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RESEARCH PAPER

A Sensitive Sensor for Nano-Molar Detection of 5-Fluorouracil by Modifying a Paste Sensor with Graphene Quantum Dots and an Ionic Liquid

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ABSTRACT

5-fluorouracil is a widely used anticancer drug with many side effects on humans, and hence its analysis in biological samples is very important. Accordingly, a novel sensitive electrochemical approach was fabricated by incorporating graphene quantum dots (GCD) and 1-butylpyridinium bromide (BPBr) in the formulation of a carbon paste electrode (GQD/BPBr/CPE). The GQD was synthesized and characterized TEM method and results confirmed them as being spherical with D~ of 5.0 nm. The applicability of the GQD/BPBr/CPE in voltammetric analysis of 5-fluorouracil was evaluated. The relations of oxidation currents and potentials of 5-fluorouracil with pH at the surface of GQD/BPBr/CPE were investigated and the results confirmed the involvement of electrons and protons in the electro-oxidation mechanism of 5-fluorouracil. In square wave voltammetry (SWV) analyses, the GQD/BPBr/CPE showed good sensitivity for 5-fluorouracil over a wide linear range of 0.001–400 µM and a detection limit of 0.5 nM was achieved. The GQD/BPBr/CPE was successfully applied for the determination of 5-fluorouracil in pharmaceutical samples and acceptable results were obtained.

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INTRODUCTION

The determination of pharmaceutical components and especially anticancer drugs such as doxorubicin, epirubicin, 5-fluorouracil is very important due to the adverse effects of these compounds on human body [1-5]. Although, some analytical methods such as spectroscopy, chemiluminescence, flow injection systems, high performance liquid chromatography and electrochemical sensors have been suggested as efficient tools for the determination of drug compounds [6-10], electrochemical methods have shown better potentials in this respect due to advantages of simplicity, low cost, fast response and ease of operation [11-18]. Electrochemists have recently introduced modified electrodes as powerful substitutes for conventional electrodes offering improved selectivity and sensitivity for trace and simultaneous determination of drugs or other biological species [19-23].

Ionic liquids, carbon nanotubes, conductive

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polymers, dendrimers and DNA are the most important electrode surface modifiers suited for electrochemical sensors [24-31], the application of which in electroanalytical sensors can greatly improve the performance [32-38].

5-Fluorouracil is an antimetabolite fluoropyrimidine analog, prescribed as a chemotherapy drug [39]. The medicine is widely used for breast, stomach, pancreatic, skin, gullet and bowel cancers. The consumption of 5-fluorouracil can cause many side effects such as nausea, diarrhea and increase the risks of infection. Consequently, controlling the dose of this drug in biological samples and studying the purity of its pharmaceutical forms can help manage its side effects. Due to the above-mentioned and the potentials of electrochemical methods, several reports have been published on preparing electrochemical sensors for 5-fluorouracil during recent years [39-44].

Fallah-Shojaei et al. used the synergic effect of 1,3-dipropylimidazolium bromide and $ZnFe_2O_4$ magnetic nanoparticles for modification of an electrode as a sensor for the electrochemical determination of 5-fluorouracil and reached a detection limit of 0.07 µM [1].

Bukkitgar et al. used a glucose modified electrode as a sensor for the determination of 5-fluorouracil and achieved a detection limit of 5.17 nM in pharmaceutical and urine samples [45].

Bukkitgar et al. used methylene blue to modify the surface of a carbon paste electrode to develop a sensor for the determination of 5-fluorouracil and reported a detection limit of 2.04 nM [39].

In this investigation, the synergic effect of graphene quantum dots and 1-butylpyridinium bromide was used for modifying a carbon paste electrode. The resulting electrode, i.e. GQD/BPBr/CPE, was found to be a powerful tool for the electrochemical determination of 5-fluorouracil in pharmaceutical samples. The results showed better detection limits as compared to previous reports on the electrochemical sensors modified with GQD and BPBr as conductive binders.

MATERIALS AND METHODS

Reagents and Instrumentation

Diethyl ether, citric acid, 5-fluorouracil, phosphoric acid and 1-butylpyridinium bromide were purchased from Sigma-Aldrich. Graphite powder was obtained from ACROS Company.

The electrochemical experiments were performed using a potentiostat/galvanostat system (Autolab). An $Ag/AgCl/KCl_{sat}$ was used as the references electrode in all voltammetric experiments.

Synthesis of GQD nanoparticles

A pyrolysis approach was used for preparing GQD. The method was based on using citric acid as the carbon source. In the first step, 2 g of citric acid was transferred to a beaker and heated for 30 min at 250 ˚C to convert the citric acid to a liquid phase with orange color (GQD).

Fabrication of GQD/BPBr/CPE

GQD/BPBr/CPE was prepared by mixing of 0.12 g of 1-butylpyridinium bromide, 0.88 g of paraffin oil, 0.04 g of GQD, and 0.96 g of graphite powder in mortar and pestle. The mixture was hand mixed for ~ 2 h and a portion of the obtained paste was packed into one end of a glass tube, while a copper wire was inserted into the tube and the paste from the other opening of the tube.

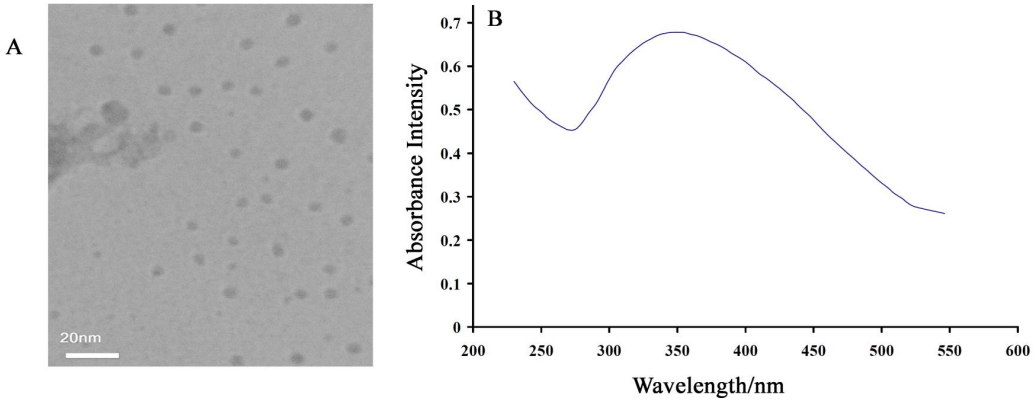

Fig. 1. A) TEM image of GQD. B) Absorbance spectra of GQD.

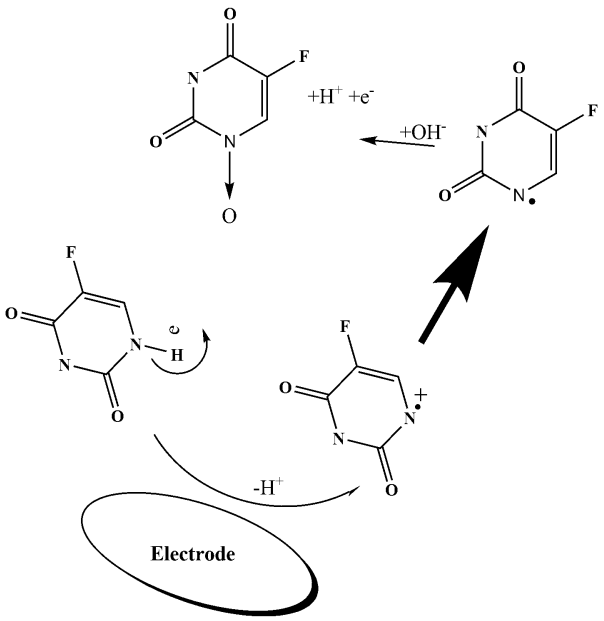

Fig. 2. The electro-oxidation mechanism of 5-fluorouracil.

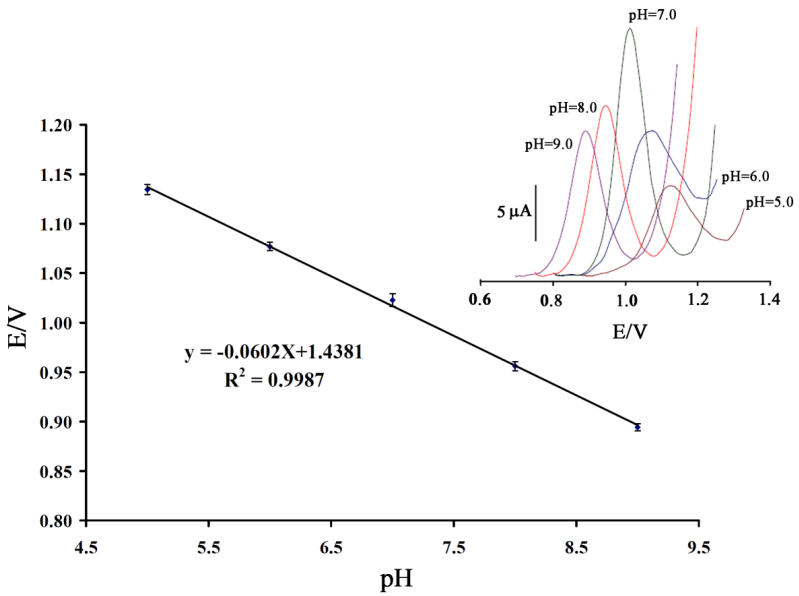

Fig. 3. The E-pH curve for electro-oxidation of 100 µM 5-fluorouracil. Insert) SWV of 100 µM 5-fluorouracil at pH ranges of 5.0-9.0.

RESULTS AND DISCUSSION

Characterization of GQD

The TEM images of GQD were recorded (Fig. 1A), indicating the presence of spherical particles of less than 5 nm in diameter. The UV-Vis spectra of GQD (e.g. Fig. 1B) contained an absorbance band at~ 350 nm relative to GQD [46].

Electrochemical behavior of 5-fluorouracil

The oxidation behavior of 5-fluorouracil was studied in the pH ranges of 5.0-9.0, through square wave voltammetry analyses (Fig. 2 insert). A linear relation between the oxidation potential of 5-fluorouracil and pH with a slope of 60.2 mV/pH was observed for the electro-oxidation of

5-fluorouracil at GQD/BPBr/CPE (Fig. 2), confirming the equal number of electrons and protons involved in the electro-oxidation of 5-fluorouracil (Fig. 3). In addition, the maximum oxidation current was observed at pH=7.0, and hence this value was applied in the next experiments.

The SW voltammograms of a 100.0 µM solution of 5-fluorouracil was recorded using GQD/BPBr/CPE (Fig. 4 curve a), BPBr/CPE (Fig. 4 curve b), GQD/CPE (Fig. 4 curve c) and CPE (Fig. 4 curve d) as the working electrodes. 5-fluorouracil produced oxidation signal at potentials of 1006, 1026, 1061 and 1071 mV with oxidation currents 21.7 µA, 14.6 µA, 10.7 µA and 5.26 µA at the surfaces of GQD/BPBr/CPE, BPBr/CPE, GQD/CPE and CPE, respectively. Moving from CPE to GQD/BPBr/CPE, the oxidation potential of 5-fluorouracil decreased and the oxidation current of the drug increased, confirming the high conductivity of GQD and BPBr at the carbon paste matrix.

In addition, the data obtained from the current density confirmed the trends in the previous

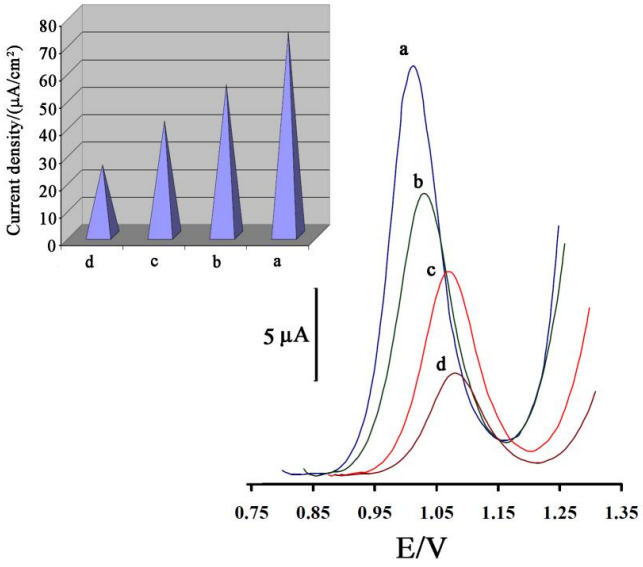

Fig. 4. The SW voltammograms of 100 µM 5-fluorouracil at surface of (a) GQD/BPBr/CPE; (b) BPBr/CPE; (c) GQD/CPE and (d) CPE. Insert) Current density diagrams obtained from recorded SW voltammograms in figure 3.

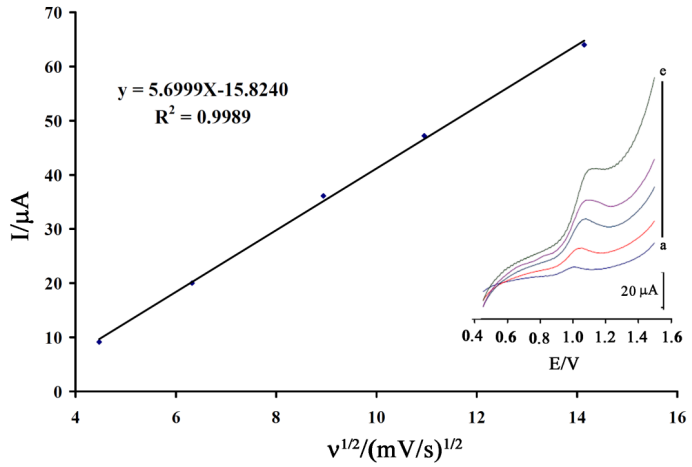

Fig. 5. The I-v1/2 curve for electro-oxidation of 250.0 µM 5-fluorouracil at pH=7.0. Insert) linear sweep voltammograms of 250.0 µM 5-fluorouracil at scan rates a) 20.0; b) 40.0; c) 80.0; d) 120.0 and e) 200.0 mV/s.

results (good electrical conductivity of mediators) (Fig. 4, insert). The respective active surface areas of GQD/BPBr/CPE, BPBr/CPE, GQD/CPE and CPE were determined to be 0.26 cm^2, 0.27 cm^2, 0.26 cm^2 and 0.21 cm^2.

The electro-oxidation behavior of 5-fluorouracil was investigated at in the scan rate range of 20-200 mV/s using GQD/BPBr/CPE (Fig. 5). The linear relation between I_{pa} and $v^{1/2}$, observed for the electro-oxidation of 5-fluorouracil, indicated the electro-oxidation of 5-fluorouracil at the modified electrode to be diffusion controlled in nature.

The diffusion coefficient (D) of 5-fluorouracil was determined by recording the chronoamperometric (applied potential of 1100 mV) signals of 1.0, 2.0 and 3.0 mM 5-fluorouracil at the surface of GQD/BPBr/CPE (see Fig. 6A). The Cottrell plots of GQD/BPBr/CPE in the presence of 1.0, 2.0 and 3.0 mM 5-fluorouracil can be seen in Fig. 6B, based on the slopes of which the D value was determined to be 2.18×10^{-6} cm^2 s^{-1}.

The analytical factors influencing the determination of 5-fluorouracil by GQD/BPBr/CPE were investigated by square wave voltammetry (Fig. 7). The GQD/BPBr/CPE showed two linear dynamic ranges of from 0.001 to 10.0 µM with a regression equation of $I = 1.004423\ C_{5\text{-fluorouracil}} + 0.77$ ($r^2 = 0.9916$); and of 10.0 to 400 µM with

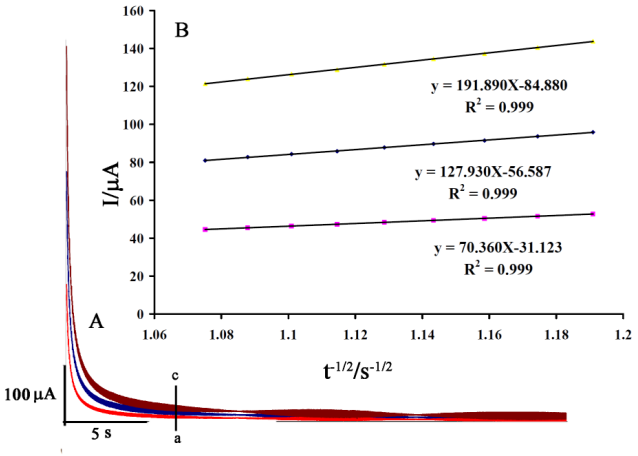

Fig. 6. (A) Chronoamperograms recorded at GQD/BPBr/CPE in the presence a) 1.0; b) 2.0 and c) 3.0 mM 5-fluorouracil. (B) The I-t-1/2 plot obtained from the chronoamperograms.

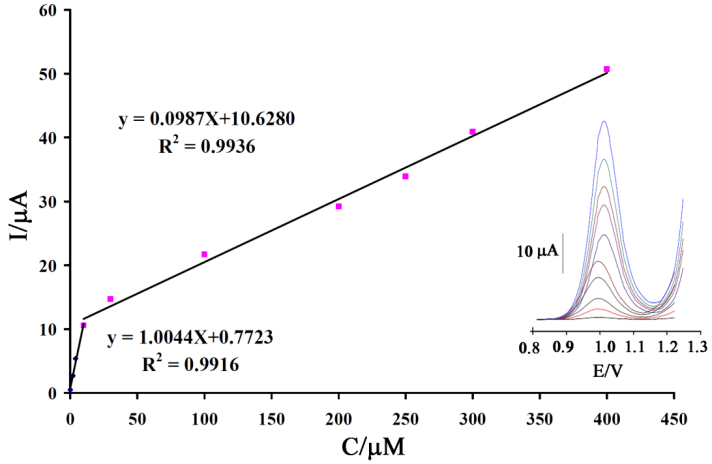

Fig. 7. The current-concentration curve for electro-oxidation of 5-fluorouracil at surface of GQD/BPBr/CPE. Insert) The SW voltammograms of GQD/BPBr/CPE in the presence of 5-fluorouracil (from inner to outer): 0.01; 2.0; 4.0; 10.0; 30.0; 100.0; 200.0; 250.0; 300.0 and 400.0 µM 5-fluorouracil.

Table 1 Comparison of the analytical parameters of GQD/BPBr/CPE with published electrochemical sensors for determination of 5-fluorouracil.

Electrode	Modifier	pH	LDR (µM)	LOD (µM)	Ref.
screen-printed carbon	Graphene oxides/multi-walled carbon nanotubes hybrid	7.0	0.05-1200	0.016	[34]
Carbon paste	porphyran-capped gold nanoparticles	8.0	29.9-234	0.66	[35]
Glassy carbon	reduced graphene oxide/chitosan	7.0	0.1-15.0	0.0049	[36]
Glassy carbon	cetyltrimethyl ammonium bromide	7.0	0.02-0.6	0.02	[37]
Carbon paste	GQD and BPBr	7.0	0.001-400	0.0005	This work

a regression equation of I = 0.0987 $C_{5\text{-fluorouracil}}$ + 10.6280 (r^2 = 0.9936). The GQD/BPBr/CPE showed a detection limit of 0.5 nM (S/N=3) for 5-fluorouracil, which is better than those of previously reported electrochemical sensors for this anticancer drug (table 1). This high sensitivity was attributed to the presence of GQD and BPBr at surface of CPE.

Stability and Selectivity

The stability of GQD/BPBr/CPE through the electrochemical determinations of 5-fluorouracil was studied by recording square wave voltammograms of 100 µM solutions of 5-fluorouracil over a period of time (Fig. 8). As can be seen, the oxidation current of 5-fluorouracil at surface of GQD/BPBr/CPE still showed 92.3% of its original oxidation signal after 14 days. This was considered as confirming the good stability of GQD/BPBr/CPE for determination of 5-fluorouracil. The selectivity of GQD/BPBr/CPE toward the determination of 20.0 µM 5-fluorouracil was found to have an acceptable error of 5%. The results presented in table 2, confirm the high selectivity of GQD/BPBr/CPE for the determination of 5-fluorouracil.

Real sample analysis

The powerful square wave voltammetric analyses were used for the determination of

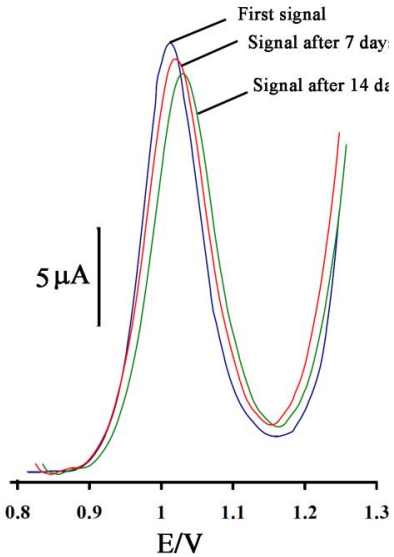

Fig. 8. The SW voltammograms of 100 µM 5-fluorouracil at different period time.

Table 2. The selectivity test of GQD/BPBr/CPE for determination of 20.0 µM 5-fluorouracil

Species	Tolerant limits ($W_{interference}/W_{5\text{-}fluorouracil}$)
Br^-, K^+, Na^+, Cl^-, Mg^{2+}	1000
glucose	700
Methionine, Glycine, ascorbic acid, Uric acid	600

Table 3. The performance of GQD/BPBr/CPE for determination of 5-fluorouracil in real samples (n=3).

Sample	Added (µM)	Expected (µM)	Founded suggested sensor (µM)	Published method (µM)	F_{tab}	$F_{exp.}$	$t_{tab.}$	$t_{exp.}$
Injection	---	5.00	4.96±0.07	5.06±0.09	19.0	7.8	3.8	1.9
	10.00	15.00	15.36±0.56	15.48±0.78	19.0	9.1	3.8	2.2
Pharmaceutical serum	---	---	<LOD	<LOD	19.0	---	3.8	---
	20.00	20.00	19.86±0.87	19.84±0.97	19.0	9.8	3.8	2.5

5-fluorouracil in injection and pharmaceutical samples through the standard addition method. The analytical data are presented in table 3. The obtained results were compared with another electrochemical strategy and F-test and t-test were used to check the accuracy of the method.

CONCLUSION

A new composite modified electrode (GQD/BPBr/CPE) was successfully designed and used as a powerful voltammetric sensor for the nano-molar determination of 5-fluorouracil. The combination of GQD and BPBr allowed for the sensitive detection of 5-fluorouracil in different samples. Using the GQD/BPBr/CPE, 5-fluorouracil could be measured over a linear calibration range of 0.45–450 µM. The GQD/BPBr/CPE showed an acceptable performance in the analysis of 5-fluorouracil in real samples.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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