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Electrochemical Oxidation and Determination of Methocarbamol at Multi-walled Carbon Nanotubes-Modified Glassy Carbon Electrode

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Abstract- A simple and rapid voltammetric oxidation of methocarbamol was investigated. In pH 3.0 phosphate buffer, methocarbamol shows an irreversible oxidation peak at about 1.28 V at a multi-walled carbon nanotube (MWCNT)-modified glassy carbon electrode. The cyclic voltammetric results indicate that MWCNT-modified glassy carbon electrode showed that methocarbamol at 12 µL of MWCNT, the oxidation sites of glassy carbon was adsorbed by MWCNT which increased only the current sensitivity. Under optimized conditions, the concentration range and detection limit are 6.0×10^{-6} to 1.0×10^{-4} M and 4.22×10^{-6} M, respectively for methocarbamol. The proposed method was successfully applied to methocarbamol determination in pharmaceutical samples. The analytical performance of this sensor has been evaluated for the detection of analyte in urine sample.

Keywords- Methocarbamol, Buffer solution, Glassy carbon electrode, Multi walled carbon nanotubes, Cyclic voltammetry

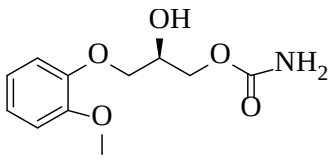
1. INTRODUCTION

Methocarbamol (MET), 2-hydroxy-3-(2-methoxyphenoxy) propyl carbomate is carbamate of guaifenesin, was developed for the treatment of skeletal muscle conditions of

pain and discomfort [1]. It is formulated as a single entity (trade name: Robaxin®) or in combination with other active ingredients such as acetaminophen (trade name: Robaxacet®), ibuprofen (trade name: Robax Platinum®), and aspirin (trade name: Robaxisal®). The mechanism it works is unknown, but it is thought to depress the nervous system [2,3]. Methocarbamol is easily absorbed from the intestine and widely distributed in all body tissues, especially the liver and kidney [4]. Its metabolism is similar in rats, dogs, and humans, which is ring hydroxylation and o-demethylation at phase I and conjugation at phase II [4,5]. The sulfoconjugate is the main metabolite recovered in the urine [6].

For pharmacokinetic or bioequivalence studies, a fast, selective and sensitive method for determination of methocarbamol concentration in plasma is highly desirable. Only a few methods of methocarbamol analysis are published in literature. Obach et al [7]. Used HPLC with UV detection to determine plasma methocarbamol concentrations to study pharmacokinetics and bioavailability of methocarbamol in rats. Alessi-Severini et al [8], reported a stereospecific HPLC method with UV detection after derivatization to quantify methocarbamol enantiomers in biological fluids. The sample preparation procedure was complicated and the derivatization step took 12 h. The run time was also long; around 50 min. A HPLC-UV method was developed [9] for the analysis of methocarbamol in human plasma and by HPLC-tendam spectrometry [10]. However, usually this method is costly, solvent usage intensive and requires a length pre-treatment of the sample prior to the chromatographic analysis. Electrochemical detection of analyte is a very elegant method in analytical chemistry [11].

Carbon nanotubes (CNTs) continue to receive remarkable attention in electrochemistry [12,13]. Since their discovery by Iijima [14]. In 1991 using transmission electron microscopy, CNTs have been the subject of numerous investigations in chemical, physical and material areas due to their novel structural, mechanical, electronic and chemical properties [15]. Subtle electronic properties suggest that CNTs have the ability to promote charge transfer reactions when used as an electrode [16]. The modification of electrode substrates with multi-walled carbon nanotubes (MWCNTs) for use in analytical sensing has been documented to results in low detection limits, high sensitivities, reduction of over potentials and resistance to surface fouling. MWCNTs have been introduced as electrocatalysts [17,18] and CNTs modified electrodes have been reported to give super performance in the study of a number of biological species [19].



Scheme 1. Chemical structure of methocarbamol

To the best of our knowledge, voltammetric determination of methocarbamol using a MWCNTs modified glassy carbon electrode (GCE) has not been reported yet. The objective of the present work is to develop a convenient and sensitive method for the determination of methocarbamol based on the unusual properties of MWCNTs-modified glassy carbon electrode. The ability of the modified electrode for voltammetric response of selected compound was evaluated. Finally, this modified electrode was used for the analysis of methocarbamol in pharmaceutical and urine samples. The resulted biosensor exhibits high sensitivity, rapid response, good reproducibility and freedom of other potentially interfering species.

2. EXPERIMENTAL

2.1. Reagents

Pure methocarbamol in powdered form was obtained from (Sigma-Aldrich; India) and used as received. A stock solution of methocarbamol (1.0×10^{-2} M) was made in doubly distilled water. Multi-walled carbon nanotubes were from Sigma-Aldrich; India, (>90%.: 10-15 nm, I.D.: 2-6 nm, length: 0.1-10μm). The phosphate buffers from pH 3.0-7.0 were prepared in doubly distilled water as described by Christian and Purdy [20]. Other reagents used were of analytical or chemical grade, and their solutions were prepared with doubly distilled water.

2.2. Apparatus

Electrochemical measurements were carried out on a CHI1110A electrochemical analyzer (CH Instrument Company, USA) coupled with a conventional three electrode cell. A three-electrode cell was used with a Ag/AgCl as reference electrode, a Pt wire as counter electrode and a glassy carbon electrode with a diameter of 2 mm (modified and unmodified) were used as working electrodes, respectively. All of the used electrodes were from CHI Co. and all the potentials in this paper are given against the Ag/AgCl (3 M KCl). Solution pH was measured with an Elico LI120 pH meter (Elico Ltd., India).

2.3. Preparation of MWCNTs modified electrode

Multi-walled carbon nanotubes was refluxed in the mixture of concentrated H_2SO_4 and HNO_3 for 4-5 h. then washed with doubly distilled water and dried in vacuum at room temperature. The MWCNTs suspension was prepared by dispersing 2 mg MWCNTs in 10 mL acetonitrile using ultrasonic agitation to obtain a relative stable suspension. The GCE was carefully polished with 0.30 and 0.05 μm α-alumina slurry on a polishing cloth, and then washed in an ultrasonic bath of methanol and water, respectively. The cleaned GCE was coated by casting 12 μL of the black suspension of MWCNT and dried in air. The

electroactive areas of the MWCNT-modified GCE and the bare GCE were obtained by cyclic voltammetry (CV) using 1.0 mM $K_3Fe(CN)_6$ as a probe at different scan rates. For a reversible process, the Randles-Sevcik formula has been used [21].

$$i_{pa} = (2.69 \times 10^5)\, n^{3/2}\, A D_R^{1/2} C o \upsilon^{1/2} \quad (1)$$

where i_{pa} refers to the anodic peak current, n is the number of electrons transferred, A is the surface area of the electrode, D_R is diffusion coefficient, ν is the scan rate and Co is the concentration of $K_3Fe(CN)_6$. For 1.0 mM $K_3Fe(CN)_6$ in 0.1 M KCl electrolyte, n=1, $D_R=7.6\times10^{-6}$ cm^2s^{-1}, then from the slope of the plot of i_{pa} versus $\nu^{1/2}$, relation, the electroactive areas were calculated. In bare GCE, the electrode surface was found to be 0.04638 cm^2 and for MWCNT-modified GCE, the surface was nearly 2.5-3.0 times greater.

2.4. Analytical procedure

The MWCNT-modified GCE was first activated in phosphate buffer (pH 3.0) by cyclic voltammetric sweeps between 0.0 and 2.0 V until stable cyclic voltammograms were obtained. Then electrode was transferred into another 10 ml of phosphate buffer (pH 3.0) containing proper amount of methocarbamol. After accumulating for 60 s at open circuit under stirring and following quiet for 10 s, potential scan was initiated and cyclic voltammograms were recorded between +0.4 and +1.4, with scan rate of 50 mVs^{-1}. All measurements were carried out at room temperature of 25±0.1 C.

2.5. Sample preparation

Ten pieces of methocarbamol tablets were powdered in a mortar. A portion equivalent to a stock solution of a concentration of about 1.0 mM was accurately weighed and transferred into a 100 mL calibrated flask and completed to the volume with double distilled water. The content of the flask were sonicated for 10 min to affect complete dissolution. Appropriate solutions were prepared by taking suitable aliquots of the clear supernatant liquid and diluting them with phosphate buffer solutions. Each solution was transferred to the voltammetric cell and analyzed by standard addition method. To study the accuracy of the proposed method and to check the interferences from excipients used in the dosage form, recovery experiments were carried out. The concentration of methocarbamol was calculated using standard addition method.

3. RESULTS AND DISCUSSION

3.1. Cyclic voltammetric behavior of methocarbamol

The cyclic voltammograms of methocarbamol at a bare GCE and at MWCNT-modified GCE were shown in Fig. 1. It can be seen that the methocarbamol oxidation peak at the bare

GCE was weak and broad due to slow electron transfer, while the response was considerably improved at the MWCNT-modified GCE. At the bare GCE, the peak was at about 1.22 V (Fig. 1b), but on the MWCNT-modified GCE, the peak appeared at about 1.28 V (Fig. 1a), blank CVs of MWCNT-modified GCE (Fig. 1c), and bare GCE (Fig. 1d), with considerable enhancement in the peak current and slight change in oxidation potential. In general, the trend of using MWCNT decreases the oxidation potential and increases the current sensitivity, which was attributed to the electro catalytic effect caused by MWCNTs. However, our experimental results showed that MWCNTs modified glassy carbon electrode increased the current with slight change in the potential. This was attributed to the fact that methocarbamol at 12 µL of MWCNT, the oxidation sites of glassy carbon was adsorbed by MWCNTs, which increases only current sensitivity. The reason for the better performance of the MWCNT-modified GCE may be due to the nanometer dimensions of the MWCNTs, the electronic structure and the topological defects present on the MWCNTs surfaces [22]. Meanwhile the MWCNTs also increase the effective area of the electrode.

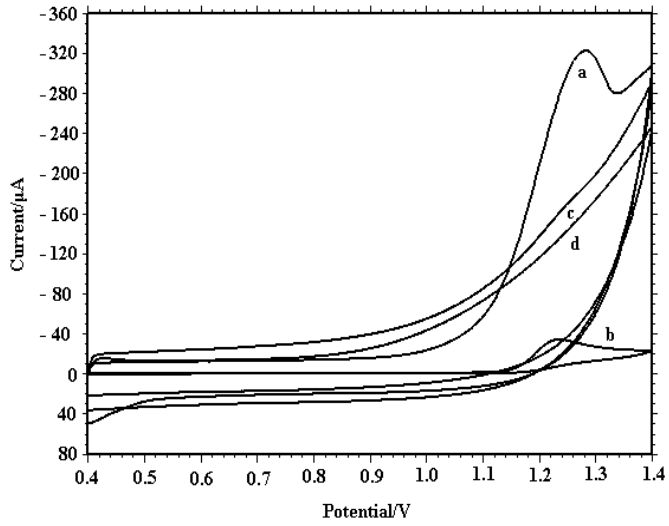


Fig. 1. Cyclic voltammograms of 1×10^{-3} MET on MWCNT-modified GCE (a) and bare GCE (b), Blank CVs of MWCNT-modified GCE (c), and bare GCE (d). Scan rate: 50 mVs^{-1}; supporting electrolyte: 0.2 M phosphate buffer with pH 3.0; accumulation time: 60 s (at open circuit); volume of MWCNTs suspension: 12 µL

It also showed that no reduction peak was observed in the reverse scan, suggesting that the electrochemical reaction was a totally irreversible process. Nevertheless, it was found that the oxidation peak current of methocarbamol showed a remarkable decrease during the successive cyclic voltammetric sweeps (Fig. 2). After the successive scan, the peak current decreased greatly and finally remained unchanged. This phenomenon may be attributed to the adsorption of oxidative product of methocarbamol at the modified electrode surface. This

experiment clearly indicated the adsorption of methocarbamol on the electrode surface before electrochemical oxidation. Therefore, the voltammograms corresponding to the first anodic cycle and peak was generally recorded [23].

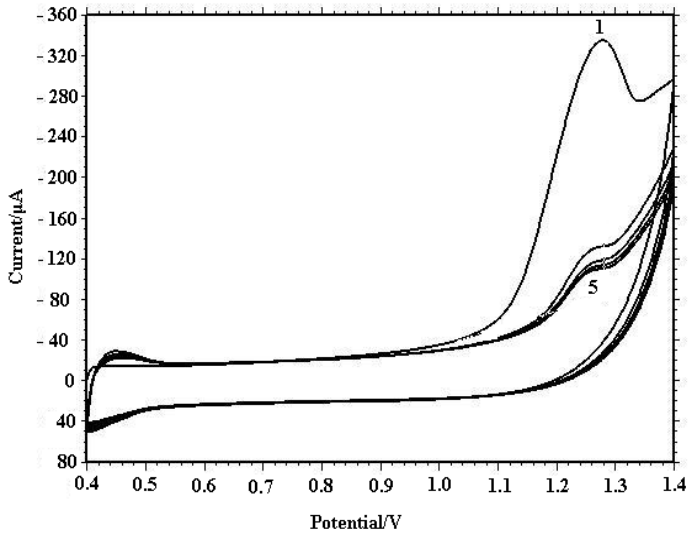


Fig. 2. Successive cyclic voltammograms of 1.0×10^{-3} M MET on MWCNT-modified GCE

3.2. Influence of amount of MWCNTs

The amount of MWCNTs has influence on the peak current. At 12 μL of MWCNTs, the peak current was highest. After that amount, it decreases. This is related to the thickness of the film. If the film was too thin, the MET amount adsorbed was small, resulting in the small peak current. When it was too thick, the film conductivity reduced and the film became not as stable as MWCNTs could leave off the electrode surface. Thus it blocks the electrode surface and hence the peak current decreases. Therefore, 12 μL MWCNTs suspension solution was used in the remaining studies [24-26].

3.3. Influence of accumulation potential and time

It was important to fix the accumulation potential and time when adsorption studies were undertaken. Both conditions could affect the amount of adsorption of MET at the electrode. Bearing this in mind, the effect of accumulation potential and time on peak current response was studied by CV. The concentration of MET used was 1.0×10^{-3} M. When accumulation potential was varied from +0.4 to -0.4 V, the peak current changed a little, hence accumulation at open circuit was adopted. The peak current increased very rapidly with increasing accumulation time, which induced rapid adsorption of MET on the surface of the modified electrode. The peak current reached the maximum after 60 s and then decreases, this indicates the saturation accumulation. As long accumulation time might reduce the stability of MWCNTs film, 60 s was chosen as accumulation time [27].

3.4. Influence of pH

The electrode reaction might be affected by the pH of the medium. The electro-oxidation of 1.0×10^{-3} M MET was studied over pH range 3.0 -7.0 in phosphate buffer solution by cyclic voltammetry. The results showed that high peak current was obtained in phosphate buffer with pH 3.0 as shown in Fig. 3. Within the range of pH 3.0 to 7.0, dramatically decreased peak current response was found with a peak broadening. Hence we selected pH 3.0 for remaining studies. The peak potential was pH independent from pH 3.0 to 5.0, there after the peak potential was almost pH dependent. Above pH 7.0 we have not found any peak [28-30].

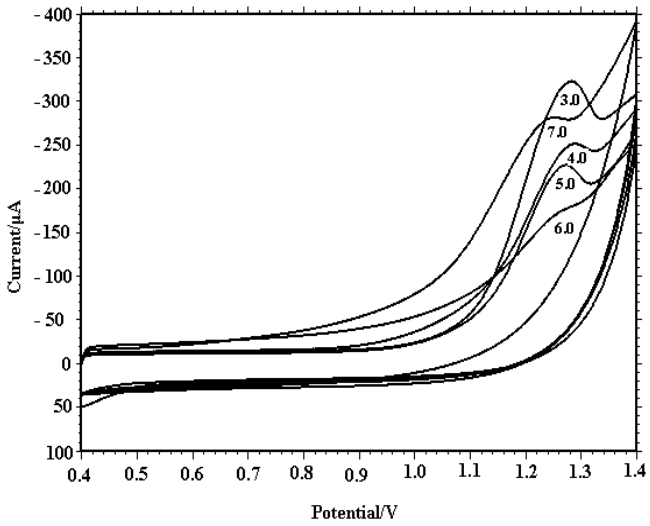


Fig. 3. Influence of pH on the shape of anodic peak of 1.0×10^{-3} M MET on MWCNTs glassy carbon electrode at scan rate 50 mVs^{-1} in phosphate buffer

3.5. Influence of scan rate

Useful information involving electrochemical mechanism usually can be acquired from the relationship between peak current and scan rate. Therefore, the electrochemical behavior of MET at different scan rate10 to 120 mVs^{-1} in (Fig. 4), was also studied. There is a good linear relationship between peak current and scan rate. The equation representing this was I_p=507.63 ν+58.9; r=0.9913 as shown in Fig. 5. This indicates that the electrode process was controlled by adsorption rather than diffusion. In addition, there was a linear relation between log I_p and log ν, corresponding to the following equation: log I_p=0.9684 log ν+2.7092; r=0.9936. The slope of 0.9684 was very close to the theoretically expected value of 1.0 for an adsorption-controlled process [31].

The peak potential shifted to more positive values with increasing the scan rates. The linear relation between peak potential and the logarithm of scan rate can be expressed as E_p=0.1251+1.3163 log ν; r=0.9954. As for an irreversible electrode process, according to Laviron [32]. E_p is defined by the following equation.

$$E_P = E^{0'} + \left(\frac{2.303RT}{\alpha nF}\right)\log\left(\frac{RTk^0}{\alpha nF}\right) + \left(\frac{2.303RT}{\alpha nF}\right)\log\nu \quad (2)$$

where α is the transfer coefficient, k^0 the standard heterogeneous rate constant of the reaction, n the number of electrons transferred, ν the scan rate and E^0 is the formal redox potential. Other symbols have their usual meanings. Thus the value of αn can be easily calculated from the slope of Ep *vs*. log ν. In this system, the slope was 0.1251, taking T=298, R=8.314 and F=96,480, αn was calculated to be 0.4819. Generally, α is assumed [33] to be 0.5 in totally irreversibly electrode process.

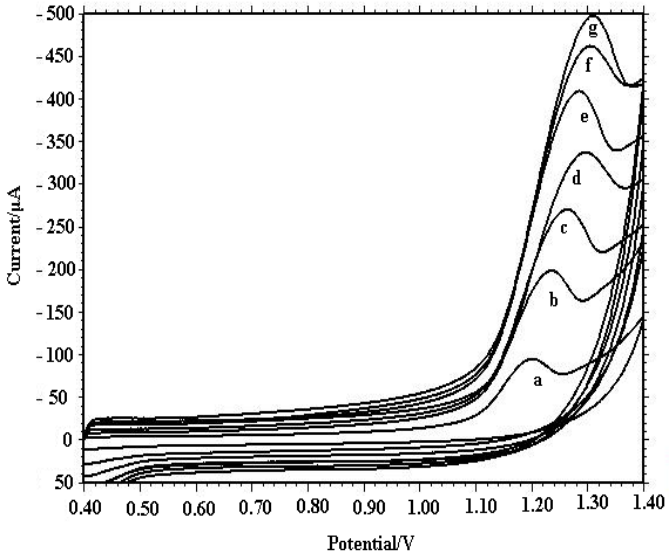


Fig. 4. Cyclic voltammograms of 1.0×10^{-3} M MET on MWCNT-modified GCE with different scan rates. (a)-(g) 10, 20, 40, 50, 60, 80 and 120 mVs^{-1}, respectively

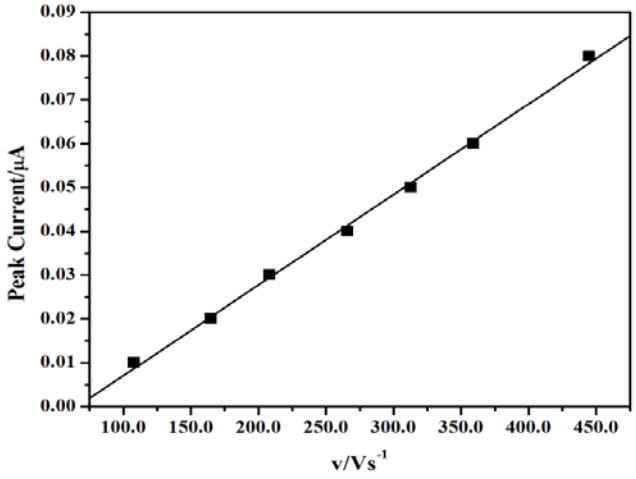
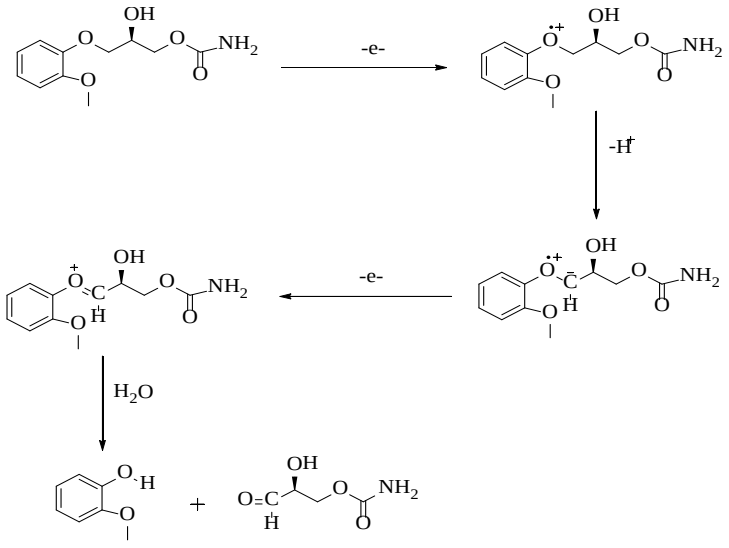


Fig. 5. Dependence of the oxidation peak current on scan rate

Further, the number of electrons (n) transferred in the electro oxidation of MET was calculated to be 0.9454≈1. The value of k^0 can be determined from the intercept of the above plot if the value of $E^{0'}$ known. The value of E^0 in Eq. (2) can be obtained from the intercept of E_p *vs.* ν curve by extrapolating to the vertical axis at ν=0 [34]. The intercept for E_p *vs.* log ν plot was 1.316 and $E^{0'}$ was obtained to be 1.1871; the k^0 was calculated to be 70.0 s^{-1}.

3.6. Mechanism

Taking into account that methocarbamol contains an ether linkage in its molecular structure it presents a basic center with the availability of non-bonding electron pair as donor. So, we may assume that the oxidation step of compound is located on the oxygen which is linked to 2^0 carbons. Methocarbamol loses an electron from non-bonding electron pair of the oxygen attached to the secondary carbon to form radical cation, which on losing a proton and an electron in subsequent steps to form an oxonium ion. The resulted oxonium ion was rapidly hydrolysed to the substituted 2-methoxy phenol and 2-hydroxy-3-oxo-propyl ester. A possible electrode reaction mechanism of MET might be expressed as shown in Scheme 2. The voltammetric studies show that oxidative pathways of electrochemical and chemical process are different. The proposed mechanism is based on earlier work [35,36].



Scheme 2. Possible electrode reaction mechanism of MET

3.7. Calibration curve

In order to develop a voltammetric method for determining the drug, according to the obtained results, it was possible to apply this technique to quantitative analysis of MET. The phosphate buffer solution of pH 3.0 was selected as supporting electrolyte for the quantification of MET as it gave maximum peak current at pH 3.0. The peak at about 1.28V

was considered for the analysis. The cyclic voltammograms obtained with increasing amounts of MET showed that the peak current increased linearly with increasing concentration, as shown in Fig. 6. Using the optimum conditions described above, linear calibration curve were obtained for MET in the range of 6.0×10^{-6} to 1.0×10^{-4} M (Fig. 6. Inset): The linear equation was Ip (μA)=1.4227+55.616 C (r=0.9926, C is in μM). Deviation from linearity was observed for more concentrated solutions, due to the adsorption of MET or its oxidation product on the electrode surface. Related statistical data of the calibration curves were obtained from the five different calibration curves. The limit of detection (LOD) and quantification (LOQ) were 4.22×10^{-6} and 1.41×10^{-5} M, respectively. The LOD and LOQ were calculated using following equations respectively.

LOD=3 s/m

LOQ=10 s/m

where s is the standard deviation of the peak currents of the blank (five runs), and m is the slope of the calibration curve. The virtues of the reported figures for the present work are apparently analogous or much superior to other analytical systems as shown in Table 1. In order to study the reproducibility of the electrode preparation procedure, a 1.0×10^{-5} M MET solution was measured with the same electrode (renewed every time) for every several hours within day, R.S.D. of the peak current was 2.6% (number of measurements=5).

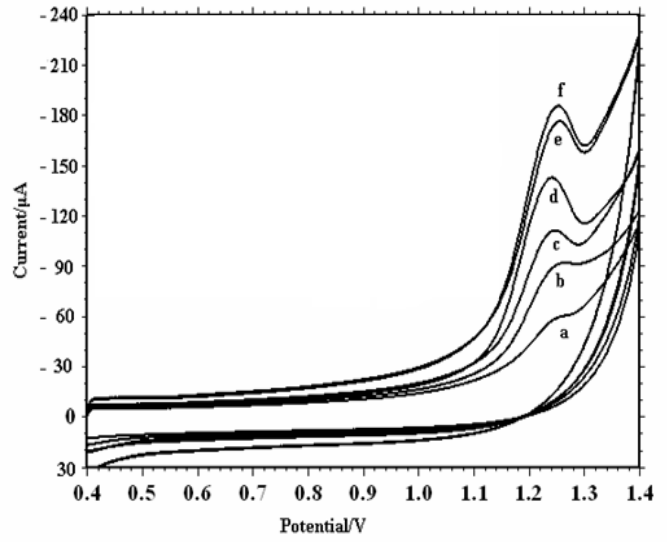


Fig. 6. Cyclic voltammograms of MWCNT-modified GCE in MET solution at different concentrations (a) 6.0; (b) 10.0; (c) 20.0; (d) 40.0; (e) 60.0; (f) 80.0 μM. Inset: Plot of the peak current against the concentration of MET

As to the between reproducibility, it was similar to that of within day if the temperature was kept almost unchanged. Owing to the adsorption of MET or its oxidative products on to the

electrode surface, the current response of the modified electrode would decrease after successive use. In this case, the electrode should be modified again.

Table 1. The limit of detection value reported for MET determination using various analytical systems

Materials	LOD mL^{-1}	Method	Reference
MMT-Ca/CPE	1.2×10^{-8}	Voltammetry	[37]
Analytical instrument	1.5×10^{-6}	MCR	[38]
Fluorescence detection	6.0×10^{-6}	RP-HPLC	[39]
Fluorescence detection	3.8×10^{-6}	HPLC	[40]
ABIL/CPE	1.5×10^{-6}	Voltammetry	[41]
[BnMIM]PF_6/CPE	3.3×10^{-6}	Voltammetry	[42]
MWCNTs/GCE	4.22×10^{-6}	Voltammetry	Present work

MCR= Mean centering ratio
MMT=Montmorillonite
ABIL=Acetylene block ionic liquid

3.8. Tablet analysis

In order to evaluate the applicability of the proposed method in the pharmaceutical sample analysis, one commercial medicinal sample containing MET viz. Robaxin (Cipla Co. India), was used to detect MET in tablets (50 mg per tablet). The procedures for the tablet analysis were followed as described in the procedural section. The detected content was 48.6 mg per tablet with 97.2% recovery.

Table 2. Recovery test of methocarbamol in tablet Robaxin

Added (M)	Found (M)[a]	Recovery (%)	S.D. ± R.S.D (%)
3.0×10^{-6}	2.98×10^{-6}	99.33	0.045±0.0636
5.0×10^{-6}	5.02×10^{-6}	100.4	0.207±0.299
8.0×10^{-6}	7.89×10^{-6}	101.39	0.060±0.0851
1.0×10^{-5}	0.99×10^{-5}	99.09	0.191±0.268
3.0×10^{-5}	3.01×10^{-5}	103.4	0.449±0.629
5.0×10^{-5}	4.98×10^{-5}	99.78	1.26±1.76
8.0×10^{-5}	8.02×10^{-5}	100.26	0.65±0.919

[a]Average of five determinations

3.9. Interference

The tolerance limit was defined as the maximum concentration of the interfering substance that caused an error less than ±5% for determination of MET. Under the optimum experimental conditions, the effects of potential interferents on the voltammetric response of 1.0×10^{-5} M, MET were evaluated. The experimental results (Table 3) showed that hundred-fold of glucose, starch, sucrose, citric acid, gum acacia and did not interfere with the voltammetric signal of MET. However magnesium stearate, talk, ascorbic acid, lactic acid, tartaric acid and oxalic acid had apparent influence on the voltammetric signal of MET.

Table 3. Influence of potential interferents on the voltammetric response of 1.0×10^{-5} M MET

Interferents	Concentration (1.0×10^{-3} M)	Signal change (%)
Glucose	0.1	+4.23
Starch	0.1	+2.61
Sucrose	0.1	+4.45
Citric acid	0.1	-2.84
Magnesium stearate	0.1	+6.68
Talk	0.1	+5.36
Gum acacia	0.1	+0.32
Ascorbic acid	0.1	+9.39
Lactic acid	0.1	+6.39
Tartaric acid	0.1	+6.79
Oxalic acid	0.1	+10.9

3.10. Detection of MET in urine samples

The developed cyclic voltammetric method for the MET determination was applied to urine samples. The recoveries from urine were measured by spiking drug free urine with known amounts of MET.

Table 4. Determination of MET in urine samples

Sample	Spiked (10^{-5} M)	Found[a] (10^{-5} M)	Recovery (%)	S.D. ± R.S.D (%)
1	0.4	0.392	100.33	0.019 ± 0.014
2	0.6	0.589	98.60	0.017 ± 0.012
3	0.8	0.802	97.50	0.0155 ± 0.011
4	2.0	1.986	100.22	0.036 ± 0.026
5	4.0	4.105	102.62	0.155 ± 0.109

[a] Average of five determinations

The urine samples were diluted 100 times with the phosphate buffer solution before analysis without further pretreatments. A quantitative analysis can be carried out by adding the standard solution of MET into the detect system of urine sample. The calibration graph was used for the determination of spiked MET in urine samples. The detection results of five

urine samples obtained are listed in Table 4. The recovery determined was in the range from 97.5% to 102.63% and the standard deviation and relative standard deviation are listed in Table 4.

4. CONCLUSION

In this work, a multi-walled carbon nanotubes modified glassy carbon electrode has been successfully developed for the oxidation of MET in phosphate buffer solution (pH=3.0). The cyclic voltammetric results indicate that MWCNT-modified glassy carbon electrode showed that methocarbamol at 12 µl of MWCNT, the oxidation sites of glassy carbon was adsorbed by MWCNT which increased only the current sensitivity. The enhancement of the peak current was probably due to the larger surface area and edge plane like sites/defects of MWCNTs. A suitable electrochemical oxidation mechanism for MET was proposed. This sensor can be used for voltammetric determination of selected analyte as low as 4.22×10^{-6} M with good reproducibility. The modified electrode has been used to determine MET in pharmaceutical and real samples.

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