# A multipurpose Voltammetric Sensor for the Determination of Chlorpromazine in Presence of Acetaminophen, Uric Acid, Dopamine and Ascorbic Acid

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We report the fabrication and characterization of a voltammetric sensor for the determination of chlorpromazine (CPM) based on multiwalled carbon nanotube-polyethyleneimine (MWCNT-PEI) composite modified glassy carbon electrode (GCE). The MWCNT-PEI composite was prepared by a simple ultrasonication method without any pretreatment of MWCNT. CPM shows irreversible oxidation peak at MWCNT and MWCNT-PEI modified GCE in pH 7 at 0.685 V. MWCNT-PEI shows excellent electroanalytical properties towards CPM and can detect as low as 10 nM level by differential pulse voltammetry (DPV) with a sensitivity of  $1.3 \ \mu A \ \mu M^{-1} \ cm^{-2}$ . The MWCNT-PEI film does not show any peak for ascorbic acid. However, it shows well defined and well separate peaks for dopamine, uric acid, acetaminophen and CPM in the same solution. Therefore, this sensor may be used for the determination of all these compounds individually or simultaneously. The fabrication method shows good reproducibility and the film exhibits good stability and appreciable performance in real sample analysis.

**Keywords:** multiwalled carbon nanotube, polyethyleneimine, composite, chlorpromazine, differential pulse voltammetry

# **1. INTRODUCTION**

Chlorpromazine (CPM) is an antipsychotic drug which is widely used for the treatment of acute and chronic psychoses, including schizophrenia and bipolar disorder [1,2]. CPM also shows superior effects to other drugs in the treatment of mania [3]. A recent study reveals that patients undergoing treatment with antipsychotic drugs are less likely to develop cancer than the general population [4]. Chlorpromazine ( $\alpha$ -2-chloro-10-(3-dimethylaminopropylidine)-phenothiazine comes under the drug

category of phenothiazine. It is a nitrogen- and sulfur-containing tricyclic compound with an aliphatic side chain attached to the 2 and 10 positions [5]. Therefore, monitoring of CPM is necessary for effective therapy. Several analytical methods have been developed for the determination of CPM. Analytical methods such as high performance liquid chromatography [6-9], chemiluminescence [10,11], chemiluminometric [12], spectrophotometric [13-15], spectrofluorimetric [16], voltammetric [17], polarography [18], gas chromatography [19], phosphorimetry [20] etc. have been reported. Conventional methods are usually expensive; involve time consuming process, use solvents, expensive instruments and need special training for the analyses. Among the various methods electrochemical methods have been found very effective due to their low cost, ease of fabrication, easy handling and fast response and sensitivity. Recently, Parvin et al reported the detection of CPM at graphene paste electrode by differential pulse voltammetry (DPV) with a detection limit of 6.0 nM [21]. The detection of CPM by electrochemical oxidation at GCE in pH 2 has also been reported [22]. Use of mediator like alizarin red has been reported for the determination of CPM [23]. The electrochemical techniques are excellent for the determination of pharmaceutical compounds in different matrices.

Carbon nanotubes (CNT) have been extensively used in electrode modification for electrochemical studies, due to their high specific surface area, excellent structural, electronic and mechanical properties. However, producing homogeneous dispersion of CNT in polar solvents is difficult due to its hydrophobic nature. Therefore, in many cases CNT is used after acid pretreatment or functionalization. Unmodified CNT may be dispersed in suitable surfactants like sodium dodecyl sulfate [24, 25] and polymer solutions like nafion [26, 27] and chitosan [28, 29] CNT modified electrodes also provide a faster electron transfer rate and catalytic activity towards many important biomolecules [30, 31]. PEI is an excellent material for preparing homogeneous multilayer films that can be used in various pH values [32]. Pristine CNT can be effectively dispersed in polycationic polyethylenimine (PEI) solution and it can form CNT-PEI composite on drying [33, 34]. CNT-PEI modified glassy carbon electrode shows an enhanced electroactivity of analytes for the determination of neurotransmitters, phenolic compounds, herbicides, etc, [35]. We reported the fabrication of MWCNT modified GCE [36-47]. In this work we report the fabrication of MWCNT-PEI modified GCE, characterization and its application for the voltammetric determination of CPM in pharmaceutical preparations.

#### 2. EXPERIMENTAL

# 2.1 Apparatus

The cyclic voltammetric experiments were carried out using a CHI 1205A model electrochemical workstation. A conventional three electrode system with MWCNT, PEI and MWCNT-PEI modified GCEs as working electrodes, a thin Pt wire as auxiliary electrode and Ag/AgCl (sat. KCl) as reference electrode was used for electrochemical studies. Electrochemical impedance spectroscopy (EIS) measurements were done using IM6ex ZAHNER (Kroanch, Germany). Scanning electron microscopy (SEM) was performed using a Hitachi S-3000 H Scanning Electron Microscope.

Differential pulse voltammetric (DPV) experiments were done with a CHI 900A electrochemical workstation.

## 2.2 Materials and reagents

Chlorpromazine and MWCNT with O.D. 10 - 15 nm, I.D. 2-6 nm and length  $0.1-10 \mu m$  were obtained from Sigma–Aldrich. PEI (50% (w/v) in water, average M 750,000) was obtained from Sigma-Aldrich. 0.1 M phosphate buffer solution (PBS) was prepared from 0.1 M Na<sub>2</sub>HPO<sub>4</sub> and NaH<sub>2</sub>PO<sub>4</sub> in deionized water to get pH 7. Real sample (Winsumin, 50 mg/tablet) was purchased from a local pharmaceutical company in Taiwan. Inert atmosphere was set by passing N<sub>2</sub> over the solution during experiment. All the experiments were conducted at ambient temperature ( $25^{\circ}C \pm 2^{\circ}C$ ).

## 2.3. Preparation of MWCNT-PEI composite modified electrode

The MWCNT was used as such without any pretreatment. The MWCNT-PEI composite solution was prepared by following the procedure reported elsewhere [48]. 4 mg of PEI (50% w/v) was dissolved in 1 mL of Ethanol to prepare the PEI solution. A uniform dispersion of MWCNT in PEI solution was prepared by dispersing 1 mg of MWCNT in 1mL of PEI solution and ultrasonication for 30 min. A homogeneous black solution was obtained. To fabricate the MWCNT-PEI composite modified electrodes, the GCE was polished using 0.05  $\mu$ m alumina slurry and Buehler polishing cloth. The GCE was washed and then ultrasonicated in deionized water and ethanol for 5 min each to remove any adsorbed alumina particles on the electrode surface. 5  $\mu$ L of MWCNT-PEI dispersion was drop casted onto the well polished GCE surface and dried at 50°C. Same conditions were used to fabricate MWCNT modified GCE and PEI modified GCE for comparison.

# **3. RESULTS AND DISCUSSION**

## 3.1 Surface morphological characterization of modified electrodes

Fig. 1 shows the SEM images of MWCNT and MWCNT-PEI films coated on indium tin oxide electrode with identical conditions mentioned for the GCE modification in section 2.2. Fig. 1(a) shows the SEM image of MWCNT film prepared from 1 mg/mL MWCNT dispersion in DMF. Fig. 1 (b) is the SEM image of MWCNT-PEI composite film. On comparing the SEM images of the two films it is clear that some morphological differences exist between them. MWCNT appears as thin nanofibers with random distribution on the ITO. The sonication process helps to unlock the MWCNT bundles into more simple strands of MWCNTs. The PEI coated MWCNT (Fig. 1b) appears as more bulky than the pristine MWCNT. Also, the MWCNT-PEI film has porous structure which is very helpful for the diffusion of the analyte for catalysis. Therefore, it is clear that PEI has formed as a coating on the surface of MWCNT and forms a stable MWCNT-PEI composite.



Figure 1. SEM images of MWCNT and MWCNT-PEI composite films

3.2 EIS studies of different films



**Figure 2.** EIS of bare GCE, MWCNT, PEI and MWCNT-PEI modified GCE in 5 mM  $Fe(CN)_6^{3-}$ /Fe(CN)<sub>6</sub><sup>4-</sup> in 0.1 M KCl. Applied AC voltage: 5 mV, frequency: 0.1 Hz to 100 kHz.

The electrochemical impedance properties of the bare GCE, MWCNT, PEI, MWCNT-PEI modified GCEs are recorded in 5 mM  $\text{Fe}(\text{CN})_6^{3-}/\text{Fe}(\text{CN})_6^{4-}$  in 0.1 M KCl and are represented as Nyquist plot ( $Z_{\text{im}}$  vs.  $Z_{\text{re}}$ ) in Fig. 2. The inset of Fig. 2 shows the Randles equivalence circuit model used to fit the experimental data. Where  $R_s$  is the electrolyte resistance,  $R_{\text{et}}$  is charge transfer resistance,  $C_{\text{dl}}$  double layer capacitance and  $Z_w$  is Warburg impedance. The semicircle appeared in the Nyquist plot indicates the parallel combination of  $R_{\text{et}}$  and  $C_{\text{dl}}$  resulting from electrode impedance.

The semicircles obtained at lower frequency represent a diffusion limited electron transfer process and those at higher frequency represent a charge transfer limited process. From Fig. 2, it is evident that bare GCE exhibits a larger semicircle compared to other electrodes indicating a higher charge transfer resistance. PEI and MWCNT also show good charge transfer properties. MWCNT-PEI shows very small semicircle suggesting a lower charge transfer resistance. This improved facile electron transfer is due to the formation of highly conducting MWCNT-PEI composite film on the GCE [49].

## 3.3 Electrochemical behavior of CPM at different electrodes



Figure 3. Cyclic voltammograms of  $4.76 \times 10^{-5}$  M CPM in 0.1 M PBS (pH 7) a) MWCNT-PEI/GCE, b) MWCNT/GCE, d) PEI/GCE and e) bare GCE. c) is MWCNT-PEI/GCE in 0.0 M CPM. Scan rate:  $0.05 \text{ Vs}^{-1}$ .

Fig. 3 shows the cyclic voltammetric behavior of CPM at various electrodes in N<sub>2</sub> saturated 0.1 M PBS (pH 7). Cyclic voltammograms were recorded in the potential range of 0 to 0.9 V vs. Ag/AgCl reference electrode at a scan rate of 0.05 Vs<sup>-1</sup>. In prior to each experiment, purified N<sub>2</sub> was purged into PBS containing  $4.76 \times 10^{-5}$  M CPM for 10 min. CPM shows an irreversible oxidation peak at bare GCE and PEI/GCE in pH 7 with almost same peak current. At MWCNT/GCE the peak current has been enhanced by 6.2 times than that of bare GCE and PEI/GCE. While MWCNT-PEI shows a 15.7 times increase in peak current. This enormous increase in peak current shows the high conducting nature and increased active surface area of the MWCNT-PEI composite modified electrode. As evident

from the EIS results in section 3.2, PEI forms a conducting composite with MWCNT and facilitates a fast electron transfer thereby increasing the efficiency of the electrode for the electrocatalysis of CPM.



3.4 Effect of pH on the electrochemical behavior of CPM at MWCNT-PEI/GCE

**Figure 4.** Cyclic voltammograms of  $4.76 \times 10^{-5}$  M CPM at MWCNT-PEI/GCE in different pH solutions a) 7, b) 3, c) 9 and d) 5 at a scan rate of 0.05 Vs<sup>-1</sup>. Inset is the pH vs. peak current.

Fig. 4 represents the cyclic voltammograms of  $4.76 \times 10^{-5}$  M CPM at MWCNT-PEI/GCE in the pH range from 3 - 9 at a scan rate of 0.05 Vs<sup>-1</sup>. CPM exhibits well defined anodic peak in pH 7 at 0.685 V. It also shows a second oxidation peak at 0.79 V in pH 7. CPM shows feeble oxidation peaks at pH 3, 5 and 9, however, does not show second oxidation peak. As can be seen from the inset of Fig. 4 in pH 7 CPM shows 9.6 times higher current than pH 3, 6.2 times higher than in pH 5 and 13.6 times higher in pH 9. Therefore, pH 7 has been chosen for all the electrochemical experiments in the work. CPM does not show any consistent peak potential shift with the change in pH.

#### 3.5 Different scan rate studies for MWCNT-PEI/GCE

Different scan rate experiment has been conducted to understand the nature of electrochemical process taking place at the electrode surface. The different scan rate studies were conducted for MWCNT-PEI/GCE using CV in 0.1 M PBS (pH 7) containing  $4.76 \times 10^{-5}$  M CPM in the potential range of 0.4 – 0.9 V. Fig. 5 shows the cyclic voltammograms obtained for CPM at different scan rates from 0.01 to 0.6 Vs<sup>-1</sup>. The anodic peak current increases with the increase in scan rate. The linear dependence of the peak current with the scan rate is given in the inset of Fig. 5.  $I_{pa}$  increases linearly with the square root of scan rate. The linear regression equation can be written as  $I_{pa}$  ( $\mu$ A) = 28.496 ( $v^{1/2}$ ) – 2.3415, R<sup>2</sup> = 0.9903. This result shows that the electrochemical oxidation of CPM at MWCNT-PEI/GCE is a diffusion controlled process [22].



Figure 5.Cyclic voltammograms recorded at MWCNT-PEI/GCE in N<sub>2</sub> saturated 0.1 M PBS (pH 7) in presence of  $4.76 \times 10^{-5}$  M CPM at different scan rates. From  $a \rightarrow j$ : 0.01, 0.03, 0.05, 0.07, 0.09, 0.15, 0.25, 0.35, 0.45 and 0.60 Vs<sup>-1</sup>. The inset shows the plot of  $I_{pa}$  vs. v<sup>1/2</sup>.

3.6 Electrocatalytic behavior of CPM at MWCNT-PEI/GCE



**Figure 6.** Cyclic voltammograms obtained for CPM in N<sub>2</sub> saturated 0.1 M PBS (pH 7) at MWCNT-PEI/GCE for various concentrations inner to outer: 1.49, 1.99, 3.99, 6.95, 9.90, 19.60, 29.13, 38.46, 47.62, 56.60, 74.07, 90.91, and 115.04  $\mu$ M. Scan rate: 0.05 Vs<sup>-1</sup>. Inset shows the plot of  $I_{pc}$  vs. [CPM]

Fig.6 shows the cyclic voltammograms obtained for various concentrations of CPM at MWCNT-PEI/GCE in pH 7. The CPM concentration in the solution was increased by adding several volumes of  $1 \times 10^{-3}$  M CPM solution. The anodic peak current increases with the increase in concentration of CPM from 1.49 – 115.4 µM. The linear dependence of  $I_{pa}$  to concentration of CPM is given in inset of Fig. 6.  $I_{pa}$  increases linearly with CPM concentration with a slope of 0.22 µA µM<sup>-1</sup> and the linear regression coefficient,  $R^2 = 0.986$ . The above result shows the stability of the film for electrocatalytic applications in which the analyte is added continuously for many additions. At higher concentrations, the second oxidation peak is also visible. MWCNT-PEI film shows a sensitivity of 3.11 µA µM<sup>-1</sup> cm<sup>2</sup>. Thus the film shows promising properties for its application for electroanalytical purposes. Differential pulse voltammetric technique could improve the sensitivity and linear range of the sensor.



3.7 Electroanalytical properties MWCNT-PEI/GCE towards CPM determination by DPV

**Figure 7.** Differential pulse voltammograms obtained at MWCNT-PEI/GCE for different concentrations of CPM in N<sub>2</sub> saturated PBS.  $a \rightarrow j$  is from 19 nM to 9.2  $\mu$ M. Inset shows the liner plot of  $I_{pa}$  vs. [CPM].

Fig. 7 shows the DPV of CPM at various concentrations in pH 7. Various volumes of  $1 \times 10^{-4}$  M CPM was added to pH 7 and the differential pulse voltammograms were recorded. The  $I_{pa}$  of CPM increased linearly with the increase in concentration. The inset of Fig. 7 shows the increase in peak current with the concentration of CPM. The linear regression equation can be written as  $I_{pa}$  ( $\mu$ A) = 0.12 + 0.0917 C ( $\mu$ M). R<sup>2</sup> = 0.9859. The linear range of detection of CPM is 19 nM to 9.2  $\mu$ M. The sensitivity of the electrode for CPM determination by DPV is 1.3  $\mu$ A  $\mu$ M<sup>-1</sup> cm<sup>-2</sup> in the linear range concentrations. The limit of detection (LOD) is 10 nM which was calculated as LOD =  $3S_b/S$  and the limit of quantification (LOQ) is 33.3 nM which was calculated as LOQ =  $LOQ = 10S_b/S$ , where,  $S_b$  is

the standard deviation of blank signal and *S* is the sensitivity of the electrode. These results show that the proposed electrode can be used effectively for the determination of CPM in real samples.



3.8 Selectivity of MWCNT-PEI composite film towards the determination of CPM

**Figure 8.** Differential pulse voltammograms recorded for various concentrations of a mixture of dopamine, uric acid, acetaminophen and CPM in N<sub>2</sub> saturated PBS. From a  $\rightarrow$ k are [UA] = [DA] = [PA] = [CPM] = 0.0, 0.199, 0.398, 0.596, 0.793, 0.99, 1.185, 1.38, 1.574, 1.768, 1.96  $\mu$ M.

In order to test the selectivity of MWCNT-PEI composite towards the detection of CPM, DPV response of CPM was recorded in presence of common interferrants such as uric acid, dopamine and acetaminophen. The DPV was run in pH 7 in the potential range of 0.0 to 0.9 V with amplitude of 0.05 V and pulse width of 0.05 s. A mixture of equal concentrations of all the aforementioned analytes were prepared and definite volumes of the the mixture were added and the DPV responses were recorded. Fig. 8 shows the DP voltammograms of all the anlaytes from 0.0 to 1.96 µM. The oxidation peaks of all the analytes are well defined and well separated. Oxidation peaks of UA, DA, PA and CPM increases linearly with the increase in concentration. Ascorbic acid does not show any characteristic peak in this potential range. Therefore this study suggests that CPM can be detected in presence of UA, DA and PA. Moreover, since the peaks are well separated and independent of the concentration of other analytes, UA, DA, PA and CPM can be simultaneously determined by DPV in pH 7. Therefore, MWCNT-PEI could be a promising material for real sample analysis.

## 3.9 Reproducibility and real sample analysis

To understand the reproducibility of the sensor, four individual electrodes were fabricated and the peak current was measured for a series of CPM concentrations by cyclic voltammetry. The sensor shows a relative standard deviation of 4.54% which shows the excellent reproductionity of the sensor fabrication and its application for CPM determination. To validate the possibility of practical application of the sensor, CPM in Winsumin tablets has been analyzed by DPV with the same conditions mentioned for lab sample analysis. Ten winsumin tablets containing 50 mg of CPM per tablet was dissolved in 1000 mL of buffer solution to prepare 1.40 M real sample solution. Definite volumes of the real sample solutions were added and the DP voltammograms were recorded. The error bars for the real sample measurements are given in Fig. 9. The error bars are small with RSD 3.15% to 15.2%. The result shows the high capability of the developed sensor in achieving high sensitivity and reproducibility for pharmaceutical sample analysis. The linear regression coefficient for the real sample is  $R^2 = 0.9879$ .



Figure 9. Error bars plot for CPM determination in real sample for 3 trials by DPV

# 4. CONCLUSIONS

A voltammetric sensor for the determination of chlorpromazine has been constructed by a simple procedure. The MWCNT-PEI film showed very low electron transfer resistance. Therefore, it is a good choice of electrode material for electrochemical sensors and biosensors. The proposed electrode can detect CPM in presence of uric acid, dopamine and acetaminophen. Also, it does not show any peak for ascorbic acid and it shows very high peak current for acetaminophen. Therefore, this sensor may be used as a acetaminophen sensor. Further, this sensor can also be used for the simultaneous determination of uric acid, dopamine, acetaminophen and CPM in presence of ascorbic. This wide choice of sensing properties of this sensor makes it attractive for further investigation and application.

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