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ELECTROCHEMICAL OXIDATION OF ANTIBIOTIC, ANTIHISTAMINE, ANALGESIC AND CNS STIMULANT PHARMACEUTICALS

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BY

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ABSTRACT

Electrochemical oxidation is a common method for the degradation of chemicals by applying potential at a definite value. In this research, 'cyclic voltammetry' experiments were conducted to find out the oxidation potential for 8 different pharmaceuticals. Mainly, 3 different pH solutions (pH 6.0, 7.5, 9.0) and 9 different concentrations (1, 2, 5, 10, 20, 50, 100, 200, 500 µM) were studied for each of the pharmaceuticals in this experiments. Acetaminophen, Ibuprofen, Naproxen Sodium, Caffeine showed oxidation peak at 0.34-0.79V, 1.37- 1.39V, 0.94-1.01V, 1.44-1.55V respectively at different pH and concentrations. Antibiotic and antihistamine pharmaceuticals i.e. Erythromycin Hydrate, Triclosan, Sulfanilamide, Diphenhydramine Hydrochloride showed oxidation peak at 0.91-1.19V, 0.58-1.03V, 0.86-1.11V, 0.79-1.22V respectively at different pH and concentrations. The oxidation potential varies with both pH and concentration for every pharmaceutical. The chronoamperometry experiments were performed to determine the relationship between the concentration of the pharmaceuticals and the current. The sensor curves have been developed from the data of the chronoamperometry experiments. To observe the electrochemical degradation, the potential (higher than the oxidation potential found by the cyclic voltammetry experiments) have been applied to the pharmaceutical

solutions and samples were collected at different time from the solutions during the period of applying potential. The samples were then analyzed in HPLC instrument. Triclosan and Sulfanilamide have shown successful degradation. The 1^{st} order reaction constants are 0.0039 min^{-1} and 0.0148 min^{-1} for the degradation of sulfanilamide and Triclosan respectively.

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CHAPTER 1 INTRODUCTION

Pharmaceuticals are so much widely used worldwide that these can be found in terrestrial and aquatic system in considerable amount [1]–[5]. This amount is still increasing slowly, but continuously [6], [7]. The presence of the pharmaceuticals or their derivatives can cause adverse effects on aquatic lives, plants and even on humans [6], [8]. Since we cannot avoid medication, thus it is now a concern to reduce the concentration of the pharmaceuticals from environment. Different approaches were discovered over the years to degrade the pharmaceuticals from the wastewater. In this work, electrooxidation method have been applied to degrade and remove the pharmaceuticals.

1.1. What is CEC

CEC stands for ‘Contaminants of Emerging Concern’. Pharmaceuticals are now found in such a considerable amount in natural water sources that these are now being considered as CEC. CEC also includes some other types of chemicals and materials which can have negative effect on the animal being or on environment. CEC includes pesticides, industrial effluents, pharmaceuticals, personal care products etc. Most of these compounds reach the environment through municipal wastewater treatment plant where these compounds are not being removed completely [5]. That is why scientists are now researching on how to remove or degrade those CEC compounds from municipal wastewater. Since, CEC is a

broad area of compounds, in my research I concentrated on the degradation of few of the pharmaceuticals which are commonly used in urban area.

1.2. Background

The consumption of pharmaceuticals is increasing with time. One report showed that the antibiotic consumption was increased by an average of 36% in 71 countries and even it was as high as 76% for few other countries during the period of 2000 to 2010 [9].

Pharmaceuticals can enter the environment by different pathways such as excretion and metabolism [10], unused or expired medicine thrown as solid waste, discharge of treated wastewater, seepage from sewer lines, landfills and septic systems etc. In general, pharmaceuticals are metabolized in the body by different mechanisms such as oxidation, reduction, conjugation, hydrolysis etc. and transformed into more polar and water soluble derivatives which have a reduced pharmacological activity compared to the original compound [11]. The pharmaceuticals or other chemical compounds which are detected at low levels in surface water are called as Contaminants of emerging concern (CEC) which may also act as endocrine disruptors (EDCs). The presence of CECs can be detected by High Performance Liquid Chromatography (HPLC), Mass Spectrometry, Isotope-Dilution Mass Spectrometry (ISTD) etc. Generally, CECs concentration in wastewater is found to be in the range between ppt (ng L^{-1}) to ppm (mg L^{-1}).

The veterinary pharmaceuticals can enter the surface water [12], [13]. The concentration of different pharmaceuticals in several countries have been shown in previous studies [6]. Different anti-inflammatories and analgesics i.e. diclofenac, ibuprofen etc. have been found in groundwater and aquifers in Germany, England and Spain [14]–[17]. Caffeine was also found in the wastewater, sewage effluent, groundwater and surface water [18], [19].

The presence of the pharmaceuticals in water system can bio-accumulate within the food chain and affect aquatic lives as well as human health in long term. This can hinder normal function of hormones and thus can have reproductive effects in aquatic organisms [20]. These can be reactive to non-target organisms [3], [21]–[23]. Different researches showed the negative impact of the pharmaceuticals on the reproduction of aquatic lives and the growth of algae and phytoplankton [24], [25]. The presence of antibiotic pharmaceuticals can promote the antibiotic resistance in bacteria which can be detrimental for human and animals [25]–[27]. The long time exposure of the pharmaceuticals in water can impair health condition of fish such as kidney, grill disease etc. [3], [8], [28], [29]. Some pharmaceuticals like Carbamazepine does not generally undergo to the degradation or adsorption process and thus can be found in groundwater or surface water in higher concentration [30]. For these reasons, this is now very important to successfully degrade the pharmaceuticals as well as CEC into harmless compound.

1.3. Type of Pharmaceuticals used

Different kinds of pharmaceuticals are found in the aqueous environment such as analgesics, antibiotics, anti-inflammatories, steroids, antipyretics, stimulants, antihistamines etc. [6], [8], [31]. In this work, 8 pharmaceuticals from 4 different categories have been used to study. The list of pharmaceuticals along with their categories are shown below.

Category-1: Analgesic and Anti-inflammatory Drugs

i. Acetaminophen
ii. Ibuprofen
iii. Naproxen Sodium

Categoory-2: Central Nervous System (CNS) Stimulant Drugs

i. Caffeine

Category-3: Antibiotic Drugs

i. Erythromycin Hydrate
ii. Triclosan
iii. Sulfanilamide

Category-4: Antihistamine Drugs

i. Diphenhydramine Hydrochloride

Acetaminophen [IUPAC name: N-(4-hydroxyphenyl)acetamide] is the prescription and non-prescription analgesic and antipyretic drug which is widely used to reduce fever and pain. Acetaminophen is non-carcinogenic and prescribed for the patients who cannot tolerate aspirin [32]. Ibuprofen (Ibu) [IUPAC name: 2-[4-(2-methyl propyl) phenyl] propanoic acid] is a non-prescription, non-steroidal anti-inflammatory drug (NSAID) used for treating arthritis, fever, pain and inflammation [33]. Naproxen sodium [IUPAC name: sodium;(2S)-2-(6-methoxynaphthalen-2-yl)propanoate] is the sodium salt form of naproxen which is non-steroidal anti-inflammatory drugs (NSAIDs) with anti-inflammatory analgesic and antipyretic properties. It is used to moderate pain relief and in the treatment of arthritis, other rheumatic or musculoskeletal disorders etc. [34]. This is both prescription and non-prescription drug.

CNS stimulant drugs e.g. Caffeine, Modafinil etc. are generally used to treat excessive sleepiness and restore alertness. Caffeine [IUPAC name: 1,3,7-trimethylpurine-2,6-dione] is the world's most widely consumed psychoactive substance [35]. It is present in cocoa, tea, chocolate, soft and energy drinks, coffee and certain medicines. Caffeine's pharmacological usage is to increase alertness, produce agitation, relax smooth muscle and stimulate diuresis and cardiac muscle etc. It was found also to be useful in the treatment of some types of headache [36].

Antibiotics are used to treat bacterial infections. Erythromycin Hydrate ($C_{37}H_{69}NO_{14}$) or Erythromycin is a prescribed drug used for the treatment of mouth

infections, skin infections, urine infections, respiratory infections etc. Triclosan [IUPAC name: 5-chloro-2-(2,4-dichlorophenoxy)phenol] is an antiseptic which is used in soap, toothpaste, cosmetics etc. Sulfanilamide [IUPAC name: 4-aminobenzenesulfonamide] is used in the treatment of vaginal infections. It reduces vaginal burning and itching.

Antihistamine drugs acts to reduce the activity of histamjne receptors and to treat allergies. Diphenhydramine Hydrochloride [IUPAC name: 2-benzhydryloxy-N,N-dimethylethanamine; hydrochloride] or Diphenhydramine is used in the treatment of common cold, allergy, hay fever etc.

1.4. Review of Previous Researches

There are several common methods to degrade the CECs such as electrochemical oxidation, advanced oxidation (Fenton, cavitation, radiation etc.) and biological degradation (MBBR, ASR, MBR etc.) [11], [37], [38]. Different researchers followed different methods to degrade CEC compounds. In this work, electrochemical method has been applied to observe the degradation.

In advanced oxidation processes (AOP), hydroxyl radical is produced. This radical acts as a oxidant to degrade CEC. Several researches showed that AOP has very high degradation efficiency (mostly over 90%) [39]–[46]. But there are also some disadvantages

of these processes. In Fenton process, large amount of byproduct sludge is produced through the process [39], [44]. On the other hand, cavitation or radiation processes are expensive. Biological degradation is also an effective method to degrade CEC from wastewater. In this method, biological organisms i.e. bacteria, fungi etc. are used in different ways. Moving bed biofilm reactor (MBBR) uses biofilm carriers which are kept moving in reactor with aerobic condition. Membrane bioreactor (MBR) was used in parallel with wastewater treatment plant in different researches [47], [48]. The results showed that this method cannot fully degrade for all types of CEC. Some pharmaceuticals can be removed almost completely and some other are instead more recalcitrant and difficult to degrade [47]–[49]. Researchers found that naproxen was removed 40-55% using biological treatment [50]. In comparison with these processes, electrochemical oxidation is the better because this is inexpensive and no byproduct sludge is produced electrochemically. Also, the biological methods may take a long time to degrade CEC at a desired level whereas the electrochemical degradation method might be quite faster.

Electrochemical oxidation is also a common method to degrade pharmaceuticals. Different researchers used different electrodes such as porous Ti, boron doped diamond [51], Ti/Pt/PbO_2 [52], glassy carbon electrodes modified with poly(4-aminobenzoic acid) [53], platinum nanoparticles coated FTO glass [54], ZnO nanoparticles and multiwalled carbon nanotubes modified carbon paste electrode [55], modified reticulated vitreous carbon electrodes with $TiO_2$and $CuO/TiO_2/Al_2O_3$ [46], graphite-poly vinyl chloride (PVC) composite electrode [56], Nafion–Gr modified glassy carbon electrode [57], multi-walled carbon nanotubes-epoxy composite electrode [58], etc. to increase the oxidation efficiency.

L. Yang et al. showed that acetaminophen has been degraded more than 95% in 80 min using TiO_2 loading as photocatalysis [59]. Researchers found that conductive diamond electrochemical oxidation (CDEO) technology can efficiently and possibly completely degrade caffeine even at very low concentration [60]. It has also been found that with the increase of the applied voltage, the removal efficiency of caffeine increases very significantly and chloride media is better for its removal [56]. According to the experimental result of S. Motoc et al., Ibuprofen can be degraded by applying potential at 1.2 and 1.75V vs. Ag/AgCl using multi-walled carbon nanotubes-epoxy (MWCNT) and silver-modified zeolite-multi-walled carbon nanotubes-epoxy (AgZMWCNT) composites electrodes [58]. Xiang Li et al. showed that ibuprofen could be completely degraded in 5-15min using the electro-peroxone process [61].

In this work, we used electrochemical oxidation process to degrade three analgesic drugs i.e. Acetaminophen, Ibuprofen, Naproxen Sodium and one CNS stimulant drugs i.e. Caffeine. Particularly, we identified the oxidation peaks of those CECs of interests at different operating conditions i.e. concentration and pH. We applied electrical potential to the solution containing CEC using different methods i.e. cyclic voltammetry (CV), chronoamperometry to determine the applicability of this method.

CHAPTER 2 EXPERIMENTAL METHODS

2.1. Reagents and Materials

Carbon fiber paper was supplied by Fuel Cell Store, USA. Acetaminophen, Ibuprofen, Naproxen Sodium and Caffeine were obtained from Sigma-Aldrich . The structural formulas of the pharmaceuticals are shown in Figure 1 and Figure 2. Gradient grade Methanol (OmniSolv MX0488) and water (OmniSolv WX0004) were used to prepare the solutions and to wash the equipments. KH_2PO_4, K_2HPO_4, NaCl, KCl, Na_2HPO_4, NaH_2PO_4 were supplied by EMD Chemicals Incorporation. In order to control the pH in buffer solution, KOH or H_3PO_4 was used which were also supplied by EMD Chemicals Incorporation.

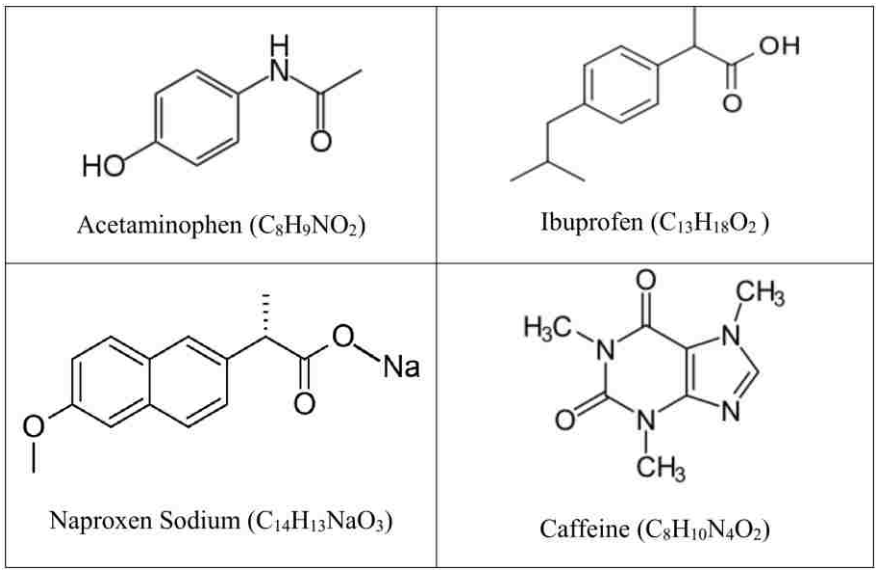


Figure 1. Chemical structures of the analgesic and CNS stimulant pharmaceuticals

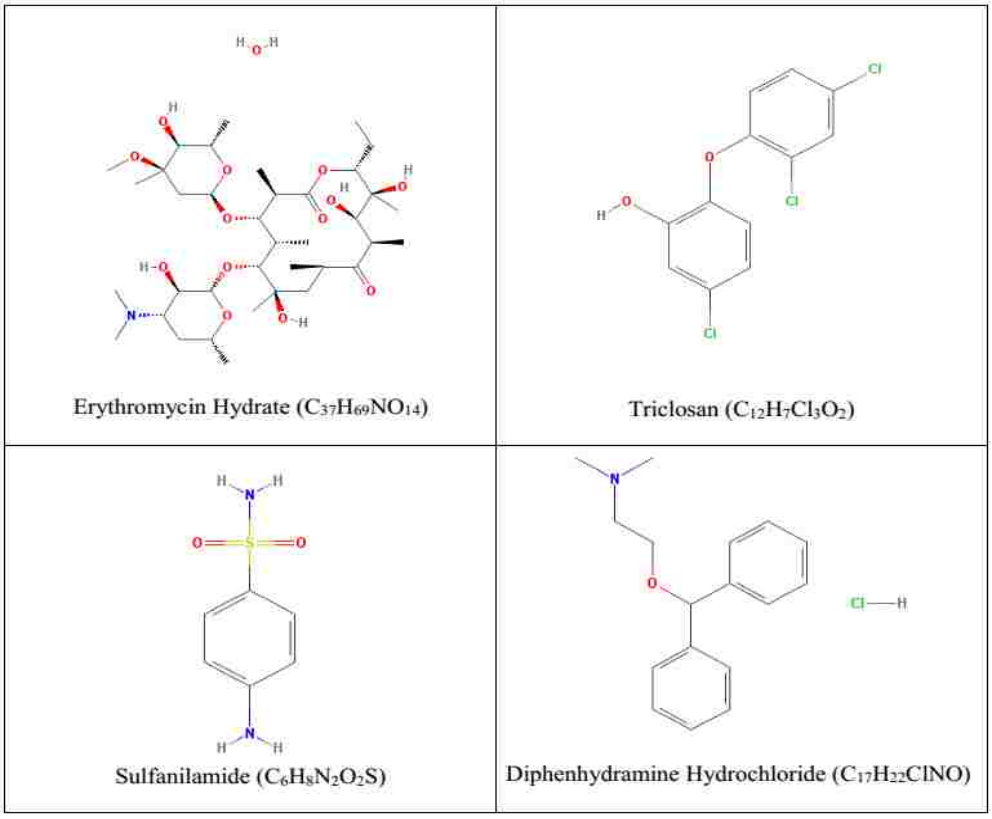


Figure 2. Chemical structures of the antibiotic and antihistamine pharmaceuticals [62]–[65]

2.2. Sample Preparation

Sample solutions of the pharmaceuticals were prepared by adding them into the mixture (approx. 50-50%V) of methanol and HPLC grade water. The concentration was 10mM for each of the stock solutions. The prepared solutions were kept in dark and closed plastic test tube to avoid undesired change in concentration.

As a reagent, potassium phosphate buffer (K-PB) solution (0.1M) was prepared at pH 4.5, 6.0, 7.5 and 9.0 using KH_2PO_4 and K_2HPO_4 in proper ratio. As the supporting

electrolyte, 0.1M KCl was added in the phosphate buffer solution. K_2HPO_4, H_2SO_4, NaCl/KCl were used to prepare the buffer solution of pH 1.0, 3.0. And, for the preparation of buffer solutions of pH 11.0, 13.8, $Na_2HPO_4/NaH_2PO_4.H_2O$, NaOH, NaCl were used.

2.3. Experimental Set up

Pyrex 100mL bottle with screw cap was used as the electrochemical oxidation reactor. In order to measure cyclic voltammetry (CV) and chronoamperometry, VersaSTAT MC potentiostat (Princeton Applied Research) was used in a three electrode configuration (working electrode, counter electrode and reference electrode). In our experiment, carbon fiber paper with micro-porous layer coating, titanium wire and Ag/AgCl 3M KCl (+210 mV vs SHE) were used as the working electrode, counter electrode and the reference electrode respectively. Four small holes were created in the cap in order to accommodate working, counter and reference electrode and a small tube for flushing nitrogen into the solution. The size of the working electrode (WE) or carbon fiber paper for each experiment was the same (2×5 cm). The carbon fiber paper was connected with the connecting copper wire in which epoxy glue was used to isolate the connection and avoid cupper corrosion in the liquid solution. The pH value was measured using pH meter (Omega PHB-600R). The chemicals and pharmaceuticals were weighed in Semi-Micro Analytical Balance (Ohaus DV215CD-US) to prepare buffer solutions and sample solutions respectively.

2.4. Experimental Procedures and description

100 mL of buffer solution was taken into the Pyrex bottle. The working electrode, counter electrode and reference electrode were placed into the solution and connected with

the VersaSTAT MC potentiostat. In order to avoid unwanted reaction or interaction with oxygen, the liquid solution was flushed with nitrogen for at least 20 minutes before starting the experiment.

2.4.1. Cyclic Voltammetry

CV was performed at each different concentration of the pharmaceuticals to identify the oxidation peak of the pharmaceutical of interest. CV was performed in the range between 0V to 1.8V (vs Ag/AgCl) at $100mVs^{-1}$. Pharmaceuticals were added from the sample solution by definite known concentrations in the buffer solution. The CV experiments were run at pH 1.0, 3.0, 4.5, 6.0, 7.5, 9.0, 11.0, 13.8.

2.4.2. Chronoamperometry

Once the oxidation peak was determined from the CVs, chronoamperometry experiments were run at a potential slightly higher than the oxidation peak to guarantee that degradation was taking place. The pharmaceuticals of interest were added from the stock solution every 5 minutes to observe the variation of current at a fixed potential. The variation of current in function of the pharmaceuticals concentration allowed to draw concentration-response graphs simulating a non-selective biosensor for pharmaceuticals detection. The chronoamperometry experiments were done for the pharmaceuticals at pH 6.0, pH 7.5 and pH 9.0. All experiments were performed at room temperature (25℃). Before each experiments, the working electrode was soaked in the buffer solution for 1-2

hours to increase the interaction between liquid and solid and diminish the electrode hydrophobicity.

2.4.3. High-Performance Liquid Chromatography (HPLC)

High Performance Liquid Chromatography (HPLC) Agilent 1100 series was used for detecting the concentration of the pharmaceuticals in the samples. The overall HPLC system was equipped by: i) a degasser, ii) a pump, iii) an auto-sampler, and iv) UV-vis detector. Fixed wavelength (210 nm) was used for detection. Waters Xterra MS-C18 15mm column was used during the experiments and a thermostat kept the temperature of the column stable at 28°C.

Ibuprofen, Triclosan, Sulfanilamide and Caffeine were purchased from Sigma Aldrich. The pharmaceuticals were dissolved into stock solution composed of HPLC grade 50%:50% methanol:water. Then the stock solutions were added in the 0.1M potassium buffer solution to make the concentration as 100 µM. Chronoamperometry experiments were conducted at the potential higher than the oxidation potential. The samples were taken during the chronoamperometry experiment after 5, 10, 20, 30, 45, 60 and 90 minutes. The sample collected was 0.5 mL and was mixed with 0.5 mL of methanol.

Samples were run into the HPLC following different methods. The first method was used for Ibuprofen, Naproxen Sodium and Triclosan and it was based on an isocratic flow of 0.2 $mLmin^{-1}$ with a mixture ratio of 80% acetonitrile and methanol (50% each) and 20% water with 0.1% TFA. The duration of the first method was 30 minutes. The second method instead was used for Sulfanilamide and Caffeine and it was based on an isocratic flow of 0.2 $mLmin^{-1}$ with a mixture ratio of 60% methanol and 40% water. The duration of the first method was 25 minutes. Water, methanol and acetonitrile were HPLC graded.

CHAPTER 3 RESULTS AND DISCUSSION

3.1. Effect of CEC concentration on electrochemical oxidation

The oxidation peak in the CV experiment indicates the electrochemical oxidation of the pharmaceuticals. The pharmaceuticals were investigated at the range between 1 to 500 μM. CVs were initially run on blank solutions based on the buffer solution (without adding any pharmaceuticals) within the applied potential range of 0 to 1.8V (vs Ag/AgCl). No oxidation peak was detected in the absence of pharmaceuticals. But, the current increased after 1-1.25V (vs Ag/AgCl) probably because the oxygen evolution reaction (OER) was occurring. After then the pharmaceuticals were added gradually in the buffer solution and CV was run each time after the addition. In Figure 3, the cyclic voltammetry behavior has been shown for Acetaminophen at pH 6.0. The CVs related to other pharmaceuticals at pH 6.0, 7.5 and 9.0 are instead presented in the supporting information.

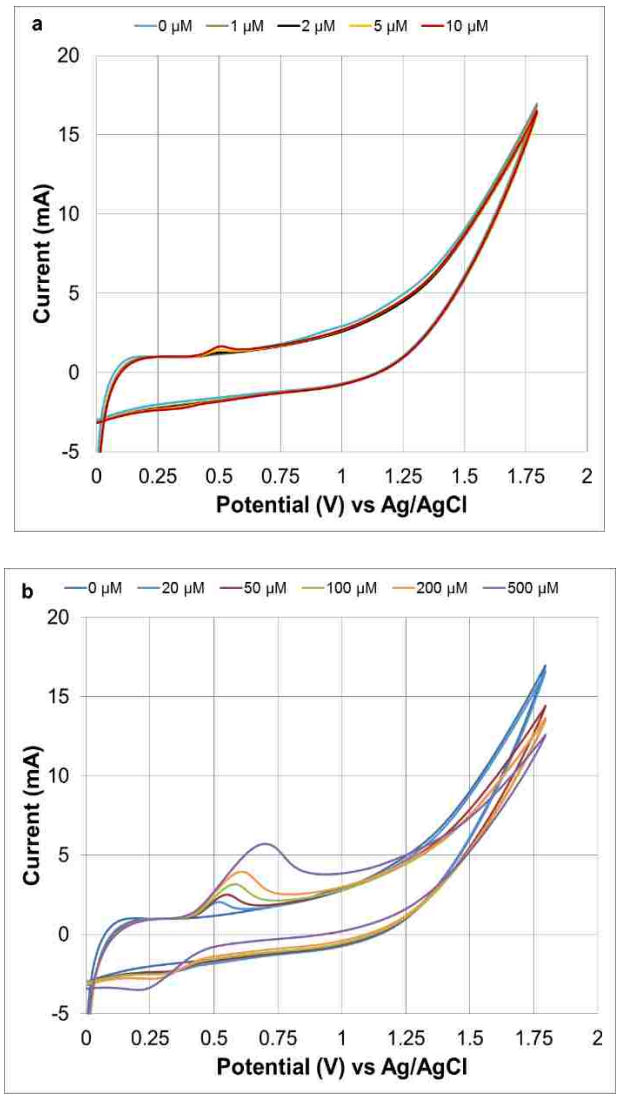


Figure 3. Cyclic voltammogram for Acetaminophen at the concentration of (a) 0µM, 1µM, 2µM, 5µM, 10 µM and (b) 0µM, 20µM, 50µM, 100µM, 200µM, 500µM at pH 6.0.

From this figure, it is clear that the oxidation peak gets higher with the increase of the pharmaceutical concentration. That is because at higher concentration high amount of the reactant (pharmaceuticals) is available to be oxidized and thus higher current is produced which can be seen as the oxidation peak. Higher concentration also shifts the

potential towards higher values. Acetaminophen shows the oxidation peak potential nearly at 0.5 to 0.7V (vs Ag/AgCl) at pH 6.0. The similar experiments were done for three other pharmaceuticals which have been shown in the supporting information. From the experimental data, it was also observed that at pH 6.0, the oxidation peak of Naproxen Sodium shifted from 0.97 to 1.01 V (vs Ag/AgCl). From the experiment, no oxidation peak was detected for caffeine at pH 6.0 and 7.5 using carbon fiber paper electrode. Distinguishable peak for Ibuprofen was detected at pH 9.0 only at very high concentration (500 μM) investigated at 1.39 V vs Ag/AgCl. In conclusion, the lower the oxidation peak, the easier is to breaking down the pharmaceutical and consequently their degradations.

In literature, other researchers have found the oxidation peak potential for Acetaminophen from 0.25V to 1.05V (vs Ag/AgCl) using different electrodes at different pH solutions [51], [53], [66]–[71]. The oxidation peak potential for Caffeine, Ibuprofen and Naproxen has been found from 1.30V to 1.60V (vs Ag/AgCl) [71]–[76] , 1.20V to 1.75V (vs Ag/AgCl) [52], [58] and 0.85V to 1.10V (vs Ag/AgCl) [55], [77] respectively at different pH solutions using different electrodes.

3.2. Effect of pH on electrochemical oxidation

Researchers showed that the degradation efficiency of Naproxen is better at lower pH solution [54]. Effect of pH on the electrochemical oxidation has been studied in our work. Particularly, three different pHs (6, 7.5 and 9) were studied and used to simulate conditions

of the municipal or industrial wastewater. Oxidation peaks are summarized in Table 1, 2 and 3. CVs are showed in the Supporting Information.

Table 1. Oxidation peak potential (V vs Ag/AgCl) at pH 6.0

Pharmaceuticals/ Concentration	10μM	20μM	50μM	100μM	200μM	500μM
Acetaminophen	0.51 ± 0.03	0.52 ± 0.03	0.55 ± 0.03	0.58 ± 0.05	0.61 ± 0.05	0.69 ± 0.05
Ibuprofen	-	-	-	-	-	1.39 ± 0.05
Naproxen Sodium	0.97 ± 0.05	0.97 ± 0.05	0.97 ± 0.05	0.98 ± 0.05	0.96 ± 0.05	1.01 ± 0.05
Caffeine	-	-	-	-	-	-
Erythromycin H.	-	-	-	1.05 ± 0.03	1.05 ± 0.03	1.19 ± 0.03
Triclosan	-	0.79 ± 0.03	0.89 ± 0.05	0.93 ± 0.05	0.96 ± 0.05	1.03 ± 0.05
Sulfanilamide	1.06 ± 0.03	1.09 ± 0.03	1.09 ± 0.03	1.08 ± 0.03	1.09 ± 0.05	1.11 ± 0.05
Diphenhydramine H.	0.99 ± 0.05	1.00 ± 0.05	1.02 ± 0.05	1.04 ± 0.05	1.12 ± 0.05	1.22 ± 0.05

Table 2. Oxidation peak potential (V vs Ag/AgCl) at pH 7.5

Pharmaceuticals/ Concentration	10μM	20μM	50μM	100μM	200μM	500μM
Acetaminophen	0.49 ± 0.03	0.52 ± 0.03	0.56 ± 0.03	0.60 ± 0.05	0.63 ± 0.05	0.72 ± 0.05
Ibuprofen	-	-	-	-	-	1.38 ± 0.05
Naproxen Sodium	0.96 ± 0.05	0.95 ± 0.05	0.99 ± 0.05	0.99 ± 0.05	1.01 ± 0.05	0.99 ± 0.05
Caffeine	-	-	-	-	-	-
Erythromycin H.	-	-	-	-	1.04 ± 0.02	1.1 ± 0.03
Triclosan	-	0.67 ± 0.03	0.71 ± 0.05	0.72 ± 0.05	0.71 ± 0.05	0.75 ± 0.05
Sulfanilamide	0.93 ± 0.03	0.97 ± 0.03	0.98 ± 0.03	1.01 ± 0.03	1.03 ± 0.05	1.08 ± 0.05
Diphenhydramine H.	-	0.85 ± 0.05	0.92 ± 0.05	1.03 ± 0.05	0.98 ± 0.05	1.04 ± 0.05

Table 3. Oxidation peak potential (V vs Ag/AgCl) at pH 9.0

Pharmaceuticals/ Concentration	10μM	20μM	50μM	100μM	200μM	500μM
Acetaminophen	0.34 ± 0.03	0.35 ± 0.03	0.34 ± 0.03	0.36 ± 0.05	0.38 ± 0.05	0.44 ± 0.05
Ibuprofen	-	-	-	-	-	1.37 ± 0.05
Naproxen Sodium	0.94 ± 0.05	0.95 ± 0.05	0.96 ± 0.05	0.96 ± 0.05	0.96 ± 0.05	0.96 ± 0.05
Caffeine	1.44 ± 0.05	1.41 ± 0.05	1.43 ± 0.05	-	1.55 ± 0.05	-
Erythromycin H.	-	-	-	0.91 ± 0.03	0.91 ± 0.03	0.92 ± 0.03
Triclosan	0.63 ± 0.03	0.64 ± 0.03	0.62 ± 0.03	0.61 ± 0.05	0.61 ± 0.05	0.58 ± 0.05
Sulfanilamide	0.86 ± 0.03	0.87 ± 0.03	0.87 ± 0.03	0.92 ± 0.03	0.94 ± 0.05	0.99 ± 0.05
Diphenhydramine H.	-	0.79 ± 0.05	0.83 ± 0.05	0.89 ± 0.05	0.96 ± 0.05	1.04 ± 0.05

In Figure 4, the voltammograms of the pharmaceuticals have been shown at different pHs (6, 7.5 and 9) at a fixed concentration of 10 μM for Caffeine, 50 μM for Naproxen Sodium, 100 μM for Acetaminophen and 500 μM for Ibuprofen. The results showed that Acetaminophen and Naproxen Sodium have higher oxidation current and peak potential in buffer solution of pH 7.5 than pH 6.0 and 9.0. Caffeine does not show oxidation peak in the buffer solution of pH 6.0 and 7.5 using carbon fiber paper electrode probably because the oxidation reaction takes place in the window in which oxygen evolution reaction(OER) occurs and most likely is hindered by the OER peak itself. In literature it has been showed that caffeine has an oxidation peak at 1.35-1.45V vs SCE at pH2.0 using Nafion–Gr modified glassy carbon electrode [57].

At pH 9.0, Naproxen Sodium and Acetaminophen shows the lowest oxidation current, whereas at pH 7.5 it shows the highest oxidation current as shown in Fig. 4b and Fig. 4c. Ibuprofen shows the lowest oxidation current at pH 6.0 and the highest oxidation current at pH 9.0. Ibuprofen shows oxidation peak only at very high concentration (500μM) using carbon fiber paper electrode. From Figure 4d, it is clear that oxidation current or oxidation peak potential does not vary substantially with the change of pH for Ibuprofen, but still the highest oxidation peak potential is shown at pH 6.0 which is different from Acetaminophen and Naproxen Sodium. It might be speculated that, as for caffeine, the oxidation peak occurs at high potentials in which OER occurs.

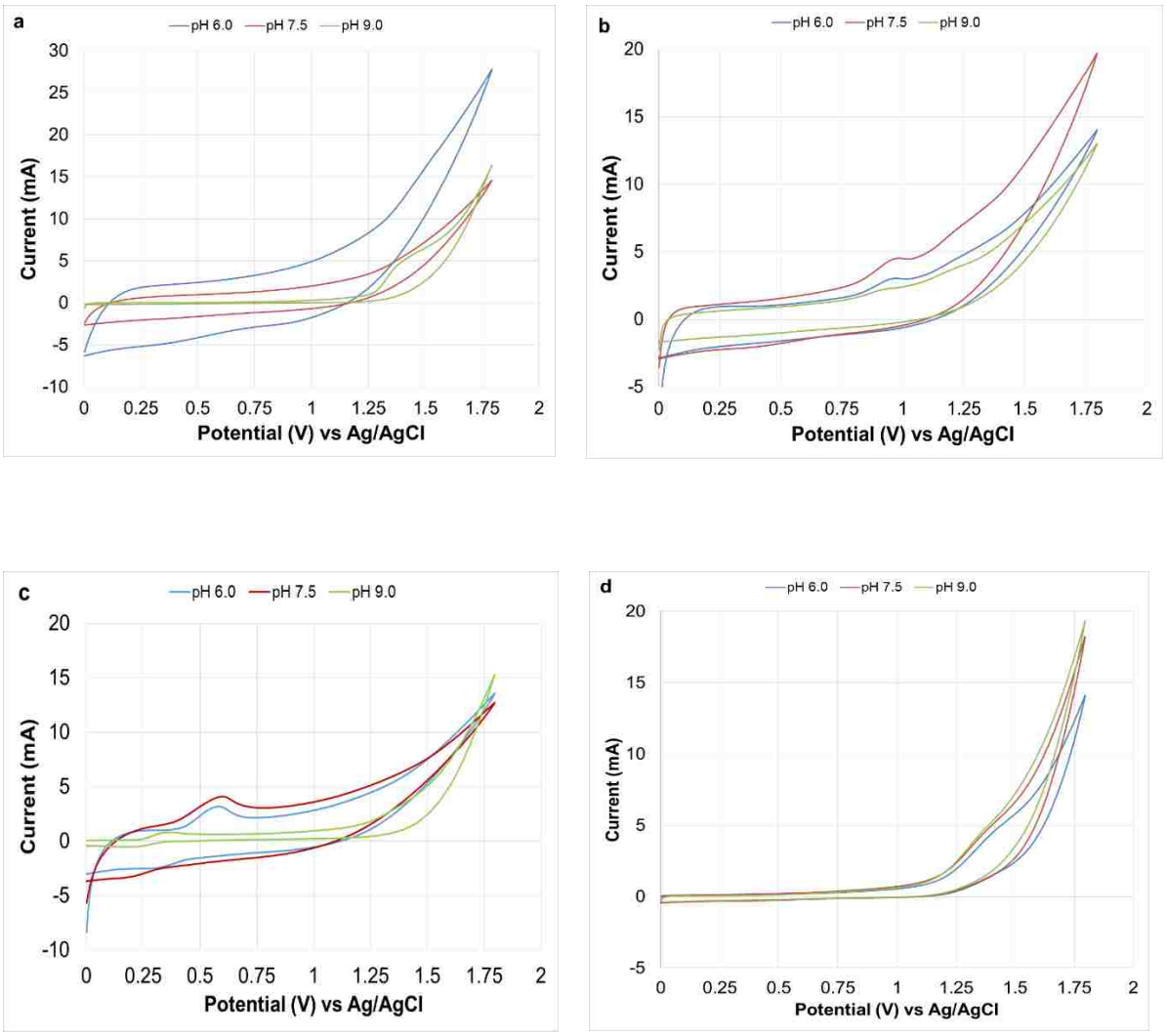


Figure 4. Cyclic voltammogram showing the Effect of pH on electrochemical oxidation of a) Caffeine (10µM) b) Naproxen Sodium (50µM) c) Acetaminophen (100µM) d) Ibuprofen (500µM)

In Figure 5, the voltammograms of the pharmaceuticals have been shown at different pHs (6, 7.5 and 9) at a fixed concentration of 200 µM. It has been observed that pH 6.0 showed higher oxidation peak potential than pH 7.5 and 9.0. Also, pH 9.0 buffer

solution showed the lowest oxidation peak potential among them. Thus we can conclude that oxidation peak potential is not linearly related to pH in the circumneutral pH range. The following figures depict the effect of circumneutral pH on the oxidation peak potential and current.

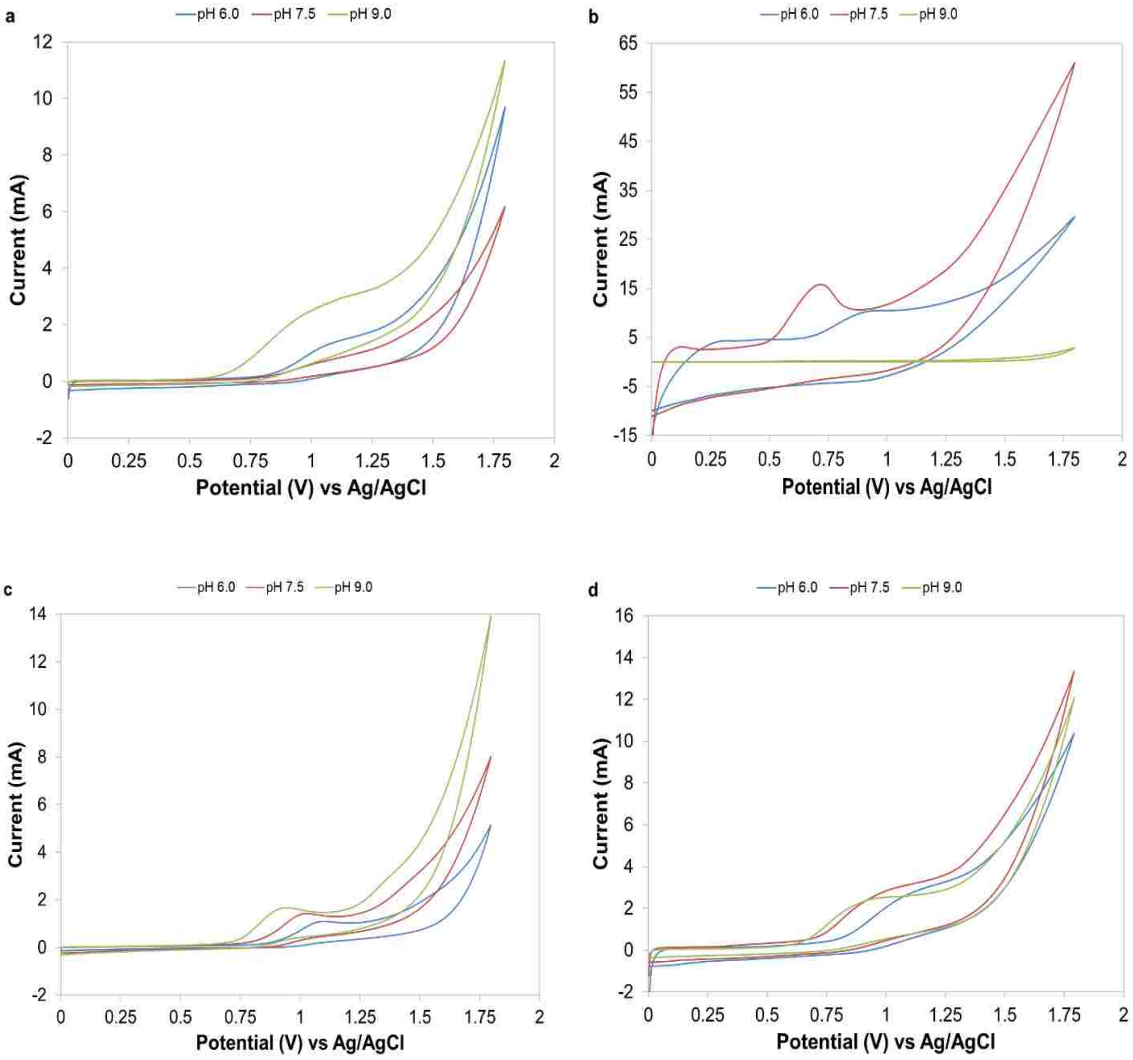


Figure 5. Effect of pH on electrochemical oxidation of a) Erythromycin Hydrate b) Triclosan c) Sulfanilamide d) Diphenhydramine Hydrochloride at the fixed concentration of 200 μM.

To further investigate the relation between the oxidation peak potential and pH, CVs were run in the buffer solutions of different pH from 1.0 to 13.7 with concentration of 100 μM. In agreement with the data presented above, Ibuprofen and Caffeine had oxidation peak potential above 1.25 V vs Ag/AgCl and consequently the peak might be hindered by the OER and thus the oxidation peak was not clear. That is why this study was not performed on them. Also, Erythromycin Hydrate and Diphenhydramine Hydrochloride did not show clear oxidation in the full range from pH of 1.0 to 13.7. Thus the experimental results of the change of oxidation peak potential (V vs Ag/AgCl) with pH for Acetaminophen, Naproxen Sodium, Triclosan and Sulfanilamide have been shown in Figure 6 and Figure 7.

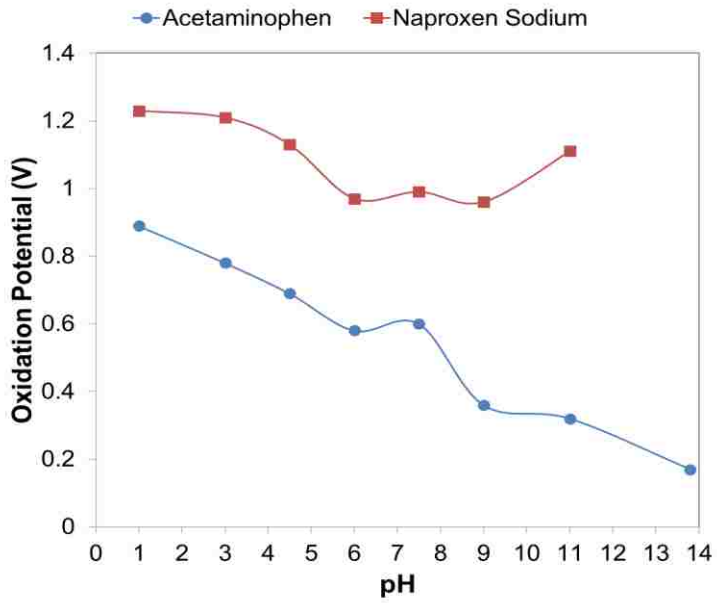


Figure 6. The change in oxidation peak potential of Acetaminophen and Naproxen Sodium with pH in the circumneutral region at the fixed concentration of 100μM.

Concerning Acetaminophen, it can be noticed that the oxidation peak potential decreases linearly with the increase of pH from acidic to basic mediium. But in the neutral pH region, the oxidation peak potential shows fluctuation in the oxidation peak potential as shown in Figure 6. In the case of Naproxen Sodium, the oxidation peak potential decreases with pH in the acidic medium following a non-linear trend. In the experiments, Naproxen Sodium did not show any oxidation peak potential in pH 13.7 using carbon fiber paper electrode, so the correlation between oxidation peak potential and pH for Naproxen Sodium cannot be established in the basic medium. But, in the neutral pH medium, it also shows fluctuation in the oxidation peak potential with the change of pH. Single CV regarding each pH are presented in the Supporting information.

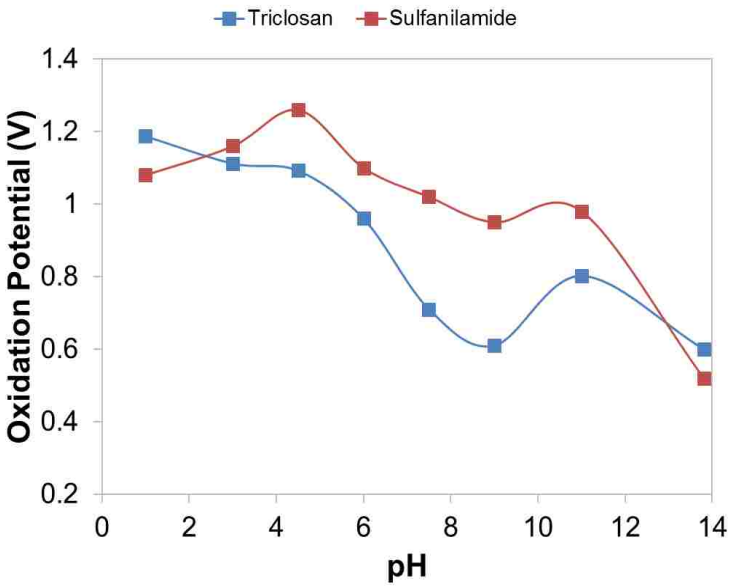


Figure 7. The change in oxidation peak potential of Triclosan and Sulfanilamide with pH at the fixed concentration of 200µM.

It is also observed that oxidation peak potentials for Triclosan and Sulfanilamide were not absolutely linear with pH. There was a sudden increase of oxidation peak potential at pH 5 and pH 11. But in overall, it is clear that the oxidation potential decreases with pH.

3.3. Cumulative oxidation peaks with simultaneous presence of several pharmaceuticals in the electrolyte

In real conditions, different pharmaceuticals may exist together in the wastewater. To achieve the similar condition, the four pharmaceuticals from the analgesic and CNS stimulant category were mixed together in the same proportion and added in the buffer solution of pH 6.0, 7.5 and 9.0 at different concentrations (each pharmaceuticals of 100μM, 150μM and 200μM). Then, CVs were run to detect the oxidation peaks. CVs showed that the solution mixture of four pharmaceuticals had only two clear oxidation peak potentials at 0.6 and 1.1V respectively at pH 6.0 as shown in Figure 8.

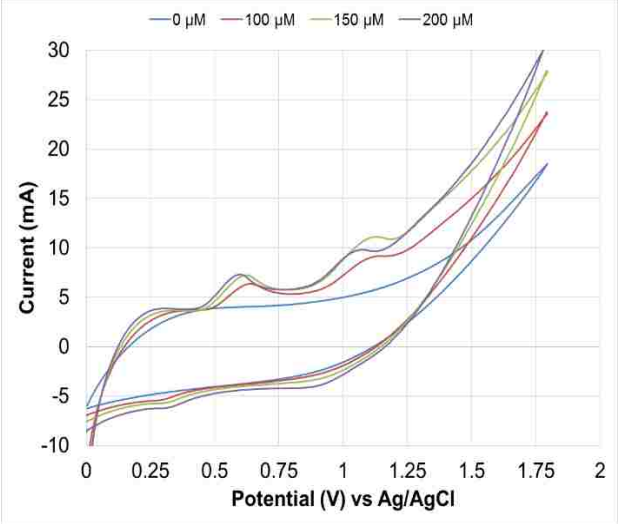


Figure 8. Cyclic voltammogram of the mixed solution of the analgesic pharmaceuticals at different concentration at pH 6.0.

These two oxidation peak potentials resemble with Acetaminophen and Naproxen Sodium as shown in Figure 4 or Table 1. Caffeine and Ibuprofen did not show any detectable oxidation peak at those concentrations at pH6.0. in this mixed solution probably because that was hindered or overlapped by the OER window. The results from pH 7.5 and 9.0 have been included in appendix.

The similar experiments have also been done for the four antibiotic and antihistamine pharmaceuticals which is shown in Figure 9. From the figure, it can be seen that CV does not show four distinct oxidation peaks, rather it shows a single oxidation peak at 1.0-1.15 V. The probable reason is that the oxidation peak for the pharmaceuticals are close to each other. That is why the four different oxidation are overlapping at near to 1.0

V. Since, they are showing a clear oxidation peak, so it can be concluded that electrochemical degradation is applicable in the mixture of multiple pharmaceuticals or CEC.

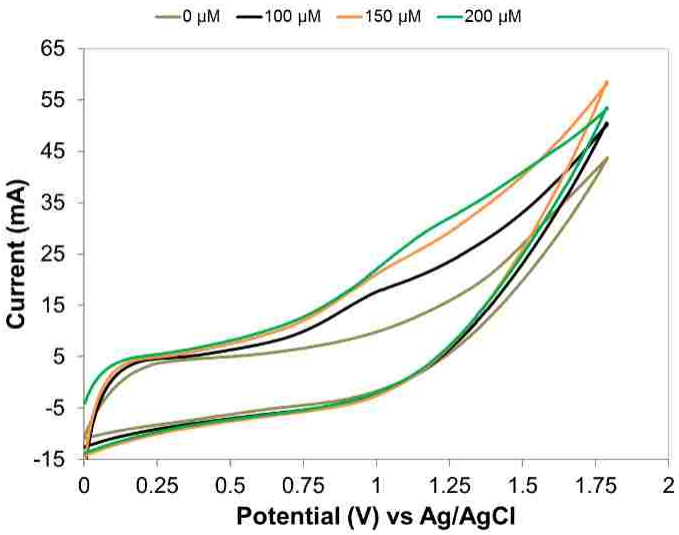


Figure 9. Cyclic voltammetry of the mixed solution of the pharmaceuticals at different concentration at pH 6.0.

3.4. Determination of Concentration using Chronoamperometry Data

In the chronoamperometry experiments, the variation of current was observed with the change of the concentration of the pharmaceuticals at a constant applied potential. The fixed potential was chosen a higher value than the oxidation peak potential of the pharmaceuticals. Concentration and current response relationships have been built from the experimental data and this relation can be used as non-selective biosensors for detecting pharmaceuticals in aqueous media. Considering that Ibuprofen and Caffeine have high oxidation peak potential within the range in which OER occurs, these two pharmaceuticals were then excluded from chronoamperometry experiment.

At pH 7.5 (Figure 11), Naproxen Sodium has higher background current compared to Acetaminophen probably due to the higher applied potential. The measured current has been shown. Current increased with the increase of the pharmaceutical concentration in buffer solution (from 0 to 50 µM every 5 minutes). The interval time between the additions of the pharmaceutical was kept relatively low (5 min) in order to evaluate the change in current due to the pharmaceutical concentration and to avoid the degradation effect.

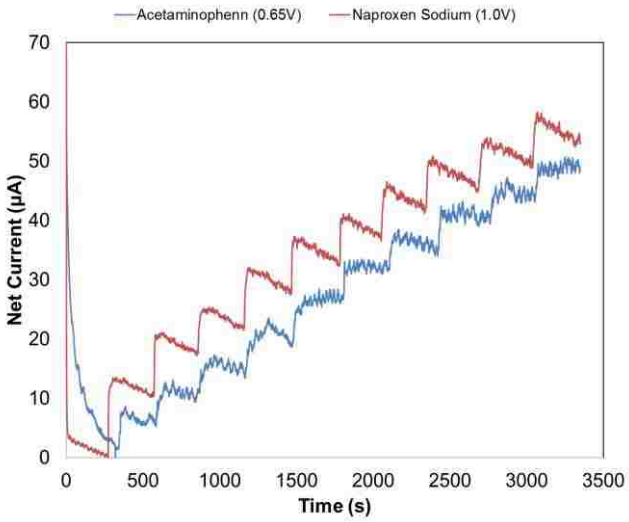


Figure 10. Chronoamperometry Data for Acetaminophen and Naproxen Sodium at pH 7.5

Current produced vs concentration linear relationships are here presented for Acetaminophen (Figure 12.a) and Naproxen Sodium (Figure 12.b) at pH 6.0, 7.5 and 9.0. Current signal was determined by subtracting the background current from the actual current. From the figure, pH 9.0 has higher slope than others which indicates that Acetaminophen and Naproxen Sodium can be easily ionized in alkaline medium. On the other hand, the lowest slope is found in the neutral (pH 7.5) medium.

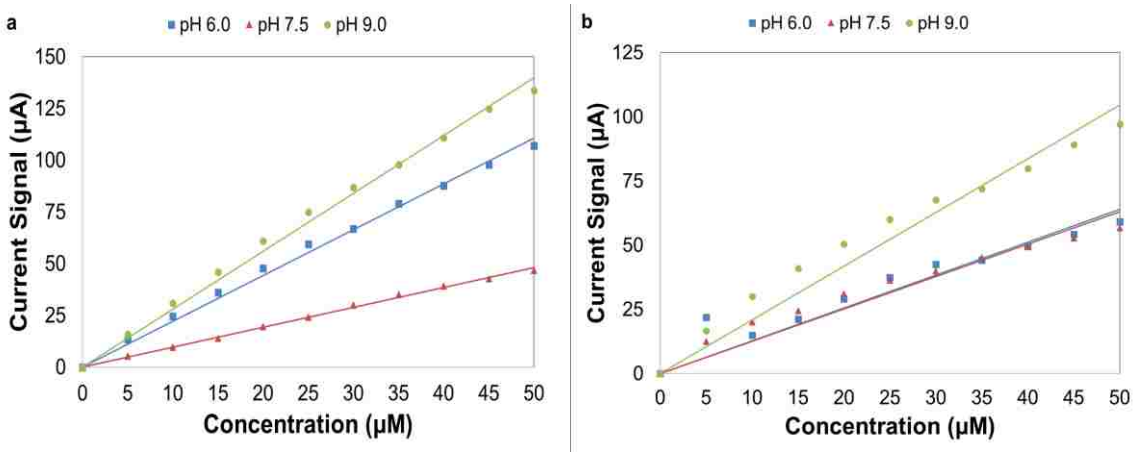


Figure 11. Current versus concentration linear trend for a) Acetaminophen b) Naproxen Sodium at pH 6, 7.5 and 9.

In the chronoamperometry experiments, the variation of current was observed with the change of the concentration of the pharmaceuticals at a constant applied potential. The fixed potential was chosen a higher value than the oxidation peak potential of the pharmaceuticals. Concentration and current response relationships have been built from the experimental data. Chronoamperometry graphs have been shown in Figure 11 and Figure 12. The current increased with the increase of the pharmaceutical concentration in buffer solution (from 0 to 50 µM every 5 minutes). The interval time for the pharmaceutical addition was kept relatively low (5 min) in order to evaluate the change in current due to the pharmaceutical concentration and to avoid the degradation effect.

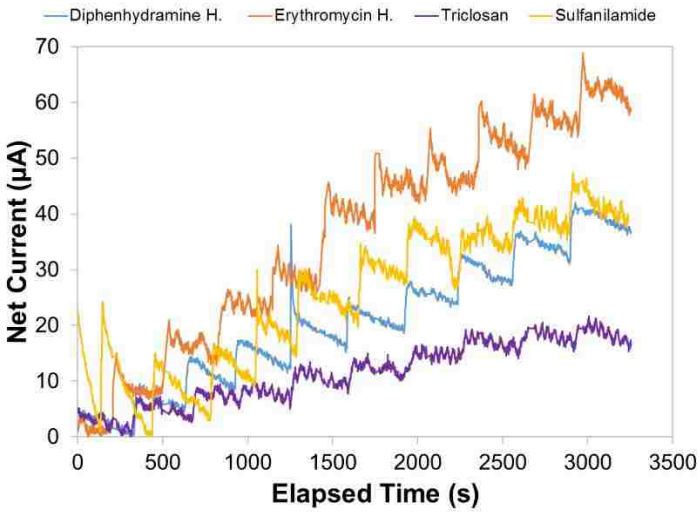


Figure 12. Chronoamperometry Data for Diphenhydramine Hydrochloride (1.10V), Erythromycin Hydrate (1.05V), Triclosan (0.95V) and Sulfanilamide (1.02V) and at pH 7.5.

From the Figure 12, it is clear that the increase of current is not the same for the different pharmaceuticals with the addition of equal moles. The current is increased by approximately 20µA and 5µA for the addition of 5µM of Erythromycin Hydrate and Triclosan respectively. This indicates that Erythromycin Hydrate can be easily ionized in the aqueous solution. Using the data from chronoamperometry experiment, non-selective biosensors can be developed for detecting pharmaceuticals in aqueous media.

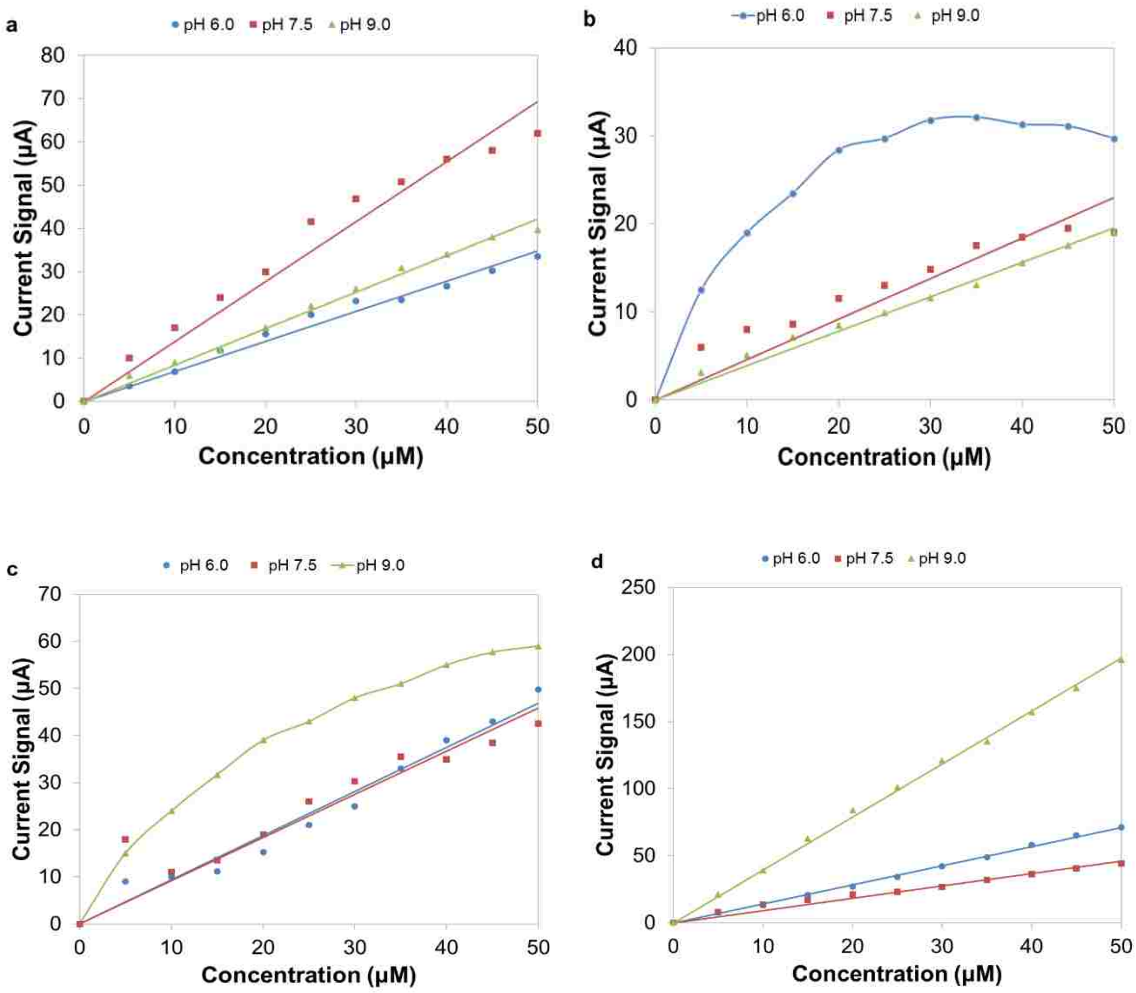


Figure 13. Change of current with CEC concentration at different pH for a) Erythromycin Hydrate (1.05V) b) Triclosan (0.85V) c) Sulfanilamide (1.06V, 1.02V, 1.0V) d) Diphenhydramine Hydrochloride (1.10V)

The linear relationship between the produced current and concentration for the pharmaceuticals are presented for Erythromycin hydrate, Triclosan, Sulfanilamide, and Diphenhydramine in Figure 13. But it was not linear for Triclosan at pH 6.0 and Sulfanilamide at pH 9.0. From this figure, we can also get the idea of the effect of pH on the produced current for the presence of the pharmaceuticals. Sulfanilamide and

Diphenhydramine Hydrochloride show the similar effect of pH where the slope is high at pH 9 (initially) and low at 7.5. This indicates that at pH 9, Sulfanilamide and Diphenhydramine Hydrochloride can be ionized more than at pH 6 and 7.5. But, for Erythromycin Hydrate the slope is higher at pH 7.5 and lower at pH 6. For Triclosan, the higher slope is found at pH 6 (initially), but after increasing concentration at 30 µM current signal became stable and does not increase anymore. The lower slope for Triclosan is found at pH 9.

3.5. Determination of electrochemical degradation rate using HPLC Data

The pharmaceutical solutions were put under an applied potential higher than the oxidation potential, so the solution should have gone under the oxidation as well as degradation. To verify the degradation of the pharmaceuticals, HPLC experiments were performed. Since, HPLC experiments cannot tell the real concentration of any elements in the solution, rather it can only give the peak and the area which is dependent on the concentration. So firstly calibration curves were prepared from the known concentration of the pharmaceuticals. Calibration curves for Sulfanilamide and Triclosan are shown in Figure 14 & Figure 16.

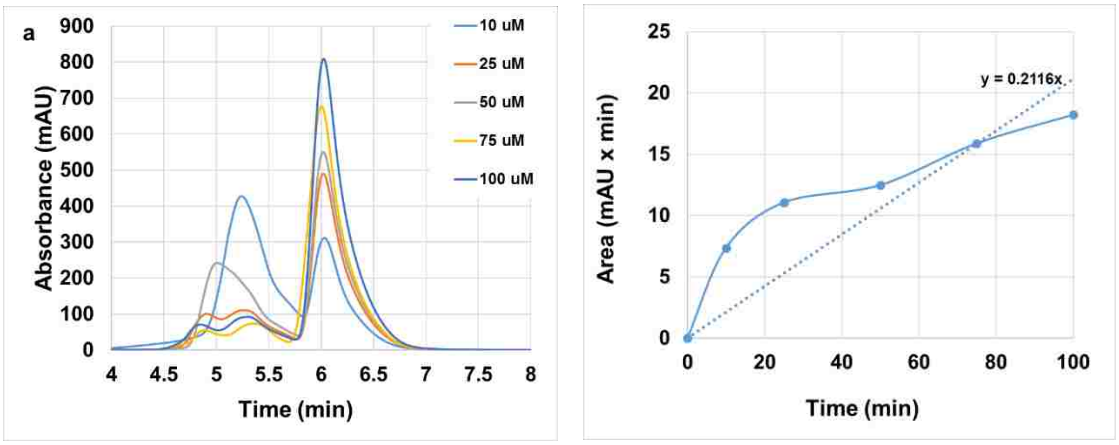
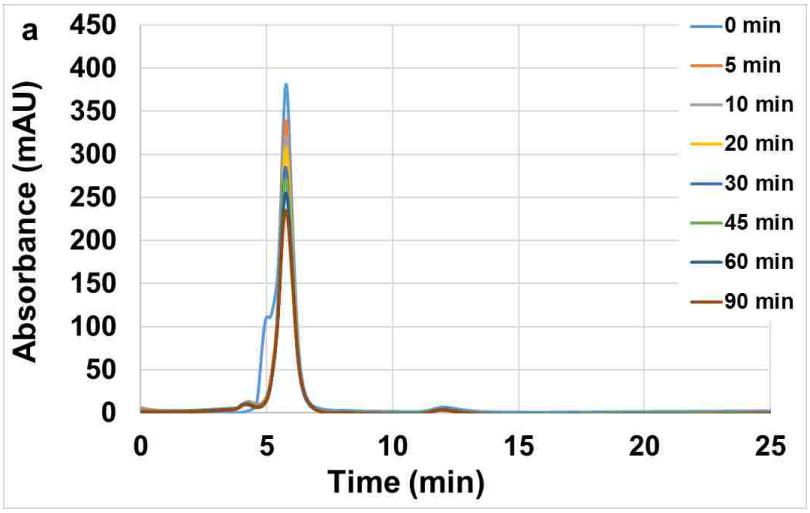
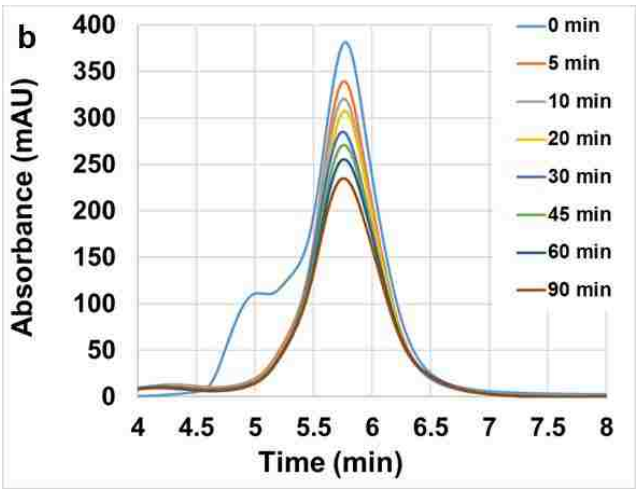


Figure 14. a) Chromatogram for Standard solution and b) Calibration Curve for Sulfanilamide.





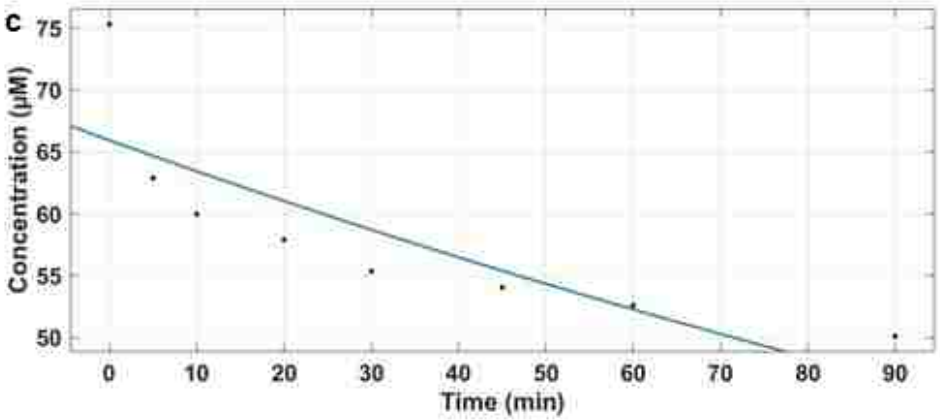


Figure 15. a) Chromatogram for the samples taken at different time after applying potential (1.1V) in pH 7.5 potassium buffer solution containing sulfanilamide b) Enlarged Chromatogram at region of interest c) Degradation curve for Sulfanilamide.

From Figure 14, we got a relationship between the area of the chromatograph and the concentration of sulfanilamide. In Figure 15, chromatogram for the samples taken at different time after applying potential has been shown for sulfanilamide. The correlation that we have found from the calibration curve has been used to determine the concentration of sulfanilamide in the samples. From the degradation curve in Figure 15 c, we can determine the 1st order reaction constant for Sulfanilamide. k = 0.0039 min^{-1} and half lifetime, $t_{1/2}$ = 177.7 min

In Figure 16, chromatogram and the calibration curve for Triclosan have been shown. Using the correlation from the calibration curve, the degradation curve has been developed, which is shown in Figure 17.

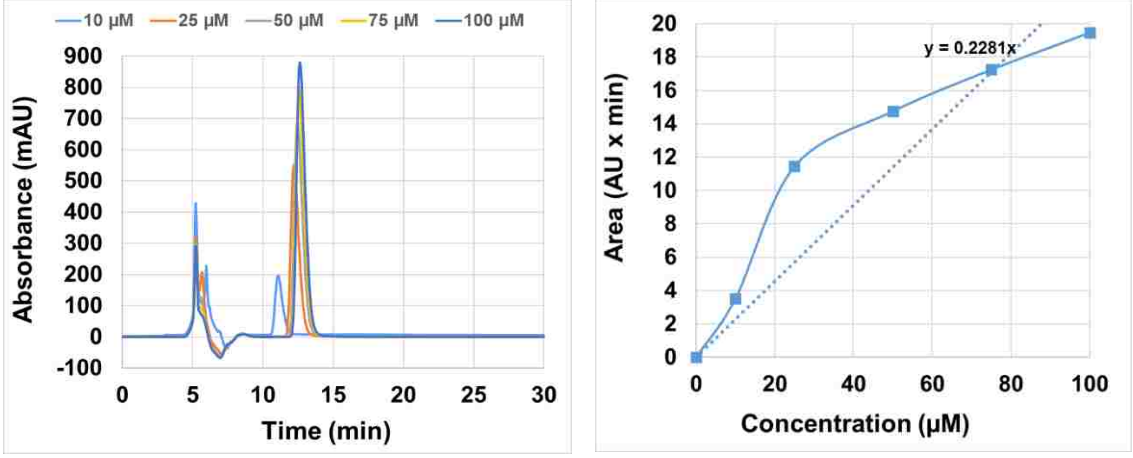


Figure 16: a) Chromatogram for Standard solution and b) Calibration Curve for Triclosan.

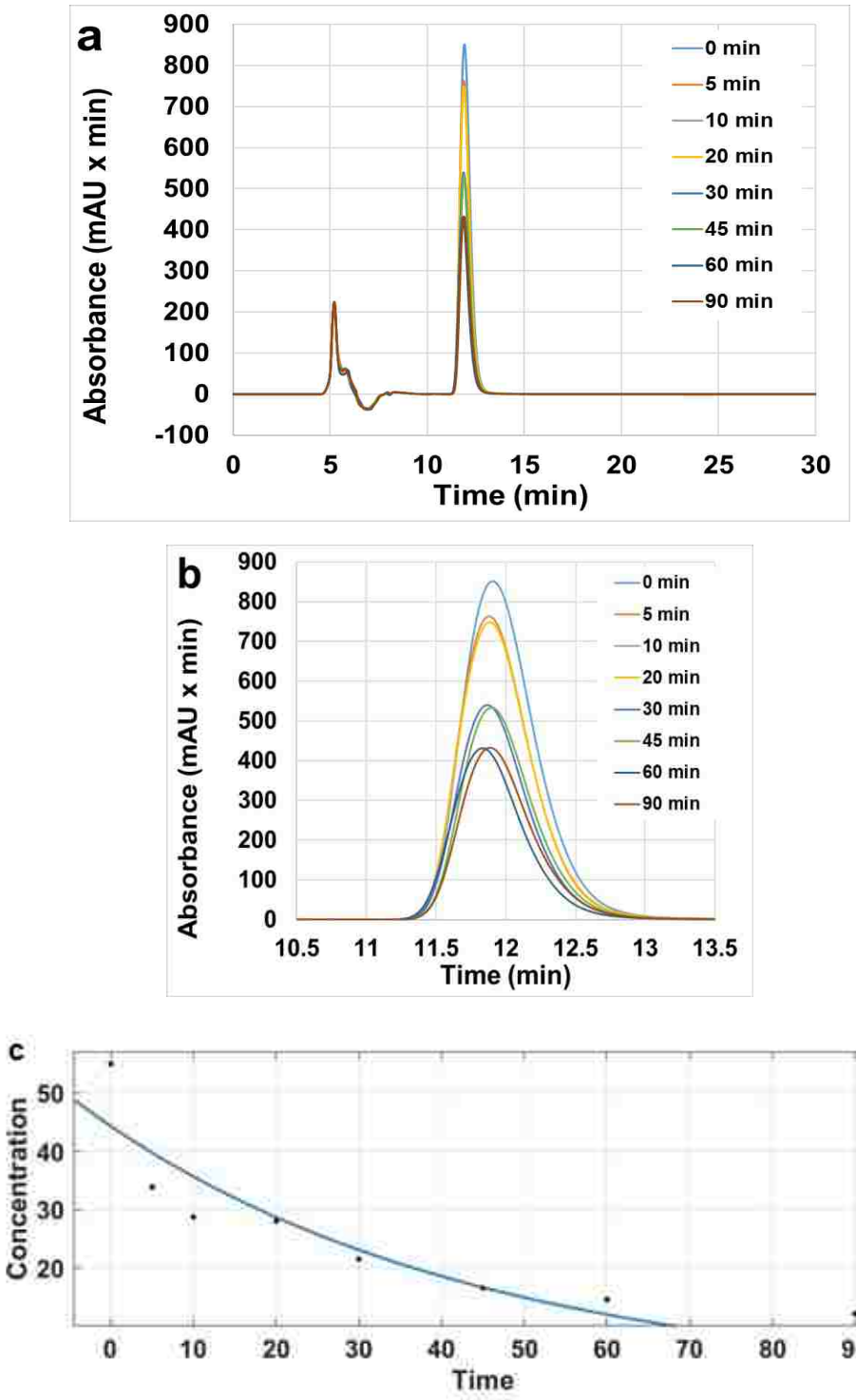


Figure 17: a) Chromatogram for the samples taken at different time after applying potential (0.85V) in pH 7.5 potassium buffer solution containing Triclosan b) Enlarged Chromatogram at region of interest c) Degradation curve for Triclosan.

From the degradation curve, 1st order reaction constant for Triclosan. k = 0.0148 min^{-1} and half lifetime, $t_{1/2}$ = 46.82 min were determined.

CHAPTER 4 CONCLUSION

In this research, 8 different pharmaceuticals have been studied for the electrochemical degradation. To determine the oxidation potential, CV experiments have been performed using 'carbon fiber paper' as working electrode. From the experiments, Analgesic and CNS stimulant pharmaceuticals i.e. Acetaminophen, Ibuprofen, Naproxen Sodium, Caffeine showed oxidation peak at 0.34-0.79V, 1.37- 1.39V, 0.94-1.01V, 1.44-1.55V respectively at different pH and concentrations.

Antibiotic and antihistamine pharmaceuticals i.e. Erythromycin Hydrate, Triclosan, Sulfanilamide, Diphenhydramine Hydrochloride also showed oxidation peak at 0.91-1.19V, 0.58-1.03V, 0.86-1.11V, 0.79-1.22V respectively at different pH and concentrations. Sensor curves have been developed for 6 pharmaceuticals which is shown in Figure 11 and Figure 13. Electrochemical degradation was measured using HPLC instrument. The 1^{st} order reaction constants are 0.0039 min^{-1} and 0.0148 min^{-1} for sulfanilamide and Triclosan respectively.

4.1. Limitations

The 1st order reaction rate constants were found only for Triclosan and Sulfanilamide. Ibuprofen and caffeine have very high oxidation potential over the OER window. For which the samples were not prepared for these two pharmaceuticals. For other pharmaceuticals, proper method of separation was not established.

The derivatives which are being produced after degrading the pharmaceuticals have not been analyzed. If the derivatives themselves are harmful, then the degradation by this way cannot be followed. But generally, the derivatives from the pharmaceuticals are more polar and water soluble which should have a reduced pharmacological activity compared to the original compound.

At every pH, oxidation potentials could not be found for the pharmaceuticals. Also, the oxidation potential for some pharmaceuticals are very high which cannot be applied in real conditions. Further analysis is required to find out lower oxidation potential or to find in other pH using different electrodes.

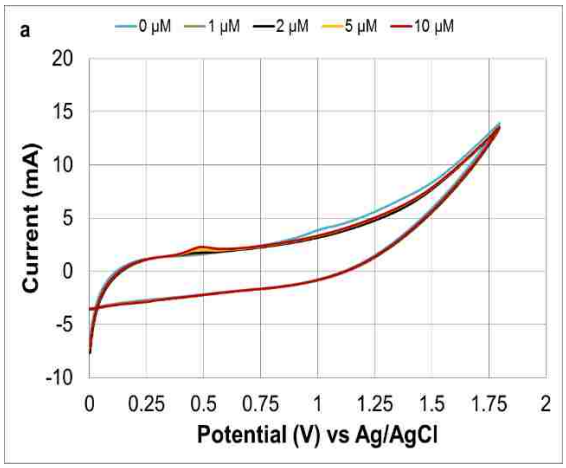
4.2. Future Work

Different other electrodes such as activated glassy carbon electrode, boron doped diamond, Ti etc. can be studied for the better result in some cases where the oxidation potential could not be found using carbon fiber paper electrode. Catalyst can also be applied on the electrode to observe better performance. The derivatives that are produced from the electrochemical oxidation should also be studied whether those are harmless or not. Since, there are many other major pharmaceuticals present in the aquatic environment, those compounds should also be studied in the similar way.

CHAPTER 5 APPENDICES

Appendix A

Cyclic Voltammetry Data



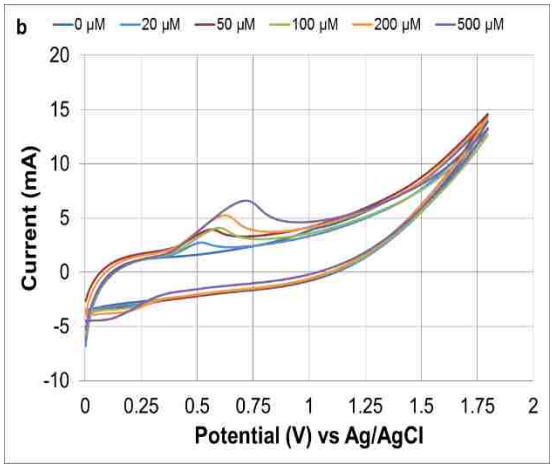


Figure A. 1. Cyclic voltammogram for Acetaminophen at pH7.5 at different concentration.

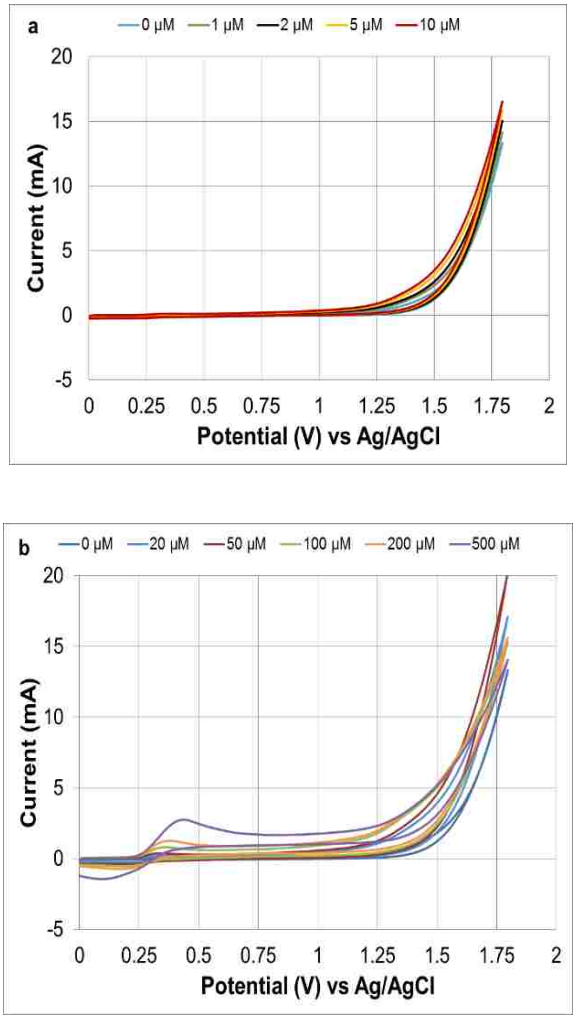


Figure A. 2. Cyclic voltammogram for Acetaminophen at pH9.0 at different concentration.

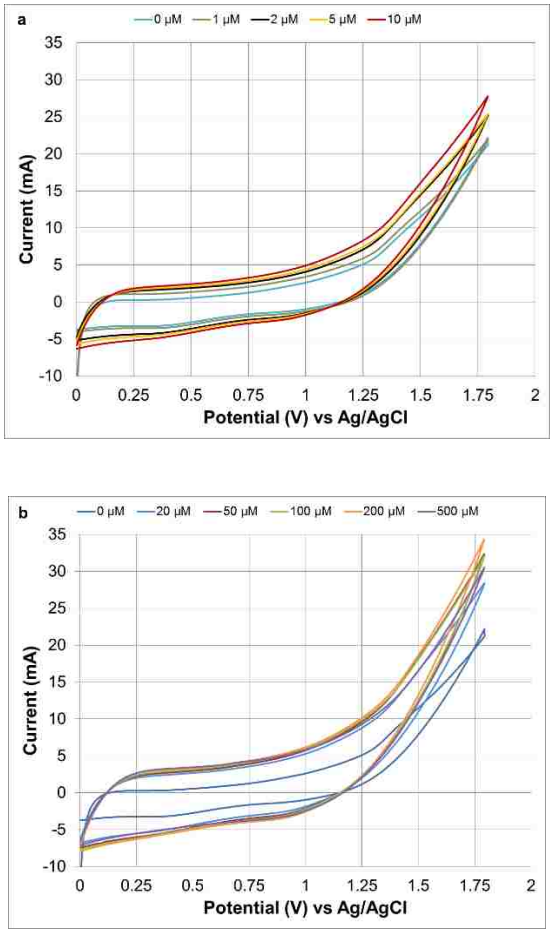


Figure A. 3. Cyclic voltammogram for Caffeine at pH6.0 at different concentration.

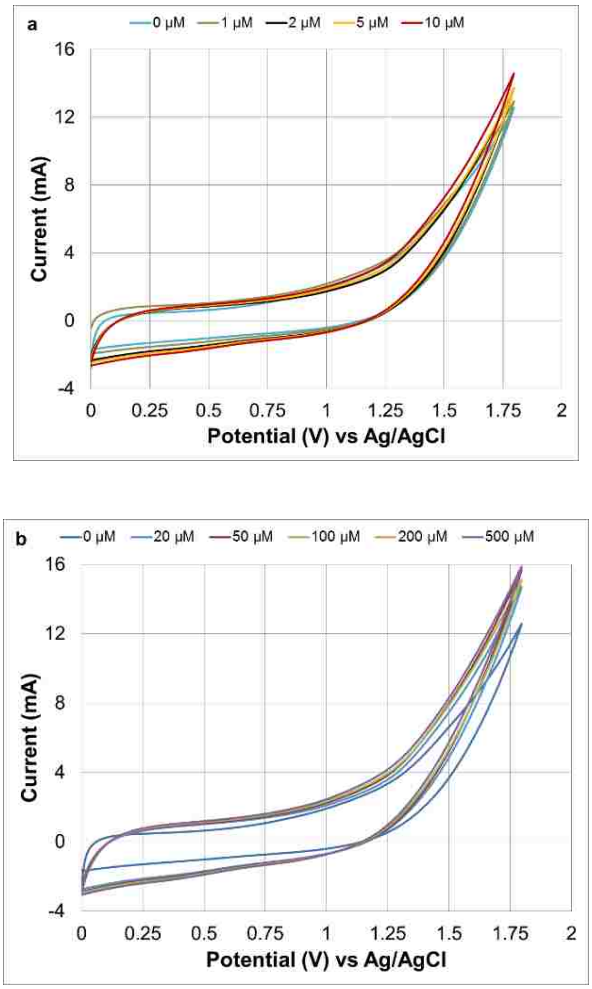


Figure A. 4. Cyclic voltammogram for Caffeine at pH7.5 at different concentration.

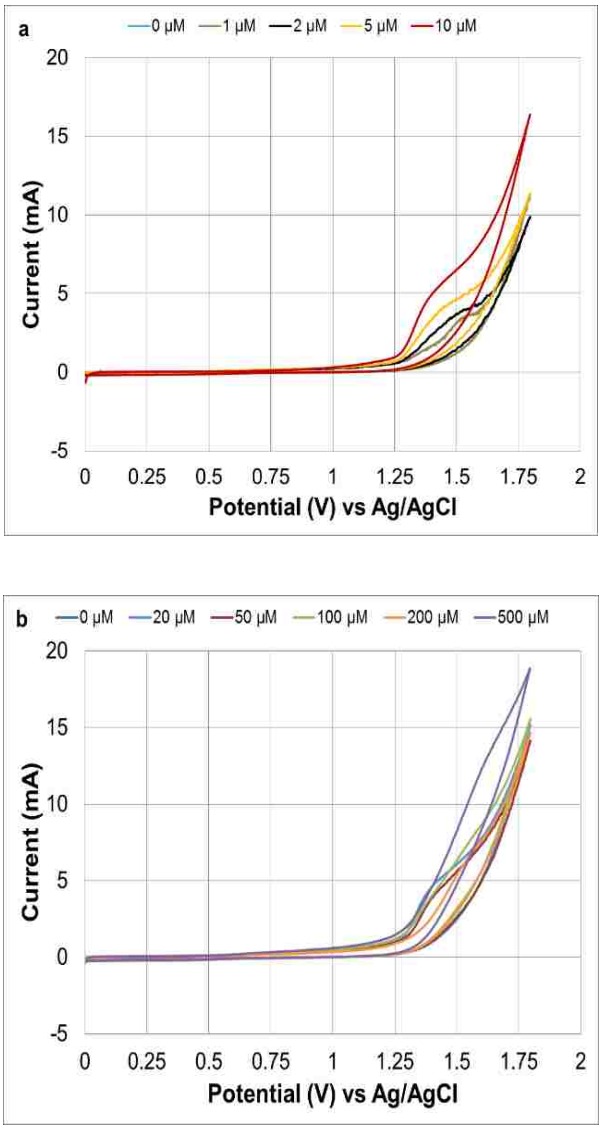


Figure A. 5. Cyclic voltammogram for Caffeine at pH9.0 at different concentration.

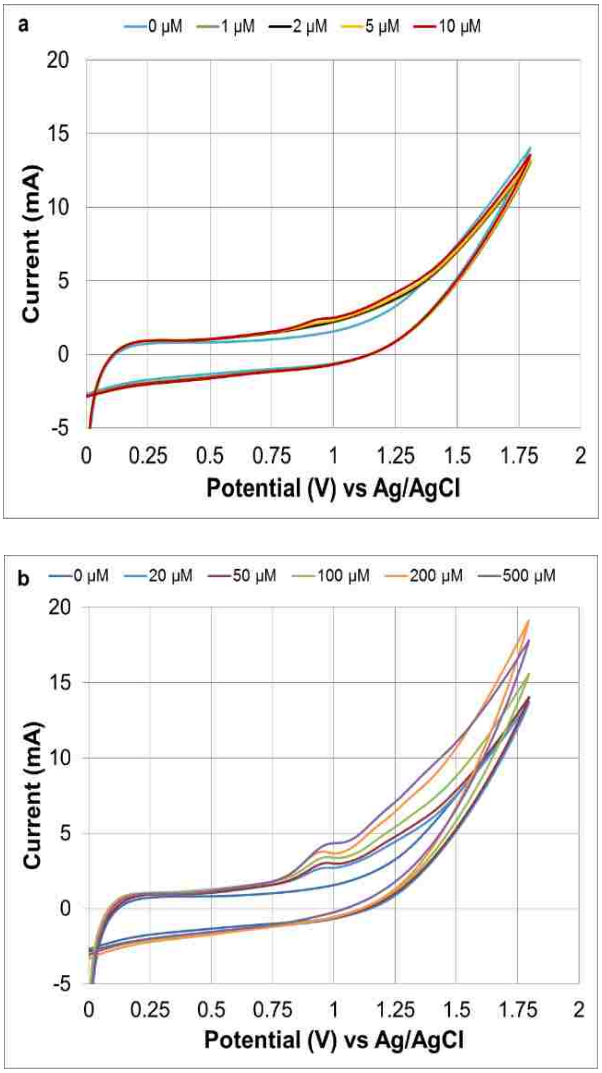


Figure A. 6. Cyclic voltammogram for Naproxen Sodium at pH6.0 at different concentration.

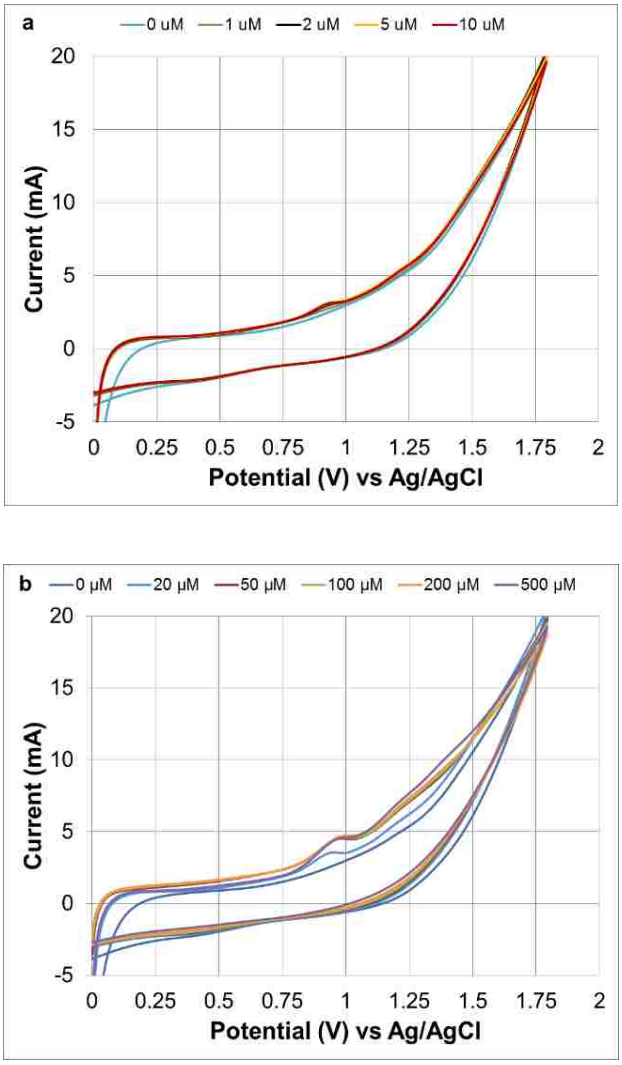
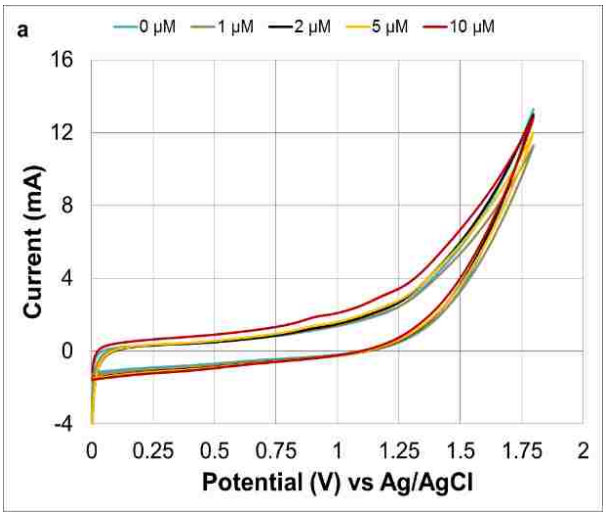


Figure A. 7. Cyclic voltammogram for Naproxen Sodium at pH7.5 at different concentration.



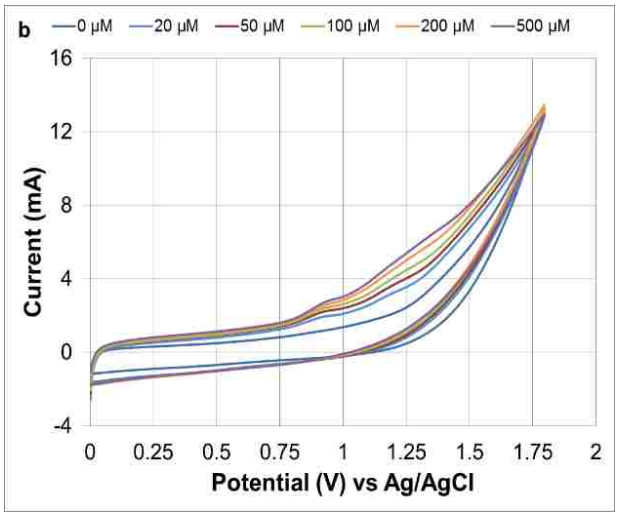


Figure A. 8. Cyclic voltammogram for Naproxen Sodium at pH9.0 at different concentration.

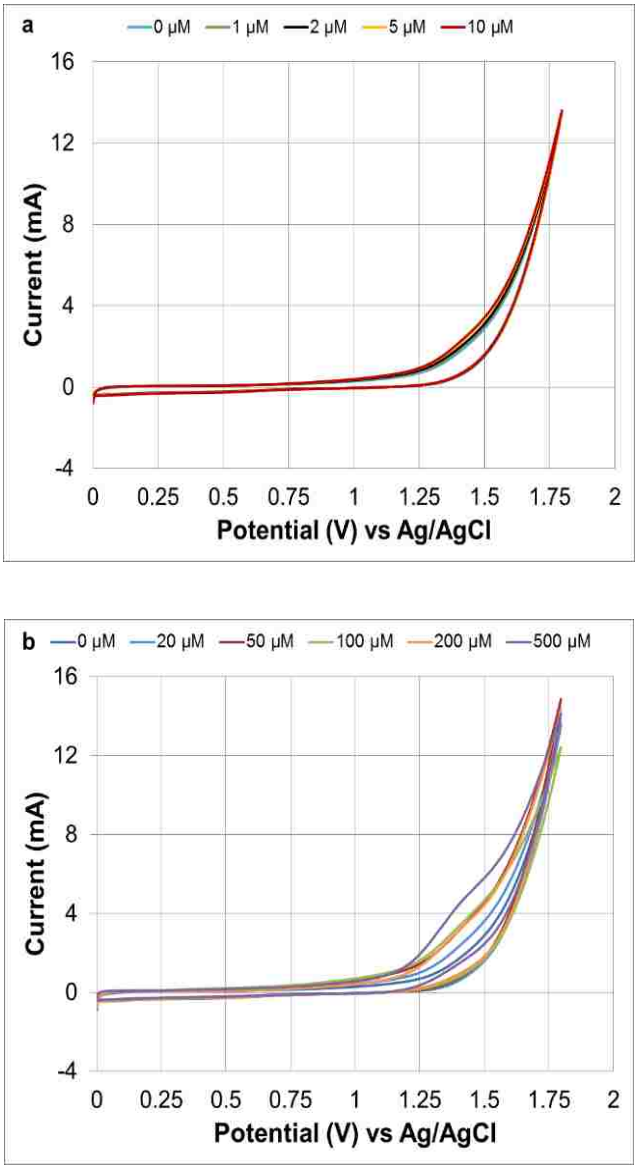
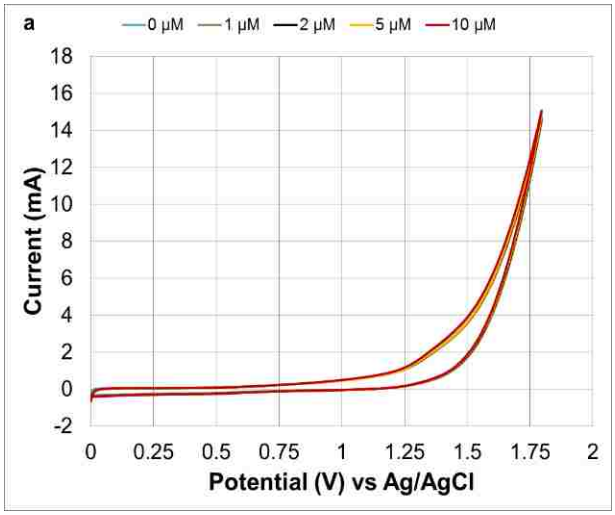


Figure A. 9. Cyclic voltammogram for Ibuprofen at pH6.0 at different concentration.



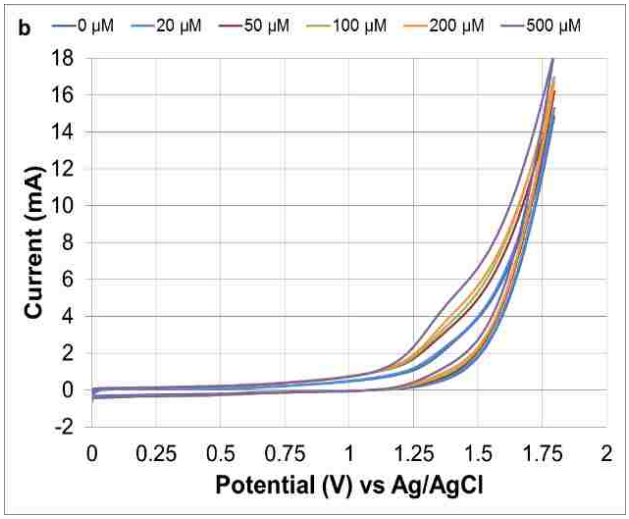


Figure A. 10. Cyclic voltammogram for Ibuprofen at pH7.5 at different concentration.

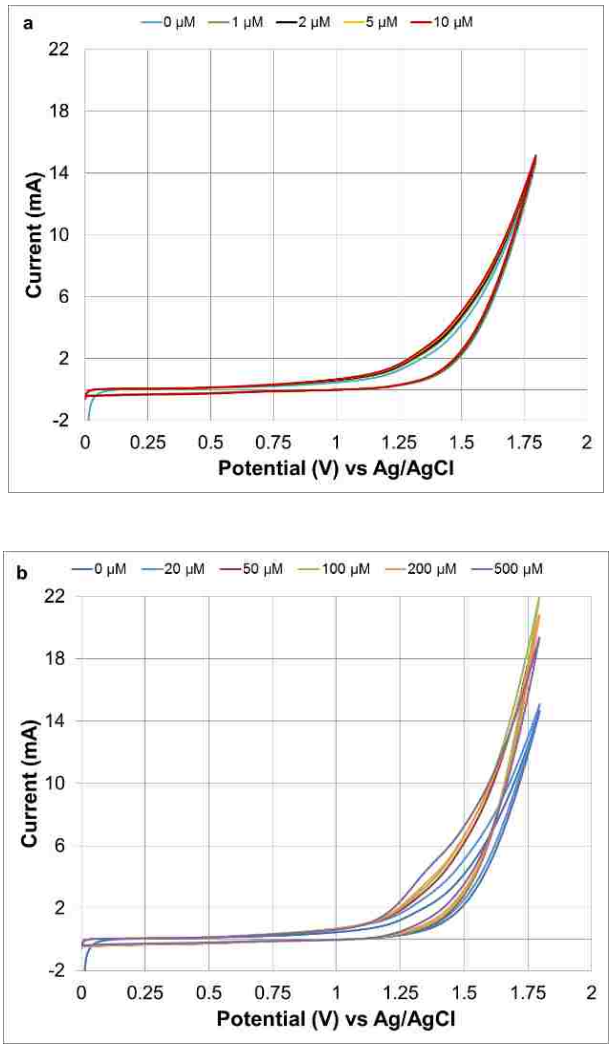


Figure A. 11. Cyclic voltammogram for Ibuprofen at pH9.0 at different concentration.

Antibiotic + Antihistamine:

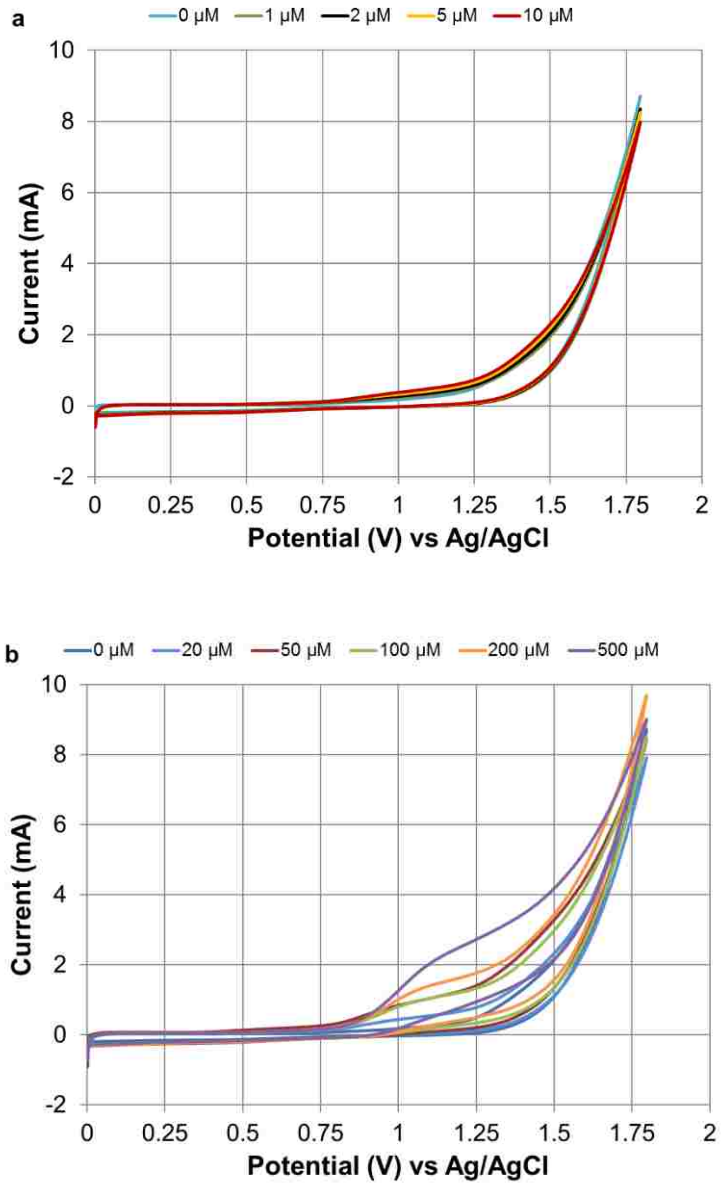


Figure A. 12. Cyclic voltammogram of Erythromycin Hydrate at pH6.0 at different concentration.

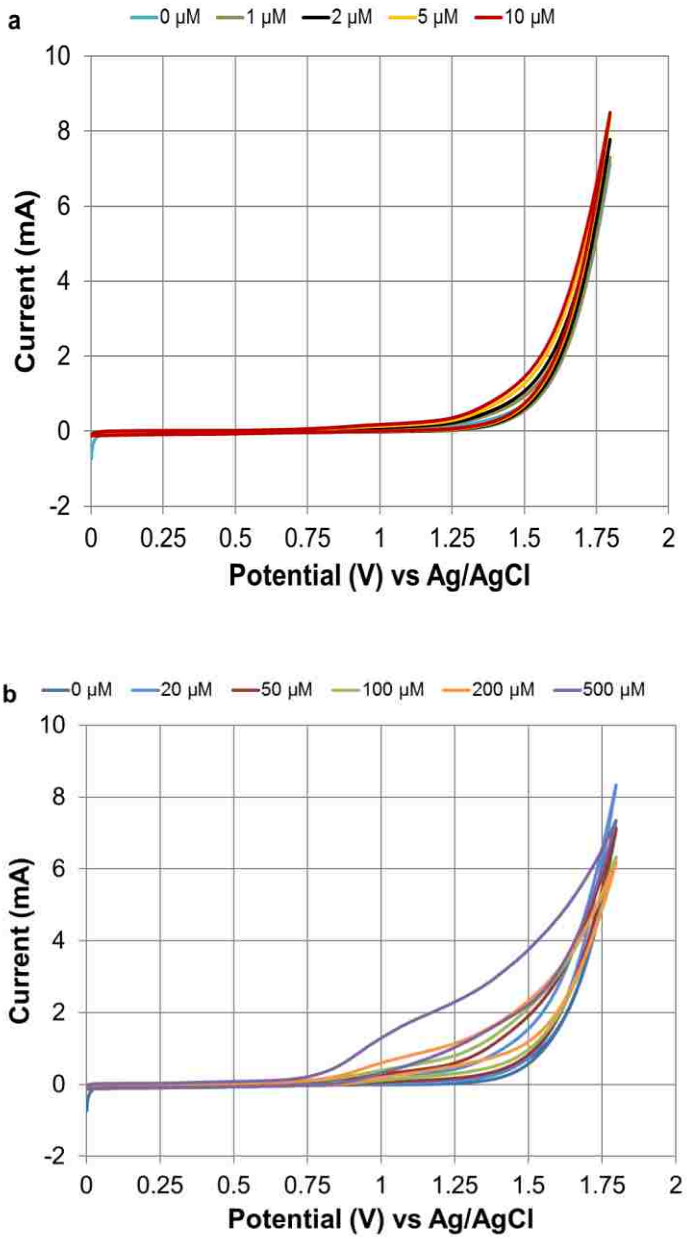


Figure A. 13. Cyclic voltammogram of Erythromycin Hydrate at pH7.5 at different concentration.

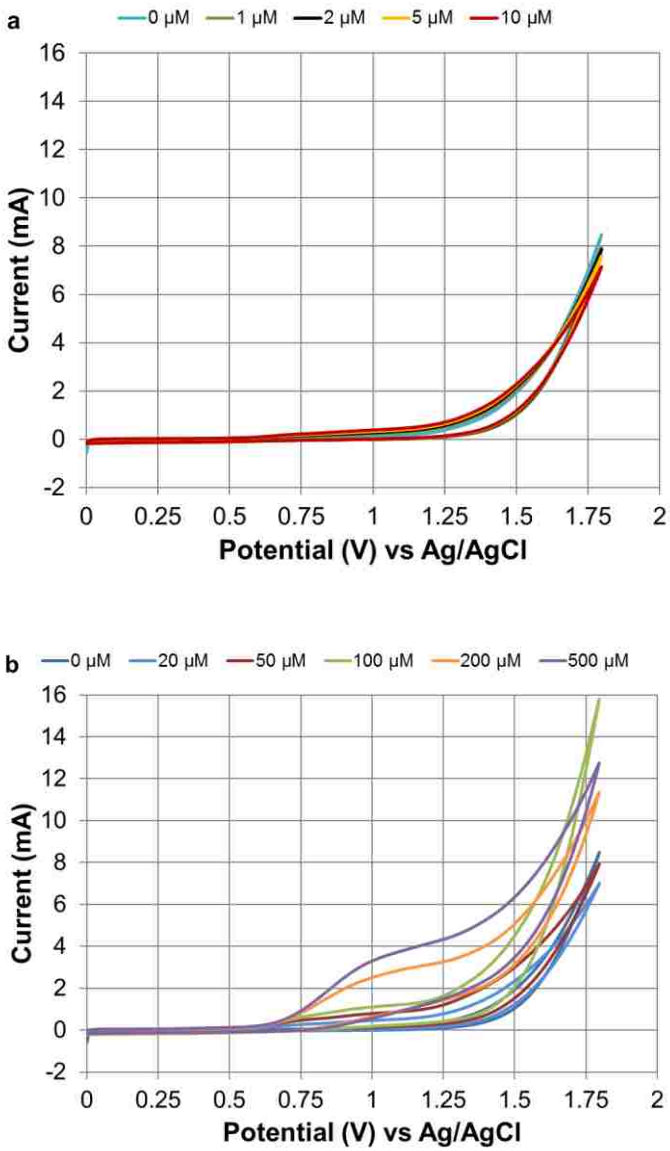


Figure A. 14. Cyclic voltammogram of Erythromycin Hydrate at pH9.0 at different concentration.

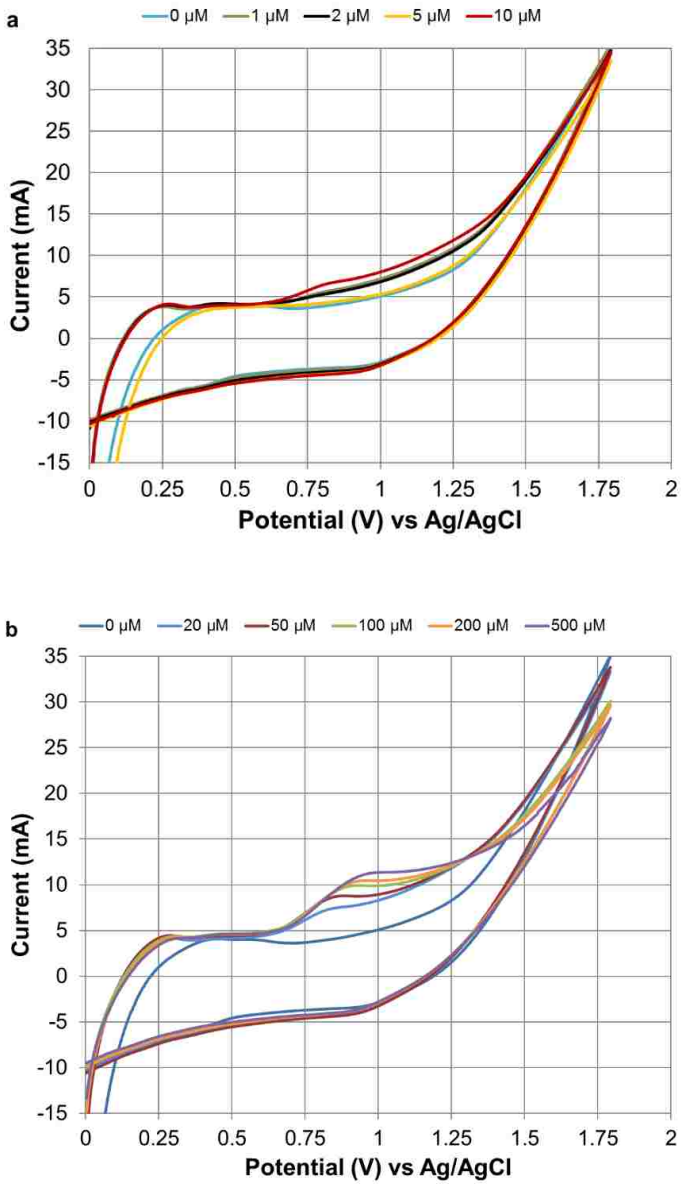


Figure A. 15. Cyclic voltammogram of Triclosan at pH6.0 at different concentration.

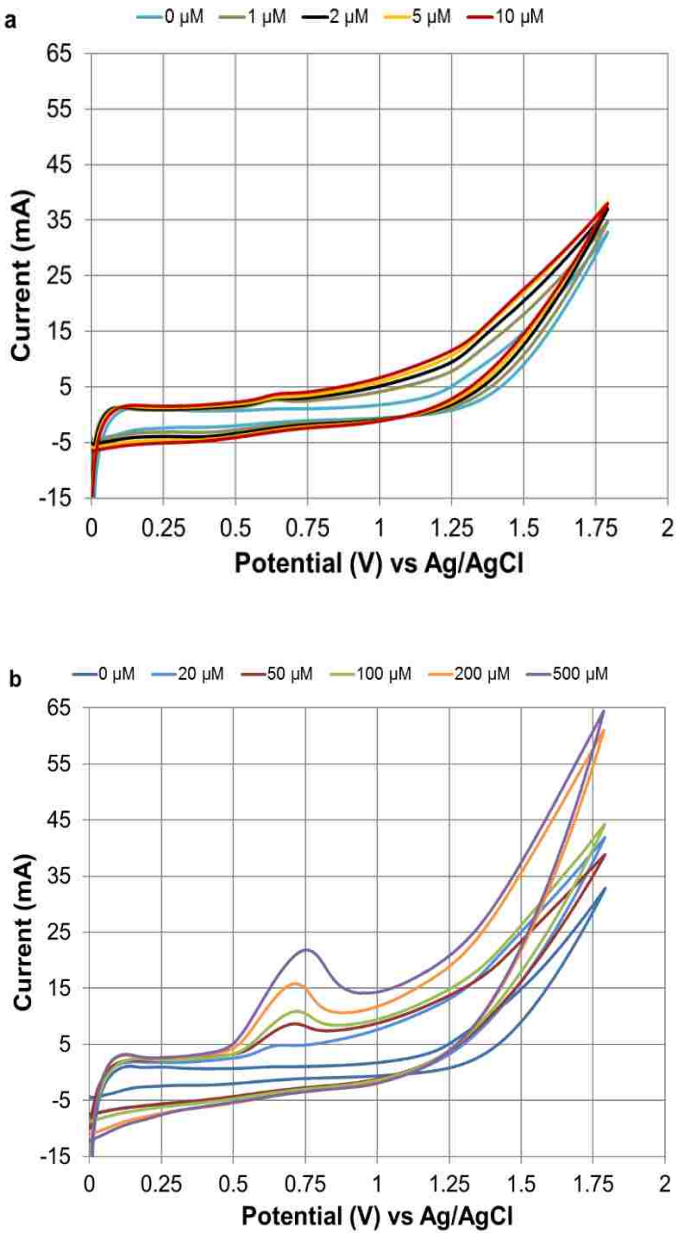


Figure A. 16. Cyclic voltammogram of Triclosan at pH7.5 at different concentration.

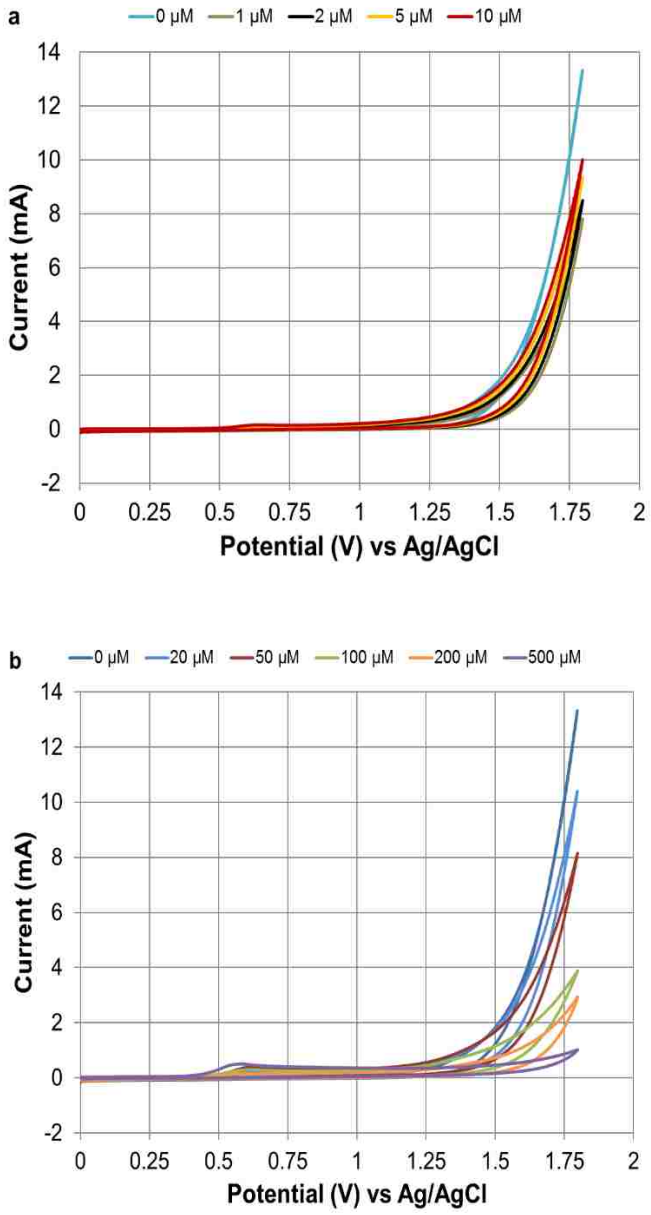


Figure A. 17. Cyclic voltammogram of Triclosan at pH9.0 at different concentration.

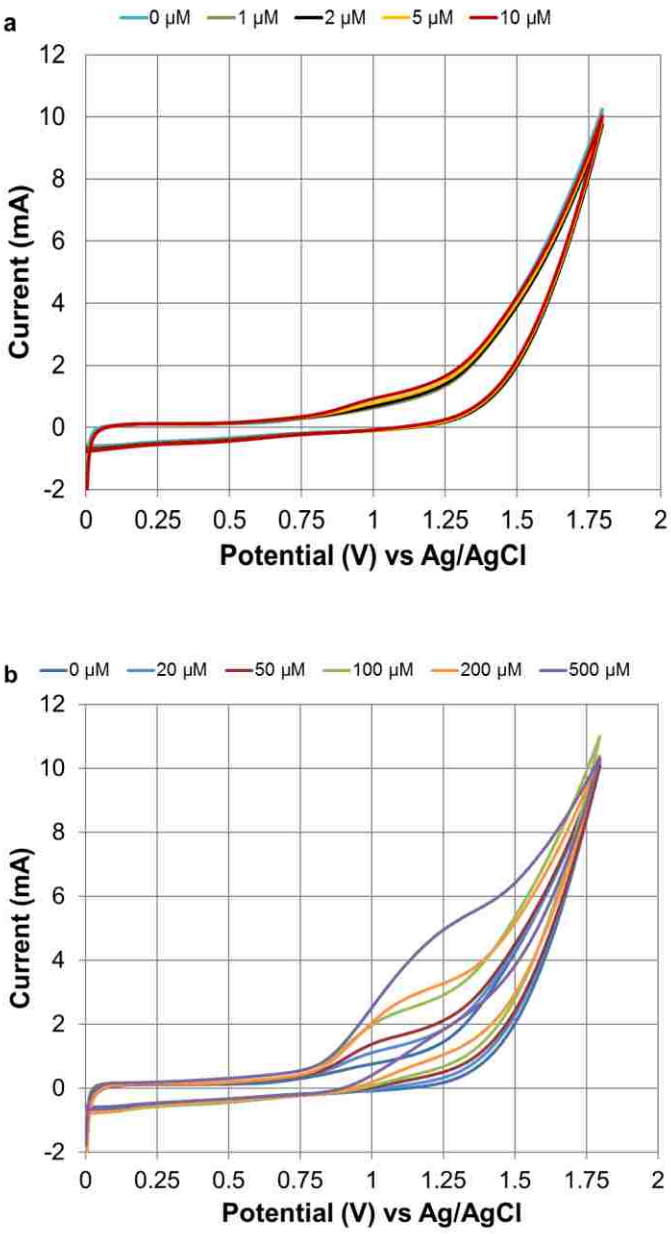


Figure A. 18. Cyclic voltammogram of Diphenhydramine Hydrochloride at pH6.0 at different concentration.

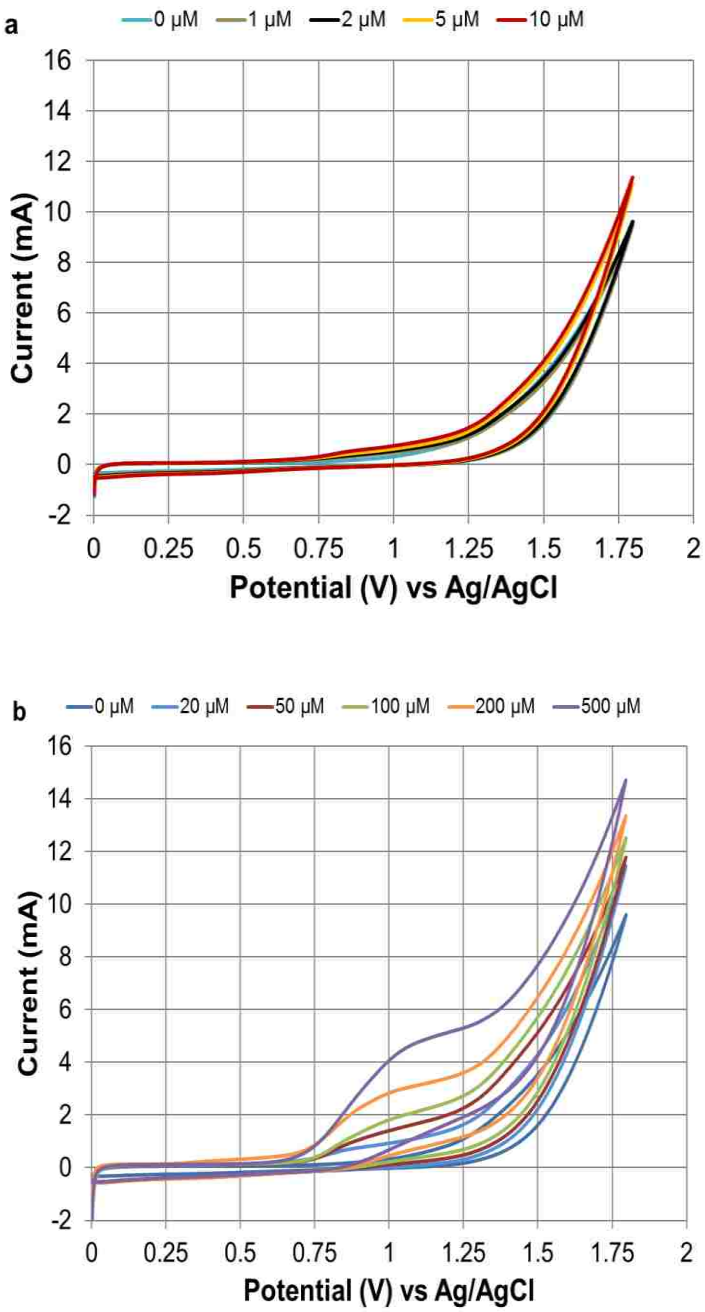


Figure A. 19. Cyclic voltammogram of Diphenhydramine Hydrochloride at pH7.5 at different concentration.

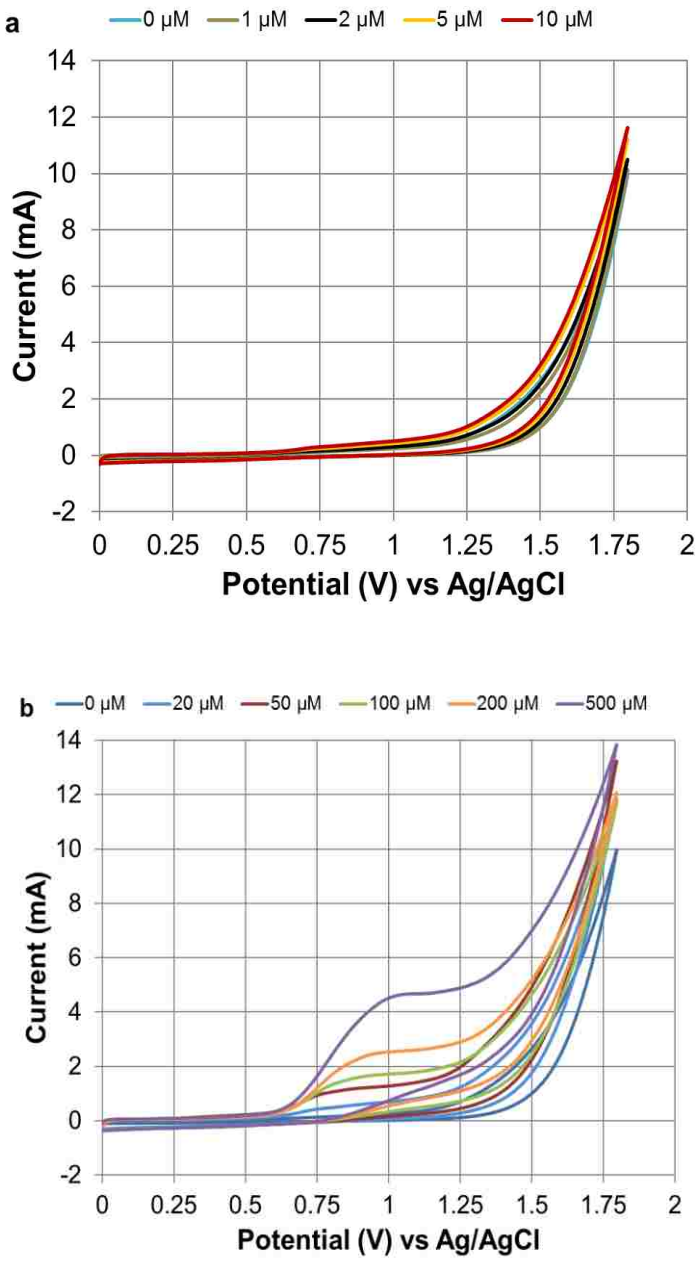


Figure A. 20. Cyclic voltammogram of Diphenhydramine Hydrochloride at pH9.0 at different concentration.

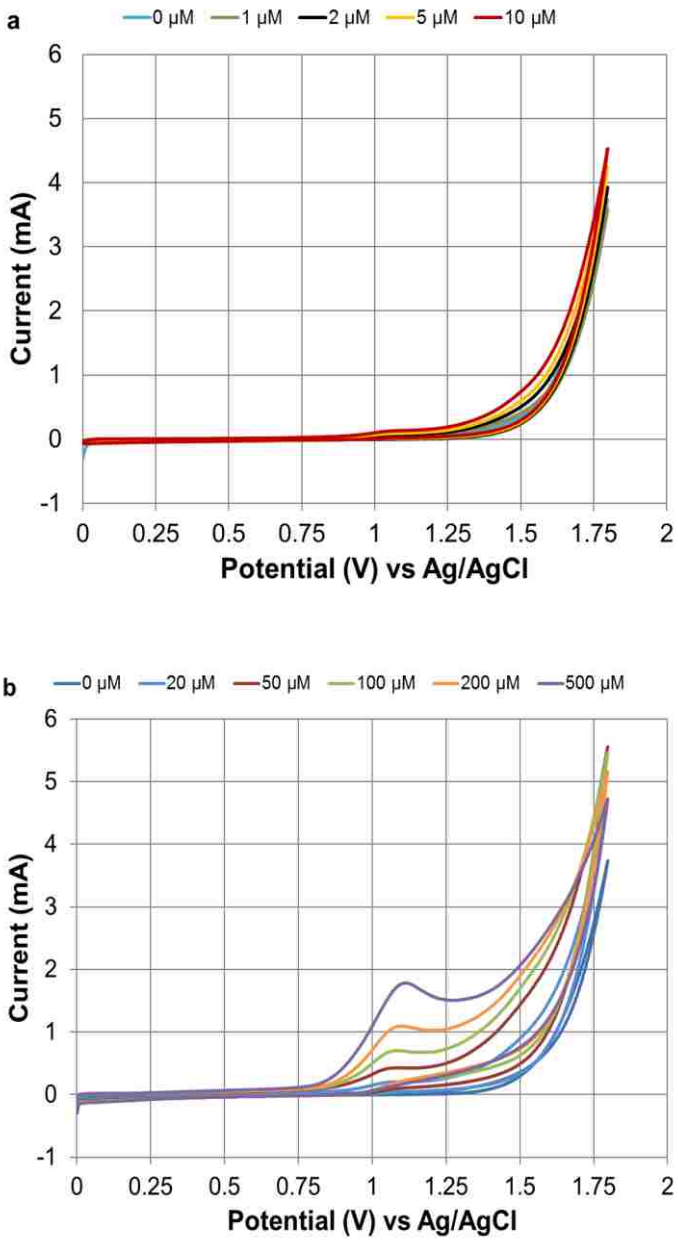


Figure A. 21. Cyclic voltammogram of Sulfanilamide at pH6.0 at different concentration.

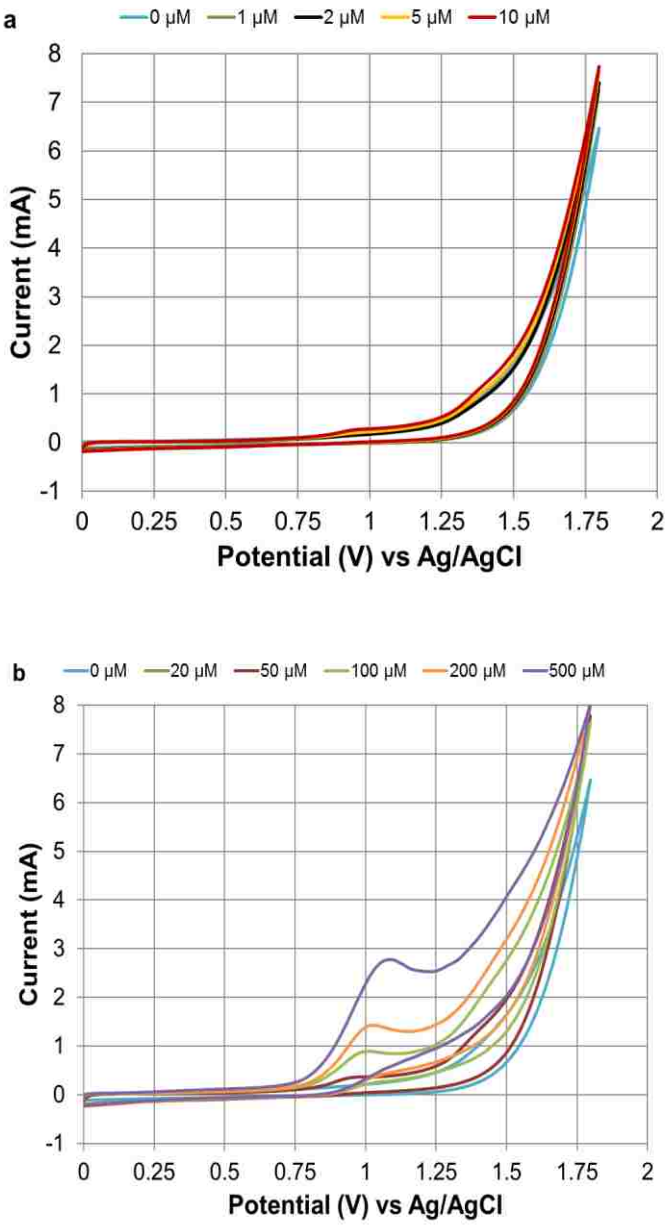


Figure A. 22. Cyclic voltammogram of Sulfanilamide at pH7.5 at different concentration.

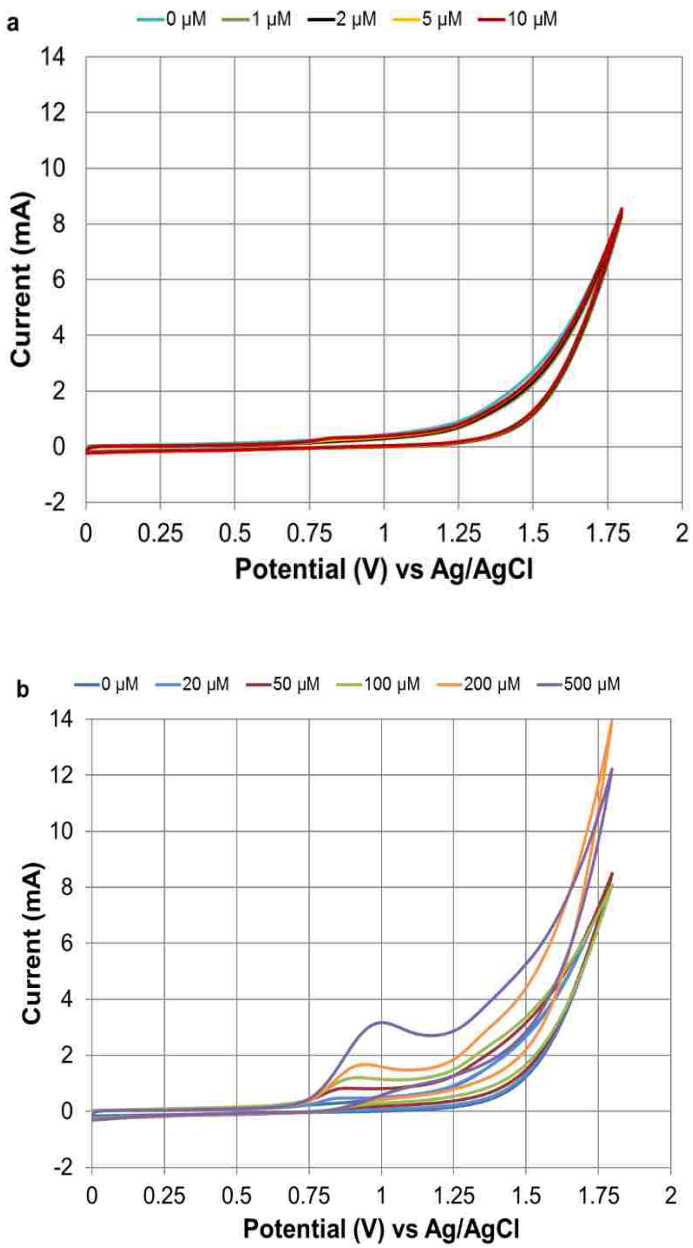
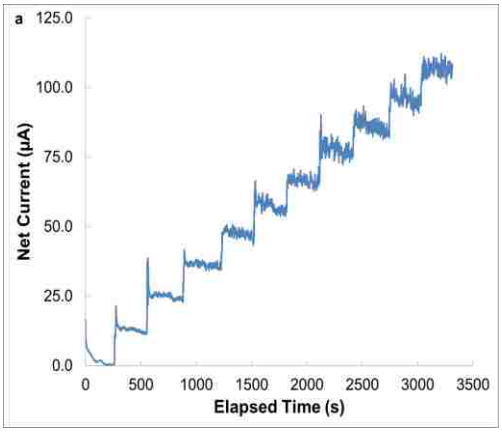
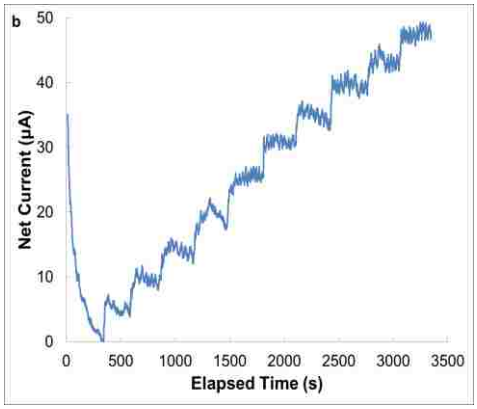


Figure A. 23. Cyclic voltammogram of Sulfanilamide at pH9.0 at different concentration.

Appendix B

Chronoamperometry Data





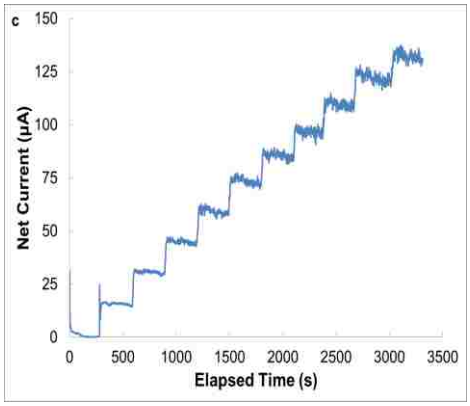
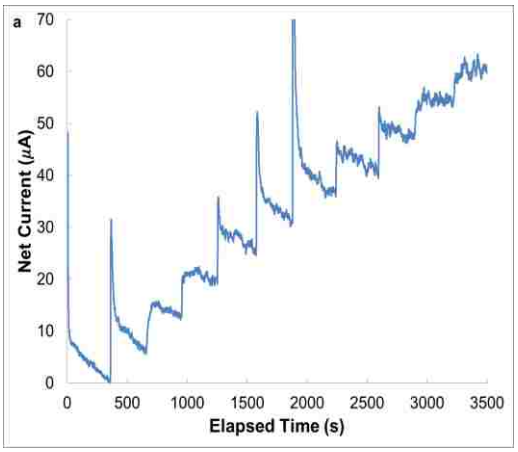
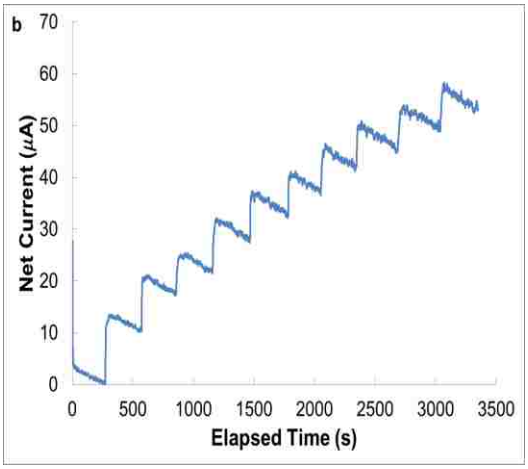


Figure B. 1. Chronoamperometry of Acetaminophen at (a) pH6.0 at applied potential 0.65V (b) pH7.5 at applied potential 0.65V (c) pH9.0 at applied potential 0.5V.





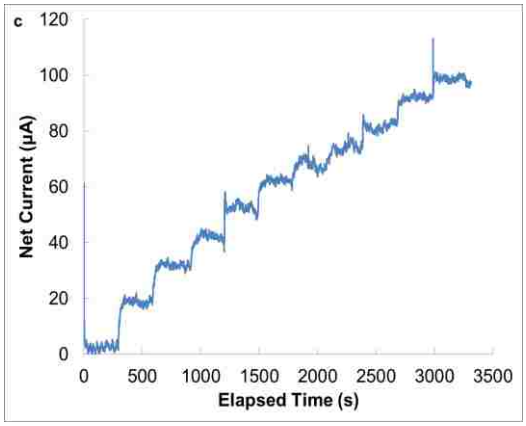


Figure B. 2. Chronoamperometry of Naproxen Sodium at applied potential 1.0 V at (a) pH6.0 (b) pH7.5 (c) pH9.0

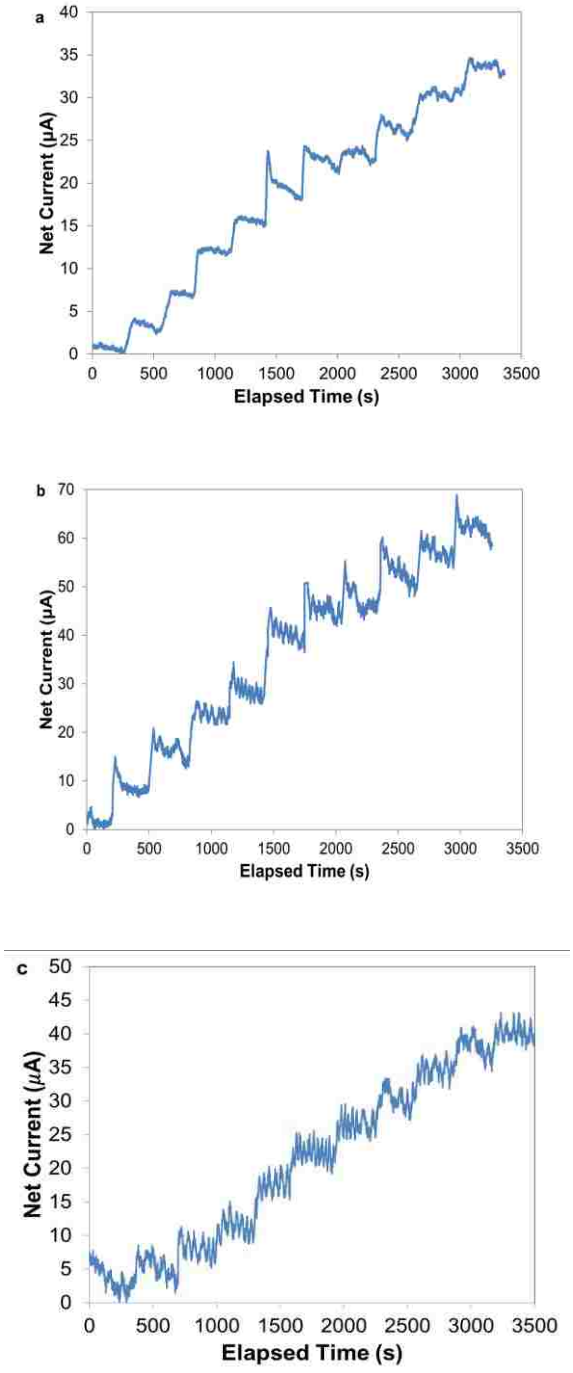


Figure B. 3. Chronoamperometry of Erythromycin Hydrate at Potential 1.05 V at (a) pH6.0 (b) pH7.5 (c) pH9.0

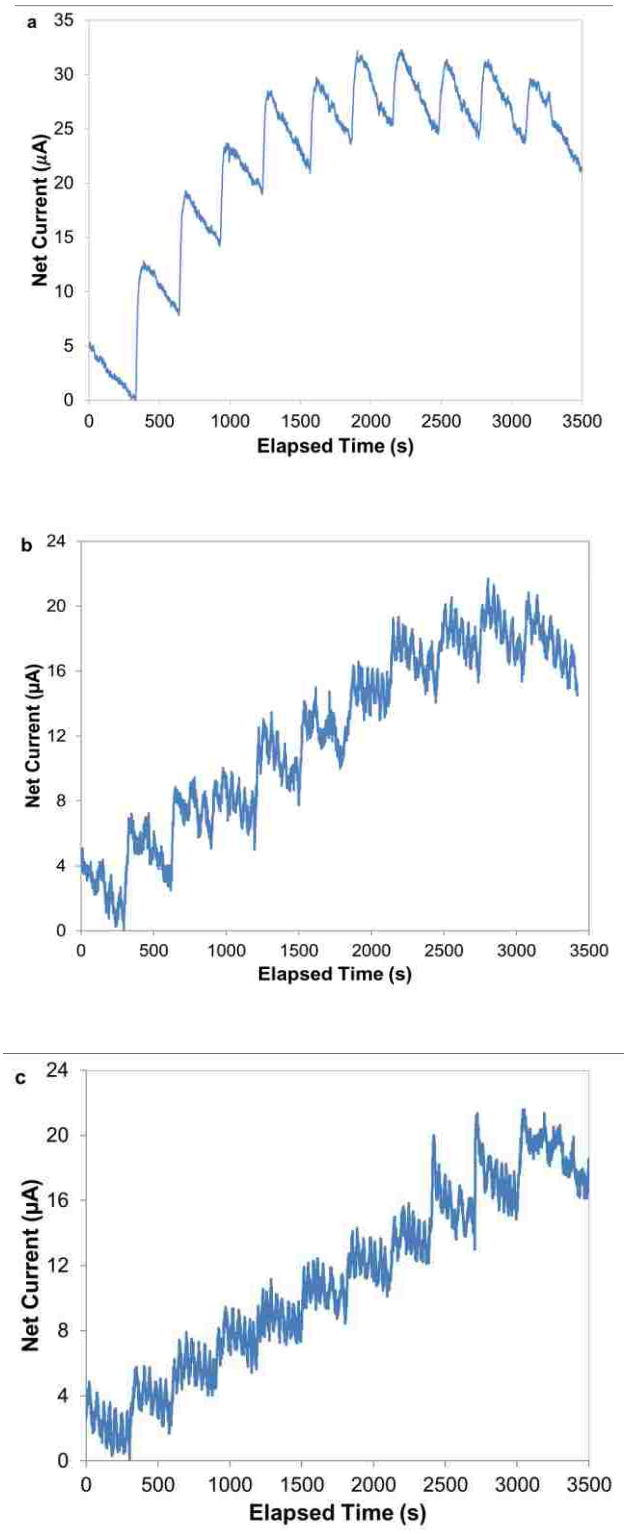


Figure B. 4. Chronoamperometry of Triclosan at Potential 0.85 V at (a) pH6.0 (b) pH7.5 (c) pH9.0

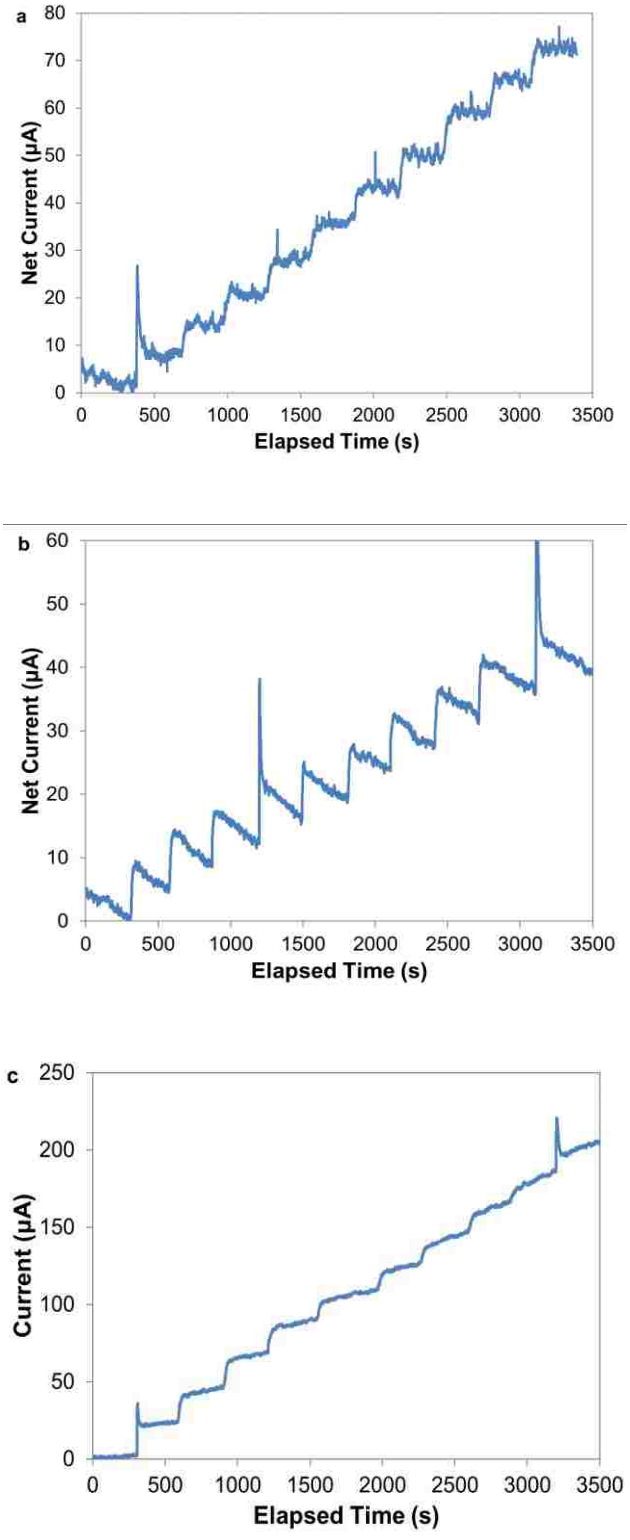


Figure B. 5. Chronoamperometry of Diphenhydramine Hydrochloride at Potential 1.10V at (a) pH6.0 (b) pH7.5 (c) pH9.0

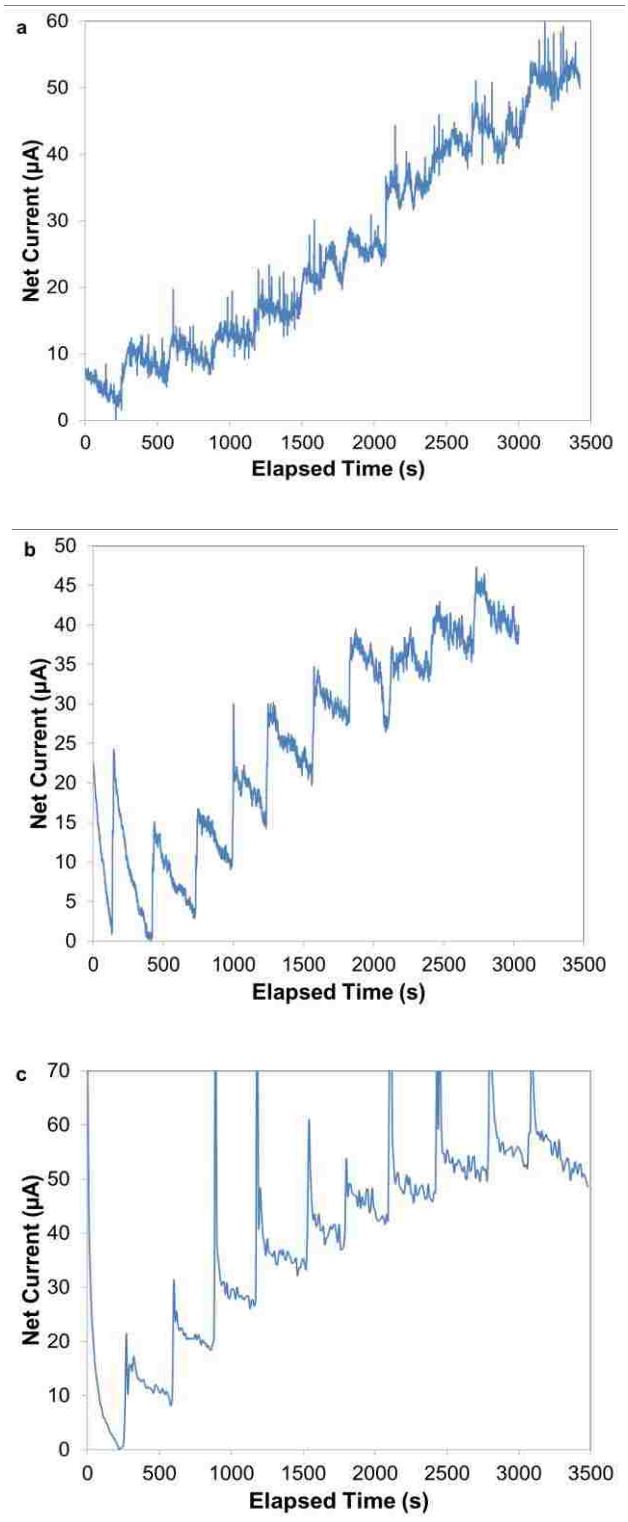


Figure B. 6. Chronoamperometry of Sulfanilmide at (a) pH6.0 at 1.06V (b) pH7.5 at 1.02V (c) pH9.0 at 1.0V

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