

# Electrochemical Determination of Methyldopa by Graphene Quantum Dot / 1-butyl-3-methylimidazolium hexafluoro phosphate Nanocomposite Electrode

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Methyldopa is one the important catecholamines used for treatment of high blood pressure. In this study, a nanocomposite electrode was made using graphene quantum dots (GQD) and 1-butyl-3-methylimidazolium hexafluorophosphate (1B3MIPF<sub>6</sub>) in a carbon paste matrix (GQD/1B3MIPF<sub>6</sub>/CPE). The used GQD was synthesized and characterized using transmission electron microscopy (TEM). The electro-oxidation behavior of Methyldopa was investigated on the surface of GQD/1B3MIPF<sub>6</sub>/CPE and finally it was used as a working electrode for the electrochemical determination of Methyldopa in some pharmaceutical and biological samples. The results showed an improvement of ~3.2 times in electro-oxidation peak of methyldopa in a dynamic linear range of 0.04-750.0 μM (limit of detection 0.01 μM).

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**Keywords:** Graphene quantum dots, Methyldopa, Carbon paste electrode, Voltammetry

## 1. INTRODUCTION

Methyldopa with a catechol chemical structure is a medication used for the treatment of gestational hypertension, pre-eclampsia and renal impairment [1]. The mechanism of action of methyldopa is proposed to be converted to alpha-methylnorepinephrine in central adrenergic neurons, and then released and stimulates central adrenoceptors, particularly alpha-2 adrenoceptors in the medulla so this agent reduced sympathetic activity [2,3]. Methyldopa is capable of including a number of psychological and physiological adverse side effects such as depression, anxiety, nausea, impotence,

fever and decreased heart rate [4,5]. Up to now, methyldopa have been studied with different analytical methods consist of electrochemical [6-8], high-performance liquid chromatography [9, 10], spectrophotometry [11,12], NMR spectroscopy [13]. Among these methods, electrochemical have gained wide attention due to their sensitivity, simplicity, accuracy and reliability, lower cost, easy to operate and high dynamic range [14-28]. Since Methyldopa is an electroactive molecule, electrochemical techniques can provide fast methods for Methyldopa detection.

Beytak and et al. [29] reported a novel modified electrode based on terbium oxide and CNT for electrochemical detection of methyldopa. The offered sensor provided  $1.5 \times 10^{-9}$  M limit of detection for methyldopa and the anodic peak currents were linear with concentrations in the range of  $5.0 \times 10^{-9}$  M to  $1.0 \times 10^{-6}$  M. Ramirez and et al. studied on electrochemical oxidation of methyldopa on fluorine doped SnO<sub>2</sub> substrates that their suggested sensor demonstrated two linear ranges with limit of detection of  $0.15 \times 10^{-6}$  and  $2.9 \times 10^{-6}$  mol L<sup>-1</sup> [30].

Progress of nanomaterials in electrochemistry created a remarkable developments. They have been widely used for the fabrication of electrochemical sensors/biosensors, supercapacitors and fuel cells because of their excellent properties such as enhancement of the active surface, electrocatalytic activities and high electrical conductivities [31-44]. In the past few years, graphene derivatives have been practical as a huge substrate in electrochemical investigation owing to a large specific surface area, ecofriendly, low toxicity, and especially due to a great electrical conductivity [45-51]. With the best of our knowledge, there is not any instance for determination of methyldopa with GQD modified electrode. Thus, based on the above mentioned, we used the GQD as modifier in carbon paste electrode to study the electrochemical behavior of Methyldopa. This modified nanocomposite electrode showed a rather wide dynamic range, low limit of detection and high sensitivity in Methyldopa analysis. Finally, we appraise the analytical efficiency of the suggestion sensor for determination of methyldopa in real samples such as pharmaceutical tablet and urine.

## 2. MATERIALS AND METHODS

### 2.1. Apparatus

An electrochemical systems (Autolab) consisting of a counter electrode (Pt wire), a working electrode (GQD/1B3MIPF<sub>6</sub>/CPE) and a reference electrode (an Ag/AgCl/KCl<sub>sat</sub>) was used for recording electrochemical signals. A Transmission electron microscopy (Philips, CM30, 300 Kv) was used for morphological investigation.

### 2.2. Reagents and materials

Citric acid, methyldopa, diethyl ether, phosphoric acid, 1-butyl-3-methylimidazolium hexafluorophosphate and sodium hydroxide were purchased from Sigma-Aldrich Company. For fabrication of carbon paste electrode graphite powder and paraffin oil were prepared from Merck Company. GQDs were synthesized according to the previous published work [52].

### 2.3. Real sample preparation

Eleven tablets (250 mg per tablet) were grinded to form a uniform powder. Then appropriate amounts of the tablet were dissolved in 100 mL ethanol/water (1:1) solution under sonication. Also, urine samples ready for real sample analysis according to our previous published paper [52].

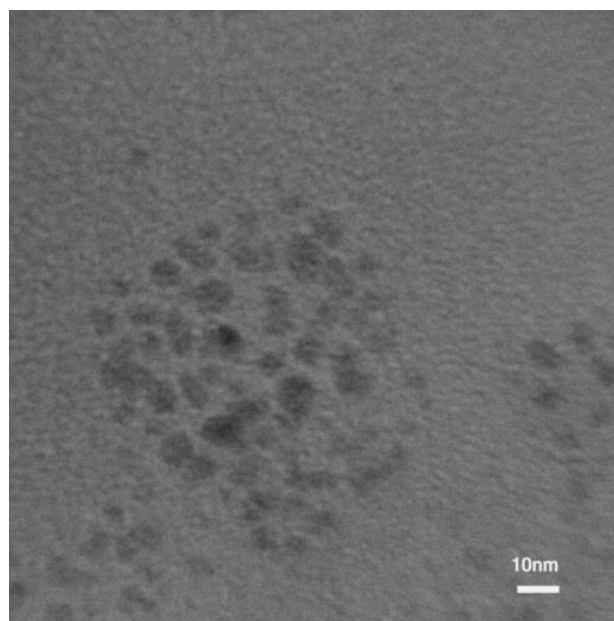
### 2.4. Fabrication of GQD/1B3MIPF<sub>6</sub>/CPE

GQD/1B3MIPF<sub>6</sub>/CPE was prepared by mixing of 0.1 g GQD and 0.9 g graphite powder in the presence of suitable amount of paraffin oil and 1B3MIPF<sub>6</sub> as binders. The mixt powder uniform for ~ 1.5 h and filled into end of glass tube in the presence a copper wire as a conductive matter.

## 3. RESULTS

### 3.1. GQD Characterization

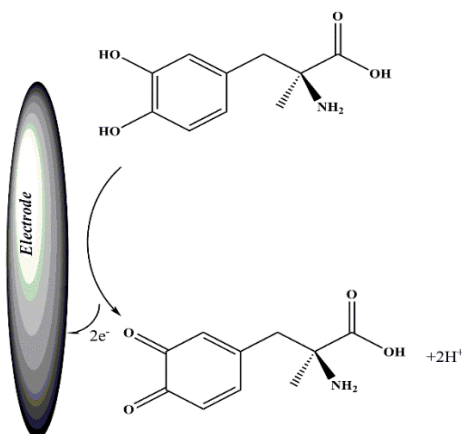
The morphology of GQD was characterized by TEM method. As can be seen in figure 1 GQD synthesized in spherical shape with diameter ~ 3-5 nm.



**Figure 1.** TEM image of GQD synthesized in this work

### 3.2. Electrochemical investigation

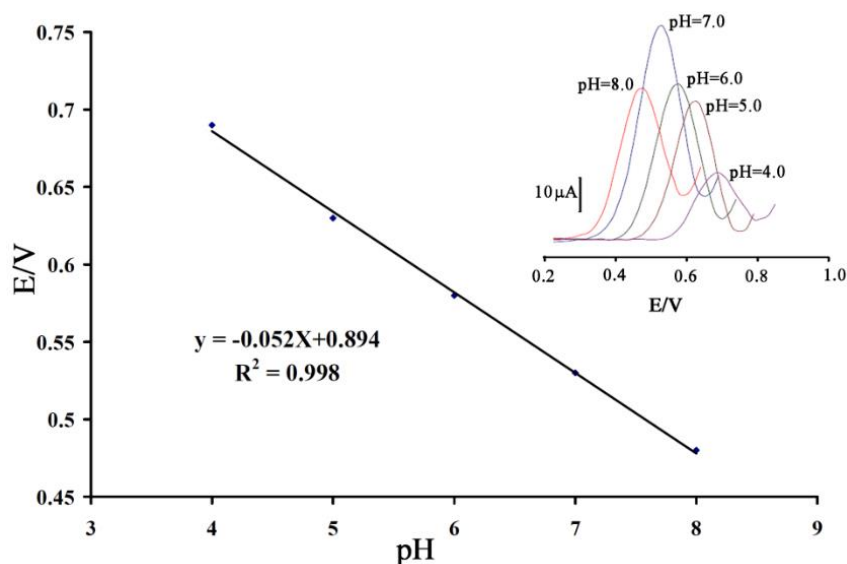
According to previous published papers [53, 54] and Scheme 1, we found that electro-oxidation of methyl dopa is pH dependent.



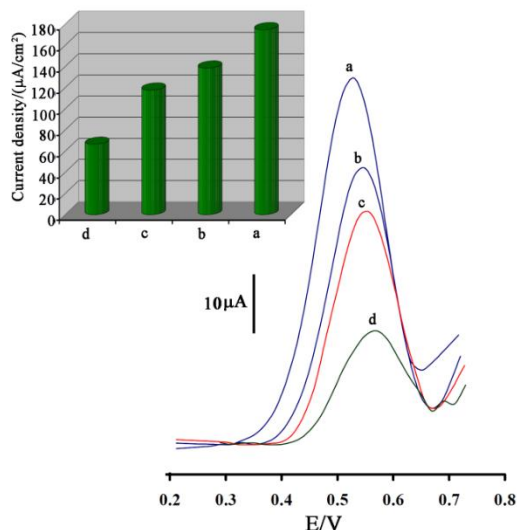
**Scheme 1.** Electro-oxidation mechanism of methyldopa

For pH investigation, square wave voltammograms of 80.0  $\mu\text{M}$  methyldopa at a different pH in the range 4.0-8.0 (Figure 2 insert) was recorded. As can be seen, the oxidation potential shift to the negative value with increasing in pH that confirm above mechanism for methyldopa oxidation at a surface of GQD/1B3MIPF<sub>6</sub>/CPE. As can be seen, the plot of oxidation potential vs. pH showed a slope 0.052 V/pH that confirm two electrons and two protons for methyldopa. On the other hand, the maximum oxidation current was observed at pH=7.0 that selected as optimum condition.

The square wave voltammograms of 80.0  $\mu\text{M}$  methyldopa was recorded at a surface of GQD/1B3MIPF<sub>6</sub>/CPE (Fig. 3, curve a), 1B3MIPF<sub>6</sub>/CPE (Fig. 3, curve b), GQD/CPE (Fig. 3, curve c) and bare carbon paste electrode (Fig. 3, curve d). Moving from carbon paste electrode (curve d) to GQD/1B3MIPF<sub>6</sub>/CPE (curve a) oxidation current increase and over-potential for methylopa reduce.



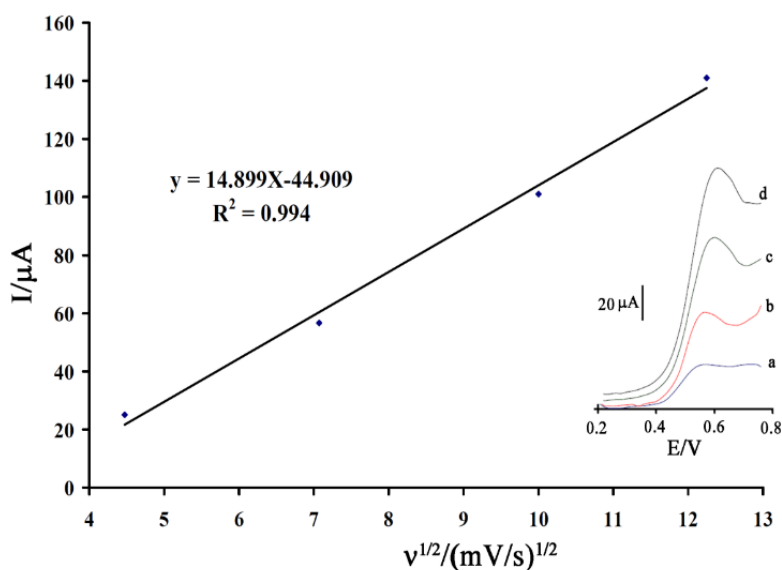
**Figure 2.** Potential-pH curve for electro-oxidation of 80.0  $\mu\text{M}$  methyldopa at a surface of GQD/1B3MIPF<sub>6</sub>/CPE. Insert: Square wave voltammograms of 80.0  $\mu\text{M}$  methyldopa at a different pH



**Figure 3.** Square wave voltammograms of 80.0  $\mu\text{M}$  methyl dopa at a surface of GQD/1B3MIPF<sub>6</sub>/CPE (curve a), 1B3MIPF<sub>6</sub>/CPE (curve b), GQD/CPE (curve c) and bare carbon paste electrode (curve d), pH=7.0

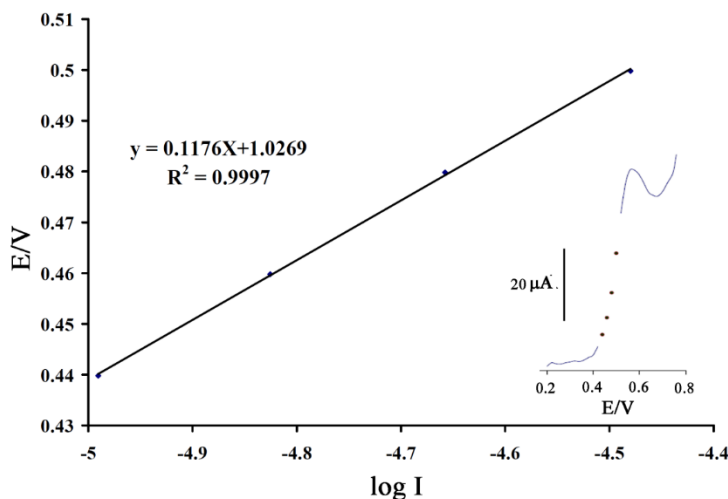
This data confirm high electrical conductivity GQD and 1B3MIPF<sub>6</sub> for modification of carbon paste electrode. The current density investigation is presence in figure 3 insert that confirm GQD and 1B3MIPF<sub>6</sub> increase active surface area and electrical conductivity of carbon paste electrode.

The effect of scan rates on the response of the GQD/1B3MIPF<sub>6</sub>/CPE shows in figure 4. Where, the anodic peak currents were increasing with increase in  $v^{1/2}$  (20 - 150 mV/s) suggesting a diffusion process for electro-oxidation of methyl dopa.



**Figure 4.** The current- $v^{1/2}$  plot for electro-oxidation of 700  $\mu\text{M}$  methyl dopa at surface of GQD/1B3MIPF<sub>6</sub>/CPE (pH=7.0). Insert: linear sweep voltammograms of 700  $\mu\text{M}$  methyl dopa at a different scan rate. a) 20.0; b) 50.0, c) 100.0 and d) 150.0 mV/s.

Tafel plot was used for the methyldopa at a surface of GQD/1B3MIPF<sub>6</sub>/CPE (Fig. 5). The slope of the Tafel plot is equal to  $n(1-\alpha)F/2.3RT$  which comes up to 0.1176 V decade<sup>-1</sup>. We obtained  $\alpha$  as 0.75.



**Figure 5.** Tafel plot for electro-oxidation of 700  $\mu\text{M}$  methyldopa at surface of GQD/1B3MIPF<sub>6</sub>/CPE and scan rate 50 mV/s (pH=7.0).

The effect of concentration of methyldopa on GQD/1B3MIPF<sub>6</sub>/CPE has been studied in 0.1 M PBS (pH 7.0) by square wave voltammetric method (Not shown). Where anodic peak current increase with increasing in the concentration (0.04 – 750  $\mu\text{M}$ ) with limit of detection 0.01  $\mu\text{M}$  for methyldopa.

Since methyldopa is one of the electroactive substance, it was previously determined by electrochemical methods. Table 1 compare the values of linear range and limit of detection of the proposed modified electrode to the similar previous reported ones used in analysis of methyldopa. As can be seen, the new composition has superiority to the compared ones. Besides, the used materials can be easily prepared.

**Table 1.** The analytical data reported by some different electrochemical sensors for methyldopa analysis

The Modified Electrode	pH	Linear range ( $\mu\text{M}$ )	Limit of detection ( $\mu\text{M}$ )	Reference
MgO-IL-Carbon paste	7.0	0.08-380	0.03	[6]
Fe:Co Nanoalloy Carbon paste	7.0	0.06-600	0.03	[54]
MWCNTs-IL-Carbon paste	7.0	0.4-400	0.1	[55]
GQDs-IL-Carbon paste	7.0	0.04-750	0.01	This work

One of the most significant advantages of GQD/1B3MIPF<sub>6</sub>/CPE is having good selectivity. We check selectivity of GQD/1B3MIPF<sub>6</sub>/CPE for analysis of methyldopa in the presence of some

biological or pharmaceutical samples and obtained data are presence in Table 2. As can be seen, the GQD/1B3MIPF<sub>6</sub>/CPE showed good selectivity for analysis of methyldopa.

**Table 2.** Interference study for the determination of 50.0  $\mu\text{M}$  Methyldopa

Species	Tolerant limits ( $W_{\text{Substance}}/W_{\text{Analytes}}$ )
Glucose, phenylalanine, tryptophan and glutamic acid	500
$\text{Mg}^{2+}$ , $\text{Br}^-$ , $\text{Li}^+$ , $\text{K}^+$ , $\text{Na}^+$ , $\text{Cl}^-$	200
Starch	Saturation

The GQD/1B3MIPF<sub>6</sub>/CPE was applied to determination of methyldopa in two pharmaceutical drugs and urine samples by standard addition method. The obtained data were compared with a published method and the results are summarized in Table 3. As can be seen, the GQD/1B3MIPF<sub>6</sub>/CPE showed good ability for analysis of methyldopa in two pharmaceutical drugs and urine samples.

**Table 3.** Determination of methyldopa in real samples (n=3)

Sample	Added ( $\mu\text{M}$ )	expected ( $\mu\text{M}$ )	Found ( $\mu\text{M}$ )	Published method ( $\mu\text{M}$ ) [55]	$F_{\text{tab}}$ (0.05; 95%)	$F_{\text{exp}}$	$t_{\text{tab}}$ (98%)	$t_{\text{exp}}$
Tablet	---	5.00	4.85 $\pm$ 0.54	5.56 $\pm$ 0.66	19.0	9.3	3.8	1.9
	10.00	15.00	15.55 $\pm$ 0.89	14.78 $\pm$ 0.98	19.0	10.6	3.8	2.8
Serum	---	---	<LOD	<LOD	---	---	---	---
	50.00	50.00	50.89 $\pm$ 1.02	50.59 $\pm$ 1.05	19.0	13.5	3.8	3.5

#### 4. CONCLUSION

In this paper, an electrochemical sensor amplified with graphene quantum dots and 1-butyl-3-methylimidazolium hexafluorophosphate in carbon paste matrix has been successfully developed to investigate methyldopa at pH 7.0. The GQD/1B3MIPF<sub>6</sub>/CPE has great capability in determine methyldopa relative to bare carbon paste electrode. We found a linear dynamic range (0.04-750.0  $\mu\text{M}$ ) with 0.01  $\mu\text{M}$  limit of detection. The GQD/1B3MIPF<sub>6</sub>/CPE was used for analysis of methyldopa in real samples.

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