THE REPUBLIC OF TURKEY
HARRAN UNIVERSITY
GRADUATE SCHOOL OF
APPLIED AND NATURAL SCIENCES

MASTER OF SCIENCE (MSc) THESIS

A NOVEL MODIFIED ELECTRODE BASED ON NANOCOMPOSITE MATERIAL FOR THE DETERMINATION OF PARACETAMOL

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DEPARTMENT OF CHEMISTRY

ŞANLIURFA
2022

A study entitled **''A novel modified electrode based on a nanocomposite material for the determination of paracetamol''** prepared by **Sherzad Ahmed M. Salih MOHAMMED SALIH** under the supervision of Prof. Dr. Mehmet ASLANOĞLU was approved as a Master of Science thesis on 25/01/2022 by the following committee in Graduate School of Natural and Applied Sciences at the University of Harran.

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This study was supported by HÜBAP.
Project No: 21011

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NANOKOMPOZIT TEMELLI YENI BIR MODIFIYE ELEKTROT ILE PARASETAMOLUN SAPTANMASI

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Yıl: 2022, Sayfa:37

Karbon nanotop ve samaryum oksit nanoparçacıklar ile yeni bir malzeme hazırlanmıştır. Elde edilen malzeme elektrot kaplama da kullanılmış ve yeni bir modifiye elektrot hazırlanmıştır. Hazırlanan elektrot platform (Sm_2O_3/CNBs/GCE) parasetamol saptanması için kullanılmıştır, Sm_2O_3/CNBs/GCE sistemi parasetamol elektrot reaksiyonunu hızlandırmıştır. Sm_2O_3/CNBs/GCE sistemi, parasetamol için $2.0x10^{-7}$ M ile $3.7x10^{-5}$ M aralığında doğrusal bir ilişki göstermiştir. Modifiye elektrot ile $5.7\ x10^{-9}$ M'lık bir saptama sınırı elde edilmiştir. Ayrıca, yöntemin tekrarlanabilirlik, kesinlik ve doğruluk parametreleri mükemmeldir.

ANAHTAR KELİMELER: Parasetamol, samaryum oksit, voltametri, elektroanaliz, sensör

ABSTRACT

MSc Thesis

A NOVEL MODIFIED ELECTRODE BASED ON NANOCOMPOSITE MATERIAL FOR THE DETERMINATION OF PARACETAMOL

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A novel material was prepared by using carbon nanoballs and samarium oxide. The material was used for coating an electrode and a new platform was obtained. The electrode prepared was used for detecting paracetamol. The Sm_2O_3/CNBs/GCE system accelerated the electrode reaction of paracetamol. The Sm_2O_3/CNBs/GCE system exhibited a linear relationship between $2.0x10^{-7}$ M and $3.7x10^{-5}$ M for paracetamol. A detection limit of $5.7\ x10^{-9}$ M was obtained for paracetamol at proposed modified electrode. In addition, the analytical parameters of the method such as reproducibility, precision and accuracy were excellent.

KEY WORDS: Paracetamol, samarium oxide, voltammetry, electroanalysis, sensor

ACKNOWLEDGEMENT

I would like to thank to Prof. Mehmet Aslanoğlu for supporting me in last 2 years. I also wish to thank to following friends for their kind help and assistance in lab work. Tuğçe and Şehriban. I also wish to thank my family for theri great support during my education at Harran University.

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LIST OF SYMBOLS and ABBREVIATIONS

CV	Cyclic Voltammetry
DA	Dopamine
GCE	Glassy Carbon Electrode
mV	Milivolt
n	Number of Electrons
nM	Nanomolar
PAR	Paracetamol
PBS	Phosphate Buffer
R.S.D	Relative Standard Deviation
Sm_2O_3	Samarium Oxide
XRD	X-Ray Diffraction

1. INTRODUCTION

Paracetamol is an analgesic drug and has antipyretic properties. It is used widely to reduce fever. It also acts as a painkiller for the relief of pains such as arthritis, backache, headache, and post-surgical pain (Anderson, 2008). Figure 1.1 shows the chemical structure of paracetamol. Overdoses of paracetamol might produce side effects especially in pregnancy such as accumulating toxic oxidative substances leading to fatal hepatoxicity and nephrotoxicity (Langhendries et al., 2016; Allegaert and van den Anker, 2017; Avinash et al., 2019).

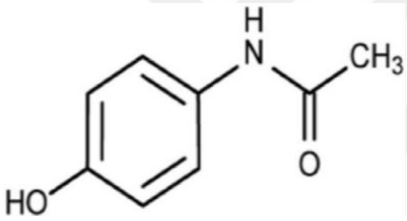

Figure 3.1. Chemical structure of paracetamol

Authors have reported that some body tissues, kidney and liver may be damaged by using overdose of paracetamol leading to generation of toxic metabolites (Charpiat et al., 2013). Analysis of pharmaceuticals and body fluids is important for medical reasons. Quantitative methods including spectrophotometry (Dinç et al., 2002; Criado et al., 2000), liquid chromatography (Abdelaleem et al., 2015) electrochemistry (Baccarin et al., 2017; Zhao et al., 2006) and chemiluminescence (CL) (Zhao et al., 2006) were reported for quantification of paracetamol.

Pharmaceuticals are important chemicals that are utilized for the relief of pains or preventing and treatment of diseases (Karaman, 2013). It has been issued that drug is mainly extracted from plants (Wadud et al., 2007). Historically, some unconventional methods based on plants, animal products and minerals were utilized for treating

diseased. The analysis of drugs consists of tests for materials, raw application or application applications, and animal product. assortment, such as blood, birth and tissues

Analysis of methods for drug contents includes tests on pharmaceutical or veterinary formulations, and more complex matrices including foods of animal origin, beverages, and food items that are performed for clinical and forensic purposes which involve a variety of matrices such as samples of blood and urine, (Martinez Calatayud, 2005). The main issue for ensuring the safety of drug therapy is the control and minimization of their effects. Because side effects are inherent characteristics of substances, drug analyzers cannot be affected by them. In addition, drug analysts exhibit a major role to ensure the quality of pharmaceuticals which is related to the safety of drugs (Görög, 2008).

Electrochemical sensors offer promising devices for monitoring and controlling of a wide range of analytes as a result of their accuracy, specificity and the ease of use, fast analysis, low-cost, reliable and reproducible measurements with miniaturized and portable devices (Wang, 2002; Patel et al., 2020), the interest in their application in the clinical, pharmaceutical and environmental field substantially has increased. The stability, sensitivity and selectivity of the platforms for impurities are mostly dependent on surface area of electrodes and modifiers (Sandulescu, 2011).

Voltammetry was subjected to the analysis of samples more than other analytical techniques for the determination of analytes, because of several benefits i.e. low cost, high efficiency, rapid response, simplicity of analytical procedures, speed, higher sensitivity and reproducibility (Bard and Faulkner, 2001). Voltammetry, a family of electroanalytical techniques, is based on electrolytic reduction or oxidation mainly for the analyte detection or investigation of mechanism and kinetics of redox reactions. It measures current as a function potential. Initially, Jaroslav Heyrovsky introduced the first voltammetric technique in the early 1920s for which uses only two electrodes.

However, modern voltammetry uses a three-electrode system. Results for a voltammetric experiment are presented by a voltammogram which is the based on the current generated by the analyte versus applied potential (Bard and Faulkner, 2001).

An oxidation/reduction process occurring on a platform is related to the applied potential. The potential forces the ions in the solution to gain or lose an electrons (Joshi and Sutrave, 2018) .Thus, voltammetry is a potential technique to acquire voltammetric behavour of chemicals through a systematic study of the measurement of current versus applied voltage of a particular electrochemical cell as given in Figure 1.2. The graph of current response against potential is known as the cyclic voltammogram.

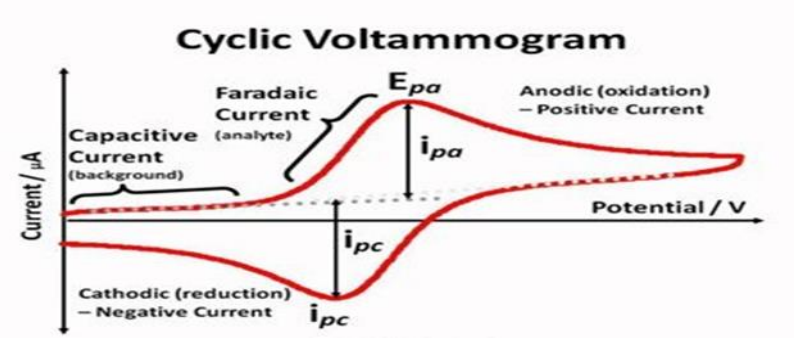

Figure 1.4. CV graph with forward and reverse scan

An electrochemical cell represented in Figure 1.3 consists of working, auxiliary, and a reference electrode (Elgrishi et al., 2018; Gomaa et al., 2018) The auxiliary electrode is usually a platinum rod however reference electrode can be silver/silver chloride or saturated calomel electrode electrode. However, materials such as gold, mercury, silver, platinum and carbon can be used as working electrodes (Wang et al., 2019; Lee et al., 2017). The voltammetric cell also includes a N_2-purge line for removing dissolved oxygen.

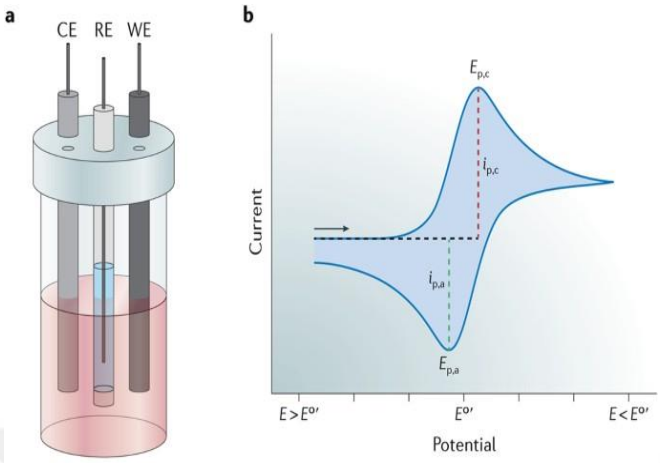

Figure 1.3. Autolab electrochemical workstation

Voltammetric experiments are characterized b, accuracy, high sensitivity and simplicity. Also, a number of nanostructured materials such as metallic nanoparticles, and carbon nanotube were utilized for improving properties of electrodes (Shahmiri et al., 2013; Fouladgar and Mohammadzadeh, 2014). However, the selectivity for electrochemical platforms may be sometimes restricted in the presence of interferences that display similar redox behavior with chemicals including paracetamol (Kutluay and Aslanoglu 2013; Hosseinzadeh et al., 2009). An important strategy for minimization of interferences from other molecules in solution is to modify the surface of working electrodes using various materials (Raoof et al., 2007; Keyvanfard et al., 2013)

Voltammetric procedures at electrodes have been extensively applied as sensitive analytical tools in detecting trace amounts of species. The most important characteristics of electrodes is the capability to stimulate redox reactions through the significant drop in overvoltage when compared to the conventional electrodes (Luo et al., 2013; Taleat et al., 2008; Shangguan and Li, 2013; Thomas et al., 2013a; Raoof et al., 2006; de Oliveira et al., 2013, Beitollahi et al., 2011a; Thomas et al., 2013b; Mohammadi et al., 2013; Beitollahi et al., 2014a; Li et al., 2012; Ghoreishi et al., 2012; Yildiz et al., 2014; Beitollahi et al., 2011b; Sanghavi et al., 2013).

Carbon nanotubes have promising electronic properties and can be used as attractive modification materials for fabricating electrochemical platforms due to their ability to provide good catalytic activity and reduce surface contamination (Keyvanfard et al., 2014). Modification of electrodes with materials including carbon nanotubes has also been reported for use in analytical sensing resulting in lower detection limits, good sensitivities, reduced overpotentials, large surface area and excellent conductivity. They are very attractive as a support for heterogeneous catalysis (Lu and Tsai, 2011; Campbell and Compton, 2010; He et al., 2004; Vairavapandian et al., 2008). In addition, the uniform dispersion of nanoparticles of metals or metal oxides on carbon nanotubes surfaces enable promise as nanoelectrocatalysts for use in electroanalysis (Yánez-Sedeno et al., 2010; Wang et al., 2007).

Several platforms were reported for quantification of paracetamol including carbon nanotubes modified electrode (Babaei et al., 2011), an electrode coated with carbon nanoparticles (Ghorbani-Bidkorbeh et al., 2010), NiFe2O4/graphene modified CPE (Afkhami et al., 2014), composite of carbon nanotube and polymer modified GCE (Deiminiat et al., 2017; Afkhami et al., 2013) and resin-gold nanoparticles modified GCE (Sanghavi and Srivastava, 2011).

The nanoparticle production exhibited significant advantages such as higher electroactive surface area for electrode reactions. They also exhibited good selectivity over conventional electrodes in sensing applications (Arai et al., 2004; Han et al., 2004). Experimental parameters such as deposition potential, period of duration, and solution consistency can be controlled for controlling growth rate of nanoparticles for the electrodeposition of metallic oxides (Day et al., 2007; Wildgoose et al., 2006).

Nanostructured materials have recently received potential interest of research as having unique structure-dependent behavior and therefore can be utilized in potential applications in applied fields (Jia et al., 2013; Beitollahi et al., 2014a). Materials of metallic oxides have been utilized in potential applications great interest owing to their

non-toxicity, chemical stability, ease of preparation and good electrocatalytic effect (Mohammadi et al., 2011).

Various shapes of carbon nanoballs such as spheres, microbeads and carbon black are available as modifier (Calderón-Moreno et al., 2007; Mao et al., 2018). Recent articles have revealed their importance in critical applications like batteries, fuel cells, reinforcement,catalyst support materials, composites and purification processes.

The carbon nanoballs normally are avaiable as agglomerates of several nanoballs through van der Waals bonding. Nanoballs have a brown to black colour as the thickness increases. The carbon balls have a BET surface area ranging from as low as 2 to 1200 m^2 g -1 (Jin et al., 2005; Deshmukh et al., 2010).The density ranges from as low as 0.4 to 1.6 g cm-3 depending on the synthesis procedures (Mhlanga et al., 2010).The chemical reactivity of carbon spheres is somewhat similar to those of graphitic materials. They appear to be insoluble in non polar solvents and sparingly soluble in most solvents because of their hydrophobic nature. However, solvents such as chloroform, benzene, methanol and toluene might produce in miscibility (Sobkowicz et al., 2009).The presence of dangling bonds has enabled carbon balls to be functionalised by acids like nitric acid (Kang and Wang, 1996).

2. LITERATURE REVIEW

The major target for ensuring the safety of pharmaceuticals is the control and minimization of their effects. Since their side effects are inherent characteristics of substance, drug analyzers cannot be affected by them. In addition, drug analysts exhibit a key role to ensure the quality of drug materials and pharmaceuticals which reflects to the safety of drugs (Görög, 2008). Analysis of pharmaceuticals is traditionally related to chemical analysis that deals with drugs as drug substances and pharmaceutical products (Dispas et al., 2021). Several procedures were employed for analyzing paracetamol. High performance liquid chromatography (Hewavitharana et al., 2008), cyclic voltammetry (Tungkananuruk et al., 2005), spectrophotometry (Behera et al., 2012), flow injection analysis (Vieira et al., 2003),and electroanalysis (Asadpour-Zeynali and Mollarasouli, 2016; Moccelini et al., 2011) were performed. Some of previously studied procedures are time consuming and may involve strict experimental conditions or suffer from interferences and are therefore not appropriate for routine analysis of drugs. Voltammetric procedures present alternative means for determination of drugs and provide advantages such as high sensitivity and portable devices for rapid monitoring purposes (Shahrokhian et al., 2011; Salmanipour et al., 2012).

A spectrophotometry procedure for determining paracetamol in pharmaceuticals was proposed by Eustaquio et al. (1999). The procedure is simple, relatively accurate, precise and sensitive, using the fewest number of reagents and reaction sequences and contains two multivariate calibration methods which is measured over wavelength of 600-1900 nm.

A flow injection spectrophotometry procedure for the determination of methyldopa in pharmaceuticals has been proposed by Knochen et al. (2003). The procedure is simple, fast, relatively inexpensive, accurate, precise and sensitive, using

the fewest number of reagents and reaction sequences and contains the formation of a yellow-colored product which is measured at wavelength of 430 nm,

Hewavitharana et al. (2008), prepared an HPLC–MS/MS method, in order to accurately quantify traces of paracetamol in urine. The procedure found to provide a highly sensitive quantification for the determination of submicromolar amounts of paracetamol with a column limit of 1.2 pmol.

Ranifam et al. (2019), prepared a sensitive CL method, in order to accurately quantify traces of paracetamol in pharmaceuticals. The procedure found to provide a highly sensitive quantification for the determination of submicromolar amounts of paracetamol with a detection limit of 8.7×10^{-7}M.

Tungkananuruk et al. (2005), prepared a cyclic voltammetric method, in order to accurately quantify traces of paracetamol in drugs. The procedure found to provide a highly sensitive quantification for quantifying submicromolar amounts of paracetamol with a range of 3-2240 μg/ml and a detection limit of 10 nM.

Goyal and Singh, (2006), developed a C-60 modified electrode for sensitive quantification of paracetamol in biological and drugs. Article presented that paracetamol oxidation on the surface of the GCE coated with carbon nanotubes significantly improved peak response compared to conventional platform. A linear working range (0.05–1.5 μM) was reported. The sensitivity of procedure was 13.04.

Ghadimi et al. (2013), developed a platform for the electroanalysis of pharmaceutical and urine samples. The study exhibited that peak current for paracetamol exhibited a working range of 0.02–450 μM. The authors also reported an LOD of 1.69 nM.

Fan et al. (2011), reported a novel platform using an electrode coated with a mixture of graphene acid and TiO_2 nanoparticles. The response of the proposed novel sensor to the catalytic current for the concentration of paracetamol exhibited a linear relationship over a range from 1–100 μM. Fan et al. (2011), also presented an LOD of 2.1×10^{-7} M.

Gowda et al. (2015), proposed a paracetamol -sensitive identification nanosensor using carbon nanotubes decorated with cetyltrimethyl ammonium bromide. The composite material based nanosensor exhibited a synergistic activity for methyldopa electrode reaction. The authors reported peak current was linear with a range of 4.0×10^{-7} M-4.0×10^{-6} M for methyldopa and a detection limit of 4.82×10^{-9} M.

Kalambate et al. (2015), reported a new sensing platform by modifying a GCE with platinum nanoparticles (PtNPs) and CNTs. The novel sensing platform was applied for quantification of paracetamol. The procedure yielded working ranges from 8.2×10^{-6}–1.6×10^{-9} M for methyldopa and paracetamol, respectively. The detection limit presented for paracetamol was 1.06×10^{-10}.

Zhang et al. (2019), developed a poly caffeic-Zn/Ni-ZIF material for the oxidation and the determination of methyldopa in pharmaceuticals. The pH-dependent electrochemical behavior of paracetamol exhibited a detection limit of 0.0291 μM.

Yan et al. (2020), utilized thiol-grafted PEDOT/N-doped graphene electrode to determine paracetamol content in pharmaceuticals. A linear range from 0.4 to 1280 μM was reported with a detection limit of 1.0 μM using voltammetric methods..

Xu et al. (2019), described a new method using MnO_2 and poly(3,4-ethylenedioxythiophene) coated carbon platform. The procedure was successfully applied for determining methyldopa in a solution containing folic acid, with a linear response of concentration from 0.06 to 435 μM and a detection limit of 31 nM.

Engin et al. (2015), developed a platform for electroanalysis of pharmaceutical samples. The study exhibited that peak current for paracetamol exhibited a working range of $4x10^{-6}$ M to $1x10^{-4}$ M. The authors also reported an LOD of $3.69x10^{-7}$ mol/L.

A nanosheet-assembled lindgrenite microflower has also been synthesized to modify the surface of an electrode which was applied for electrochemically quantifying paracetamol in a media. The authors reported a calibration curve of 0.01 to 1000.0 μM for paracetamol with detection limit of 0.01 nM (Fu et al. 2020).

The aim of this study is to develop a sensing material for quantifying paracetamol. A glassy carbon electrode was utilized as the platform which was modified with samarium (III) oxide (Sm_2O_3) nanoparticles, and carbon nanoblack (CNBs) to enhance the stability, sensitivity and selectivity in the analysis of samples containing methyldopa. Cyclic voltammetry was successfully performed as the analytical technique with the proposed electrode /CNBs Sm_2O_3-NPs /GCE) for the analysis of drug samples.

3. MATERIAL and METHOD

3.1. Material

There are several tools used for the current study. Some of these are listed below;

- An Epsilon brand potentiostat (BASi, US) was used for voltammetric studies.
- A glassy carbon electrode (GCE) (Bioanalytical systems, USA) served as working electrode, A Metrohm silver/silver chloride (Ag/AgCl) was served as reference electrode while a Pt rod served as counter electrode.
- The pH studies were performed using Metrohm 744 pH Meter (Metrohm, Switzerland).
- Composite of carbon nanoballs-metal nanoparticules was prepared using a KUDOS (SK3301OHP) model ultrasonic bath.
- SHIMADZU (AY-220) model balances was used for analtytical weighing.
- X-ray diffraction was used for the characterization of carbon nanoballs and samarium oxide

The reagents used without additional purification and obtained from Sigma–Aldrich, Fluka or Merck and are listed below:

- Acetic acid (≥ 99.8 %, Merck),
- Acetonitrile (99.9 %, Merck),
- Acetone (≥ 99.8 %, Merck),
- Alumina powder, (0.3; 1.0 micron, Buehler),
- Paracetamol powder (99.0%, Sigma Aldrich),

- Chloroform (99.0 %,Merck),
- Carbon black nanoballs (95.0%, Nano Lab),
- Na_2HPO_4 (99.5 %, Merck),
- Ethanol (≥99.5%, Merck),
- Samarium(III) oxide nano powder (99.995%, US-Nano),
- Parol tablet (Local pharmacy)
- Hydrochloric acid (37-38 %, Merck),
- Multiwalled carbon nanotubes (MWCNTs) (95.0 %, Nano Lab),
- Nitric acid (65.0 %, Merck),
- KCl (99.5 %, Merck),
- KH_2PO_4 (99.5 %, Merck),
- NaOH (≥99.0 %, Merck)

3.2. Method

3.2.1. Preparation of solutions

Phosphate buffer (PBS) was prepared by addition of 6.8 g/L of KH_2PO_4, 8.8 g/L of $Na_2HPO_4.2H_2O$, and 0.75 g/L of KCl into a 1 L flask. The solution was then diluted to 1 L using ultra pure water. Then, the pH was adjusted using diluted HCl or diluted NaOH. Stock solutions were freshly prepared. Stock solutions of sunset yellow, uric acid and paracetamol were prepared using 0.1 M PBS. The working solution was deoxygenated using N_2 gas before each run. Ionic strength of solutions was kept constant. Fresh stock solutions were prepared before use and the all stock solutions were kept in amber bottles for protecting from day-light. Dilutions of stock solutions were made using phosphate buffer. Electrochemical experiments were carried out under oxygen-free nitrogen.

3.2.2. Activation of glassy carbon electrodes

Prior to develop an electrochemical platform, GCE was polished with alumina slurries of 1 μm and 0.3 μm on polishing pad. A simple way to polish electrodes is using alfa motion of electrode in alumina slurry on the polishing pad (Elgrishi et al., 2018) as ilustrated in Figure 3.1. Then, polished glassy carbon electrodes were sonicated in a mixture acetone-ethanol for 10 min. The electrode was rinsed using double-distilled water. The activation of platform was carried out in 0.1 M PBS by cyclic voltammetry. The potential range varies from −0.2 to +1.0 V at 0.1 V/s. The activation was completed upon the observation of a stable voltammogram.

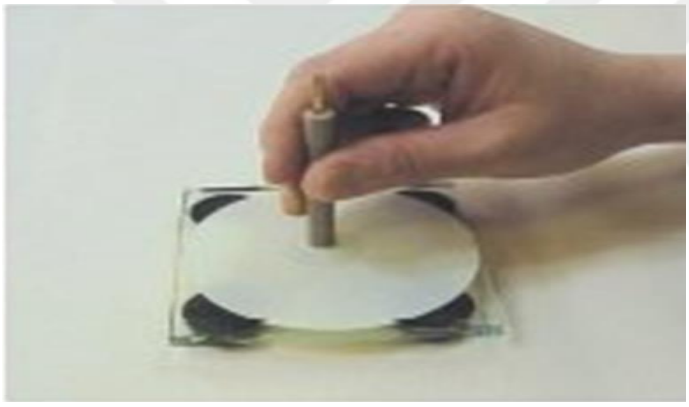

Figure 3.2. Polishing glassy carbon electrode

3.2.3. CNBs/ Sm_2O_3-NPs /GCE platform preparation

Prior to the modification the electrode, carbon black nanoballs neodymium oxides nanoparticle were weighed and dispersed in chloroform. The mixture was then sonicated for 45 minutes to obtain a black suspension. Afterwards, 5 μL of black suspension (CNBs/ Sm_2O_3-NPs) was dispersed on the electrode by using a micropipette. Then, the electrode left to dry in air for 5 min. The platform was denoted as CNBs/ Sm_2O_3-NPs /GCE. The platform was washed with pure water before use. Then, voltammetry was used to activate electrochemical platform and to obtain a stable

voltammogram for blank solution. A schematic preparation of the platform has been illustrated in Scheme 3.1.

Figure 3.2 shows the XRD spectrum of Sm_2O_3/CNBs. Peaks at 2θ = 28.5°, 31.0°, 32.0° and 44.0° correspond to Sm_2O_3, and peak at 2θ = 26° corresponds to the diffraction of carbon nanoballs.

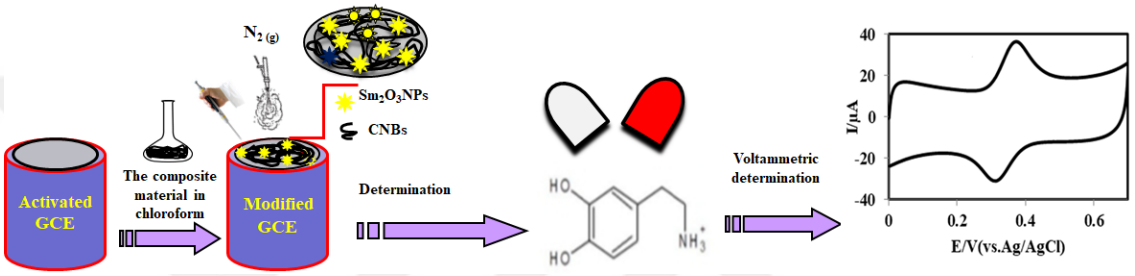

Figure 3.2. Schematic illustration of the proposed electrode

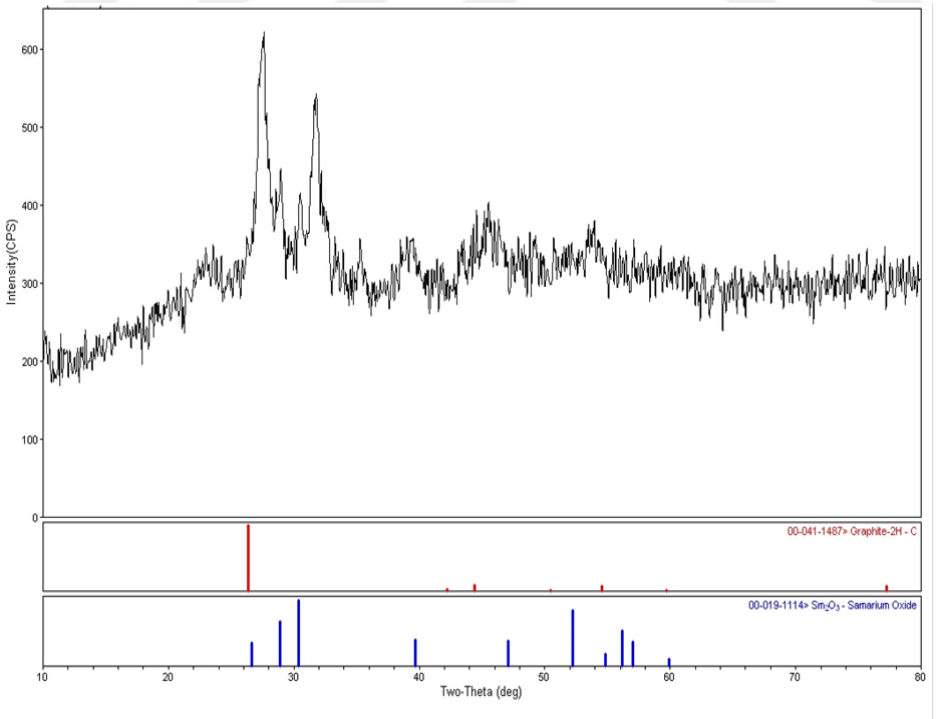

Figure 3.3. XRD pattern of the proposed electrode

3.2.4. Optimization of platform

The sensitivity of the method was high when the ratio of 1:10 for the mixture of Nd_2O_3NPs and carbon nanoballs was dispersed in chloroform. The sonication of Sm_2O_3 and CNBs should not be less than 45 min. In addition the electrode should be coated with only 5 µL of black suspension for high response towards methyldopa.

3.2.5. Voltammetric measurement

The electrode was activated by cyclic voltammetry in PBS in a potential range of -0.2 to +1.0 V. The procedure was completed upon the observation of a stable background voltammogram. Voltammograms of methyldopa were recorded at at several electrodes for comparison. The mechanism of methyldopa at CNBs/Sm_2O_3-NPs/ GCE was determined by the effect of scan rate. Furthermore, influence of pH value on the peak potential was studied to determine the redox reaction of methyldopa. Then, linear working range was obtained for methyldopa using a current response against the various concentrations by using cyclic voltammetry.

4. RESULTS and DISCUSSIONS

4.1. Cyclic Voltammetry of Paracetamol

Cyclic voltammograms of 6.0×10^{-6} M paracetamol studied at various surfaces by cyclic voltammetry are presented in Figure 4.1. Electrodes such as (a) conventional naked GCE, (b) GCE modified with CNBs and (c) GCE coated with CNBs/Sm_2O_3-NPS are compared in 0.1 M phosphate buffer.

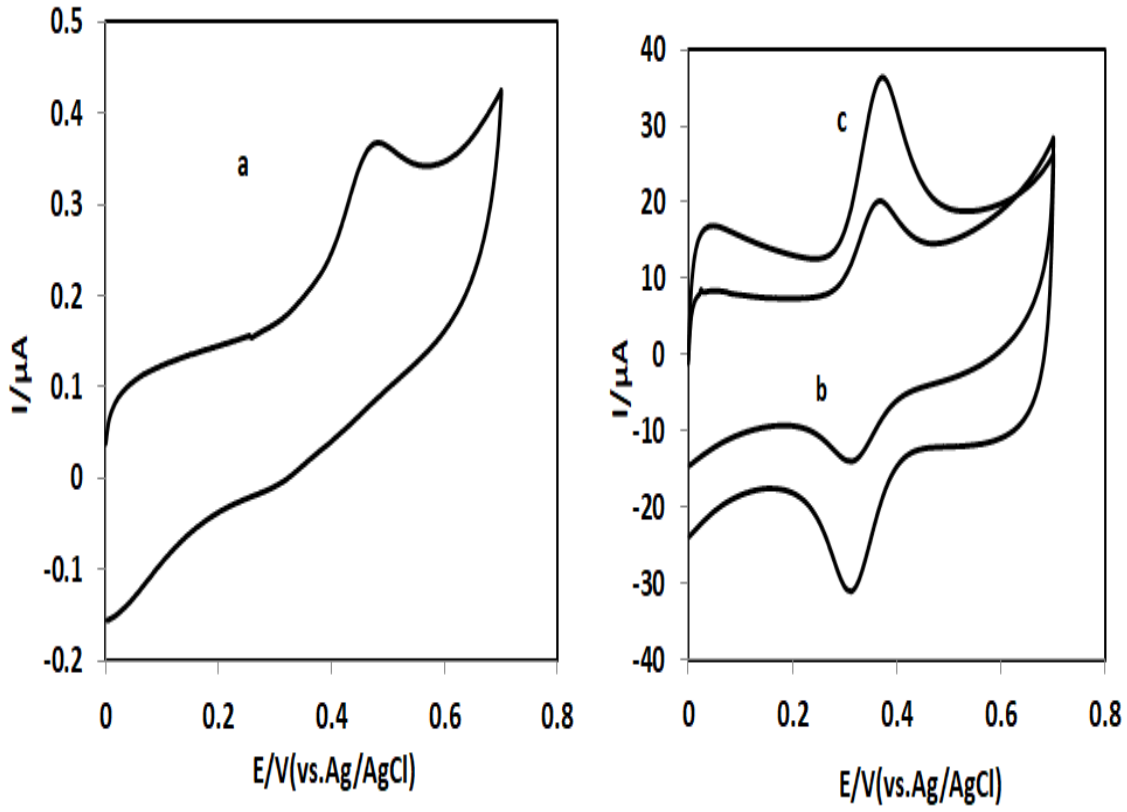

Figure 4.4. CVs of 6.0×10^{-6} M PAR at bare GCE (a); CNBs/GCE (b) and CNBs/Sm_2O_3/GCE (c) in 0.1 M PBS at pH 7.0. Scan rate: 50 mV/s

Data indicated that bare GCE showed a poor voltammogram towards paracetamol. The separation between oxidation/reduction peak potentials (ΔEp) was found to be 164 mV (Epa = 0.481V, Epc = 0.317 V) as shown in Figure 4.1a. The electrode coated with

carbon nanoballs (CNB/GCE) showed an oxidation at a potential of 0.363 V. The CNB/GCE produced a reversed peak at 0.324 V. ΔEp was about 39 mV for PAR at electrode coated with carbon nanoballs as presented in Figure 4.1b. However, a surface modified with a carbon nanoballs and samarium oxide nanoparticles (CNBs/Sm_2O_3-NPs /GCE) produced a sharp peak at 0.361 V. A reversed peak was observed at 0.334 V using the proposed electrode (Figure 4.1c). ΔEp was 27 mV for PAR process. Obviously, ΔEp was decreased to 27 mV at CNBs/Sm_2O_3-NPs /GCE when compared to other electrodes. The decrease in ΔEp at the proposed electrode system was a clear indication of the acceleration of electrochemical reaction of PAR. Decrease in ΔEp and high response for methyldopa at the proposed electrode indicated that the CNBs/Sm_2O_3-NPs /GCE was more appropriate for studying electrode reaction of methyldopa , such an improvement of parecetamol process is due to increment of surface area with carbon nanoballs and samarium oxide nanoparticles (Teker and Aslanoglu, 2019; Kutluay and Aslanoglu, 2016; Fathi et al., 2020).

4.2. Effect of Scan Rate

Voltammetry of paracetamol at various scan rate was studied. The peak potential and peak response was dependent on scan rate using the proposed platform. The experimental results were used to determine possible reaction mechanism for paracetamol.

Voltammograms of 6.0×10^{-6} M paracetamol in phosphate buffer for various scan rates. Voltammograms are given in Figure 4.2. This indicated an adsorption controlled mechanism for paracetamol (Figure 4.3). The calibration equation was Ipa (μA) = 0.2638 υ (mV s^{-1})+4.82. A correlation coefficient of 0.998 was obtained. Peak potential shifted with increase in scan rate. This is an indicative of a quasi-reversible electrode reaction at voltammetric platform (Rezaei et al., 2013).

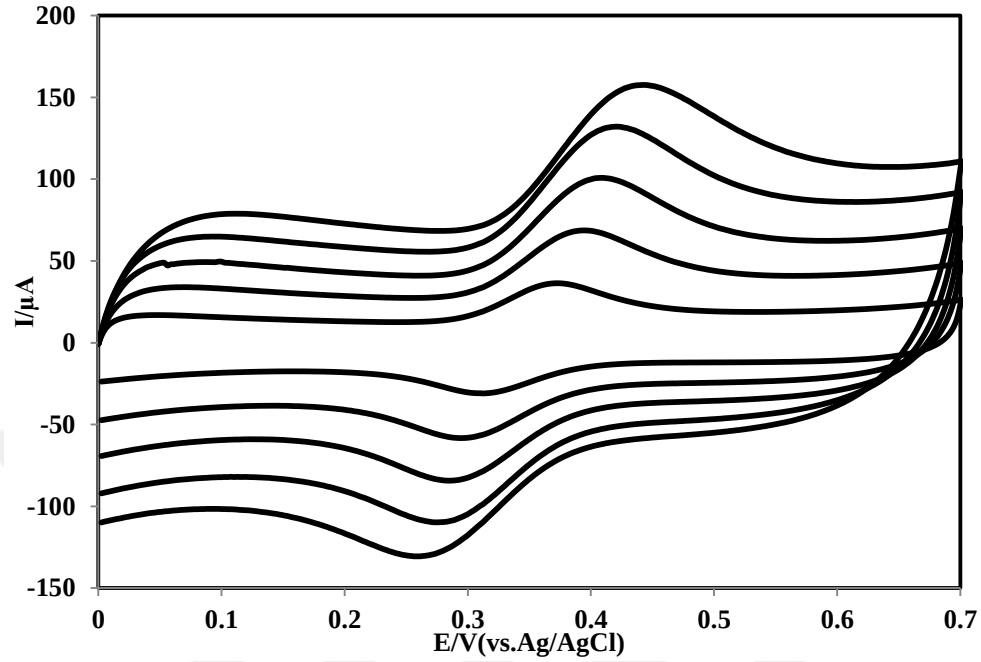

Figure 4.5. CVs of 6.0×10^{-6} M PAR at CNBs/Sm2O3/GCE at various scan rates

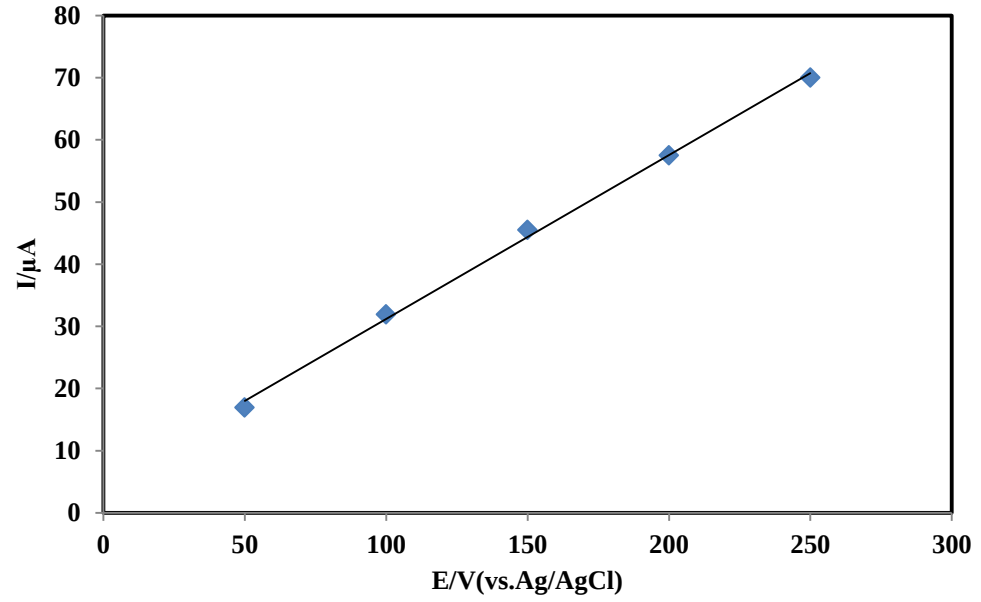

Figure 4.6. Plot of current response of 6.0×10^{-6} M paracetamol versus scan rates

4.3. Effect of pH

The peak potential of paracetamol is influenced by solution pH, Therefore, the oxidation of paracetamol was performed to obtain the significant pH value for the further studies and to acquire the number of protons involved in its reaction by cyclic voltammetry. For this purpose, various pH solutions containing 6.0×10^{-6} M methyldopa at the proposed electrode are presented in Figure 4.4.

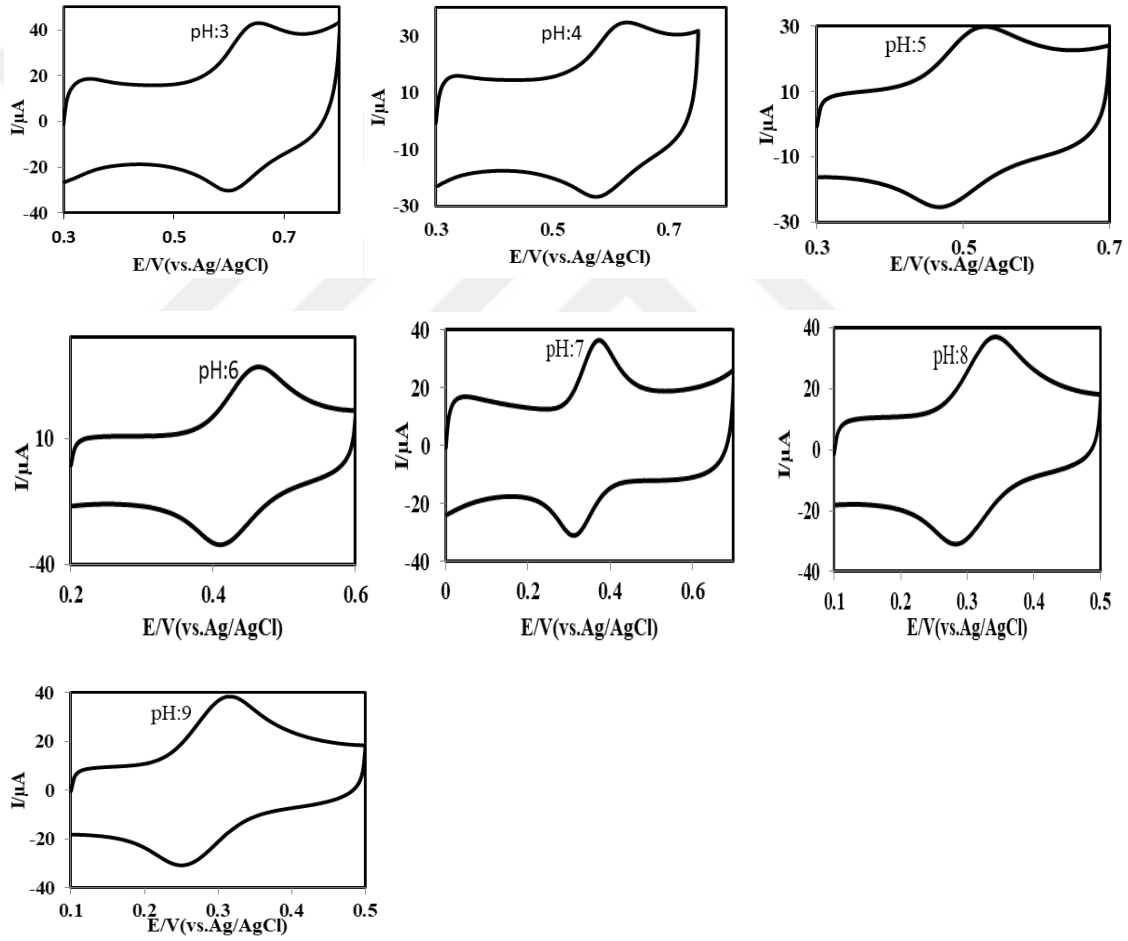

Figure 4.7. CVs of 6.0×10^{-6} M paracetamol at CNBs/Sm_2O_3/GCE in phosphate buffer at various pH values

The linear equation was E(V) = 0.8293 – 0.0618 pH for PAR at the proposed electrode. The correlation coefficient was 0.9908. The potential shifted toward the

negative voltage with increasing pH values indicated that paracetamol oxidation included proton transfer.

The anodic peak potential (E_{pa}) was plotted versus pH and a slope -0.0618 V/ pH^{-1} was obtained (Figure 4.5). This indicates that the ratio for electron/proton participating in redox couple is 1:1. This reveals equal number of electron and proton. Thus, it can be concluded that two protons are involved in electrode reaction of paracetamol. Figure 4.6 shows the proposed electrode reaction for paracetamol. The results of pH studies at the proposed electrode also showed that the highest value of response was obtained at pH 7 (Fouladgar and Ahmadzadeh, 2016).

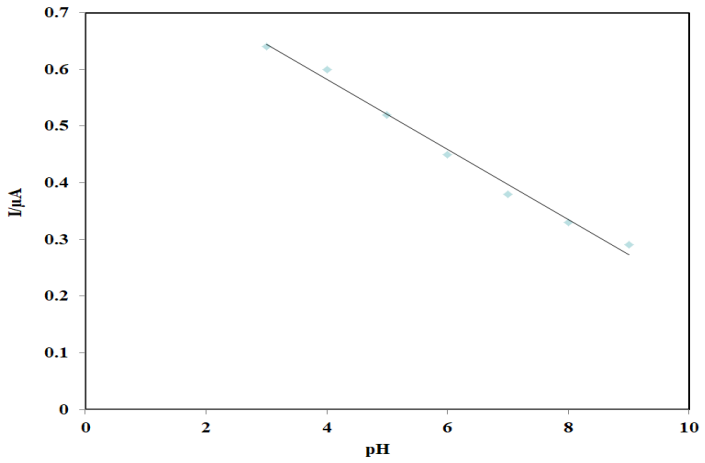

Figure 4.8. A plot of peak potentials of paracetamol versus solution pH

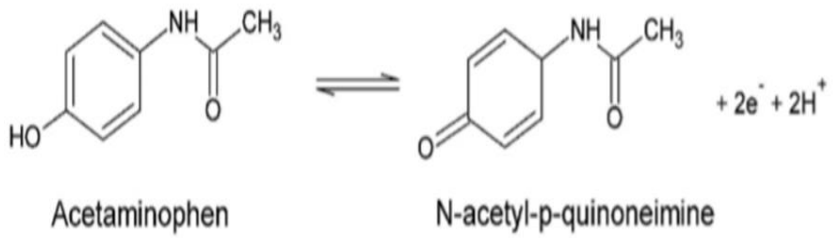

Figure 4.6. The electrode reaction of paracetamol

4.4. Interference study

Voltammetry is an accurate approach to evaluating drugs (Schmidt et al., 2014; Chen et al., 2018; Baytak et al., 2019).Voltammograms of increaing concentrations of PAR in the presence dopamine and sunset yellow at CNBs /Sm_2O_3-NPs/ GCE in buffer at pH 7 exhibited three well-defined anodic peaks for PAR, DA, and SSY as shown in Figure 4.7. Dopamine has similar voltammetric behavior like PAR, which exhibits at similar potential. Electrochemical oxidations of DA, SSY and PAR were investigated by cyclic voltammetry. Three well-defined peaks were obtained whowing DA, and SSY had no interfere with its determination.

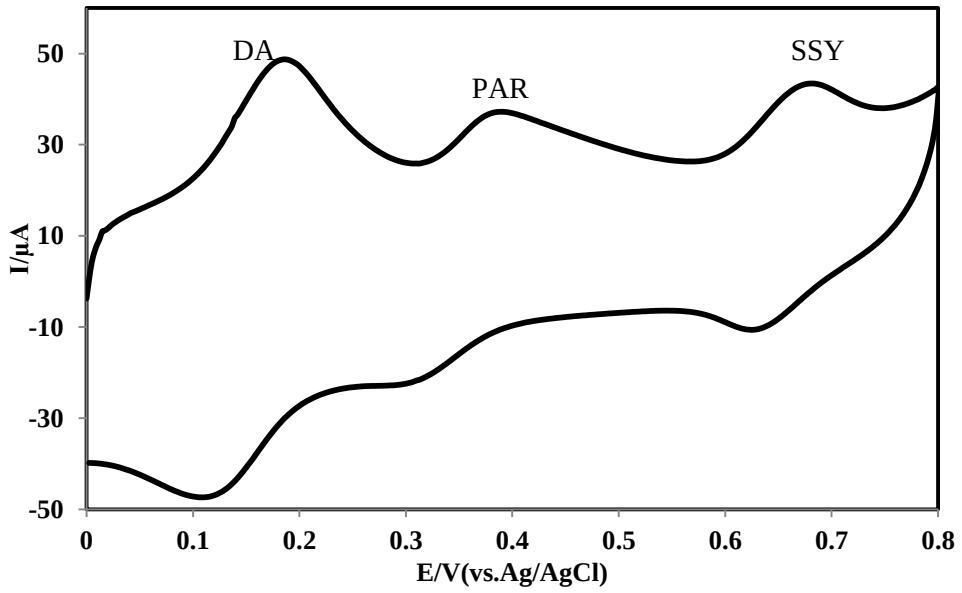

Figure 4.7. CVs of 8.0×10^{-6} M DA, 2.0×10^{-5} M PAR and 2.0×10^{-5} M SSY using CNBs/Sm_2O_3/GCE

4.5. Determination of Paracetamol

Cyclic voltammetry at CNBs/Sm_2O_3- NPs/GCE was performed for study of calibration plot of paracetamol. Voltammograms for various concentrations of PAR are given in Figure 4.8. The current response was plotted against the concentration of PAR

as shown in Figure 4.9. The current was shown to be linear with in the range of 2.0×10^{-7}M - 3.7×10^{-5} M. The corresponding regression equation with a correlation cofficient were represented as Ip(μA) = Ip(μA) = 3.06(μM)+ 2.46, R^2 = 0.999, respectivly. A detection limit (LOD) = 5.7×10^{-9} M was obtained for paracetamol.

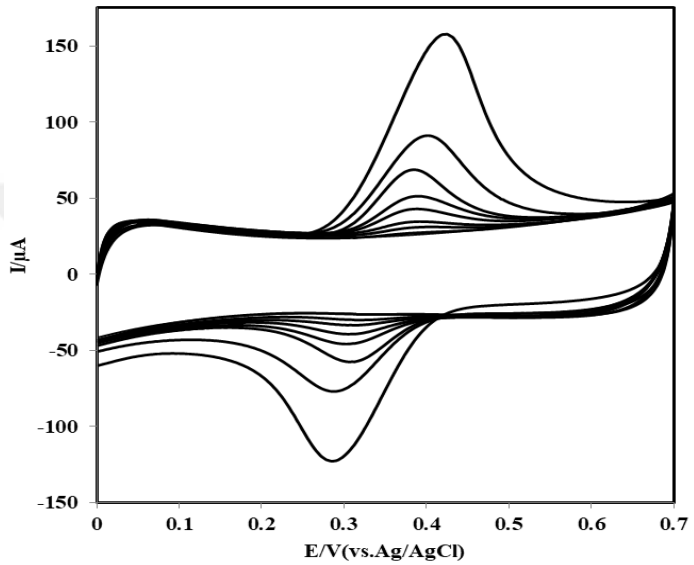

Figure 4.8. Voltammograms for concentrations of PAR at CNBs/Sm_2O_3/GCE. a) 2.0×10-7; b) 6.0×10-7 M; c) 1.2×10^{-6} M; d) 2.4×10^{-6} M; e) 4.7×10^{-6} M; f) 9.5×10^{-6} M; g) 1.9×10^{-5} M; h) 3.7×10^{-5} M.

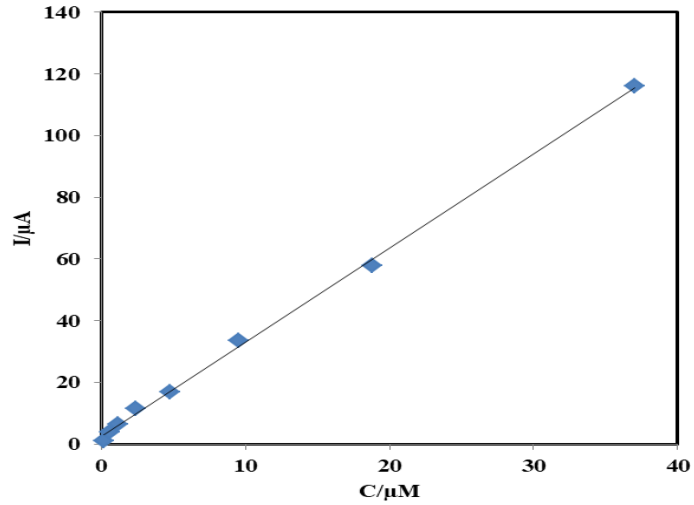

Figure 4.9. Calibration plot of paracetamol

4.6. Analysis of drug sample

The determination of cyclic voltammetric (CV) of paracetamol in drugs refers to regression equation. Data summarized are shown in Table 4.1. Average recovery was 100.15% with an RSD of 0.8%. The drug analysis at proposed platform showed good agreement to the declared value These results showed that the CNBs/Sm_2O_3/GCE was accurate and precise for quantifying paracetamol in drug sample.

Table 4.1. Determination of paracetamol in drug sample

Sample	**Added (mg)**	**Found (mg)**	**Recovery%**	**RSD%**
Parol Tablet	500	500.7	100.15	0.8

Mean± standard deviation (n= 4)

5. CONCLUSIONS and RECOMMENDATIONS

In this study, a novel platform for sensitive quantification of paracetamol in drug samples was developed using a GCE modified with CNBs and samarium oxide nanoparticles. The electrochemical platform exhibited remarkable electrocatalytic activity paracetamol compared with conventional naked GCE and CNBs/GCE, the CNBs/Sm_2O_3 /GCE showed high performance in point of peak potential difference and current response for PAR. The proposed electrode was used for detection of paracetamol in a presence of dopamine and sunset yellow. Measurements proved that high concentration of dopamine and sunset yellow did not interfere with paracetamol. CNBs/Sm_2O_3/GCE was successfully performed for determination of calibration equation for PAR using cyclic voltammetry. The response increased linearly with PAR concentrations. A linear range of 2.0×10^{-7}M - 3.7×10^{-5} M was obtained. The proposed sensor exhibited a detection limit of 5.7×10^{-9} M.

Further measurements may be conducted on a composite of nanotubes and graphene to improve the sensitivity of the proposed electrode and enable the study of paracetamol in samples containing ascorbic acid, trypyophan and uric acid. Also, equilibrium time may also be considered for further studies of modified platforms.

REFERENCES

AVINASH, B., RAVIKUMAR, C., KUMAR, M. A., NAGASWARUPA, H., SANTOSH, M., BHATT, A. S. and KUZNETSOV, D., 2019. Nano CuO: Electrochemical sensor for the determination of paracetamol and D-glucose. Journal of Physics and Chemistry of Solids, 134**:** 193-200.

ABDELALEEM, E. A., NAGUIB, I. A., HASSAN, E. S. and ALI, N. W., 2015. HPTLC and RP-HPLC methods for simultaneous determination of Paracetamol and Pamabrom in presence of their potential impurities. Journal of Pharmaceutical and Biomedical Analysis, 114**:** 22-27

AFKHAMI, A., GHAEDI, H., MADRAKIAN, T., AHMADI, M. and MAHMOOD-KASHANI, H., 2013. Fabrication of a new electrochemical sensor based on a new nano-molecularly imprinted polymer for highly selective and sensitive determination of tramadol in human urine samples. Biosensors and Bioelectronics, 44**:**34-40.

AFKHAMI, A., KHOSHSAFAR, H., BAGHERI, H. and MADRAKIAN, T., 2014. Preparation of NiFe2O4/graphene nanocomposite and its application as a modifier for the fabrication of an electrochemical sensor for the simultaneous determination of tramadol and acetaminophen. Analytica Chimica Acta, 831**:**50-59.

ALLEGAERT, K. and VAN DEN ANKER, J. N. Perinatal and neonatal use of paracetamol for pain relief. Seminars in Fetal and Neonatal Medicine., 2017. Elsevier:308-313.

ANDERSON, B. J., 2008. Paracetamol (Acetaminophen): mechanisms of action. Pediatric Anesthesia, 18**:**915-921.

ARAI, S., ENDO, M. and KANEKO, N., 2004. Ni-deposited multi-walled carbon nanotubes by electrodeposition. Carbon, 42**:**641-644.

ASADPOUR-ZEYNALI, K. and MOLLARASOULI, F., 2016. A novel and facile synthesis of TGA-capped CdSe@ Ag2Se core-shell quantum dots as a new substrate for high sensitive and selective methyldopa sensor. Sensors and Actuators B: Chemical, 237**:** 387-399.

AVINASH, B., RAVIKUMAR, C., KUMAR, M. A., NAGASWARUPA, H., SANTOSH, M., BHATT, A. S. and KUZNETSOV, D., 2019. Nano CuO: Electrochemical sensor for the determination of paracetamol and D-glucose. Journal of Physics and Chemistry of Solids, 134**:**193-200.

BABAEI, A., TAHERI, A. R. and AFRASIABI, M., 2011. A multi-walled carbon nanotube-modified glassy carbon electrode as a new sensor for the sensitive simultaneous determination of paracetamol and tramadol in pharmaceutical preparations and biological fluids. Journal of the Brazilian Chemical Society, 22**:** 1549-1558.

BACCARIN, M., SANTOS, F. A., VICENTINI, F. C., ZUCOLOTTO, V., JANEGITZ, B. C. and FATIBELLO-FILHO, O., 2017. Electrochemical sensor based on reduced graphene oxide/carbon black/chitosan composite for the simultaneous

determination of dopamine and paracetamol concentrations in urine samples. Journal of Electroanalytical Chemistry, 799**:** 436-443.

BARD, A. J. and FAULKNER, L. R., 2001. Fundamentals and applications. Electrochemical methods, 2**:**580-632.

BAYTAK, A. K., AKBAŞ, E. and ASLANOGLU, M., 2019. A novel voltammetric platform based on dysprosium oxide for the sensitive determination of sunset yellow in the presence of tartrazine. Analytica Chimica Acta, 1087**:** 93-103.

BAYTAK, A. K. and ASLANOGLU, M., 2015. Voltammetric quantification of tryptophan using a MWCNT modified GCE decorated with electrochemically produced nanoparticles of nickel. Sensors and Actuators B: Chemical, 220**:**1161-1168.

BEHERA, S., GHANTY, S., AHMAD, F., SANTRA, S. and BANERJEE, S., 2012. UV-visible spectrophotometric method development and validation of assay of paracetamol tablet formulation. J Anal Bioanal Techniques, 3**:** 151-7.

BEITOLLAHI, H., RAOOF, J.-B. and HOSSEINZADEH, R., 2011a. Electroanalysis and simultaneous determination of 6-thioguanine in the presence of uric acid and folic acid using a modified carbon nanotube paste electrode. Analytical Sciences, 27**:** 991-991.

BEITOLLAHI, H., RAOOF, J. B. and HOSSEINZADEH, R., 2011b. Application of a carbon-paste electrode modified with 2, 7-bis (ferrocenyl ethyl) fluoren-9-one and carbon nanotubes for voltammetric determination of levodopa in the presence of uric acid and folic acid. Electroanalysis, 23**:** 1934-1940.

BEITOLLAHI, H., TAHER, M. A., AHMADIPOUR, M. and HOSSEINZADEH, R., 2014. Electrocatalytic determination of captopril using a modified carbon nanotube paste electrode: Application to determination of captopril in pharmaceutical and biological samples. Measurement, 47**:** 770-776.

CALDERÓN-MORENO, J. M., LABARTA, A., BATLLE, X., PRADELL, T., CRESPO, D. and BINH, V. T., 2007. Magnetic properties of dense carbon nanospheres prepared by chemical vapor deposition. Chemical Physics Letters, 447**:** 295-299.

CAMPBELL, F. W. and COMPTON, R. G., 2010. The use of nanoparticles in electroanalysis: an updated review. Analytical and bioanalytical chemistry, 396**:** 241-259.

CHARPIAT, B., BEDOUCH, P., ROSE, F. X., JUSTE, M., ROUBILLE, R., CONORT, O. and ALLENET, B., 2013. Overdosed paracetamol (acetaminophen) prescriptions and subsequent pharmacist interventions in French hospitals. Annales Pharmaceutiques Françaises, 71**:** 410-417.

CHEN, Y., ZHENG, G., SHI, Q., ZHAO, R. and CHEN, M., 2018. Preparation of thiolated calix [8] arene/AuNPs/MWCNTs modified glassy carbon electrode and its electrocatalytic oxidation toward paracetamol. Sensors and Actuators B: Chemical, 277**:** 289-296.

CRIADO, A., CÁRDENAS, S., GALLEGO, M. and VALCÁRCEL, M., 2000. Continuous flow spectrophotometric determination of paracetamol in

pharmaceuticals following continuous microwave assisted alkaline hydrolysis. Talanta, 53**:** 417-423.

DAY, T. M., UNWIN, P. R. and MACPHERSON, J. V., 2007. Factors Controlling the Electrodeposition of Metal Nanoparticles on Pristine Single Walled Carbon Nanotubes. Nano Letters, 7**:** 51-57.

DE OLIVEIRA, K. M., DOS SANTOS, T. C., DINELLI, L. R., MARINHO, J. Z., LIMA, R. C. and BOGADO, A. L., 2013. Aggregates of gold nanoparticles with complexes containing ruthenium as modifiers in carbon paste electrodes. Polyhedron, 50**:**410-417.

DEIMINIAT, B., ROUNAGHI, G. H. and ARBAB-ZAVAR, M. H., 2017. Development of a new electrochemical imprinted sensor based on poly-pyrrole, sol–gel and multiwall carbon nanotubes for determination of tramadol. Sensors and Actuators B: Chemical, 238**:** 651-659.

DEROCO, P. B., FATIBELLO-FILHO, O., ARDUINI, F. and MOSCONE, D., 2019. Effect of Different Carbon Blacks on the Simultaneous Electroanalysis of Drugs as Water Contaminants Based on Screen-printed Sensors. Electroanalysis, 31**:** 2145-2154.

DESHMUKH, A. A., MHLANGA, S. D. and COVILLE, N. J., 2010. Carbon spheres. Materials Science and Engineering: R: Reports, 70**:**1-28.

DINÇ, E., YÜCESOY, C. and ONUR, F., 2002. Simultaneous spectrophotometric determination of mefenamic acid and paracetamol in a pharmaceutical preparation using ratio spectra derivative spectrophotometry and chemometric methods. Journal of Pharmaceutical and Biomedical Analysis, 28**:** 1091-1100.

ELGRISHI, N., ROUNTREE, K. J., MCCARTHY, B. D., ROUNTREE, E. S., EISENHART, T. T. and DEMPSEY, J. L., 2018. A Practical Beginner's Guide to Cyclic Voltammetry. Journal of Chemical Education, 95**:** 197-206.

ENGIN, C., YILMAZ, S., SAGLIKOGLU, G., YAGMUR, S. and SADIKOGLU, M., 2015. Electroanalytical investigation of paracetamol on glassy carbon electrode by voltammetry. Int. J. Electrochem. Sci, 10**:** 1916-1925.

EUSTAQUIO, A., BLANCO, M., JEE, R. D. and MOFFAT, A. C., 1999. Determination of paracetamol in intact tablets by use of near infrared transmittance spectroscopy. Analytica Chimica Acta, 383**:** 283-290.

ENGIN, C., YILMAZ, S., SAGLIKOGLU, G., YAGMUR, S. and SADIKOGLU, M., 2015. Electroanalytical investigation of paracetamol on glassy carbon electrode by voltammetry. Int. J. Electrochem. Sci, 10**:** 1916-1925.

EUSTAQUIO, A., BLANCO, M., JEE, R. D.and MOFFAT, A. C., 1999. Determination of paracetamol in intact tablets by use of near infrared transmittance spectroscopy. Analytica Chimica Acta, 383**:**283-290.

FAN, Y., LIU, J.-H., LU, H.-T. and ZHANG, Q., 2011. Electrochemical behavior and voltammetric determination of paracetamol on Nafion/TiO2–graphene modified glassy carbon electrode. Colloids and Surfaces B: Biointerfaces, 85**:** 289-292.

FATHI, M., SALEM, S. E., GOMAA, E. A., KILLA, H. M. and FAROUK, A., 2020. Study of Electrochemical Redox Reaction of CuSO4 Salt with Amoxicillin at

Different Temperatures Using Glassy Carbon Electrode. Egyptian Journal of Chemistry, 63**:** 5239-5249.

FOULADGAR, M. and AHMADZADEH, S., 2016. Application of a nanostructured sensor based on NiO nanoparticles modified carbon paste electrode for determination of methyldopa in the presence of folic acid. Applied Surface Science, 379**:** 150-155.

FU, R., SHEN, M., DING, Y., LI, M., LI, L., REN, Z. and WU, Q., 2020. Electrocatalytic Oxidation and Sensitive Determination of Paracetamol Based on Nanosheets Self-assembled Lindgrenite Microflowers. Electroanalysis, 32**:** 978-985.

GHADIMI, H., M.A.TEHRANI, R., ALI, A. S. M., MOHAMED, N. and AB GHANI, S., 2013. Sensitive voltammetric determination of paracetamol by poly (4-vinylpyridine)/multiwalled carbon nanotubes modified glassy carbon electrode. Analytica Chimica Acta, 765**:**70-76.

GOWDA, J. I., GUNJIGANVI, D. G., SUNAGAR, N. B., BHAT, M. N. and NANDIBEWOOR, S. T., 2015. MWCNT–CTAB modified glassy carbon electrode as a sensor for the determination of paracetamol. RSC Advances, 5**:**49045-49053.

GOYAL, R. N. and SINGH, S. P. 2006. Voltammetric determination of paracetamol at C60-modified glassy carbon electrode. Electrochimica Acta, 51**,** 3008-3012.

GHADIMI, H., M.A.TEHRANI, R., ALI, A. S. M., MOHAMED, N. & AB GHANI, S. 2013. Sensitive voltammetric determination of paracetamol by poly (4-vinylpyridine)/multiwalled carbon nanotubes modified glassy carbon electrode. Analytica Chimica Acta, 765**,** 70-76.

GHORBANI-BIDKORBEH, F., SHAHROKHIAN, S., MOHAMMADI, A. and DINARVAND, R. 2010. Simultaneous voltammetric determination of tramadol and acetaminophen using carbon nanoparticles modified glassy carbon electrode. Electrochimica Acta, 55**,** 2752-2759.

GHOREISHI, S. M., BEHPOUR, M. and GOLESTANEH, M. 2012. Simultaneous determination of sunset yellow and tartrazine in soft drinks using gold nanoparticles carbon paste electrode. Food chemistry, 132**,** 637-641.

GOMAA, E. A., NEGM, A. and ABU-QARN, R. M., 2018. Cyclic voltammetry study of the electrochemical behavior of vanadyl sulfate in absence and presence of antibiotic. Measurement, 125**:** 645-650.

GÖRÖG, S., 2008. Drug safety, drug quality, drug analysis. Journal of Pharmaceutical and Biomedical Analysis, 48**,** 247-253.

GOWDA, J. I., GUNJIGANVI, D. G., SUNAGAR, N. B., BHAT, M. N. and NANDIBEWOOR, S. T., 2015. MWCNT–CTAB modified glassy carbon electrode as a sensor for the determination of paracetamol. RSC Advances, 5**:** 49045-49053.

GOYAL, R. N. and SINGH, S. P., 2006. Voltammetric determination of paracetamol at C60-modified glassy carbon electrode. Electrochimica Acta, 51**:** 3008-3012.

HAN, L., WU, W., KIRK, F. L., LUO, J., MAYE, M. M., KARIUKI, N. N., LIN, Y., WANG, C. and ZHONG, C.-J., 2004. A Direct Route toward Assembly of

Nanoparticle−Carbon Nanotube Composite Materials. Langmuir, 20**:** 6019-6025.

HE, Z., CHEN, J., LIU, D., ZHOU, H. and KUANG, Y., 2004. Electrodeposition of Pt–Ru nanoparticles on carbon nanotubes and their electrocatalytic properties for methanol electrooxidation. Diamond and Related Materials, 13**:** 1764-1770.

HEWAVITHARANA, A. K., LEE, S., DAWSON, P. A., MARKOVICH, D. and SHAW, P. N., 2008. Development of an HPLC–MS/MS method for the selective determination of paracetamol metabolites in mouse urine. Analytical Biochemistry, 374**:** 106-111.

HOSSEINZADEH, R., SABZI, R. E. and GHASEMLU, K., 2009. Effect of cetyltrimethyl ammonium bromide (CTAB) in determination of dopamine and ascorbic acid using carbon paste electrode modified with tin hexacyanoferrate. Colloids and Surfaces B: Biointerfaces, 68**:** 213-217.

HEWAVITHARANA, A. K., LEE, S., DAWSON, P. A., MARKOVICH, D. and SHAW, P. N., 2008. Development of an HPLC–MS/MS method for the selective determination of paracetamol metabolites in mouse urine. Analytical Biochemistry, 374**:** 106-111.

IRANIFAM, M., KHODAEI, S. and SAADATI, M., 2019. Chemiluminescence reaction of graphene oxide–luminol–dissolved oxygen and its application for determination of isoniazid and paracetamol. Microchemical Journal, 146**:** 850-855.

JIA, L., DUAN, Z., FAN, D., MI, Y., HUI, J. and CHANG, L., 2013. Human-like collagen/nano-hydroxyapatite scaffolds for the culture of chondrocytes. Materials Science and Engineering: C, 33**:** 727-734.

JIN, Y. Z., GAO, C., HSU, W. K., ZHU, Y., HUCZKO, A., BYSTRZEJEWSKI, M., ROE, M., LEE, C. Y., ACQUAH, S., KROTO, H. and WALTON, D. R. M. 2005. Large-scale synthesis and characterization of carbon spheres prepared by direct pyrolysis of hydrocarbons. Carbon, 43**:** 1944-1953.

JOSHI, P. and SUTRAVE, D., 2018. Building an arduino based potentiostat and instrumentation for cyclic voltammetry. J. Appl. Sci. Comput, 5**:** 163-167.

KALAMBATE, P. K., SANGHAVI, B. J., KARNA, S. P. and SRIVASTAVA, A. K., 2015. Simultaneous voltammetric determination of paracetamol and domperidone based on a graphene/platinum nanoparticles/nafion composite modified glassy carbon electrode. Sensors and Actuators B: Chemical, 213**:** 285-294.

KEYVANFARD, M., AHMADI, M., KARIMI, F.and ALIZAD, K., 2014. Voltammetric determination of cysteamine at multiwalled carbon nanotubes paste electrode in the presence of isoproterenol as a mediator. Chinese Chemical Letters, 25**:** 1244-1246.

KEYVANFARD, M., SHAKERI, R., KARIMI-MALEH, H. and ALIZAD, K., 2013. Highly selective and sensitive voltammetric sensor based on modified multiwall carbon nanotube paste electrode for simultaneous determination of ascorbic acid, acetaminophen and tryptophan. Materials Science and Engineering: C, 33**:**811-816.

KNOCHEN, M., GIGLIO, J. and REIS, B. F., 2003. Flow-injection spectrophotometric determination of paracetamol in tablets and oral solutions. Journal of Pharmaceutical and Biomedical Analysis, 33**:** 191-197.

KUTLUAY, A. and ASLANOGLU, M., 2013. Selective detection of albuterol in the presence of uric acid using a glassy carbon electrode modified with multi-walled carbon nanotubes and poly(pivalic acid). Sensors and Actuators B: Chemical, 177**:** 703-709.

KUTLUAY, A. and ASLANOGLU, M., 2016. Quantification of methyldopa in pharmaceuticals using a glassy carbon electrode modified with carbon nanotubes. Chinese Chemical Letters, 27**:** 91-95.

LANGHENDRIES, J. P., ALLEGAERT, K., VAN DEN ANKER, J. N., VEYCKEMANS, F. and SMETS, F., 2016. Possible effects of repeated exposure to ibuprofen and acetaminophen on the intestinal immune response in young infants. Medical Hypotheses, 87**:** 90-96.

LEE, K. J., ELGRISHI, N., KANDEMIR, B. and DEMPSEY, J. L., 2017. Electrochemical and spectroscopic methods for evaluating molecular electrocatalysts. Nature Reviews Chemistry, 1**:** 0039.

LI, B. L., WU, Z. L., XIONG, C. H., LUO, H. Q. and LI, N. B., 2012. Anodic stripping voltammetric measurement of trace cadmium at tin-coated carbon paste electrode. Talanta, 88**:** 707-710.

LU, T.-L. and TSAI, Y.-C., 2011. Sensitive electrochemical determination of acetaminophen in pharmaceutical formulations at multiwalled carbon nanotube-alumina-coated silica nanocomposite modified electrode. Sensors and Actuators B: Chemical, 153**:** 439-444.

LUO, J. H., JIAO, X. X., LI, N. B. and LUO, H. Q. ,2013. Sensitive determination of Cd (II) by square wave anodic stripping voltammetry with in situ bismuth-modified multiwalled carbon nanotubes doped carbon paste electrodes. Journal of Electroanalytical Chemistry, 689**:** 130-134.

MAO, H., CHEN, X., HUANG, R., CHEN, M., YANG, R., LAN, P., ZHOU, M., ZHANG, F., YANG, Y. and ZHOU, X., 2018. Fast preparation of carbon spheres from enzymatic hydrolysis lignin: Effects of hydrothermal carbonization conditions. Scientific reports, 8**:** 1-10.

MHLANGA, S. D., COVILLE, N. J., IYUKE, S. E., AFOLABI, A. S., ABDULKAREEM, A. S. and KUNJUZWA, N., 2010. Controlled syntheses of carbon spheres in a swirled floating catalytic chemical vapour deposition vertical reactor. Journal of Experimental Nanoscience, 5**:**40-51.

MIRHADI, E., RAMAZANI, A., ROUHANI, M. and JOO, S. W., 2013. Perlite-SO. Chemija, 24**:** 320-324.

MOCCELINI, S. K., FRANZOI, A. C., VIEIRA, I. C., DUPONT, J. and SCHEEREN, C. W., 2011. A novel support for laccase immobilization: cellulose acetate modified with ionic liquid and application in biosensor for methyldopa detection. Biosensors and Bioelectronics, 26**:** 3549-3554.

MOHAMMADI, A., BADRAGHI, J., MOGHADDAM, A. B., GANJKHANLOU, Y., KAZEMZAD, M., HOSSEINI, S. and DINARVAND, R., 2011. Synthesis of

Er2O3 nanoparticles and Er2O3 nanoparticle/polyaniline deposition on the surface of stainless steel by potentiostatic deposition. Chemical Engineering & Technology, 34**:** 56-60.

MOHAMMADI, S., BEITOLLAHI, H. and MOHADESI, A., 2013. Electrochemical behaviour of a modified carbon nanotube paste electrode and its application for simultaneous determination of epinephrine, uric acid and folic acid. Sensor Letters, 11**:** 388-394.

PATEL, B. R., NOROOZIFAR, M. and KERMAN, K., 2020. Review—Nanocomposite-Based Sensors for Voltammetric Detection of Hazardous Phenolic Pollutants in Water. Journal of The Electrochemical Society, 167**:** 037568.

RAHMAN, M. M., BALKHOYOR, H. B., ASIRI, A. M. and MARWANI, H. M., 2016. A gold electrode modified with silver oxide nanoparticle decorated carbon nanotubes for electrochemical sensing of dissolved ammonia. Microchimica Acta, 183**:** 1677-1685.

RAOOF, J.-B., OJANI, R., BEITOLLAHI, H. and HOSSEINZADEH, R., 2006. Electrocatalytic oxidation and highly selective voltammetric determination of L-cysteine at the surface of a 1-[4-(ferrocenyl ethynyl) phenyl]-1-ethanone modified carbon paste electrode. Analytical Sciences, 22**:**1213-1220.

RAOOF, J. B., OJANI, R. and BEITOLLAHI, H. 2007. L-Cysteine voltammetry at a carbon paste electrode bulk-modified with ferrocenedicarboxylic acid. Electroanalysis: An International Journal Devoted to Fundamental and Practical Aspects of Electroanalysis, 19**:** 1822-1830.

SADRI, F., RAMAZANI, A., MASSOUDI, A., KHOOBI, M., TARASI, R., SHAFIEE, A., AZIZKHANI, V., DOLATYARI, L. and JOO, S. W., 2014. Green oxidation of alcohols by using hydrogen peroxide in water in the presence of magnetic Fe3O4 nanoparticles as recoverable catalyst. Green Chemistry Letters and Reviews, 7**:** 257-264.

SANGHAVI, B. J., MOBIN, S. M., MATHUR, P., LAHIRI, G. K. and SRIVASTAVA, A. K., 2013. Biomimetic sensor for certain catecholamines employing copper (II) complex and silver nanoparticle modified glassy carbon paste electrode. Biosensors and Bioelectronics, 39**:** 124-132.

SANGHAVI, B. J. and SRIVASTAVA, A. K., 2011. Simultaneous voltammetric determination of acetaminophen and tramadol using Dowex50wx2 and gold nanoparticles modified glassy carbon paste electrode. Analytica Chimica Acta, 706**:** 246-254.

SCHMIDT, A. C., DUNAWAY, L. E., ROBERTS, J. G., MCCARTY, G. S. and SOMBERS, L. A., 2014. Multiple scan rate voltammetry for selective quantification of real-time enkephalin dynamics. Analytical chemistry, 86**:** 7806-7812.

SHAHMIRI, M. R., BAHARI, A., KARIMI-MALEH, H., HOSSEINZADEH, R. and MIRNIA, N., 2013. Ethynylferrocene–NiO/MWCNT nanocomposite modified carbon paste electrode as a novel voltammetric sensor for simultaneous

determination of glutathione and acetaminophen. Sensors and Actuators B: Chemical, 177**:** 70-77.

SHANGGUAN, E. and LI, Q., 2013. A pre-anodized inlaying ultrathin carbon paste electrode for simultaneous determination of uric acid and folic acid. Electrochimica Acta, 89**:** 600-606.

SOBKOWICZ, M. J., DORGAN, J. R., GNESHIN, K. W., HERRING, A. M. and MCKINNON, J. T., 2009. Controlled dispersion of carbon nanospheres through surface functionalization. Carbon, 47**:** 622-628.

TALEAT, Z., ARDAKANI, M. M., NAEIMI, H., BEITOLLAHI, H., NEJATI, M. and ZARE, H. R., 2008. Electrochemical behavior of ascorbic acid at a 2, 2′-[3, 6-dioxa-1, 8-octanediylbis (nitriloethylidyne)]-bis-hydroquinone carbon paste electrode. Analytical Sciences, 24**:** 1039-1044.

TEKER, T. and ASLANOGLU, M., 2019. Sensitive Determination of Terbutaline Using a Platform Based on Nanopartices of Europium Oxide and Carbon Nanotubes. Electroanalysis, 31**:** 146-152.

THOMAS, T., MASCARENHAS, R. J., D'SOUZA, O. J., MARTIS, P., DALHALLE, J. and SWAMY, B. K. ,2013a. Multi-walled carbon nanotube modified carbon paste electrode as a sensor for the amperometric detection of L-tryptophan in biological samples. Journal of Colloid and Interface Science, 402**:** 223-229.

THOMAS, T., MASCARENHAS, R. J., SWAMY, B. K., MARTIS, P., MEKHALIF, Z. and SHERIGARA, B., 2013b. Multi-walled carbon nanotube/poly (glycine) modified carbon paste electrode for the determination of dopamine in biological fluids and pharmaceuticals. Colloids and Surfaces B: Biointerfaces, 110**:** 458-465.

TUNGKANANURUK, K., TUNGKANANURUK, N. and BURNS, D. T., 2005. Cyclic voltammetric determination of acetaminophen in paracetamol tablets. Current Applied Science And Technology, 5**:**547-551.

. VAIRAVAPANDIAN, D., VICHCHULADA, P. and LAY, M. D., 2008. Preparation and modification of carbon nanotubes: Review of recent advances and applications in catalysis and sensing. Analytica Chimica Acta, 626**:** 119-129.

VIEIRA, I. C., LUPETTI, K. O. and FATIBELLO-FILHO, O., 2003. Determination of paracetamol in pharmaceutical products using a carbon paste biosensor modified with crude extract of zucchini (Cucurbita pepo). Química Nova, 26**:**39-43.

WADUD, A., PRASAD, P., RAO, M. and NARAYANA, A., 2007. Evolution of drug: a historical perspective. Bull Indian Inst Hist Med Hyderabad, 37**:** 69-80.

WANG, J., 2002. Portable electrochemical systems. Trends in Analytical Chemistry, 21**:** 226-232.

WANG, J., TANGKUARAM, T., LOYPRASERT, S., VAZQUEZ-ALVAREZ, T., VEERASAI, W., KANATHARANA, P. and THAVARUNGKUL, P. 2007. Electrocatalytic detection of insulin at RuOx/carbon nanotube-modified carbon electrodes. Analytica Chimica Acta, 581**:** 1-6.

WANG, Y., HUANG, L., WANG, Z., WANG, L., HAN, Y., LIU, X. and MA, T., 2019. Application of Polypyrrole flexible electrode for electrokinetic

remediation of Cr(VI)-contaminated soil in a main-auxiliary electrode system. Chemical Engineering Journal, 373: 131-139.

WILDGOOSE, G. G., BANKS, C. E. and COMPTON, R. G., 2006. Metal nanoparticles and related materials supported on carbon nanotubes: Methods and Applications, 2: 182-93.

XU, Z., TENG, H., SONG, J., GAO, F., MA, L., XU, G. & LUO, X., 2019. A nanocomposite consisting of MnO 2 nanoflowers and the conducting polymer PEDOT for highly sensitive amperometric detection of paracetamol. Microchimica Acta, 186**:** 1-8.

YAN, Y., JAMAL, R., YU, Z., ZHANG, R., ZHANG, W., GE, Y., LIU, Y. and ABDIRYIM, T., 2020. Composites of thiol-grafted PEDOT with N-doped graphene or graphitic carbon nitride as an electrochemical sensor for the detection of paracetamol. Journal of Materials Science, 55**:**5571-5586.

YAN, Y., JAMAL, R., YU, Z., ZHANG, R., ZHANG, W., GE, Y., LIU, Y. and ABDIRYIM, T., 2020. Composites of thiol-grafted PEDOT with N-doped graphene or graphitic carbon nitride as an electrochemical sensor for the detection of paracetamol. Journal of Materials Science, 55**:**5571-5586.

YÁNEZ-SEDENO, P., PINGARRÓN, J. M., RIU, J. and RIUS, F. X., 2010. Electrochemical sensing based on carbon nanotubes. Trends in Analytical Chemistry, 29**:** 939-953.

YILDIZ, G., OZTEKIN, N., ORBAY, A. and SENKAL, F., 2014. Voltammetric determination of nitrite in meat products using polyvinylimidazole modified carbon paste electrode. Food Chemistry, 152**:** 245-250.

ZHANG, W., LIU, S., ZHANG, Y., DING, X., JIANG, B. and ZHANG, Y., 2019. An electrochemical sensor based on electro-polymerization of caffeic acid and Zn/Ni-ZIF-8–800 on glassy carbon electrode for the sensitive detection of acetaminophen. Biosensors and Bioelectronics, 131**:** 200-206.

ZHAO, S., BAI, W., YUAN, H. and XIAO, D., 2006. Detection of paracetamol by capillary electrophoresis with chemiluminescence detection. Analytica Chimica Acta, 559**:** 195-199.