Cyclic Voltammetric Studies of Micro and Nano Paracetamol Using Glassy Carbon Electrode Modified with Multi-Walled Carbon Nanotube and Graphene

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Abstract: The glassy carbon electrode (GCE) was modified with multiwalled carbon nanotube (MWCNT) and graphene (MWCNT/GCE), (graphene/GCE) to study the electrochemical behaviour of paracetamol using cyclic voltammetric technique at different paracetamol particles size (186μm, 4-9μm, 45nm) in a 10 ml solution of (1M) KCl and (0.1mM) paracetamol at scan rate (0.1 V/s). The results of cyclic voltammogram showed the anodic current peaks of paracetamol increases with decrease particle size. Also, the solubility is enhancement with decreasing particle size. MWCNT/GCE is a good biosensor with high electrochemical sensitivity for paracetamol than graphene/GCE.

1. Introduction
Paracetamol (PAR) is a safe analgesic agent effectively used worldwide for the relieving of pain associated with backache, headache, cancer pain and as a good replacement of aspirin for patients have sensitivity to aspirin [1]. Paracetamol is electroactive and can be oxidized under suitable conditions.

The detection of paracetamol using electrochemical methods and electrochemical sensors have received a great interest in the past few decades [2]. The oxidation of paracetamol was studied at a glassy carbon electrode modified with multi-walled carbon nanotubes and a graphene. A rapid and sensitive detection of the acetaminophen based on the bare (unmodified) screen printed carbon electrode (BSPCE) was reported by [3]. The mechanism of the electro-oxidation of acetaminophen as derived for various pHs showed that the acetaminophen is not stable in strong alkaline and strong acidic and media, which is hydrolyzed and hydroxylated. But the paracetamol is stable in intermediate pHs due to the dimerization of acetaminophen.

Cyclic voltammetry is an electrochemical method based on different types of working electrodes have been reported for PAR determination in pharmaceutical formulations, biological samples, and even wastewaters [4,5].

Cyclic voltammetry is an extremely sensitive electrochemical technique used to measure the amount of pharmaceutically active compound either in dosage forms or in biological samples using glassy carbon electrode or other modified electrode [6]. Electrochemistry has always provided analytical techniques with instrumental simplicity, moderate cost, and portability characteristics [7].
Glassy carbon (GC) is very useful electrode materials due to its high chemical inertness and temperature resistance, good electrical conductivity, low porosity, dimensional stability, high hardness, and reasonable mechanical and dimensional stability [8]. Although (GCE) is a very good electrode material, many attempts have been made to improve its electronic properties and electrochemical behaviour by modification with nanomaterials, such as graphene [9], carbon nanotubes [10], and metal nanoparticles [11]. These nanomaterials exhibit extraordinary electrical and physical properties, and they are very often used for the modifications of the electrode surface.

Graphene is a 2D-structured nanomaterial consisting of a single layer of carbon atoms. Graphene was a common nanomaterial commonly used to modify various types of electrodes for electrochemical analysis due to its remarkable features. Different chemically modified electrodes were formed by adding different molecules onto graphene in order to improve detection performance [12]. Carbon nanotubes (CNT) being several nanometers in diameter and many microns in length with two well defined regions with clearly different properties, the tube and the cap [13]. In healthcare system, CNTs can be used as electrochemical sensors and biosensors due to their high electronic conductivity, mechanical strength, and better electrochemical and chemical stabilities in both aqueous and non-aqueous solutions [14]. In this work modified GCE electrodes (MWCNT/GCE and Graphene/GCE) were used to study the electrochemical behaviour of micro and nano paracetamol with different particle sizes.

2. Experiment

2.1. Materials
Paracetamol (Hebei Jiheng Groups Pharmaceutical CO., LTD., China), Multiwall Carbon Nano Tubes (MWCNT) (Intelligent Materials Pvt. Ltd., Punjab, India), Graphene (SkySpring Nanomaterials, Inc. Houston, TX. 77082. USA) and Potassium chloride (KCl, 98%) from Sinopharm Chemical Reagent Co, China. These materials were used in this study. The electrolyte solution of cyclic voltammetry cell was prepared by using deionized water with (1M) KCl and treatment with nitrogen gas for 15 min to remove oxygen.

2.2. Apparatus
Cyclic Voltammetry (EZST 12051401, NuVant Systems, Inc.Crown Point, Indiana, USA) was used to study electrochemical analysis. Planetary Ball Mill (NQM-0.4 Model Planetary Ball Mill) was used to reduce particle size of Paracetamol. Particle Size Analysis (Malvern, Mastersizer 2000s, MAN0384 Issue 1.0, United Kingdom) and Scanning Electron Microscope (SEM) (VP-FeScan, TESCAN MIRA3 XMU, Scientific and Technical Instruments, Brno, Czech Koruna) were used to measure the particle size of paracetamol. FT-IR Spectroscopy (MB3000 spectrometer Horizon MB™, ABB, England) and X-Ray Diffraction (XRD) (SHIMADZU XRD-6000, Japan) were used to characterization MWCNT and graphene. The Atomic Force Microscopy (AFM) (SPM, NT-MDT Spectrum Instruments Co, Ntegra Prima, Russia Federation) was used for to characterization.

2.3. Modified Electrodes Preparation
The GCE was polished in a smooth circular or figure-eight motion with even pressure at regular intervals to avoid uneven electrode wear. The electrode was then ultrasonically cleaned in a water bath for 10 minutes, followed by rinsing in distilled watered and then dried using hair dryer. After polishing, the GCE was modified with nanomaterials by using mechanical attachment. The modified electrode was prepared by placing a few milligrams of nanoparticles (MWCNT or graphene) on a
filter paper first and then a polished GCE electrode is tapped onto nanoparticles on a filter paper more than twenty times to ensure some nanoparticles adhere to the electrode surface.

2.3.1 MWCNT/GCE Electrode Preparation
A well-polished, clean, and dry GCE was modified by MWCNTs using the mechanical attachment method, where some of the MWCNTs adhere to the GCE surface by tapping the electrode (about thirty times) onto MWCNTs on a filter paper as shown in figure 1. The MWCNT/GCE modified electrode is the working electrode and will be used in cyclic voltammetry to study paracetamol.

Figure 1. Mechanical attachment method to prepare MWCNT/GCE.

2.3.2 Graphene/GCE Preparation
A well-polished, clean, and dry GCE was modified by graphene using the mechanical attachment method, where some of the graphene to the GCE surface by tapping the electrode (about thirty times) onto graphene on a filter paper. The modified graphene /GCE electrode is the working electrode and will be used in cyclic voltammetry to study paracetamol.

2.4. Preparation of Paracetamol for Electrochemical Analysis
The particle size of as received paracetamol was tested using particle size analyzer. The as received paracetamol has a particle size of 186μm. The as received paracetamol was then milled for 30 min using Planetary ball mill (NQM-0.4 Model Planetary Ball Mill) with 1:15 weight ratio of powder to balls. After 30 min of ball milling, the average particles size of PAR was measured with particle size analyzer. The size was changed from 186 μm to (4-9 μm). This micro paracetamol was also used to study electrochemical analysis by cyclic voltammetry.

Then, as received paracetamol was milled for 5 hrs using Planetary Ball Mill with 1:15 weight ratio (powder to ball). After ball milling for 5 hrs, the average particles size of PAR was measured by atomic force microscopy and the size was changed to nano scale (45nm). This nano paracetamol was used to study electrochemical analysis by cyclic voltammetry. In this work, the as received paracetamol (186 μm), micro paracetamol (4-9 μm), and the nano paracetamol were used.

The three particle size of paracetamol were used in this study using modified electrode (MWCNT/GCE and graphene/GCE) at solution content 10ml (1M) KCl and 100μl (0.1M) paracetamol at scan rate (0.1 V/sec).
3. Results and Discussion

3.1 X-Ray Diffraction (XRD)

3.1.1 X-Ray Diffraction (XRD) for Graphene

The diffraction pattern for graphene is shown in figure 2. According to 1997 JCPDS - International Center for Diffraction Data (ICDD) No. 14-1487, the graphene diffraction peak appears at $2\theta = \sim 26.6^\circ$ corresponding to the diffraction plane (002) which is the characteristic of $\pi-\pi$ stacking feature present in graphite corresponds to an interlayer distance of $\sim 3.34 \text{ Å}$ [15].

![Figure 2. XRD of graphene.](image)

3.1.2 X-Ray Diffraction (XRD) for MWCNTs

The XRD pattern of MWCNT, figure 3 exhibits a strong and sharp diffraction peak at $2\theta = \sim 26.43^\circ$ corresponding to the graphite diffraction plane (002) with interlayer spacing of 3.37 Å and shows that the CNTs are crystalline in nature. This sharp peak is due to interlayer stacking of graphene sheets in a concentric cylindrical nature nested together in MWCNTs [16]. The sharpness, shape, and intensity of the (002) peak are modified with the increase in diameter of MWCNTs. There is a shift in the (002) peak at $2\theta = \sim 26.6^\circ$ for the graphite to $2\theta = \sim 26.43^\circ$ for MWCNTs due to the increase in spacing between carbon layers from 3.34 Å for graphite to 3.37 Å for MWCNTs. Other small peaks were also observed in XRD for MWCNTs at, 42.83° (100), 44.98° (101), and 54.27° (004) [17-19].

![Figure 3. XRD of MWCNTs.](image)
3.2 Fourier Transform Infrared Spectrophotometer (FTIR)

3.2.1 Fourier Transform Infrared Spectrophotometer (FTIR) for Graphene

The (FTIR) spectrum for graphene was performed in the wavelength range from 500 to 40000 cm\(^{-1}\) as shown in figure 4. The oxygen functional groups in graphene occur at absorption band of 3440 cm\(^{-1}\) which is assigned to O-H group stretching vibrations. The small peak at 1324 cm\(^{-1}\) is assigned to (C-O). The (C=C) group presences at small peaks at (1640cm\(^{-1}\) to 1432cm\(^{-1}\)). This results is agreement with [20,21].

![Figure 4. FTIR of Graphene.](image)

3.2.2 Fourier Transform Infrared Spectrophotometer (FTIR) for Multiwall Carbon Nanotubes (MWCNTs)

The (FTIR) spectrum was measured peak of MWCNT by exposed to IR beam of wave length range from 500 to 4000 cm\(^{-1}\) as shown in figure 5. The FTIR spectrum exhibited hydroxyl group (O-H) at peaks 3761 cm\(^{-1}\) and 3423 cm\(^{-1}\). The FTIR spectrum appearance Alkyl C-H Stretch at peaks (2926 cm\(^{-1}\) and 2860 cm\(^{-1}\)) and appearance Aromatic C-H Bending at peak 874 cm\(^{-1}\). The FTIR spectrum appearance C=O Stretch group at peak 1712 cm\(^{-1}\) and appearance ester C-O Stretch group at peak (1261 cm\(^{-1}\) and 1097 cm\(^{-1}\)). These results are agreements with [22 - 24].

![Figure 5. FTIR of MWCNTs.](image)
3.3 Particle Size Analysis

3.3.1 Particle Size Analysis for as Received Paracetamol
The particle size distribution for as received paracetamol is shown in figure 6. Most powder (D90) has an average particle size of 186 µm and span equal 6.

![Figure 6. Particle size distribution as received paracetamol.](image)

3.3.2 Particle Size Analysis for Micro Paracetamol
The paracetamol was milled for 30 min by planetary ball mill (NQM-0.4 Model Planetary Ball Mill) with 1:15 weight ratio (powder to ball). Figure 7 shows D10, D50, and D90. The D10 represent 10% of the particle is under this size, the D50 the median is half of the particle falls below this value and likewise for D90 is represent 90% of the distribution falls under this size. The particle size of paracetamol is (D10= 4µm, D50= 5µm, and D90= 9µm). Thus, the average particles size for microPAR (4-9µm). The span calculate from the following equations. The span value commonly represents the width of the particle size distribution [21].

\[
\text{Span} = \frac{D_{90} - D_{10}}{D_{50}} \quad (1)
\]

\[
\text{Span} = \frac{8.824 - 3.955}{4.98} = 0.977 \quad (2)
\]

![Figure 7. Particle size distribution of micro paracetamol after 30 min milling.](image)
3.4 Scanning Electron Microscopy (SEM)

3.4.1 Scanning Electron Microscopy (SEM) for Micro Paracetamol

The paracetamol was analysed by scanning electron microscopy (VP-FeScan, TESCAN MIRA3 XMU, Scientific and Technical Instruments, Brno, Czech Koruna). The paracetamol was milled for 30 min by planetary ball mill (NQM-0.4 Model Planetary Ball Mill) with 1:15 weight ratio (powder to ball). The SEM images showed the particles of PAR have irregular shape, as shown in figure 8.

![Figure 8](image)

**Figure 8.** Scanning electron microscopy of microparacetamol.

3.4.2 Scanning Electron Microscopy (SEM) for Nano Paracetamol

The surface of the paracetamol was analyzed by scanning electron microscopy (VP-FeScan, TESCAN MIRA3 XMU, Scientific and Technical Instruments, Brno, Czech Koruna). The SEM image of PAR after milling by planetary ball mill (SFM-1 Desk-Top Planetary Ball Mill) at weight ratio 1:15 (powder to ball) for 5 hrs milling time was shown in figure 9.

![Figure 9](image)

(b) 5 hrs milling time

**Figure 9.** Scanning electron microscopy of nano paracetamol.

3.5 Atomic Force Microscopy (AFM)

3.5.1 Atomic Force Microscopy (AFM) for Graphene

figure 10 shows the 0.7758 nm is a single layer graphene which is in agreement with AFM image for graphene. The thickness of graphene layer has been determined to be 0.7758 nm as shown in figure 4b. The results of AFM can be used to determine single-layer graphene and the thickness of single-layer graphene is in a range 0.34–1.2 nm [22]. Figure 10 the thickness results of [23]. The thickness values of 0.7758 nm is slightly greater than that measured for ideal graphene with thickness of around 0.335 nm.
3.5.2 Atomic Force Microscopy (AFM) for Nano Paracetamol

The AFM for paracetamol is shown in figure 11. The paracetamol powder was milled using planetary ball mill for 5 hrs with 1:15 weight ratio (powder to ball). The scan was done on 3 × 3 μm area to determine the particles size distribution and the nature of the crystallites on mica surfaces. The AFM images of nano paracetamol showed the nano paracetamol has particle size approximate 45 nm in scan area 3 × 3 μm as shown in figure 11c. The 3D surface figure 11a shows the nano paracetamol has irregulars shape.
Figure 11. AFM for nano paracetamol, (a) 3D surface, scan area 3 × 3 μm, (b) 2D view of the surface, scan area 3 x 3 μm, (c) Particles size distribution, scan area 3 x 3 μm.

3.6 Electrochemical Characterization

The cyclic voltamograms results in figure 12 for particle size 186 μm, figure 13 (4-9) μm, and figure 14 for nanoparticle size (45nm) and from the table 1 and table 2 can be proved the electrochemical of paracetamol was enhancement with decrease particle size of paracetamol. The results of cyclic voltammograms for modified electrodes (MWCNT/GCE and graphene/GCE) can be show the MWCNT/GCE is best sensor than graphene/GCE.

3.6.1 Electrochemical Study for as Received Paracetamol (Particle Size 186 um)

The cyclic voltammetry for as received paracetamol (particle size 186 um), from the figure 12 can be show the current peak for MWCNT/GCE 90 μA and for the graphene/GCE 68 μA.

Figure 12. The cyclic voltammograms black is MWCNT/GCE and the green is graphene/GCE in 10(ml) solution of (1M)KCl and 100ul (0.1M) of Paracetamol at particle size 186um.

3.6.2 Electrochemical Study for Micro Paracetamol (Particle Size 4-9 um)

The cyclic voltammetry for particle size (4-9 um), from the figure 13 can be show the current peak for MWCNT/GCE approximate 155 μA and for the graphene/GCE approximate 105 μA.
3.6.3 Electrochemical Study for Nano Paracetamol

The cyclic voltammetry for nano paracetamol (45 nm) is shown in figure 14. The anodic current peak for MWCNT/GCE approximate 396 μA and for the graphene/GCE approximate 284 μA. The cathodic current peak -170 μA for MWCNT/GCE and -129 μA for graphene/GCE.

3.6.4 Relationship between particle size and electrochemical

From the table 1 and table 2 can be proved the electrochemical behaviour of paracetamol was enhancement with decrease particle size of paracetamol. The modified electrode (MWCNT/GCE) has high current compared with modified modified electrode (graphene/GCE) this result gave indicate the modified electrode (MWCNT/GCE) is best select use in study electrochemical behaviour of paracetamol.
Table 1. Relationship between particle size and anodic current peaks for modified electrode (MWCNT/GCE) in solution contain 1ml KCl (1M) and 100 μl from Paracetamol (0.1M).

| Particle size       | Ipa1 (μA) | Ipa2 (μA) |
|---------------------|-----------|-----------|
| 186um               | 90        | 22        |
| 4-9um               | 155       | 80        |
| Nanoscale (45nm)    | 396       | 122       |

Table 2. Relationship between particle size and anodic current peaks for modified electrode (graphene/GCE) in solution contain 1ml KCl (1M) and 100 μl from Paracetamol (0.1M).

| Particle size       | Ipa1 (μA) | Ipa2 (μA) |
|---------------------|-----------|-----------|
| 186um               | 68        | 20        |
| 4-9um               | 105       | 50        |
| Nanoscale(45nm)     | 284       | 117       |

4. Conclusions
Cyclic voltammetry was employed for the study of the electrochemical behavior of micro paracetamol and nano paracetamol using modified electrode (MWCNT/GCE and graphene/GCE) at solution content 10ml (1M) KCl and 100μl (0.1M) paracetamol at scan rate (0.1 V/sec). The milling process using planetary ball mill with 1:15 weight ratio (powder to ball), is a successful process in reducing paracetamol particle size from 186 μm (as received paracetamol) to nano paracetamol in 5hrs. The electrochemical studies by cyclic voltammetry with Modified GCE (MWCNT/GCE and graphene/GCE) showed:
A comparison of the voltammetric response of paracetamol at (MWCNT/GCE) is better than (graphene/GCE). Furthermore, the voltammetric response of nano paracetamol is better than that for as received paracetamol and for micro paracetamol.

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