **822** (2005) 278-284. https://doi.org/10.1016/j.jchromb.2005.06.017
[6] H. Y. Aboul-Enein, I. Ali, Determination of tadalafil in pharmaceutical preparation by HPLC using monolithic silica column, *Talanta* **65** (2005) 276-280. https://doi.org/10.1016/j.talanta.2004.06.012
[7] A. K. Shakya, A. N. A. Abu-awwad, T. A. Arafat, M. Melhim, Validated liquid chromatographic-ultraviolet method for the quantitation of tadalafil in human plasma using liquid-liquid extraction, *Journal of Chromatography B* **852** (2007) 403-408. https://doi.org/10.1016/j.jchromb.2007.01.049
[8] L. Schreiber, R. Halko, M. Hutta, Fast ultra-high-performance liquid chromatography with diode array and mass spectrometry method for determination of tadalafil drug substance and its impurities, *Biomedical Chromatography* **31** (2017) e4020. https://doi.org/10.1002/bmc.4020
[9] P. Nagaraju, B. Kodali, P. V. Datla, Selective and rapid determination of tadalafil and finasteride using solid phase extraction by high performance liquid chromatography and tandem mass spectrometry, *Journal of Pharmaceutical and Biomedical Analysis* **152** (2018) 215-223. https://doi.org/10.1016/j.jpba.2018.01.020
[10] P. Nikolaou, I. Papoutsis, S. Athanaselis, G. Alevisopoulos, A. Khraiwesh, C. Pistos, C. Spiliopoulou, Development and validation of a GC/MS method for the determination of tadalafil in whole blood, *Journal of Pharmaceutical and Biomedical Analysis* **56** (2011) 577-581. https://doi.org/10.1016/j.jpba.2011.05.036
[11] Yd. Jeong, S. Suh, J.Y. Kim, M.K. In, K.-J. Paeng, Simultaneous determination of sildenafil, tadalafil, and vardenafil in pharmaceutical preparations by high-temperature gas chromatography/mass spectrometry, *Chromatographia* **79** (2016) 1671-1678. https://doi.org/10.1007/s10337-016-3185-y
[12] M. Yunoos, D. G. Sankar, B. P. Kumar, S. Hameed, UV spectrophotometric method for the estimation of tadalafil in bulk and tablet dosage form, *E-Journal of Chemistry* **7** (2010) 833-836. https://doi.org/10.1155/2010/630576
[13] A. A. Kaf, A. A. Gouda, Spectrophotometric determination of tadalafil in pure and dosage forms, *Chemical Industry and Chemical Engineering Quarterly* **17** (2011) 125−132. https://doi.org/10.2298/CICEQ100816062A
[14] Z. G. Khan, A. S. Patil, A.A. Shirkhedkar, Estimation of tadalafil using derivative spectrophotometry in bulk material and in pharmaceutical formulation, *International Journal of Spectroscopy* **2014** (2014) 392421. https://doi.org/10.1155/2014/392421
[15] F. V. B. Nascimento, A. P. G. Ferreira, C. Gaglieri, A. de Moura, É. T. G. Cavalheiro, Degradation pathways of Tadalafil: A thermoanalytical study, *Thermochimica Acta* **747** (2025) 179955. https://doi.org/10.1016/j.tca.2025.179955
[16] R. Kumar, S. Salwan, P. Kumar, N. Bansal, B. Kumar, Electroanalysis advances in pharmaceutical sciences: Applications and challenges ahead, *Analytica* **6** (2025) 12. https://doi.org/10.3390/analytica6020012
[17] T. Yuwen, D. Shu, H. Zou, X. Yang, S. Wang, S. Zhang, Q. Liu, X. Wang, G. Wang, Y. Zhang, G. Zang, Carbon nanotubes: a powerful bridge for conductivity and flexibility in electrochemical

glucose sensors, *Journal of Nanobiotechnology* **21** (2023) 320. https://doi.org/10.1186/s12951-023-02088-7

[18] N. Parvin, S.W. Joo, J.H. Jung, T.K. Mandal, Unlocking the future: Carbon nanotubes as pioneers in sensing technologies, *Chemosensors* **13** (2025) 225. https://doi.org/10.3390/chemosensors13070225

[19] Y. Si, H. J. Lee, Carbon nanomaterials and metallic nanoparticles-incorporated electrochemical sensors for small metabolites: Detection methodologies and applications, *Current Opinion in Electrochemistry* **22** (2020) 234−243. https://doi.org/10.1016/j.coelec.2020.08.007

[20] E. R. Sartori, D. N. Clausen, I. M. R. Pires, C. A. R. Salamanca-Neto, Sensitive square-wave voltammetric determination of tadalafil (Cialis®) in pharmaceutical samples using a cathodically pretreated boron-doped diamond electrode, *Diamond and Related Materials* **77** (2017) 153-158. https://doi.org/10.1016/j.diamond.2017.07.001

[21] E. Demir, R. Inam, S. A. Ozkan, B. Uslu, Electrochemical behavior of tadalafil on TiO_2 nanoparticles-MWCNT composite paste electrode and its determination in pharmaceutical dosage forms and human serum samples using adsorptive stripping square wave voltammetry, *Journal of Solid State Electrochemistry* **18** (2014) 2709-2720. https://doi.org/10.1007/s10008-014-2529-5

[22] M. Öksüz, M. Cittan, K. Dost, Simultaneous electrochemical determination of sildenafil citrate and tadalafil using a multi walled carbon nanotubes modified glassy carbon electrode by adsorptive stripping linear sweep voltammetry, *Electroanalysis* **37** (2025) e202400224. https://doi.org/10.1002/elan.202400224

[23] N. A. Zambianco, V. A. O. P. da Silva, L. O. Orzari, E. J. Corat, H. G. Zanin, T. A. Silva, G. A. Buller, E. M. Keefe, C. E. Banks, B. C. Janegitz, Determination of tadalafil in pharmaceutical samples by vertically oriented multi-walled carbon nanotube electrochemical sensing device, *Journal of Electroanalytical Chemistry* **877** (2020) 114501. https://doi.org/10.1016/j.jelechem.2020.114501

[24] E. S. M. Abu-Nameh, N. Al Absi, M. A. Al-Wahish, H. A. Hodali, M. F. Khanfar, Electrochemical detection of tadalafil at glassy carbon electrodes modified with ruthenium(II) complex, *International Journal of Electrochemical Science* **15** (2020) 6396-6404. https://doi.org/10.20964/2020.07.70

[25] M. Ibrahim, Y. Temerk, H. Ibrahim, M. Salah, Ultrasensitive tadalafil detection with eco-friendly CeO_2/Al-pillared clay incorporated pencil graphite paste electrode, *Chinese Journal of Analytical Chemistry* **52** (2024) 100418. https://doi.org/10.1016/j.cjac.2024.100418

[26] L. Yang, H. Zhao, C.-P. Li, S. Fan, B. Li, Dual β-cyclodextrin functionalized Au@SiC nanohybrids for the electrochemical determination of tadalafil in the presence of acetonitrile, *Biosensors & Bioelectronics* **64** (2015) 126-130. https://doi.org/10.1016/j.bios.2014.08.068

[27] V. Guzsvány, O. Vajdle, M. Gurdeljević, Z. Kónya, Ag or Au nanoparticles decorated multiwalled carbon nanotubes coated carbon paste electrodes for amperometric determination of H_2O_2, *Topics in Catalysis* **61** (2018) 1350-1361. https://doi.org/10.1007/s11244-018-0986-2

[28] I. Švancara, R. Metelka, K. Vytřas, *Piston-driven carbon paste electrode holders for electrochemical measurements*, in *Sensing in electroanalysis*, K. Vytřas, K. Kalcher, Ed., University of Pardubice, Pardubice, 2005, p. 7.

[29] S. M. Moosavi, S. Ghassabian, *Linearity of calibration curves for analytical methods: A review of criteria for assessment of method reliability*, in *Calibration and validation of analytical methods: A sampling of current approaches*, M. T. Stauffer, Ed., InTechOpen, BoD - Books on Demand, 2018, pp 109-127. https://doi.org/10.5772/intechopen.72932

[30] A. Cetinkaya, S. Irem Kaya, S. A. Ozkan, A collection of the best practice examples of electroanalytical applications in education: from polarography to sensors, *Journal of Solid State Electrochemistry* **28** (2024) 869-895. https://doi.org/10.1007/s10008-023-05637-0
[31] H. Beitollahi, F. Movahedifar, S. Tajik, S. Jahani, A review on the effects of introducing CNTs in the modification process of electrochemical sensors, *Electroanalysis* **19** (2019) 1195-1203. https://doi.org/10.1002/elan.201800370
[32] A. Mijajlović, F. Vlahović, M. Ognjanović, L. Rakočević, V. Stanković, K. Kalcher, A. Ortner, D. Stanković, La-Dy_2O_3/MWCNT: Vacancy-engineered electrode for electrochemical detection of metol in environmental and biofluid samples, *ACS Applied Electronic Materials* **8** (2026) 2124-2140. https://doi.org/10.1021/acsaelm.5c02526
[33] M. Sajid, M. Asif, N. Baig, M. Kabeer, I. Ihsanullah, A.W. Mohammad, Carbon nanotubes-based adsorbents: Properties, functionalization, interaction mechanisms, and applications in water purification, *Journal of Water Process Engineering* **47** (2022) 102815. https://doi.org/10.1016/j.jwpe.2022.102815
[34] M.B. Polat, A. Doğan, N.E. Başci, Spectrophotometry, potentiometry and HPLC in determination of acidity constant for cabergoline and tadalafil, *Journal of Research in Pharmacy* **23** (2019) 177-186. https://doi.org/10.12991/jrp.2019.123
[35] I. Fejős, A. Kazsoki, T. Sohajda, E. Márványos, B. Volk, L. Szente, S. Béni, Interactions of non-charged tadalafil stereoisomers with cyclodextrins: Capillary electrophoresis and nuclear magnetic resonance studies, *Journal of Chromatography A* **1363** (2014) 348-355. https://doi.org/10.1016/j.chroma.2014.08.045
[36] Z. Bitew, M. Amare, Recent reports on electrochemical determination of selected antibiotics in pharmaceutical formulations: A mini review, *Electrochemistry Communications* **121** (2020) 106863. https://doi.org/10.1016/j.elecom.2020.106863
[37] F.H. Pilz, P. Kielb, Cyclic voltammetry, square wave voltammetry or electrochemical impedance spectroscopy? Interrogating electrochemical approaches for the determination of electron transfer rates of immobilized redox proteins, *BBA Advances* **4** (2023) 100095. https://doi.org/10.1016/j.bbadva.2023.100095
[38] P. Kokoskarova, L. Stojanov, K. Najkov, N. Ristovska, T. Ruskovska, S. Skrzypek,V. Mirceski, Square-wave voltammetry of human blood serum, *Scientific Reports* **13** (2023) 8485. https://doi.org/10.1038/s41598-023-34350-1