# VOLTAMMETRIC SENSORS OF BISPHENOL A, URIC ACID, DOPAMINE AND ACETAMINOPHEN USING LAYERED DOUBLE HYDROXIDE-MODIFIED MULTIWALLED CARBON NANOTUBES PASTE

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UNIVERSITI PENDIDIKAN SULTAN IDRIS

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# ABSTRACT

This study aimed to develop a voltammetric sensor for the determination of bisphenol A (BPA), uric acid (UA), dopamine (DA) and acetaminophen (ACT) using multiwalled carbon nanotubes incorporated with zinc/aluminium layered double hydroxide-quinmerac (Sensor 1), zinc/aluminium layered double hydroxide-quinclorac (Sensor 2) and zinc/aluminium layered double hydroxide-clopyralid (Sensor 3). The surface morphological was determined using field emission scanning electron microscope. The electrochemical properties were characterized by cyclic voltammetry, square wave voltammetry and electrochemical impedance spectroscopy. Several experimental variables of voltammetric analysis such as composition ratios, type of supporting electrolyte, pH of the solution and square wave voltammetry parameters were optimized. The effective surface area of electrodes was determined by chronocoulometry. At the optimum conditions, Sensor 1 showed three linear ranges for the single determination of BPA (30 to 700 nM, 1 to 10 µM and 30 to 300 µM) with detection limit of 4.4 nM. Sensor 2 showed simultaneous determination of UA and BPA. The linear ranges for UA is from 0.3 to 30 µM and 50 to 100 µM while for BPA is from 0.3 to 5 µM and 10 to 100 µM with detection limit are 0.065 µM and 0.049 µM, respectively. Sensor 3 showed simultaneous determination of DA, ACT and BPA with linear ranges from 7 to 500 µM, 30 to 500 µM and 3 to 500 µM and with detection limit of 0.172 µM, 0.179 µM and 0.136 µM, respectively. All the developed sensors did not interfere by several foreign ions. In a conclusion, the proposed electrodes exhibited good analytical performance with excellent sensitivity and selectivity. In its implication, these fabricated electrodes are applicable for determination of BPA, UA, ACT and DA in baby bottle, baby teether, water samples, urine and pharmaceutical tablets.

# PENDERIA VOLTAMMETRIK BISFENOL A, ASID URIK, DOPAMIN DAN ASETAMINOFEN MENGGUNAKAN PES KARBON NANOTIUB BERBILANG DINDING TERUBAHSUAI DENGAN HIDROKSIDA BERLAPIS GANDA DUA

## ABSTRAK

Kajian ini bertujuan membangun penderia voltammetrik bagi penentuan bisfenol A (BFA), asid urik (AU), dopamin (DA) dan asetaminofen (AST) menggunakan penggabungan karbon nanotiub berbilang dinding dengan zink/aluminium hidroksida berlapis ganda dua-kuinmerak (Penderia 1), zink/aluminium hidroksida berlapis ganda dua-kuinklorak (Penderia 2) dan zink/aluminium hidroksida berlapis ganda dua-klopiralid (Penderia 3). Morfologi permukaan telah ditentukan menggunakan mikroskop elektron imbasan pancaran medan. Pencirian elektrokimia telah dikaji dengan voltammetri kitaran, voltammetri gelombang segiempat sama dan spektroskopi impedans elektrokimia. Beberapa pemboleh ubah eksperimen analisis voltammetri seperti nisbah komposisi, jenis elektrolit penyokong, pH larutan dan parameter voltammetri gelombang segiempat sama telah dioptimumkan. Luas permukaan efektif elektrod telah ditentukan oleh kronokoulometri. Di bawah keadaan optimum, Penderia 1 menunjukkan tiga julat linear bagi penentuan BPA tunggal (30 hingga 700 nM, 1 hingga 10 µM dan 30 hingga 300 µM) dengan had pengesanan sebanyak 4.4 nM. Penderia 2 menunjukkan penentuan serentak AU dan BFA. Julat linear bagi AU adalah dari 0.3 hingga 30 µM dan 50 hingga 100 µM manakala bagi BFA adalah dari 0.3 hingga 5 µM dan 10 hingga 100 µM dengan had pengesanan masing-masing 0.065 µM dan 0.049 µM. Penderia 3 menunjukkan penentuan serentak DA, AST and BFA dengan julat linear dari 7 hingga 500 µM, 30 hingga 500 µM dan 3 hingga 500 µM dan had pengesanan sebanyak masing-masing 0.172 µM, 0.179 µM dan 0.136 µM. Semua penderia yang dibangunkan tidak diganggu oleh beberapa ion luar. Sebagai kesimpulan, elektrod-elektrod yang dicadangkan menunjukkan prestasi analisis yang baik dengan kepekaan dan kepilihan yang sangat cemerlang. Implikasinya, elektrod-elektrod fabrikasi ini dapat digunakan untuk penentuan BFA, AU, DA and AST di dalam botol bayi, puting bayi, sampel-sampel air, air kencing dan tablet farmaseutikal.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AA | Ascorbic acid |
| ACT | Acetaminophen |
| AdSV | Adsorptive stripping voltammetry |
| AnSV | Anodic stripping voltammetry |
| BPA | Bisphenol A |
| CC | Chronocoulometry |
| CNT | Carbon nanotubes |
| CP | Clopyralid |
| CPE | Carbon paste electrode |
| CSV | Cathodic stripping voltammetry |
| CV | Cyclic voltammetry |
| DA | Dopamine |
| DAD | Diode array detector |
| DME | Dropping mercury electrode |
| DPV | Differential pulse voltammetry |
| EIS | Electrochemical impedance spectroscopy |
| FESEM | field emission scanning electron microscopy |
| FTIR | Fourier transform infrared |
| GCE | Glassy carbon electrode |
| GCMS | Gas chromatography mass spectrometry |
| HPLC | High performance liquid chromatography |

| | |
|---|---|
| IR | Infrared |
| ISE | Ion-selective electrode |
| IUPAC | International union of pure and applied chemistry |
| LDH | Layered double hydroxide |
| LSV | Linear sweep voltammetry |
| MWCNT | Multi walled carbon nanotubes |
| NPV | Normal pulse voltammetry |
| PBS | Phosphate buffer solution |
| PC | Polycarbonates |
| PVC | Polyvinyl chloride |
| PXRD | Powder X-ray diffraction |
| QC | Quinclorac |
| QM | Quinmerac |
| RMM | Relative molecular mass |
| RSD | Relative standard deviation |
| SCV | Staircase voltammetry |
| SEM | Scanning electron microscope |
| SPE | Solid phase extraction |
| Std. | Standard |
| SV | Stripping voltammetry |
| SWCNT | Single walled carbon nanotubes |
| SWV | Square wave voltammetry |
| TEM | Transmission electron microscope |
| UA | Uric acid |

| | |
|---|---|
| US | United states |
| USA | United State of America |
| UV | Ultraviolet |

# LIST OF APPENDICES

# CHAPTER 1

# INTRODUCTION

## 1.1 Electrochemical Sensors

Electrochemical sensors are the most popular method, which work by responding to chemical solutions and generating an electrical signal proportional to the analyte concentration (Chou, 1999). Generally, in electrochemical sensors, the target analyte interacts with a recognition element that triggers a current-generating electrochemical reaction. This current is dependent on the target analyte concentration, and can be calculated (Price, 2019). They are focussing on a redox reaction occurred at a working electrode involving the electrolyte solution containing the target analyte, leading to the variation of an electrical signal. The blood glucose sensor and the respiratory carbon dioxide sensor are known examples (Dejous, Hallil, Raimbault, Rukkumani, & Yakhmi, 2017). The electrochemical sensors are widely used in environmental monitoring, industrial analysis, medicine and pharmaceutical (Lin, Li, Yang, Ye, &

Huang, 2019; Alves, Rocha, & Soares, 2017; Winiarski, Rampanelli, Bassani, Mezalira, & Jost, 2020; Gautam, Singh, & Yadav, 2018; Yao, Wu, & Ping, 2018; Ciui et al., 2018; Sappia et al., 2019; Panahi, Motaharian, Reza, Hosseini, & Mehrpour, 2018). The area of electrochemical sensors also broaden through the development and the modification of sensors materials including nanomaterials (Feng et al., 2018; Li et al., 2018; Li et al., 2017; Sapari, Hidayah, Razak, Aishah, & Yook, 2020; Shetti et al., 2018).

Generally, the interactions between recognition element and an electrochemical transducers are the basis of the electrochemical sensors. The measurement take place in an electrochemical cell which consist of electrodes and sample. The advantages of electrochemical sensors are they do not require any transformation of signal to control unit since the signal is in an electrical form. Some of the methods are rather specific while other are nonspecific. They can be used to detect the species of interest or the only certain types of compounds. Besides that, electrochemical sensors have their advantages compared to other analytical methods due to their simplicity, portability, high diversity and low cost. They also have fast and selective analysis. Other than that, this method also offered a wide linear response range as well as a low detection limits with good stability and reproducibility (Faridbod, Gupta, & Zamani, 2011; Karimi-maleh, Karimi, Alizadeh, & Sanati, 2020; Ostoji, Herenda, Besic, Milos, & Galic, 2017; Stradiotto, Yamanaka, & Zanoni, 2003)

The electrochemical sensors are categorized according to their mode of signal transduction. The major electrochemical sensors include potentiometry, conductometry and voltammetry (Figure 1.1). The names of the methods represent the measured parameters. The potentiometry measures the electric potential under the conditions of no current flow between the electrodes. Conductometry determines the conductance (the tendency of a solution to carry an electric current) between the electrodes under the constant alternating-current potential. Meanwhile, the voltammetry measures the current caused by the redox process of an electroactive species under the varied potential (Skoog, Holler, & Crouch, 2007).

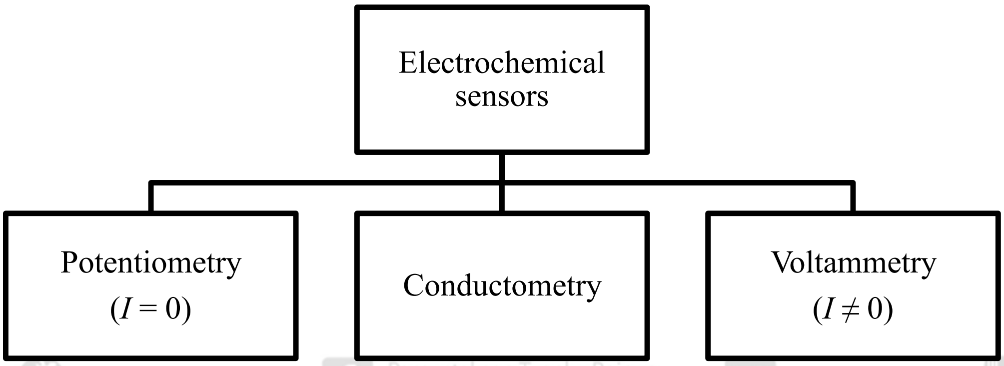


*Figure 1.1.* Types of electrochemical sensor

### 1.1.1 Potentiometry

Since the early 1930’s, potentiometry have found the most diverse practical applicability due to their low cost, easily automated for rapid sampling, and simple to use. Basically, electrochemical cell of potentiometry consists of two electrodes immersed in solution and connected to potentiostat. One of the electrodes is a reference electrode that provide a known electrode potential. The other electrode is a working electrode where the electrode potential usually depend on the analyte concentration (Stradiotto et al., 2003). Potentiometry measures the potential difference between these two electrodes in an electrochemical cell when no current flowing between them. The relationship between the concentration and the potential is given from a variation of the Nernst equation (Honeychurch, 2012).

There are several types of potentiometry or potentiometric sensors, but the most prominent is the ion-selective electrode (ISE). The typical example is pH meter. ISE is an indicator electrode capable of selectively monitoring the presence of a single ionic group. In the classic configuration, ISE are commonly membrane-based devices, consisting of permselective ion-conducting materials, separating the sample from the inner side of the electrode. ISEs are categorized into three groups, depending on the nature of the membrane; glass, liquid or solid electrode. The most common is glass electrodes which are based on a thin ion-sensitive glass membrane, and available in many shapes and sizes. Liquid electrodes are commonly used for direct potentiometric measurements based on water-immiscible liquid compounds impregnated with a polymeric membrane. Meanwhile, solid electrodes usually made up of single crystals, polycrystalline pellets, or mixed crystals that are selective to anions (Wang, 2000; Stradiotto et al., 2003).

### 1.1.2 Conductometry

As early as the 18th century, the conductive study began when Andreas Baumgartner found that the salt and mineral waters from Bad Gastein in Austria, conducted electricity. Since then, conductometry is often used in water purity measurements until today. Generally, conductometry is the study of the electrolytic conductivity of the reacting species or the resultant products by monitoring their chemical reaction. The conductometry are also used for the measurement of concentrations of electrolytes in aqueous solutions. The solution conductivity can be used to measure the electrical resistance of the solution to obtain the molar concentration an analyte. Conductometry do not require reference electrode, thus make them easy to be operated, besides low cost involved and portable (Moldoveanu & David, 2017; Shah, Arain, & Soylak, 2020).

The materials frequently used in conductometry are thin films, porous films and polymers. The thin films usually used due to their conductivity changes following surface chemisorption. For example, cadmium sulphide films is applied as oxygen sensor. Porous films of manganese tungsten oxide is used as a humidity sensor. Besides that, polymers are also used as materials in conductometry either conductive themselves or with a modifier. For example, polypyrrole is used to detect volatile amines (Smyntyna, Golovanov, Kaeiulis, Mattogno, & Righini, 1995; Qu & Meyer, 1997; Costello, Evans, & Ratcliffet, 1996).

### 1.1.3 Voltammetry

Voltammetry is one type electrochemical methods functioned in measuring the current produced at certain potential when the potential was scanned from one present to another. The applied potential give the driving force for the electron transfer reaction of the redox species. The electron transfer rate of reaction that occurred on the electrode surface is the resulting current. The current which measured as current peak in voltammetry is directly proportional to the concentration of the redox species (Skoog et al., 2007).

As shown in Figure 1.2, voltammetry consists of four basic instruments are electrode, ionic electrolyte, potentiostat and recorder. They are comprising of three electrode system immersed in a supporting electrolyte containing the target species, connected to both potentiostat and recorder, which functioning as signal converter. The three electrode of voltammetry are known as working electrode, where the reaction or electron transfer take place; reference electrode, which provides a stable potential; and counter electrode, which provides a necessary current. In this system, the potential between the working and reference electrodes is applied, while the current flow between the working and counter electrodes is measured (Tiwari, Vij, Kemp, & Kim, 2015).

In electrochemistry, the selectivity and sensitivity of the measurements usually depends on properties of the working electrode. Most of the voltammetry is based on the modification of the working electrode. The choice of a working electrode for electrochemical analysis depends on the redox behaviour of the target analyte, cost availability, surface reproducibility, electrical conductivity, mechanical properties, potential window and the background current over the potential region for the measurement. Besides, the solubility and adsorption properties of the reaction products on the surface of the electrode and the reaction

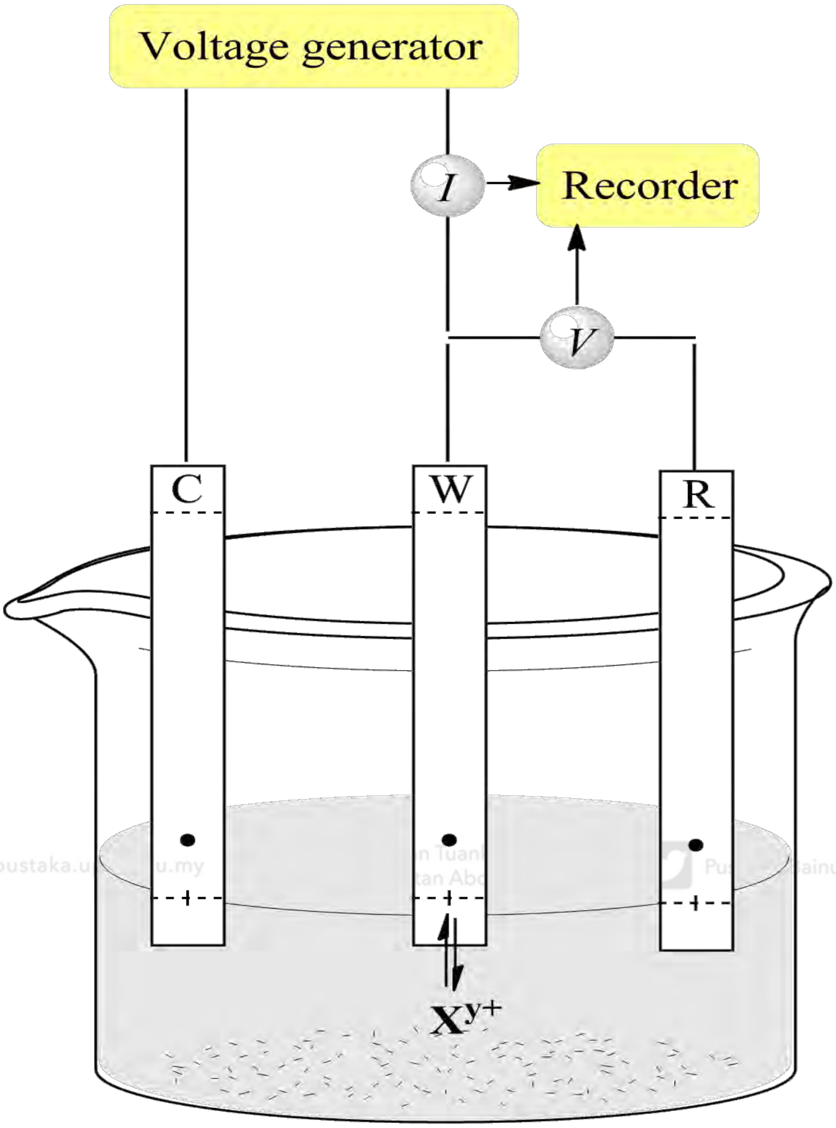


*Figure 1.2.* Schematic of A Voltammetric Sensor and Electrochemical Reaction Occur At The Surface Of A Working Electrode (Tiwari et al., 2015)

mechanism also determine the electrode type. The reference electrode keeps the potential of an electrode constant regardless of the properties of the solution. The main criteria for an electrode to be classified as a reference electrode are the capability to provide a reversible half-reaction based on Nernstian behaviour with a constant potential over time, and to be easy to assemble and maintain. The counter electrode is an electrode which a counter reaction to that of the working electrode takes place. This electrode is generally made from inert conducting material such as platinum or carbon (Scholz, 2010).

Supporting electrolytes are inert soluble substance added to the solution to avoid electrochemical reaction at the counter electrode during the electrochemical measurements. They should not be easily oxidized or reduced and must be prepared from highly purified reagents. Supporting electrolytes also act as maintaining a constant ionic strength and eliminates electromigration effects. They can be an inorganic salt, a mineral acid, a buffer or a chelating reagent (Stradiotto et al., 2003).

The potentiostat controls the applied potential that passes through the working and counter electrodes. A potentiostat can utilize variety modes of voltammetry such as cyclic voltammetry, pulse voltammetry, linear sweep voltammetry, stripping voltammetry and chronocoulometry. Each mode will secrete their typical current-potential responses and distinguished by the different form of voltammograms which the signals further be interpret by the recorder (Ötles, 2016). These various types of voltammetry will be further discuss in Chapter 2.

## 1.2 Electrochemical Impedance Spectroscopy

Electrochemical impedance spectroscopy (EIS) is a widespread analytical technique for characterizing behaviour of an electrochemical system, and therefore allows analysing several phenomena at electrode solution interfaces. EIS is also a powerful and non-destructive technique for investigating microscopic interfacial events or diffusion effects near or far from the equilibrium potential of the modified electrodes. They are able to measures the impedance of the electrode solution interface over a wide range of frequencies, from mHz to 10 kHz. The results obtained from EIS give information for determining the solution resistance, the capacitance of double layer as well as the polarization resistance (Telegdi, Shaban, & Vastag, 2018).

The two most popular plots in EIS are Bode plot and Nyquist plot (Figure 1.3A). In the Bode plot, the *x*-axis is logarithm of the frequency (*f*), the *y*-axis consist of both the logarithm of the impedance (Z) and the phase shift (Φ). Meanwhile, in the Nyquist plot, the *x*-axis is the real part of the impedance (Z') and the *y*-axis is the negative imaginary impedance (-Z"). The Nyquist plot is more complex nevertheless more popular in electrochemistry because it is very sensitive to changes and some parameter can be read directly from the plot. The EIS data are modelled using equivalent circuits, called Randles circuit (Figure 1.3B), to model electrochemical reactions at the electrode surface. Form this circuit, some parameters such as solution resistance ($R_s$), electron transfer resistance ($R_{ct}$), and double layer capacitance ($C_{dl}$) can be extract. From these parameters, valuable

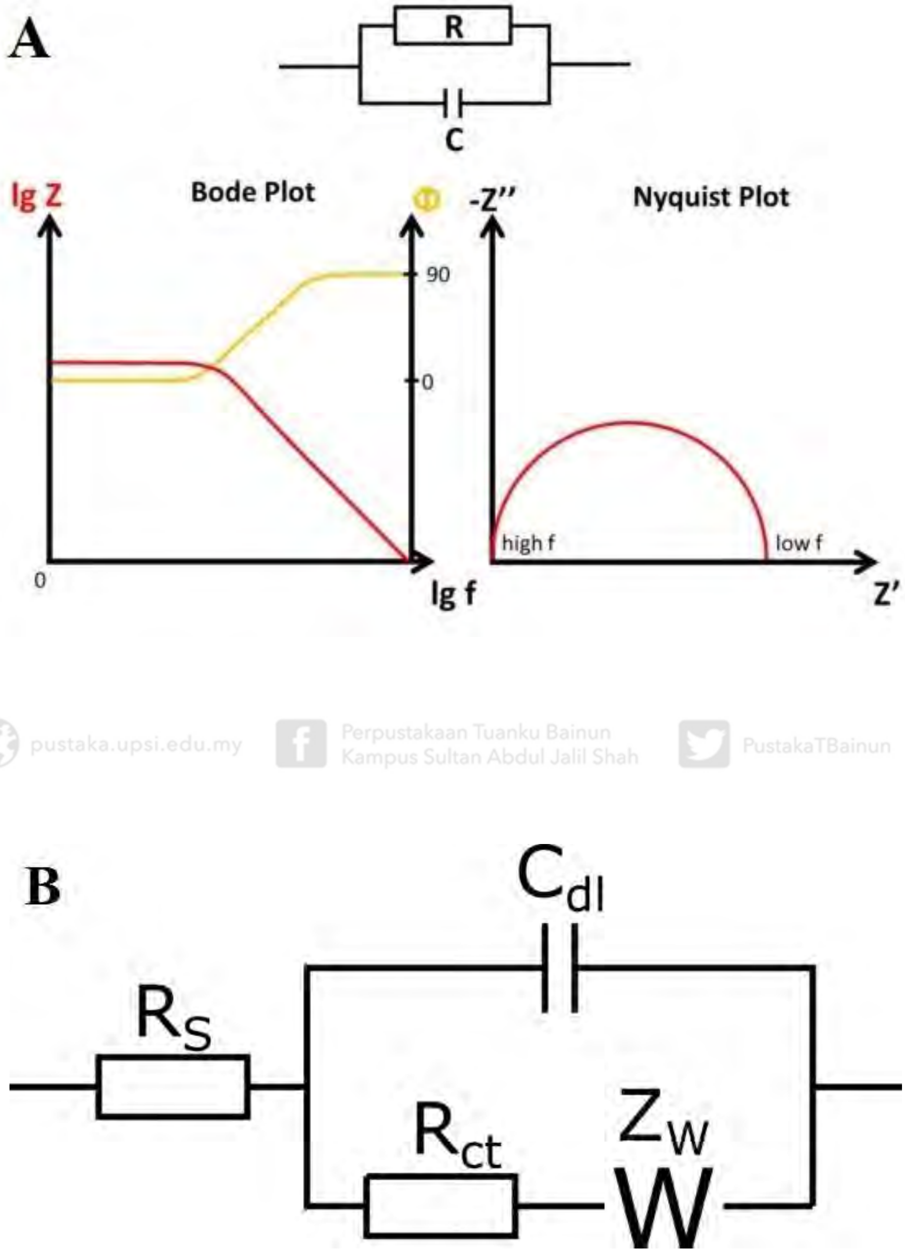


*Figure 1.3.* (A) Bode Plot and Nyquist Plot and (B) Randles Circuit in EIS (Bode, 2020; Electrochemical, 2020)

information about electrode solution interfaces can be obtained (Suni, 2008; Lasia, 1999)

Charge transfer resistance ($R_{ct}$) is related to the rate of electron transfer across the interface. In order to obtain $R_{ct}$ from which the apparent electron transfer rate constant ($k_{app}$) can be calculated, the standard procedure involves fitting impedance data to an equivalent circuit model that represents the physical interface (Ganesh, Pal, Kumar, & Lakshminarayanan, 2006). The $k_{app}$ across the interface can be obtained from $R_{ct}$ through the Equation 1.1, where R is the gas constant (8.314 J $mol^{-1}$ $K^{-1}$), T is the absolute temperature of the system (298 K), n is the number of electrons transferred in the redox reaction (n = 1 for $Fe(CN)_6^{3-/4-}$), F is the Faraday constant (96485 C $mol^{-1}$), A is the estimated surface area of electrode in $cm^2$, and C is the concentration of the $K_3[Fe(CN)_6]$ solution in mol $cm^{-3}$. The apparent electron transfer rate constant is a measure of the electron transfer kinetics across the interface (Sharma et al., 2016).

$$k_{app} = \frac{RT}{nF^2R_{ct}AC} \tag{1.1}$$

## 1.3 Carbon Paste Electrode

The most prominent forms of carbon based electrodes are carbon paste, glassy carbon, carbon film, carbon fibre, screen-printed carbon strips, graphite or other composites. They are generally fabricated from heterogeneous or homogenous materials (Wang, 2006; Dekanski, Stevanovic, Stevanovic, Nikolic, & Jovanovic, 2001; Apetrei, Apetrei, Saja, & Rodriguez-Mendez, 2011; Moscatello, Prasad, Chintala, & Yap, 2012). In 1950, Ralph Norman Adams was started the applications of carbon electrode in electroanalysis by invented the carbon paste electrode (CPE) (Lubert & Kalcher, 2010). CPE has become one of the most popular useful materials for the fabrication of various electrochemical sensors for analytical purpose (Mashhadizadeh & Akbarian, 2009).

The designation of CPE acts as an alternative to the dropping mercury electrode, because it can be used in positive potential ranges where mercury electrodes are not applicable due to the oxidation of the electrode material, and also because of the toxicity and surface fouling of the mercury electrode (Kalcher et al., 1995; Ghiaci, Rezaei, & Arshadi, 2009). CPEs have wide applicability in electrochemical studies due to their easy preparation, compatibility with various types of modifiers, biocompatibility and renewability of the surface, and more importantly is cost effectiveness (Švancara, Vytras, Barek, & Zima, 2001; Jemelkova, Barek, & Zima, 2010; Svancara, Vytras, Kalcher, Walcarius, & Wang, 2009). Owing of their wide potential window, from -1.4 V to +1.3 V, CPE has been widely used as a working electrode in electrochemical sensors field. Compare to the glassy carbon electrode or noble metallic electrodes, the residual currents of CPE are 10 times lower (Mashhadizadeh & Akbarian, 2009).

The basic ingredients of carbon paste mixtures are carbon powder and liquid binder. Carbon-based materials, especially carbon nanotubes (CNTs), are of tremendous current interest in fabrication of CPE. Carbon nanotubes can be classified into two types (Figure 1.4), which are single walled carbon nanotube (SWCNT) and multiwalled carbon nanotube (MWCNT). SWNCT is a form of one layer of graphite sheet which rolled seamlessly, and the size of an individual cylinder is 1 to 2 nm in diameter. As shown in Figure 1.5, SWCNT can be formed in three different design; armchair, zigzag and chiral. Meanwhile, MWCNT is made up of several layers of rolled graphite sheet which formed a concentric and closed graphite tubules. Their diameter typically range from 2 to 25 nm (Zhao, Gan, & Zhuang, 2002). MWCNT possess various advantages such as wide ranging use due to their limited scale, high chemical stability, high electrical and thermal conductivity, high mechanical strength and large specific surface area (Keyvanfard, Shakeri, Karimi-Maleh, & Alizad, 2013). The high specific surface area of MWCNT is contributed by reduction in their size. Materials with high surface area to volume ratio are more prone to reaction and they will react at far quicker, with a further effect on better mass transport characteristics. Besides that, the MWCNT are found to have much higher stability against electromigration compare to other small metallic structures (D’Souza et al., 2015).

The second component of carbon paste is a pasting liquid or binder. General criteria need to be fulfil by pasting liquid as a binder of carbon paste are high viscosity and low volatility, minimal solubility in aqueous solution, chemical inertness and electroinactivity, and immiscibility with organic solvents (Svancara et al., 2009). Common liquids used as binder are bromoform, bromonaphthalene, ceresin wax, silicon oil and paraffin oil. The preparation of carbon paste involve a homogenously mixing the carbon powder with the liquid binder in varies ratio. Commonly, the ratios of the liquid binder and the carbon powder varies between

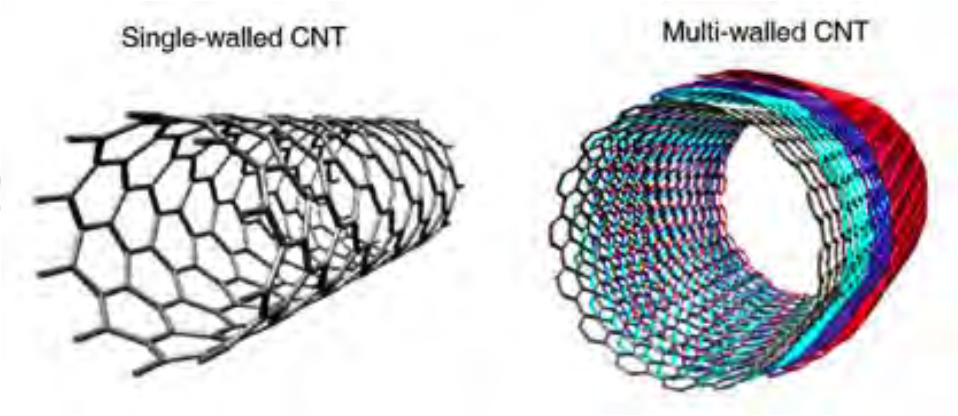


*Figure 1.4.* Molecular Structure of SWCNT and MWCNT (Xu, Shan, Cong, Shen, & Yu, 2018)

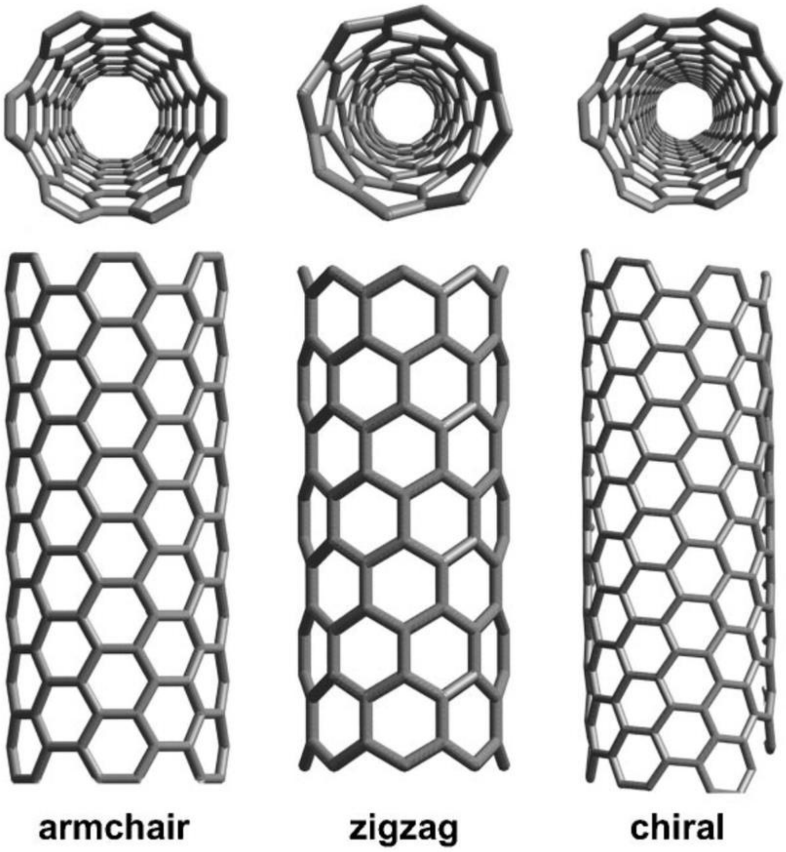


*Figure 1.5.* Schematic Model of Armchair, Zigzag and Chiral Nanotube (Gorkina et al., 2016)

0.3 to 0.5 milliliters per gram carbon for dry paste, and 0.5 to 0.9 milliliters per gram carbon for wet paste. (Kalcher, 1990; Kalcher et al., 1995)

## 1.4 Modifiers

All electrochemical sensors are based on electrochemical processes that occur at the electrode surface. Notably, electrochemical response of most of the species is poor or insensible at low concentration at ordinary bare electrodes (Ghalkhani & Ghorbani-Bidkorbeh, 2019). Thus, electrode surface modification plays an important role in the development of electrochemical sensors. Fundamentally, binary mixtures of carbon powder and liquid binder as well-known as bare ("virgin") are called unmodified CPE. In contrast, modified CPE consist of another constituent which is called modifier (Švancara et al., 2001). The main reasons of electrode modification are either to pre-concentrate or to exert a catalytic action on target analysis. According to Kalcher, four main functions of modifiers are, acting in catalytic phenomena, provide preferential entrapment of desired species, offer alteration to the surface characteristics of a CPE and acting as mediator in electrode reactions via immobilized molecules or their fragments. Other purposes of modification CPE are to enhance the analytical performance of the electrode by increasing the selectivity and sensitivity of the electrode or by shielding the surface of the electrode from undesired reactions (Kurt Kalcher, 1990). The modifier also improved the ability of electrons transfer to or from the analyte, improved some chemicals reactivity, further enhance the capability of CPE (Svancara et al., 2009).

A vast range of materials has been employed as electrode modifier aimed in improving the sensitivity and selectivity of the electrochemical responses, such as polymers, biological agents and nanomaterials. Nanomaterials can be classified into two categories which are carbon based nanomaterials and non-carbon nanomaterials (Kaya, Karabulut, Kurbanoglu, & Ozkan, 2019). Among them, one type of ionic liquid nanocomposites, which is an inorganic clay, also known as layered double hydroxides (LDHs), attract more considerable attentions as the modifier due to their perculiar properties, including large surface area, low toxicity, chemical inertness and remarkable anion exchange capability (Berber, Hafez, Minagawa, Mori, & Tanaka, 2011). Owing the structure similarities to hydrotalcite mineral, LDHs are also termed as hydrotalcite-like or anionic clays. The structure of LDH consists of octahedral positively charged edge sharing, which forming host layers with a brucite-like form as shown in Figure 1.6.

In addition, the host structure of LDH contain water which exhibit good conductivity as well as high proton mobility. LDH materials are naturally plentiful and can be readily prepared in the laboratory (Yin, Cui, Ai, Fan, & Zhu, 2010; Tonelli, Scavetta, & Giorgetti, 2013). LDHs containing various metal cations and carbonate anions. Besides that, LDHs also have good catalytic activity and adsorption property. They have diverse applications as catalyst, adsorbents, ion exchangers, catalyst support, flame retardants, polymer additives and corrosion inhibitors (Cavani, Trifiro, & Vaccari, 1991). Based on these properties and

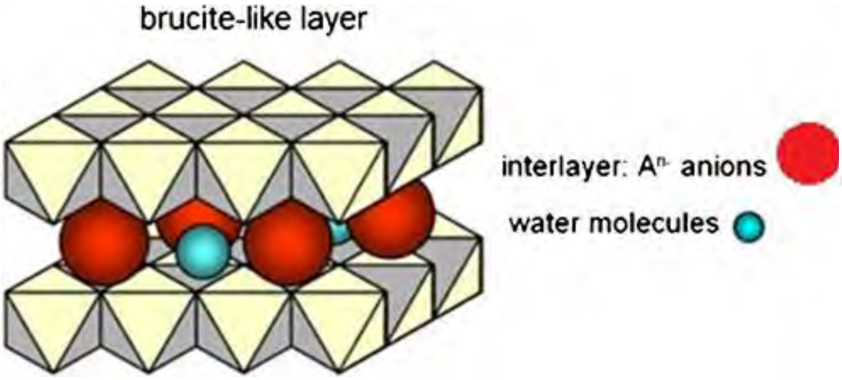


*Figure 1.6.* Structure of A Layered Double Hyrdoxide (LDH) (Tonelli et al., 2013)

applications, it is obvious that LDHs could be potentially attractive materials as electrode surface modification. The application of LDHs in electrochemical sensor will be further discuss in Sub-section 2.4 in Chapter 2.

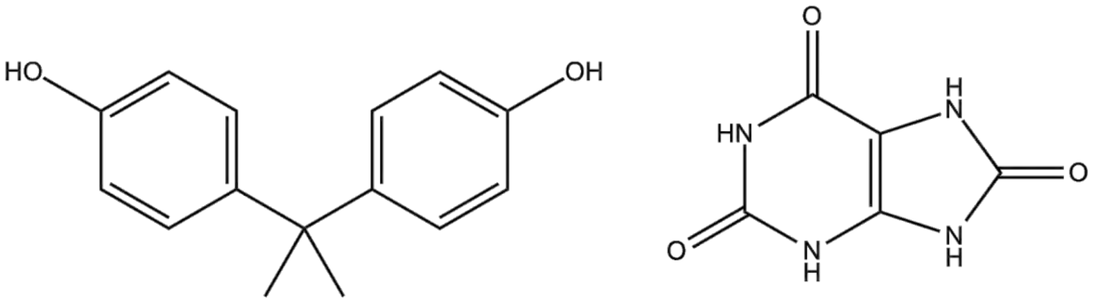
## 1.5 Bisphenol A, Uric acid, Dopamine and Acetaminophen

Bisphenol A (2,2-bis(4-hydroxyphenyl) propane, BPA), an organic compound with two phenol functional groups (Figure 1.7), is commonly used as an important monomer for the manufacture of plastics, such as epoxy resins and polycarbonates (PC). It is commonly used in adhesives and flame retardants, as well as in plasticizer antioxidants and in polyvinyl chloride polymerization inhobitors (Podlipna & Cichna-Markl, 2007; Flint, Markle, Thompson, & Wallace, 2012). During the production process, BPA is released into the environment mainly through waste water or through leaching from industrial PC or epoxy resin items, including water bottles, baby bottles, drink cans, food packaging coatings and eyeglass lenses (Staples, Dom, Klecka, Sandra, & Harris, 1998; Huang et al., 2012). BPA has also been implicated as an endocrine disruptor that is capable of mimicking natural hormones, thereby contributing to adverse health effects and increasing the risk of cancer. In addition, Canada and China have declared BPA as a toxic substance due to growing public concerns regarding the effect of BPA exposure on infants and children, and have thus banned the use of BPA in baby bottles in 2010 and 2011, respectively (Gao et al., 2012; Yonggui Li, Gao, Cao, & Li, 2012).

Uric acid (2,6,8-trihydroxypurine) is the main end product of the synthesis of purine. After primary filtration and partial secretion by the kidney, the production of uric acid from catabolism is readsorbed into the blood circulation system (Temerk & Ibrahim, 2015). The level of uric acid in healthy human being in serum and urine is from 0.24 to 0.52 mM and 1.4 to 4.4 mM, respectively (Kutzing & Firestein, 2008; Lakshmi, Whitcombe, Davis, Sharma, & Prasad, 2011; Raj & Ohsaka, 2003). The elevated level of uric acid may lead to several diseases such as gout, hyperuricemia, obesity, diabetes and Lesch-Nyhan syndrome (Ramesh & Sampath, 2004). Otherwise, the uric acid levels below normal concentration have been linked to Alzheimer's disease, Parkinson's disease, multiple sclerosis and optic neuritis (Kutzing & Firestein, 2008). The oxidation of electroactive uric acid in an aqueous solution can yield to allantoin as the major product (Khan, Haque, & Kim, 2013). Furthermore, as a reducing agent, uric acid 'scavenges' free oxygen radicals, preventing their destructive action towards tissues and cells (Huang, Jiao, & Li, 2014).

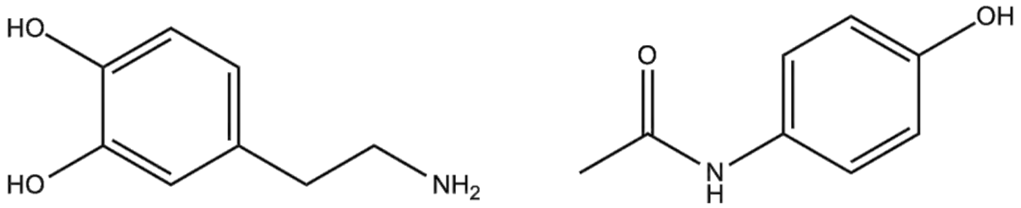
Dopamine is one of the important neurotransmitter that belongs to the catecholamine family and it exists in the mammalian central nervous system (Cheemalapati, Palanisamy, Mani, & Chen, 2013). Its plays a critical role in central nervous, cardiovascular, hormonal and renal systems. Those systems and the learning memory system may be affected by low level of dopamine in our central nervous (Kannan & Sevvel, 2017a). Normal level of dopamine in human blood is approximately 10.0 nM to 1.0 μM (Kalimuthu & John, 2011). Abnormal levels of dopamine in blood further cause neurological disorders such as Parkinsonism and Schizophrenia (Atta, Ali, El-ads, & Galal, 2013). The suffering patients of the Parkinson disease will undergo constant chronic pain due to the loss of control of motor function. In order to reduce this pain, some doctors prescribe for the patient acetaminophen as pain-killers. Hence, there are the probabilities to find both dopamine and acetaminophen together in the urine of the patient (Baccarin et al., 2017).

Acetaminophen (ACT, *N*-acetyl-*p*-aminophenol), an acylated aromatic amide, or commonly known as paracetamol, which its application in medicine was discovered in 1893 by Von Mering as a pharmaceutical analgesic and antipyretic agent (Baś, Bugajna, Jakubowska, Reczyński, & Smalec, 2013). It is internationally recognised medicine that is used to relieve pain associated with fever, headache, back pain, arthritis and postoperative pain (Su & Cheng, 2010). Acetaminophen regulates pain by disrupting the synthesis of prostaglandins in the central nervous system and sedating the centre for the regulating of hypothalamic heat (Mazloum-Ardakani et al., 2012). Acetaminophen, owing to its non-carcinogenic nature, serves as an analgesic agent in osteoarthritis and arterial hardening (D'Souza et al., 2015). This substance is useful for those who are sensitive to acetylsalicylic acid (ASA) (Prabakar & Narayanan, 2007). For humans who are normal drug user, ACT is considered safe at their therapeutic levels (Bessems & Vermeulen, 2001). However, it can cause hepatotoxicity, some cases associated with kidney and liver damage, when administrated at higher than recommended dosages, and in more severe cases; it can cause death (Su & Cheng, 2010). ACT may undergo degradation when exposed to light and give 4-aminophenol.



Bisphenol A

Uric acid



Dopamine

Acetaminophen

*Figure 1.7*. Chemical Structure of Bisphenol A, Uric Acid, Dopamine and Acetaminophen

### 1.5.1 Simultaneous determination of UA and BPA

Bisphenol A (BPA) is an essential monomer that is used in the manufacturing of plastics and is used in many consumer goods, such as bottles of water, bottles of food, and recycled food and beverage containers (Kang, Kito, & Kondo, 2003). BPA can leaches from these materials and enters into foodstuff (Brede, Fjeldal, Skjevrak, & Herikstad, 2003). In addition, studies also have shown that BPA is frequently found in waste water, river water, and sea water (Huang et al., 2012); Careghini, Mastorgio, Saponaro, & Sezenna, 2015). BPA can cause harm to human as this chemical belongs to a group of endocrine-disrupting compound, and its toxicity is widely reported in literature (Vandenberg, Hauser, Marcus, Olea, & Welshons, 2007).

Uric acid (UA), on the other hand, is the final product of purine metabolism, and oxidation of electroactive UA in an aqueous solution will give rise to allantoin as a main product that is freely removed by urination (Alvarez-Lario & Macarron-Vicente, 2010). Abnormal levels of UA are associated with gout disease, whereas the formation of UA crystal which eventually grow into stones causing harm to human organ such as kidney (Nuki & Simkin, 2006; Ferraro & Scd, 2017). Interestingly, it has been shown that the urine is a suitable marker for monitoring of BPA because almost 100% orally administered BPA is excreted via urine (Brock et al., 2001; Thayer et al., 2018). Thus, in tests like urine and blood, there is a need for simultaneous determination of UA and BPA.

### 1.5.2 Simultaneous determination of DA, ACT and BPA

DA is a molecule that has basic centers, which consists of one amino and two phenolate sites (Mirzahosseini, Palla, Orgovan, Toth, & Noszal, 2018). It is exists in central nervous system and shows a critical role in controlling our motive and cognitive systems (Westbrook & Frank, 2018). An abnormal levels of this neurotransmitter is generally known to be the cause of Parkinsonism and Schizophrenia (Macdonald et al., 2013; Howes, Mccutcheon, & Stone, 2015). The suffering patients will undergo constant chronic pain due to motor function abnormalities which related to neurological problems. Thus, for some cases, painkillers such as acetaminophen was administered to the patients (Steventon et al., 1990; Locke, Fox, Caldwell, & Caldwell, 2008)

ACT also known as paracetamol, was discovered in 1893 and has been widely used around the world as an analgesic and antipyretic. It is a worldwide known drug particularly due to its safe, effective, and available in various formulations (Yoon, Babar, Choudhary, Kutner, & Pyrsopoulos, 2016). The recommended maximum daily intake of ACT is 4 grams (Shiffman et al., 2018). However, excessive intake of ACT may cause the accumulation of toxic metabolites which further lead to liver injury (Black, 1984; Bunchorntavakul, 2013). Thus, it is important in monitoring the level of ACT in human body.

One of the endocrine disrupters capable of mimicking natural hormones is BPA (Frye et al., 2011). In the manufacturing of polycarbonate plastics such as food can linings, water tanks, baby bottles, and medical equipment, BPA functions as a monomer. Human may regularly expose to trace amounts of BPA since this compound may leach upon heating. Exposure to BPA has been associated with adverse effects against reproductive, metabolic, and developmental of humans (Rochester, 2013). Furthermore, studies found that the exposure to BPA may increase anxiety-like behaviors and alters the level of neurotransmitter specifically dopamine (Tanida et al., 2009; Cox, Gatewood, Howeth, & Rissman, 2010; Nakamura et al., 2012). In connection of clinical and pharmacological importance DA, ACT and BPA, as well as their simultaneous existence in some cases, a simple method for monitoring and determination of these compounds are required.

## 1.6 Problem Statement

As a primary monomer for the manufacture of polycarbonate polymers and epoxy resins, BPA is commonly used in the plastic industry (Saal & Hughes, 2005; Rosu et al., 2015). BPA is also ubiquitous in cans of plastic fruit, food can linings and bottles of wine, and so on. However, several experiments have shown that BPA is an endocrine-disrupting chemical that can imitate the effects of endogenous hormones (Segner, Navas, Schäfers, & Wenzel, 2003; Welshons, Nagel, & Saal, 2006) and is potentially dangerous to human health by disrupting the central nervous system and the reproductive system (Chapin et al., 2008; Vandenberg, Hauser, Marcus, Olea, & Welshons, 2007). In breast milk, on the other hand, BPA can also be found in (Ferrer et al., 2011). The risk of breast tumors in the human body can be increased by Bisphenol A. It is therefore very important to propose a highly sensitive and highly selective instrument for the determination of BPA in food samples.

A new research showed that high levels of uric acid associate with hyperthymic and irritable temperaments. (Kesebir, Yaylacı, Süner, & Gültekin, 2014). Many epidemiological studies have found that uric acid content in serum is also a risk factor for cardiovascular disease (Alderman, 2001). Besides that, UA also acts as an indicator for renal malfunction as well as renal toxicity. Thus, in biological fluids, the quantification and determination of electrochemically active UA is of clinical significance which can be used as a predictive factor for early disease detection.

Normal level of dopamine in human blood is around 0.01 μM to 1 μM (Kalimuthu & John, 2011). An acute exposure to higher level of dopamine may lead to the oxidative stress of dopaminergic neurons. The use of acetaminophen has proven by the *in vitro* studies to overcome this situation (Locke et al., 2008). While the *in vivo* studies found that the chronic usage of acetaminophen can reduce the levels of dopamine (Courade et al., 2001). Thus, the fast and precise determination of dopamine concentration in body fluid is an important issue to conveniently trace and diagnose (Zhang et al., 2013). Since dopamine is an electrochemical active species, its electrochemical detection can be easily realized, by giving dopamine-o-quinone as the oxidation product (Huang et al., 2013).

Acetaminophen is easily absorbed and metabolized in the liver through oral ingestion to reach peak plasma levels within 1 hour (Adhikari, Maduraiveeran, & Chen, 2014). Overdoses of acetaminophen may lead to the accumulation of toxic metabolites. In severe cases, it may cause nephrotoxicity and hepatoxicity (Olaleye & Rocha, 2008). Since acetaminophen is a "over the counter" drug, it is commonly used in suicide attempts (D'Souza et al., 2015). A single or combination determination of acetaminophen is a critical feature of quality management of pharmaceutical formulations. Similarly, in the medical field, where its determination is also essential in biological fluids such as blood, plasma or urine (Khaskheli et al., 2013). Besides that, it is also important to control the environmental contamination by pharmaceuticals like acetaminophen, to ensure the safety of water supply and to track the risk assessment of the environment across the human food chains. Pharmaceuticals can exist illegally in the environment through many ways such as the incorrect disposal of expired medicines and excretion by humans (Chiavazza et al., 2016). For that reason, it is indeed warranted to develop a rapid, simple, sensitive, accurate and low-cost analytical technique for the determination of acetaminophen. The development of electrochemical sensors for the determination of acetaminophen has received remarkable interest from researchers due to its readily oxidized electroactive compound.

Literature revealed that, several analytical techniques, including gas chromatography, high performance liquid chromatography, solid phase extraction and spectrophotometry, have been used to evaluate BPA, UA, DA and ACT (Correia-sá, Norberto, Delerue-matos, Calhau, & Domingues, 2018; Darmapatni, Basori, Suaniti, & Program, 2016; Caban, Lis, Kumirska, & Stepnowski, 2015; Zhou et al., 2013; Dawei et al., 2016; Li et al., 2018; Parmová, Havlíková, Chvojka, Solich, & Šatínský, 2017; Alnaimat, Barciela-Alonso, & Bermejo-Barrera, 2019; Wang et al., 2018). Unfortunately, most of these approaches are time-consuming, involving sample manipulation, relatively pricey, requiring large back-up facilities and trained operators, often difficult to use *in situ* environments. Since bisphenol A, uric acid, dopamine and acetaminophen are extremely electrochemically active, electrochemical sensors may be used for low cost, fast reaction, rapidity and on-site inspection to evaluate them.

## 1.7 Significant of Study

Those analytical techniques used in determination of BPA, UA, DA and ACT that previously discussed, such as gas chromatography, high performance liquid chromatography, solid phase extraction and spectrophotometry, require large and high-cost instruments, tedious and time-consuming sample pretreatment, also need to be operated by highly skilled technicians. Thus, this study is estimating to fabricate an electrochemical sensor which has fast response speed, more economical and simple operation. Since the electrochemical response of a bare electrode is occasionally insensible at low concentration of some analytes, this study proposes the modification of electrode surface. Carbon paste electrode consist of a peculiar mixture between multi walled carbon nanotubes (MWCNTs) and layered double hydroxide (LDH) capable in enhancing the sensitivity and selectivity of the electrochemical reaction against the determination of BPA, UA, DA and ACT. MWCNTs have a broad potential window, rich chemistry of the surface, chemical inertness, and suitability for different applications of sensing and detection. In the meantime, LDH is surprisingly sensitive to the intercalation of molecular anions with the magnetic properties of metal, which can increase the sensitivity of their identification. Hence, the incorporation of these materials produces a portable and low cost electrochemical sensor with an excellent sensitivity and selectivity.

## 1.8 Objectives of Study

The objectives of this study are as follows:

1. To fabricate multiwalled carbon nanotubes (MWCNT) modified with zinc layered hydroxide paste electrodes.
2. To study the electrochemical characterization of the Zn/Al-LDH-QC, Zn/Al-LDH-QM and Zn/Al-LDH-CP modified MWCNT paste electrodes.
3. To investigate the optimum experimental variables for the square wave voltammetry response of BPA, UA, DA and ACT at the Zn/Al-LDH-QC, Zn/Al-LDH-QM and Zn/Al-LDH-CP modified MWCNT paste electrodes.
4. To evaluate the developed MWCNT paste electrodes for the determination of BPA, UA, DA and ACT in real samples analysis.