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A highly sensitive and selective electrochemical determination of non-steroidal prostate anti-cancer drug nilutamide based on *f*-MWCNT in tablet and human blood serum sample

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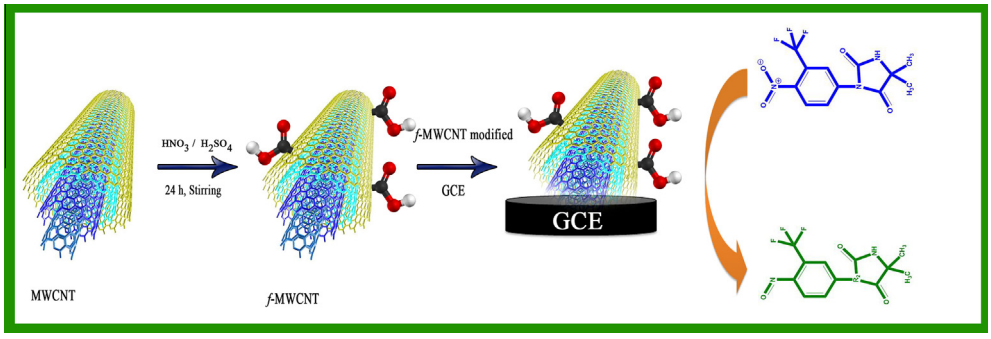
GRAPHICAL ABSTRACT



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ABSTRACT

A novel electrochemical sensor based on the functionalized multiwalled carbon nanotube (*f*-MWCNT) was successfully developed for the sensitive and selective determination of non-steroidal prostate anti-cancer drug nilutamide in tablet and blood serum samples. The *f*-MWCNT was prepared by the simple reflux method and characterized by the scanning electron microscopy (SEM), energy-dispersive X-ray spectroscopy (EDX), Raman spectroscopy, X-ray powder diffraction (XRD) and fourier transform infrared spectroscopy (FT-IR). Interestingly, the *f*-MWCNT was exhibited a superior electrocatalytic activity towards the anti-cancer drug nilutamide when compared with pristine MWCNT and unmodified electrodes. Besides, the electrochemical sensor was revealed an excellent current response for the determination of nilutamide with wide linear ranges (0.01–21 μM and 28–535 μM), high sensitivity (11.023 and 1.412 μA μM^{-1} cm^2) and very low detection limit (LOD) 0.2 nM. The developed electrochemical sensor was showed an excellent selectivity even in the presence of electrochemically active biological substances and nitro aromatic compounds. Moreover, it manifested a good reproducibility and stability. In addition, the *f*-MWCNT modified glassy carbon electrode (GCE) sensor was successfully applied for the detection of nilutamide in tablet and blood serum sample.

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1. Introduction

Nilutamide (5,5-dimethyl-3-(4-nitro-3-(trifluoromethyl)phenyl) imidazolidine-2,4-dione) (the chemical structure of nilutamide as shown in Fig. 1) is a non-steroidal, synthetic, pure anti-androgen drug and it is generally used in the treatment of advanced-stage of metastatic prostate cancer. A natural hormone of the testosterone helps to grow and spread out the normal and cancerous cells in the prostate. Nilutamide blocks the action of androgens (e.g. testosterone) of adrenal and testicular origin that arouse the growth of normal and malignant prostatic tissue as a result to extend the human life. The nilutamide dosage level is increased in human body causes severe side effects such as sexual dysfunction, interstitial pneumonitis, nocturnal amblyopia, nausea, decreased libido, visual disturbance, hemeralopia, chromatopsia, loss of body hair, blood in the urine, chest pain, difficult or labored breathing, trouble with sleeping and vomiting [1]. Aforementioned severe side effects of nilutamide, the dosage level must be controlled in pharmaceutical practices. Therefore, the determination of nilutamide in biological fluids is very significant. So far, only a limited analytical technique have been developed and reported for the determination of nilutamide including square wave voltammetry, micellar electrokinetic chromatography and spectrophotometry [2–4]. From the literature report, only one report available for the electrochemical determination of nilutamide by using square wave voltammetry method. Hence, we need to improve and develop the materials for the sensitive and selective electrochemical determination of nilutamide for the biological practices.

From the past decades carbon and carbon-based materials play a significant fundamental role in endeavors in nanotechnology, leading scientific and industrial research. The carbon material such as graphite, amorphous carbon, fullerene (C60), fullerene (C540), carbon onions, graphene, carbon nanotube (CNT- (SWCNT: MWCNT)) have been widely used in many essential applications like drug delivery [5,6], luminescent nanomaterials [5,7], nanocomposites [8–11], catalyst of chemical reaction [12] due to their good environmental stability, large surface area and thickness, etc. [13–16]. Among the carbon materials, the MWCNT attains more interest from current researchers due to their unique and physical properties such as electrochemically accessible area, large surface area, strong adsorption capability, good chemical stability, significant mechanical strength and high electrical conductivity [17]. However, the pristine CNTs are insoluble in water (aqueous) it would be discomfort for the significant applications such as electrode fabrication. Interestingly, the functionalization method has become more attractive in recent years due to the removal of impurities from CNT and also enhances the solubility and electrochemical properties. Most significantly, functionalization process creates the anchoring sites on CNT which would be more accessible to electrode fabrication. A number of applications have been developed based on *f*-MWCNT such as an electrochemical sensor, photovoltaic, biomedical and medicine, catalysis and membranes, electronics and nano-composites [18,19,20–27]. It opens the way to construct the nature-mimicking material and device at nano-scale which moving forward their applications in pharmaceuticals and industries.

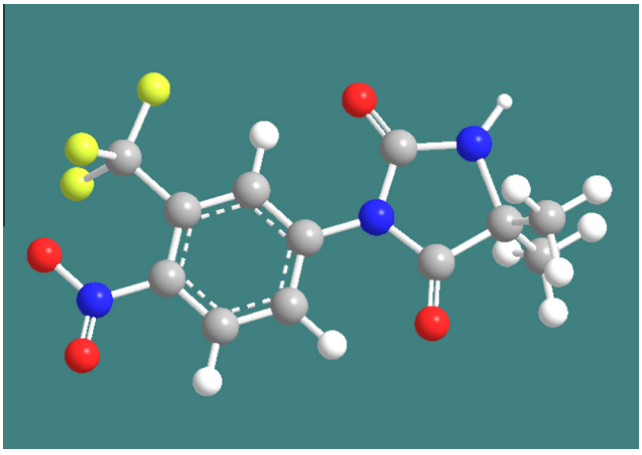


Fig. 1. The 3D chemical structure of nilutamide (5, 5-dimethyl-3-(4-nitro-3 (trifluoromethyl) phenyl) imidazolidine-2, 4-dione).

The main objective of this work is to develop a selective and sensitive method for the determinations of nilutamide based on *f*-MWCNT/GCE for the first time. The prepared *f*-MWCNT was characterized by various physicochemical characterizations. It was determined the nilutamide with the limit of detection (LOD) is 0.2 nM. To the best of our knowledge, this is the lowest LOD achieved among the entire electrochemical sensor available in the previous literature and listed in Table 1. We also demonstrated the practical applicability of real sample analysis in nilutamide tablet and human (spiked) blood serum samples based on *f*-MWCNT modified GCE and obtained acceptable recoveries.

2. Experimental section

2.1. Materials

Pristine carbon nanotube (multi-walled O.D × L 6–9 nm × 5 μM, >95%) and nilutamide were purchased from Sigma-Aldrich. Nitric acid (HNO_3), sulphuric acid (H_2SO_4), glucose, sucrose, fructose, lactose, dopamine, uric acid, ascorbic acid, catechol, nitrobenzene, 4-nitrophenol, 4-acetamido phenol and 4-nitro toluene were obtained from Sigma-Aldrich. The supporting electrolyte utilized for all experiments was prepared by using 0.05 M Na_2HPO_4 and NaH_2PO_4 solutions. All other chemicals were of analytical grade and the required solutions were prepared with double-distilled (DD) water.

2.2. Methods

FT-IR spectra were recorded by using the model Jasco FT/IR-6600 spectrophotometer. The XRD data was analyzed for the MWCNT and *f*-MWCNT in XPERT-PRO (PANalytical B.V., The Netherlands) diffractometer (Cu Ka radiation, k ¼ 1.54 Å). Raman spectra were recorded using a Raman spectrometer (Dong Woo 500i, Korea) equipped with a charge-coupled detector. The structure and surface morphological study were examined using scanning electron microscopy (SEM Hitachi S-3000 H) attached with energy-dispersive X-ray analyzer, Cylic Voltammetry (CV) and differential pulse voltammetry (DPV) experiments were performed using CHI 405A and CHI 900 work station. Amperometric measurements have been studied with analytical rotator AFMSRX (PINE instruments, USA) with a rotating disk electrode (RDE) having working area of 0.21 cm^2. Electrochemical studies were implemented in a conventional three electrode cell system using GCE as a working electrode (working area = 0.07 cm^2), platinum wire as a counter electrode and saturated Ag/AgCl (saturated KCl) as a reference electrode. All the electrochemical measurements have been executed at room temperature.

2.3. Preparation of f-MWCNT

The purchased pristine MWCNT were redispersed in a mixture of nitric acid and sulphuric acid with a volume ratio of (1:3) and the obtained mixture solution was refluxed for 24 h at ambient temperature. After that, the oxidized (Carboxylic acid-functionalized MWCNT (MWCNT-COOH)) pristine MWCNT solu-

Table 1
Comparison of the major characteristic of the different methods used in the determination of nilutamide.

Methods	Linear range	Limit of detection	Sensitivity ($\mu A\ \mu M^{-1}\ cm^2$)	Refs.
Micellar electrokinetic chromatography	–	26 μg/L	–	[3]
UV–Visible Spectrophotometric	10.0–50.0 μg/mL	0.0175 μg/mL	–	[35]
Automatic micro-flow system	–	2.26 mg/L	–	[36]
Square wave adsorptive stripping voltammetry (SWASV)	–	0.003 (μM)	–	[2]
Differential pulse voltammetry (DPV)	0.01–21 (μM) 28–535 (μM)	0.0002 (μM)	11.023	This work

tion was diluted by using a large amount of DD water. Then the *f*-MWCNT was filtered by using No. 1 Whatman filter paper and the product was washed many times with DD water until the concentration of acid-free when the pH of *f*-MWCNT is equal to the water pH. Later, the obtained products were dried in a vacuum oven at a temperature of 80 °C for 24 h.

2.4. Fabrication of f-MWCNT on the glassy carbon electrode

The final product of *f*-MWCNT (1 mg mL^{-1}) was re-dispersed in DD water and ultrasonicated for 5 h to get homogeneous *f*-MWCNT solution. Before modification, the GCE was polished with 0.05 μM alumina slurry. Then, about 8 μL (optimized concentration) of *f*-MWCNT solution was drop casted on the GCE surface and the modified GCE was allowed to dry at room temperature. After that, the dried GCE was gently washed with DD water to remove the loosely attached *f*-MWCNT on the surface of GCE. The obtained *f*-MWCNT modified GCE was used for further electrochemical experiments.

3. Results and discussion

3.1. Characterization of f-MWCNT

The structure and morphology of the MWCNTs were examined (before and after functionalization) by SEM and shown in Fig. 2. Fig. 2A shows the pristine MWCNT; it appears that the uniform morphology of nanotubes is relatively smooth. Fig. 2B shows the corresponding to the EDX spectrum of pristine MWCNT which clearly confirms that there was only a strong carbon (C) signal appeared at around 0.2 keV. After the functionalization, the morphology changes were clearly observed by the oxygen functionalities in MWCNT (Fig. 2C) surfaces and it was further confirmed by EDX spectrum. Fig. 2D shows the corresponding to the EDX spectrum of Fig. 2C, it clearly confirmed a strong signal of carbon (C) and oxygen (O) peak appeared at around 0.5 keV, it showed a good agreement with the pristine MWCNT. This result exhibited that the pristine MWCNT was successfully functionalized.

The functional groups of the as-synthesized *f*-MWCNT were characterized by FT-IR study. Fig. 3 displays the FT-IR spectrum of pristine MWCNT (A) and *f*-MWCNT (B) respectively. There were no discernible bands were observed for pristine MWCNT (Fig. 3A). After the functionalization of MWCNT, the appearance of a sharp peak at 1638 cm^{-1} ascribed to the —C=O stretching vibrations of carboxylic group and the broad peak at 3314 cm^{-1} is corresponds to the —O—H stretching of hydroxyl group attached to the MWCNT (Fig. 3B). Raman spectroscopy is a most powerful tool to analyze the defects and disorders of the carbon materials. Fig. 4 (A) and (B) show the Raman spectra of MWCNT and *f*-MWCNT, the obtained peaks at 1563 cm^{-1} and 1322 cm^{-1} corresponds to the G band (E_{2g} symmetry) of sp^2 hybridized graphitic structure

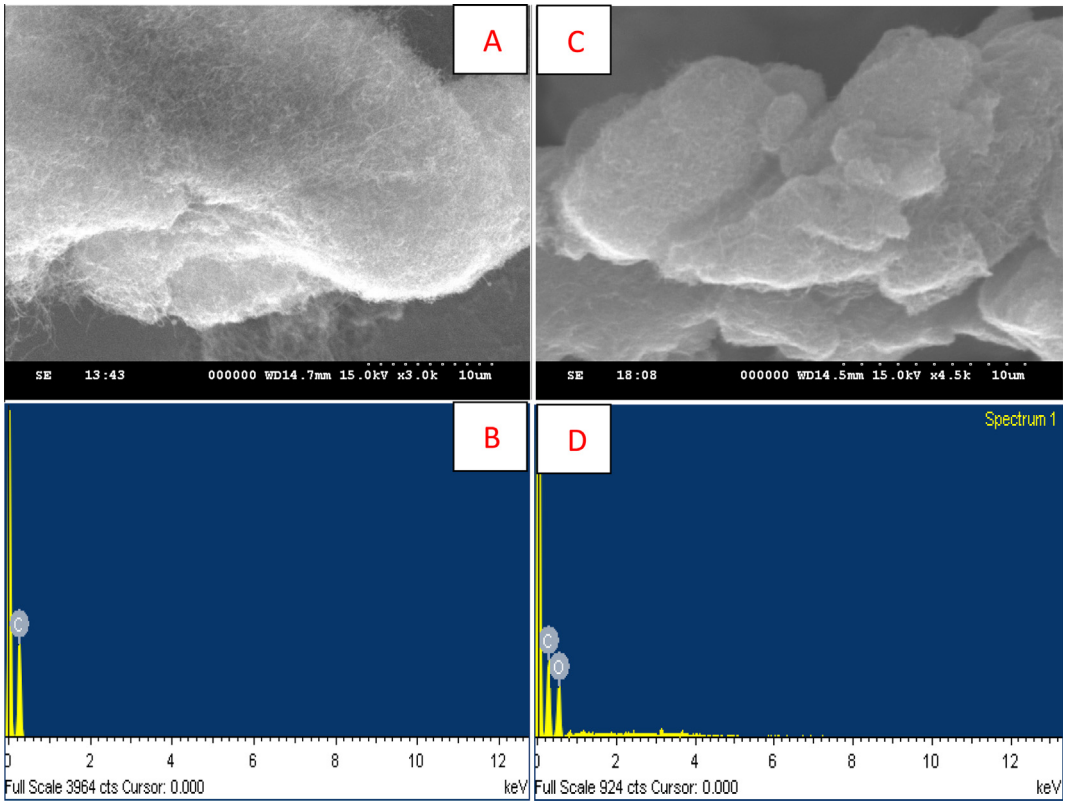


Fig. 2. SEM images and EDX spectra of (A, B) pristine MWCNT (C, D) *f*-MWCNT.

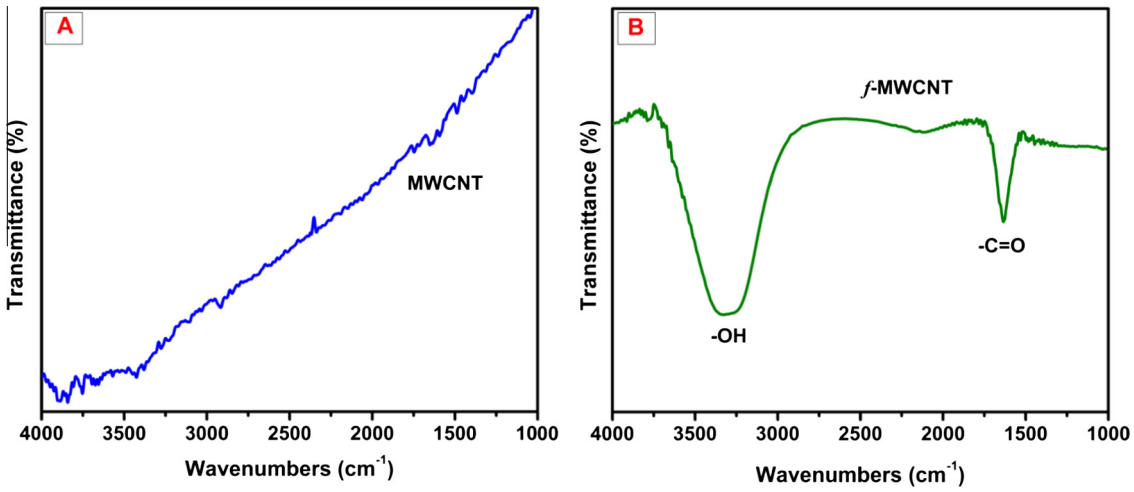


Fig. 3. FT-IR spectra of (A) pristine MWCNT and (B) *f*-MWCNT.

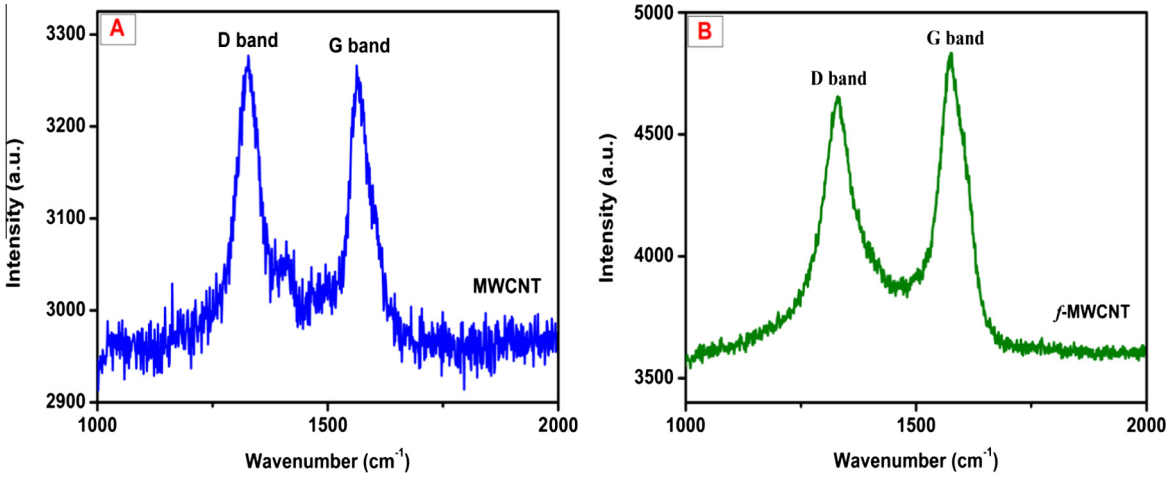


Fig. 4. Raman spectra of (A) pristine MWCNT and (B) *f*-MWCNT.

and the D band of sp^3 disordered carbon, respectively. From the Fig. 4(B), the intensity of the peak increases suggests that successful functionalization of MWCNT. Fig. 5 depicts the typical XRD spectra for MWCNT (A) and *f*-MWCNT (B), the peaks in the 2θ range at 26° and 42° attributed to the (0 0 2) and (1 0 0) reflection planes, respectively. This observation confirmed that the tubular structure of MWCNT retained after the functionalization process.

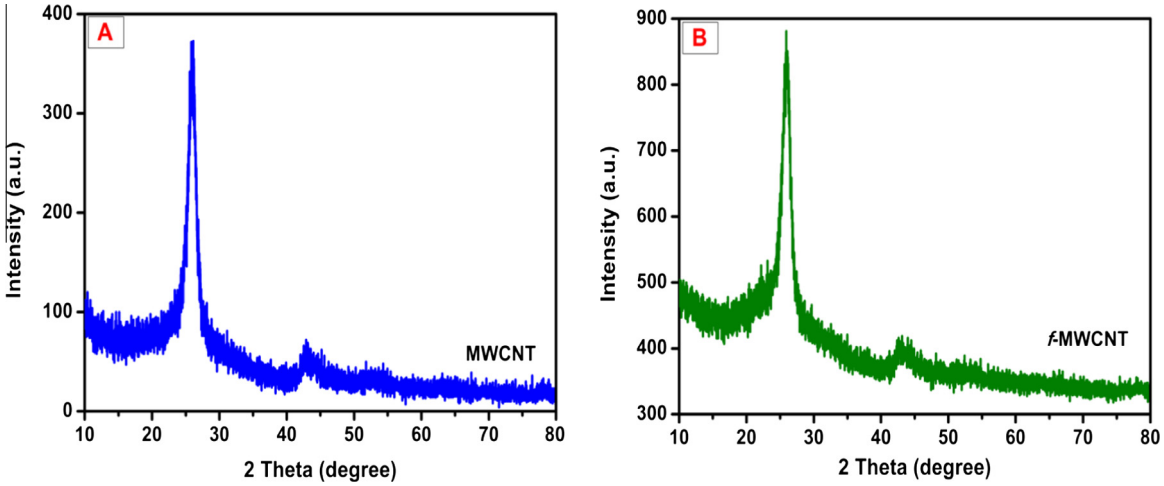


Fig. 5. XRD pattern of (A) pristine MWCNT and (B) *f*-MWCNT.

3.2. Electrochemical behavior of anti-cancer drug nilutamide at different modified electrodes

The electrochemical performance of nilutamide on various modified electrodes was investigated by CV. Fig. 6 shows the electrochemical performance of nilutamide on (a) *f*-MWCNT/GCE (b) *f*-MWCNT/GCE in the absence and (c) MWCNT/GCE (d) bare GCE in the presence of 200 μM nilutamide containing 0.05 M PB solution (pH 7) at a scan rate 50 mV/s. From the CV curves (a) (*f*-MWCNT/GCE), there is no cathodic and anodic peak was observed in the selected potential window range from 0.4 to −0.9 V. At the same time, in the presence of 200 μM nilutamide, an enhanced well-defined and very sharp cathodic peak (R_1) was observed at the potential of −0.48 V (Fig. 6b) in the same selected potential window range. The corresponding cathodic peak is related to the direct reduction of nilutamide to phenyl hydroxylamine [28]. On the reverse scan, there is no other oxidation peak was observed corresponding to the peak of R_1 it's due to the irreversible process. Even though, five more peaks are also observed at *f*-MWCNT/GCE and it was denoted as R_2, R_3, R_4, O_1 and O_2. The cathodic peak of R_4 is owing to the formation of phenylhydroxylamine to aniline. The redox couple of O_1/R_2 is due to the reversible behavior of phenylhydroxylamine to nitroso derivatives [29]. The one more reversible redox couple of O_2/R_3 is appeared at the potential of −0.06 V (anodic peak potential) and −0.06 V (cathodic peak potential) owing to the formation of by products from R_4 [30]. The cathodic peak current of R_4 is very lower compared to R_1, which suggests that the nilutamide reduction at *f*-MWCNT/GCE is more favorable to form a phenylhydroxylamine in alkaline or neutral electrolyte. On the other hand, the MWCNT/GCE (Fig. 6c) and bare GCE (Fig. 6d) was also examined in the presence of 200 μM nilutamide. The cathodic peak current of nilutamide at *f*-MWCNT/GCE was 2.0 and 7.17 fold much higher, very sharper than that of MWCNT/GCE and bare GCE. Besides, the cathodic potential of nilutamide at *f*-MWCNT/GCE (−0.48 V) was lower compared to other modified electrodes such as MWCNT/GCE (−0.52 V) and bare GCE (−0.61 V). The overall results suggest that the *f*-MWCNT exhibited the enhanced current response and lower reduction potential for the detection of nilutamide. The *f*-MWCNT modified GCE is a novel and more attractive electrode material for the determination of anti-cancer drug nilutamide than that of other modified and unmodified electrodes. The reduction mechanism of nilutamide as can be seen Scheme 1.

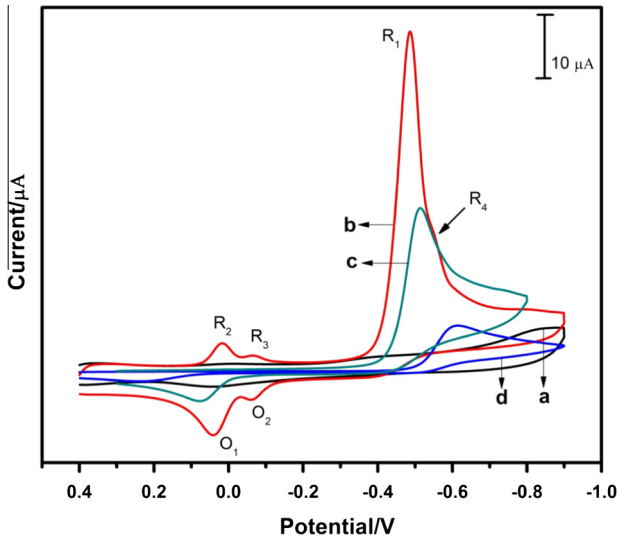
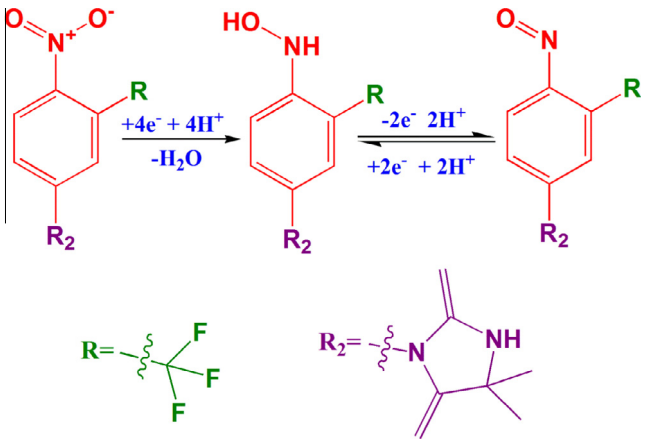


Fig. 6. CVs response of nilutamide on (a) *f*-MWCNT/GCE in absence and presence of (b) *f*-MWCNT/GCE (c) MWCNT/GCE (d) bare GCE in 200 μM nilutamide containing 0.05 M PB solution (pH 7) at a scan rate 50 mV/s.



Scheme 1. The reduction mechanism of nilutamide.

3.3. Effect of scan rate

Fig. 7A reveals that the effect of scan rate on the electrochemical performance of 200 μM nilutamide at the *f*-MWCNT modified GCE in 0.05 M PB solution (pH 7) with different scan rate ranging from 20 to 200 mV/s (a–j; 20–200 mV/s). From the figure, the cathodic peak currents increased linearly when increasing the scan rate and cathodic peak potential was also slightly shifted to the more negative side. The linear relationship plot was fitted in (Fig. 7B) scan rates *vs.* cathodic peak current with a linear regression equation of Ipc (μA) = −0.7369 × −20.615 and correlation co-efficient R^2 = 0.999, which suggesting that the reduction of nilutamide at the *f*-MWCNT modified GCE is a typical adsorption-controlled process [31].

3.4. Effect of pH

The pH of electrolyte can affect the performance of *f*-MWCNT modified GCE to the electrochemical reduction of nilutamide. The influence of pH on the cathodic peak current for nilutamide was investigated in the range of 3–11 in 0.05 M PB solution. As depict in Fig. 8A, increasing the pH value from 3 to 7 the cathodic peak current of nilutamide was increased and the cathodic peak current was decreased while increasing the pH of above 7. So, we chosen pH 7 is optimized pH for further electrochemical studies. At the higher pHs, the more hydroxyl ions are interact with the nilutamide and leads to the de-protonation, hence the electrocatalytic activity was decreased [32]. The linear plot of cathodic peak potential and different pH is shown in Fig. 8B. With increasing the pH from lower to higher the cathodic peak potential was shifted negative side and linearly (Fig. 8C). The linear equation was cathodic peak potential (V) = −0.046 + 0.1685 (R^2 = 0.9860). According the following equation [33]

$$dEpc/dpH = (-2.303\ mRT)/(nF)$$

where n is the transfer electron number, m is the proton number, R is the gas constant, T is the standard temperature, E_{pc} is the cathodic peak potential and F is the Faraday constant. Thus the ratio of the proton number against the transfer electron number was calculated to be 2, indicating that the equal number of protons and electrons transferred which associated with the reduction of nilutamide to hydroxylamine.

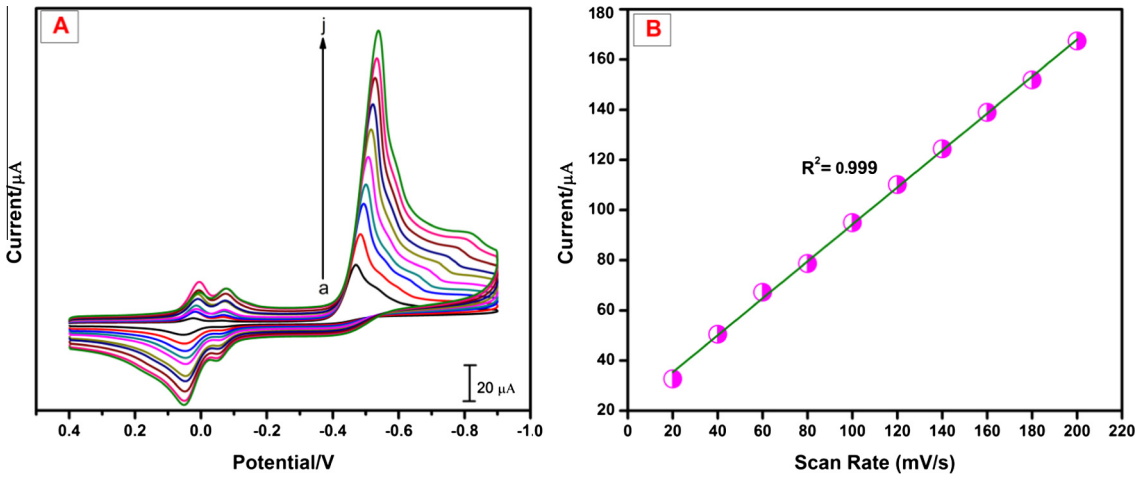


Fig. 7. (A) CVs of 200 μM nilutamide at the *f*-MWCNT modified GCE at different scan rates (a–j: 20–200 mV/s) in 0.05 M PB solution (pH 7). (B) The plots of cathodic peak currents of nilutamide *vs.* scan rates.

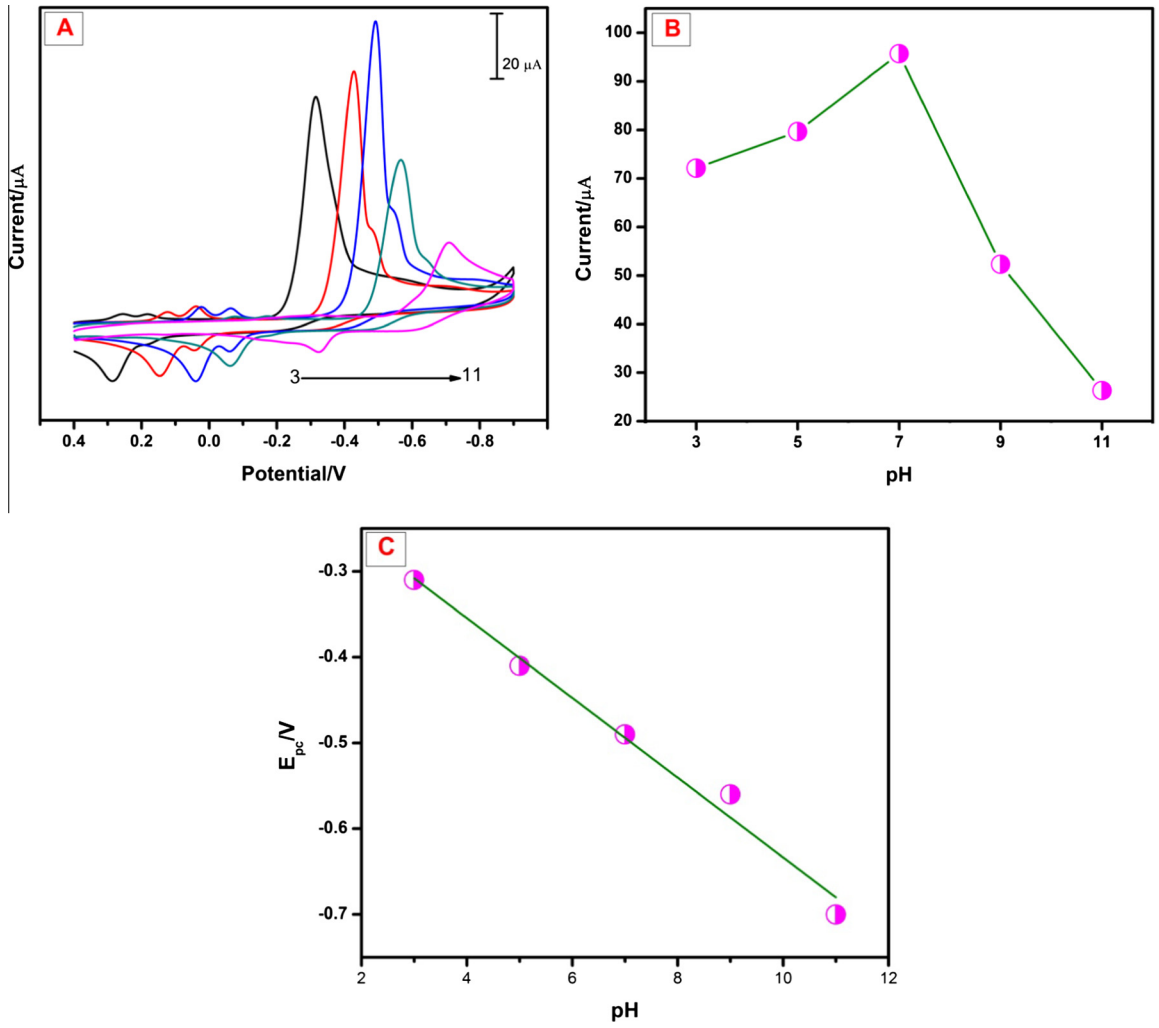


Fig. 8. (A) CVs of 200 μM nilutamide at the *f*-MWCNT modified GCE at different pH (3–11) in 0.05 M PB solution at scan rate 50 mV/s. (B) The plots of cathodic peak currents of nilutamide *vs.* pH and (C) cathodic peak potential *vs.* pH.

3.5. Calibration curve of anti-cancer drug nilutamide

As a significant electrochemical method, differential pulse voltammetry (DPV) has a more sensitive and better resolution compared than CV. On the CV experimental conditions, DPV was used to find the calibration plot for nilutamide in 0.05 M PB solution. Fig. 9 reveals that the DPV performance of various concentrations from lower to higher (0.01–675 μM) of nilutamide at

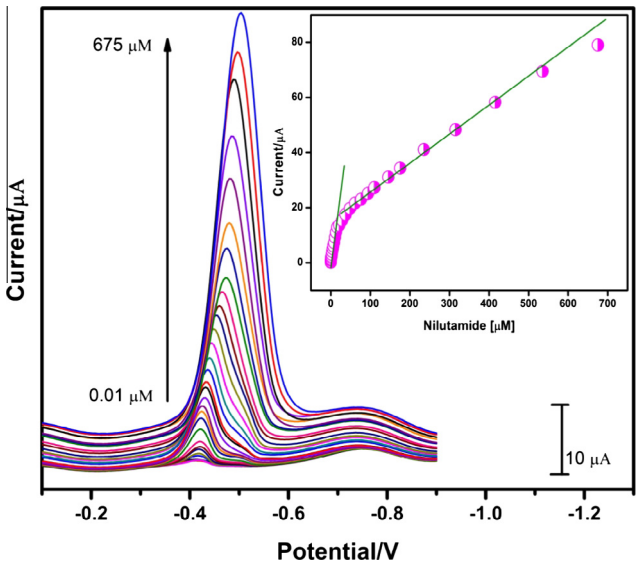


Fig. 9. DPV response at the *f*-MWCNT for different concentrations of nilutamide in PB solution (pH 7) (ranges from 0.01 to 675 μM). Inset: The plots of peak current of nilutamide *vs.* its concentrations.

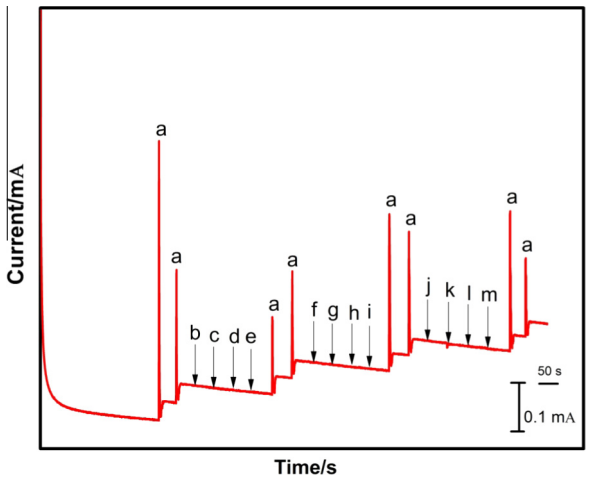


Fig. 10. Amperometric response of *f*-MWCNT/rotating disc GCE for the 80 μM addition of nilutamide (a) in the presence of 100-fold excess concentration of biological compounds glucose (b), sucrose (c), fructose (d), lactose (e), DA (f), UA (g), AA (h), catechol (i), and 50 fold excess concentration of nitro derivatives nitrobenzene (NB) (j), 4-nitrophenol (4-NP) (k), 4-acetamido phenol (l), 4-nitro toluene (j) in continues stirring 0.05 M PB solution (pH-7), the rotation speed of 1200 rpm at the applied potential −0.48 V.

f-MWCNT modified GCE. The well-defined and very sharp cathodic peak current was observed at −0.48 V with increasing the concentration of nilutamide. There are two linear ranges were obtained from the calibration plot as shown in Fig. 9 (Inset). The first linear range obtained from 0.01 to 21 μM with linear regression equation of Ipc (μA) = 0.7716 (μM) + 0.7624 (R^2 = 0.9910) with higher sensitivity and lower detection limit of 11.023 μA μM^{-1} cm^2 and 0.2 nM respectively. The second linear range obtained from 28 to 535 μM with linear regression equation of Ipc (μA) = 0.0989 (μM) + 15.647 (R^2 = 0.9920) with lower sensitivity and detection limit of 1.412 μA μM^{-1} cm^2 and 1.8 nM respectively. This two linear concentration ranges were previously reported [34] and it was possibly caused by the rapid formation of reduction products of nilutamide. At lower concentrations, the movements of nilutamide molecules are quite fast thus *f*-MWCNT/GCE responses so quickly and furnished good electrocatalytic current. However, at higher concentration, the motion of nilutamide was retard hence the response of electrocatalytic reduction was decreased. However, a good linear range, very low detection limit and good sensitivity still obtained, and the presented results revealed that the *f*-MWCNT modified GCE showed an improved or comparable performance with previously reported methods and listed in Table.1. This above result indicates that the *f*-MWCNT had the ability for the determination of anti-cancer drug nilutamide.

3.6. Anti-interference reproducibility and stability studies

The selectivity is very important for the electrochemical sensor and biosensor. In order to investigate the selectivity of the sensor for the anti-cancer drug nilutamide in the presence of various biologically co-interfering substances and some nitro content derivatives were studied in amperometric method with applied potential −0.48 V at the rotation speed of 1200 rpm in continuous stirring 0.05 M PB solution (pH 7) which shown in Fig. 10. The *f*-MWCNT/GCE showed a well-defined response for the each addition of 80 μM of nilutamide (a), at the same time, there is no considerable response were observed in the addition of 100 fold excess concentration of biological compounds such as glucose (b), sucrose (c), fructose (d), lactose (e), dopamine (DA) (f), uric acid (UA) (g), ascorbic acid (AA) (h), catechol (i), and 50 fold excess concentration of some nitro group content derivatives such as nitrobenzene (NB) (j), 4-nitrophenol (4-NP) (k), 4-acetamido phenol (l), 4-nitro toluene (j). Though, an instant response was observed upon addition of 80 μM of nilutamide into the aforementioned co-interfering biological substances coexisted electrolyte solution. Hence, the *f*-MWCNT/GCE has very good selectivity to the sensitive determination of anti-cancer drug nilutamide even in the presence of 50 and 100 fold excess concentrations of nitro compound derivatives and biological foreign substances. The reproducibility is one of the most important characters for the biosensor. To study the reproducibility with three independent electrodes were taken and used for the determination of nilutamide. The relative standard deviation (RSD) of 3.8% was obtained for a cathodic peak current of nilutamide, which indicates a good reproducibility of the proposed sensor. After that the *f*-MWCNT modified GCE was stored for 1 week, it still retained 88% of the original response of 50 μM nilutamide, suggesting acceptable storage stability.

3.7. Determination of nilutamide in real samples

In order to demonstrate the practical applicability of the *f*-MWCNT modified GCE sensor, it was explored in the real sample analysis for the nilutamide tablet and human serum samples. The sample of the nilutamide tablet and human serum samples was prepared by the appropriate dilution with 0.05 M PBS (pH 7) and directly used for determination of nilutamide. These studies demonstrated that the good recovery was achieved by *f*-MWCNT for the nilutamide tablet and human serum samples. The recover-

Table 2
Determination of nilutamide in real samples by *f*-MWCNT modified GCE.

Samples		Content (μM)	Added (μM)	Found[a] (μM)	Recovery (%)
Nilutamide tablet	1	20	–	19.8	99.0
	2	20	20	39.7	99.2
	3	20	30	49.5	99.0
Human serum (spiked)	1	–	20	19.86	99.3
	2	–	30	29.6	98.6

[a] Standard addition method.

ies were calculated by the previously reported standard addition method. The obtained recoveries were ranging from 98.6% to 99.3% for the nilutamide tablet and serum sample, and those results are summarized in Table.2. The results endorsed that the *f*-MWCNT has good recoveries for the determination of nilutamide, and can be used for the pharmaceutical formulations.

4. Conclusion

In conclusion, the *f*-MWCNT was prepared by using a mixture of pristine MWCNT and acid by a simple sonication method and used as an excellent electrode material for the fabrication of highly sensitive and selective determination of anti-cancer drug nilutamide. As-prepared *f*-MWCNT was characterized by various analytical and spectroscopic techniques. The DPV was used to assess the electrochemical properties of anti-cancer drug nilutamide which showed excellent sensitivity, wide linear ranges and very lower detection limit. The estimated sensitivity of the fabricated nilutamide sensor was 11.023 $\mu A\ \mu M^{-1}\ cm^2$ and the limit of detection 0.0002 μM. To the best of our knowledge, this is the first time report that the highly sensitive electrochemical determination of anti-cancer drug nilutamide based on *f*-MWCNT on the modified GCE.

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