Voltammetric Detection of Cinnarizine at Multi-Walled Carbon Nanotubes Modified Carbon Paste Electrode

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***Abstract:-* The voltammetric behaviour of cinnarizine was investigated. In pH 2.5 Britton-Robinson buffer, cinnarizine shows an irreversible oxidation peak at about 1.20 V at a carbon paste electrode modified with multi-walled carbon nanotubes (MWCNTs). The cyclic voltammetric results indicate that carbon paste electrode (CPE) modified with MWCNTs can remarkably enhance electro-catalytic activity towards the oxidation of cinnarizine. The electro-catalytic behavior was further exploited as a sensitive detection scheme for the cinnarizine by differential-pulse voltammetry. Under optimized conditions, the concentration range and detection limit are 8.0 x 10^{-9} to 4.5 x 10^{-7} M and 1.11 x 10^{-9} M respectively for cinnarizine. The developed method was successfully applied for detection of cinnarizine in pharmaceutical samples. The analytical performance of this sensor has been evaluated for detection of cinnarizine in urine as a real sample.**

***Keywords:* Cinnarizine; Multi-walled carbon nanotubes; Voltammetry; Carbon paste electrode**

I. INTRODUCTION

Cinnarizine (CNR), 1-(diphenylmethyl)-4-(3-phenyl-2-propenyl)piperazine (Fig. 1) is a piperazine derivative with histamine H1-receptor and calcium channel blocker. It also improves the cerebral blood flow. It is used orally for the treatment of cerebral apoplexy, cerebral arteriosclerosis and post-traumatic cerebral symptoms. It is also used to control vomiting and nausea [1]. Many studies showed that CNR is highly effective against motion sickness [2,3] and in contrast with other drugs, it should have fewer side effects. It is also used in the treatment of cerebral and peripheral vascular disorders.

There were many methods reported for the detection of CNR. It was determined spectrophotometrically in pure form [4] and in the binary mixtures [5]. It was also determined using gas chromatography [6], fluorescence spectroscopy [7] and ion selective electrode [8]. A capillary electrophoresis method [9] and a chemiluminesence method for flow injection analysis of CNR [10] were also reported. A HPTLC [11] and a chemometric [12] method were reported recently. The methods based on voltammetric behaviuor of CNR at glassy carbon electrode were also reported [13, 14]. Although spectroscopic and chromatographic methods were widely used for the analysis of various pharmaceutical drugs, most of these methods require separation and/or pretreatment steps. These methods are time consuming, solvent-usage intensive and requires expensive devices and maintenance.

Electrochemical detection of analyte is a very elegant method in analytical chemistry [15]. The interest in developing electrochemical-sensing devices for use in environmental monitoring, clinical assays or process control is growing rapidly. Electrochemical sensors satisfy many of the requirements for such tasks particularly owing to their inherent specificity, rapid response, sensitivity and simplicity of preparation.

Carbon nanotubes (CNTs) continue to receive remarkable attention in electroanalysis [16]. Since their discovery by Iijima [17], CNTs have been the subject of numerous investigations in chemical, physical and material areas due to their novel structural, mechanical, electronic and chemical properties [18]. The subtle electronic properties suggest that CNTs have the ability to promote charge transfer reactions when used as an electrode [19]. The modification of electrode substrates with multi-walled carbon nanotubes (MWCNTs) for use in analytical sensing has been documented to result in low detection limits, high sensitivities, reduction of over potentials and resistance to surface fouling. MWCNTs have been introduced as electrocatalysts [20-22] and CNTs modified electrodes have been reported to give super performance in the study of a number of biological species [23].

To the best of our knowledge, voltammetric detection of CNR using a MWCNTs modified carbon paste electrode (CPE) has not been reported yet. The objective of the present work is to develop a convenient and sensitive method for the detection of CNR based on the unusual properties of MWCNTs modified electrode. Here we report the electrochemical detection of CNR on MWCNTs modified carbon paste 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 CNR in pharmaceutical and urine samples. The resulted biosensor exhibits high sensitivity, rapid response, good reproducibility and freedom of other potentially interfering species.

II. EXPERIMENTAL

2.1. Reagents

CNR was purchased from Sigma-Aldrich and used without further purification. A 1.0 **x** 10^{-2} M stock solution was made in methanol. Multi-walled carbon nanotubes were from Sigma-Aldrich (>90%, O.D: 10-15 nm, I.D: 2-6 nm, length: 0.1-10 □m). The universal Britton-Robinson (BR) buffers (boric acid, phosphoric acid, acetic acid 0.04 M each and sodium hydroxide, 0.2 M) from pH 2.5 –5.5, 0.2 M acetate buffer from pH 3.0-5.0 and 0.2 M phosphate buffer from pH 3.0-5.0 were prepared in doubly distilled water. Neutral and alkaline media were avoided as CNR undergoes a precipitation in such media [24]. 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 self-made carbon paste electrode were used as working electrodes, respectively. All the potentials in this paper are given against the Ag/AgCl (3M KCl). Solution pH was measured with an Elico LI120 pH meter (Elico Ltd, India).

2.3. Preparation of electrode

The CPE was prepared by mixing 1.0 g graphite powder and 0.5 ml paraffin oil in a small agate mortar, and this mixture was then homogenized. After that, the paste was pressed manually into the cavity of the electrode body, and the surface was smoothed against weighing paper. Unless otherwise stated, the paste was carefully removed prior to pressing a new portion into the electrode after every measurement. The area of the electrode was obtained by cyclic voltammetric method using 1.0 x 10^{-3} M $K_3Fe(CN)_6$ as a probe at different scan rates. For a reversible process, the Randles- Sevcik formula was used and the area of electrode was calculated to be 0.028 cm^2. The modified carbon paste electrodes were prepared by mixing different amount of MWCNTs during mixing in mortar. In MWCNTs-modified CPE, the electrode surface area was found to be 0.098 cm^2. The surface area increase by nearly 3 times in MWCNTs-modified CPE.

2.4. Analytical procedure

The MWCNT-modified CPE was first activated in BR buffer (pH 2.5) in the presence of 20% methanol by cyclic voltammetric sweeps between 0 and 1.6 V until stable cyclic voltammograms were obtained. Then electrodes were transferred into another cell of BR buffer (pH 2.5) containing proper amount of CNR, keeping the final concentration of methanol constant at 20%. After accumulating for 180 s at open circuit under stirring and following quiet for 10s, potential scan was initiated and cyclic voltammograms were recorded between +0.6 and +1.6 V, with a scan rate of 50 mVs^{-1}. All measurements were carried out at room temperature of 25 ± $0.1^{o}C$.

2.5. Sample preparation

Ten pieces of CNR tablets were powdered in a mortar. A portion equivalent to a stock solution of a concentration of about 1.0 **x** 10^{-3} M was accurately weighed and transferred into a 100 ml calibrated flask and completed to the volume with methanol. The contents 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 the BR buffer solutions. Each solution was transferred to the voltammetric cell and analyzed by standard addition method. The differential pulse voltammograms were recorded between 0.60 and 1.40V after open circuit accumulation for 180 s with stirring. The oxidation peak current of CNR was measured. The parameters for differential pulse voltammetry (DPV) were pulse width of 0.06 s, pulse increment of 4 mV, pulse period of 0.2 s, pulse amplitude of 50 mV and scan rate of 20 mVs^{-1}. 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 CNR was calculated using standard addition method.

III. RESULTS AND DISCUSSION

3.1. Voltammetric behavior of CNR

The cyclic voltammograms of CNR at a bare CPE and at MWCNTs-modified CPE were as shown in Fig. 2. It can be seen that the oxidation peak or CNR at the bare CPE was weak and broad due to slow electron transfer, while the response was improved considerably at the MWCNTs-modified CPE. At the bare CPE, the peak was at about 1.30 V (Fig. 2c), but on the MWCNTs-modified CPE, the peak was present at about 1.20 V (Fig. 2a), with considerable enhancement in the anodic peak current. This was attributed to the electro-catalytic effect of MWCNTs. The reason for the better performance of the MWCNTs-modified CPE may be due to the nano dimensions of the MWCNTs, the electronic structure, more effective surface area and the topological defects present on the MWCNTs surfaces [25]. The modified electrode has no electrochemical activity in phosphate buffer solution (Fig. 2b), but the background current becomes larger, which is because of the fact that MWCNTs are increasing the surface activity. It also showed that no reduction peak was observed in the reverse scan, suggesting that the electrochemical reaction was a totally irreversible process.

But, it was found that the oxidation peak current of CNR showed a considerable decrease during the successive sweeps (Fig. 3). After the successive scan, the peak current decreased greatly and remained unchanged at the end. This phenomenon may be attributed the adsorption of oxidative product of CNR at the modified CPE surface. To know whether the CNR itself adsorbs on the electrode surface or not, a simple experiment was carried out. The MWCNT-modified CPE was placed with stirring in the 1.0 x 10^{-5} M CNR solution for 180 s. Afterwards modified CPE was taken out, placed in buffer solution of pH 2.5 and voltammogram was recorded. The peak appeared was mainly due to the already adsorbed CNR on the surface of CPE. This experiment clearly indicated the adsorption of CNR on the electrode surface before oxidation. Therefore, the voltammograms corresponding to the first anodic cycle and peak was generally recorded.

3.2. Influence of amount of MWCNTs

Fig. 4 shows that the amount of MWCNTs has influence on the peak current. At 5 mg of MWCNTs, the peak current was highest. After that amount, it decreases. This is related to the surface thickness. If the surface thickness was too thin, the CNR amount adsorbed was small, resulting in the small peak current. When it was too thick, the surface conductivity reduced and the surface became not as stable as MWCNTs could block the electrode surface. Thus it blocks the electrode surface and hence the peak current decreases. Therefore, 5 mg MWCNTs was used in the remaining studies.

3.3. Influence of accumulation potential and time

It was very important to fix the accumulation potential and time when adsorption studies were undertaken. Both conditions could affect the amount of adsorption of CNR 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 CNR used was 1.0 **x** 10^{-5} M. When accumulation potential was varied from +0.5 to -0.5 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 CNR on the surface of the modified CPE. The peak current reached the maximum after 180s and then being unchanged (Fig. 5). This indicates the saturation accumulation. As too long accumulation time might reduce the stability of MWCNTs film, 180s was generally chosen as accumulation time.

3.4. Influence of pH

The electrode reaction might be affected by the buffer solution and pH of the medium. The effect of different supporting electrolytes on the current response was investigated by CV, by taking acetate, phosphate and BR buffers. The results showed that high peak current was obtained in BR buffer with pH 2.5 (Fig. 6). Within the range of pH 2.5-5.5, dramatically decreased peak current response was found with a peak broadening. The peak potential was almost pH independent as shown in Fig. 7. From pH 6.0, CNR undergoes precipitation; hence the study was restricted to pH 2.5-5.5.

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 CNR at different scan rates from 10 to 400 mVs^{-1} was also studied (Fig. 8). There is a good linear relationship between peak current and scan rate. The equation representing this was Ip = 56.76 ν + 12.48; r = 0.992 as shown in Fig. 9. This indicates that the electrode process was controlled by adsorption rather than diffusion. In addition, there was a linear relation between log Ip and log ν (Fig. 10), corresponding to the following equation: log Ip = 0.9984 log ν + 1.32; r = 0.989. The slope of 0.9984 was very close to the theoretically expected value of 1.0 for an adsorption-controlled process [26]. The peak potential shifted to more positive values with increasing the scan rates. The linear relation between peak potential and logarithm of scan rate can be expressed as Ep = 1.4134 + 0.1537 log ν; r = 0.995 (Fig. 11). The mechanism of oxidation follows as reported earlier [14].

3.6. Calibration curve

In order to develop a detection method by voltammetric technique, we selected the differential-pulse voltammetric mode, because the peaks are sharper and better defined at lower concentration of CNR than those obtained by cyclic voltammetry, with a lower background current, resulting in improved resolution. According to the obtained results, it was possible to apply this technique to the quantitative analysis of CNR. The BR buffer solution of pH 2.5 was selected as the supporting electrolyte for the quantification as CNR gave maximum peak current at pH 2.5. The peak at about 1.12 V was considered for the analysis. Differential pulse voltammograms obtained with increasing amounts of CNR showed that the peak current increased linearly with increasing concentration, as shown in Fig. 12. Using the optimum conditions described above, linear calibration curves were obtained for CNR in the range of 8.0 **x** 10^{-9} M to 4.5 **x** 10^{-7} M. The linear equation was Ip (nA) = 0.099 + 2.256 C (r = 0.998, C is in nM). Due to the adsorption of CNR or its oxidation product on the electrode surface, deviation from linearity was observed for more concentrated solutions. Related statistical data of the calibration curves were obtained from five different calibration curves. The limit of detection (LOD) and quantification (LOQ) were 1.11 **x** 10^{-9} M and 3.71 **x** 10^{-9} M respectively. The LOD and LOQ were calculated using the following equations: 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. This method was better as compared with other reported electrochemical method [13, 14].

To check the reproducibility of the electrode preparation procedure, a 1.0 **x** 10^{-7} M CNR solution was measured with the same electrode (renewed every time) for every several hours within a day, the R.S.D. of the peak current was 1.98% (number of measurements = 10). As to the between day reproducibility, it was similar to that of within a day if the temperature was kept almost unchanged. The current response of the modified electrode would decrease after successive use because of the adsorption of oxidative product of CNR on to the electrode surface. In this case, the electrode should be modified again.

3.7. Tablet analysis

In order to check the applicability of the developed method in the pharmaceutical sample analysis, two commercial medicinal samples containing CNR viz. Vertigil (Cipla Co. India) and Vergo (Alkem Co. India) were studied. The procedures for the tablet analysis were followed as described in section 2.5. The results are in good agreement with the content marked in the label (Table. 1). The recovery test of CNR was performed using differential-pulse voltammetry ranging from 1.0 **x** 10^{-8} to 1.0 **x** 10^{-7} M. Recovery studies were carried out after the addition of known amounts of the drug to various pre-analyzed formulations of CNR. The recoveries in different samples were found to lie in the range from 98.32 % to 102.3 %, with RSD of 2.94 %.

3.9. Detection of CNR in urine samples

The developed differential-pulse voltammetric method for the CNR detection was applied to urine samples. The recoveries from urine were measured by spiking known amounts of CNR to drug free urine. The urine samples were diluted 100 times with the BR buffer solution before analysis without any pretreatments. A quantitative analysis was carried out by adding the standard solution of CNR into the urine sample. The calibration graph was used for the determination of spiked CNR in urine samples. The detection results of four urine samples obtained are listed in Table.2. The recovery determined was in the range from 98.7 % to 100.6 % and the standard deviation and relative standard deviation are listed in Table.2.

IV. CONCLUSIONS

In this work, we reported a multi-walled carbon nanotubes modified carbon paste electrode for detection of CNR. MWCNTs showed electro-catalytic action for the oxidation of CNR, characterizing by the enhancement of the peak current, which was probably due to the larger surface area of MWCNTs. The peak at about 1.12 V was suitable for analysis and the peak current was linear to CNR concentrations over a certain range under the selected conditions. This eco-friendly sensor can be used for voltammetric detection of CNR as low as 1.11 **x** 10^{-9} M with good reproducibility and accuracy. The modified CPE has been used to detect CNR in pharmaceutical samples. The developed method offered the advantages of accuracy and time saving as well as simplicity of reagents and apparatus. In addition, the results obtained in the analysis of CNR in spiked urine samples demonstrated the applicability of the method for real sample analysis.

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FIGURE LEGENDS

Fig. 1. Chemical structure of cinnarizine.

Fig. 2. Cyclic voltammograms of 1.0 X 10^{-5} M CNR on MWCNTs-modified CPE (a) and bare CPE (c). Blank CVs of MWCNT-modified CPE (b) and bare CPE (d). Scan rate: 50 mVs^{-1}; supporting electrolyte: BR buffer with pH 2.5; accumulation time: 180s (at open circuit); amount of MWCNTs: 5 mg.

Fig. 3. Successive cyclic voltammograms of 1.0 X 10^{-5} M CNR on MWCNTs-modified CPE. Other conditions are as in Fig. 2.

Fig. 4. Influence of amount of MWCNTs used on the anodic peak current. Other conditions are as in Fig. 2.

Fig. 5. Variation of the anodic peak current with accumulation time. Other conditions are as in Fig. 2.

Fig. 6. Variation of peak currents of CNR with pH. Other conditions are as in Fig. 2.

Fig. 7. Influence of pH on the peak potential of CNR. Other conditions are as in Fig. 2.

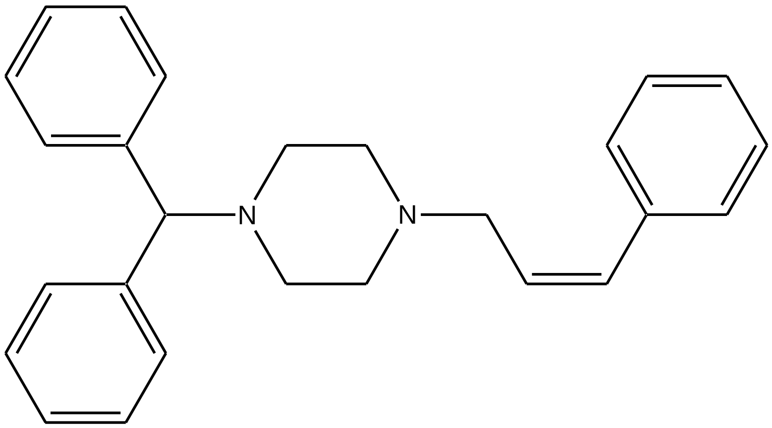
Fig. 8. Cyclic voltammograms of 1.0 X 10^{-5} M CNR on MWCNTs-modified CPE with different scan rates. (a) to (g) were 10, 50, 100, 150, 200, 300 and 400 mVs^{-1}, respectively. Other conditions are as in Fig. 2.

Fig. 9. Dependence of the oxidation peak current on the scan rate.

Fig. 10. Dependence of the logarithm of peak current on logarithm of scan rate.

Fig. 11. Relationship between peak potential and logarithm of scan rate.

Fig. 12. Differential-pulse voltammograms of MWCNTs-modified CPE in CNR solution at different concentrations: 8.0 (1), 20.0 (2), 60.0 (3), 100.0 (4), 150.0 (5) and 450.0 (6) nM. Inset: Plot of the peak current against the concentration of CNR.



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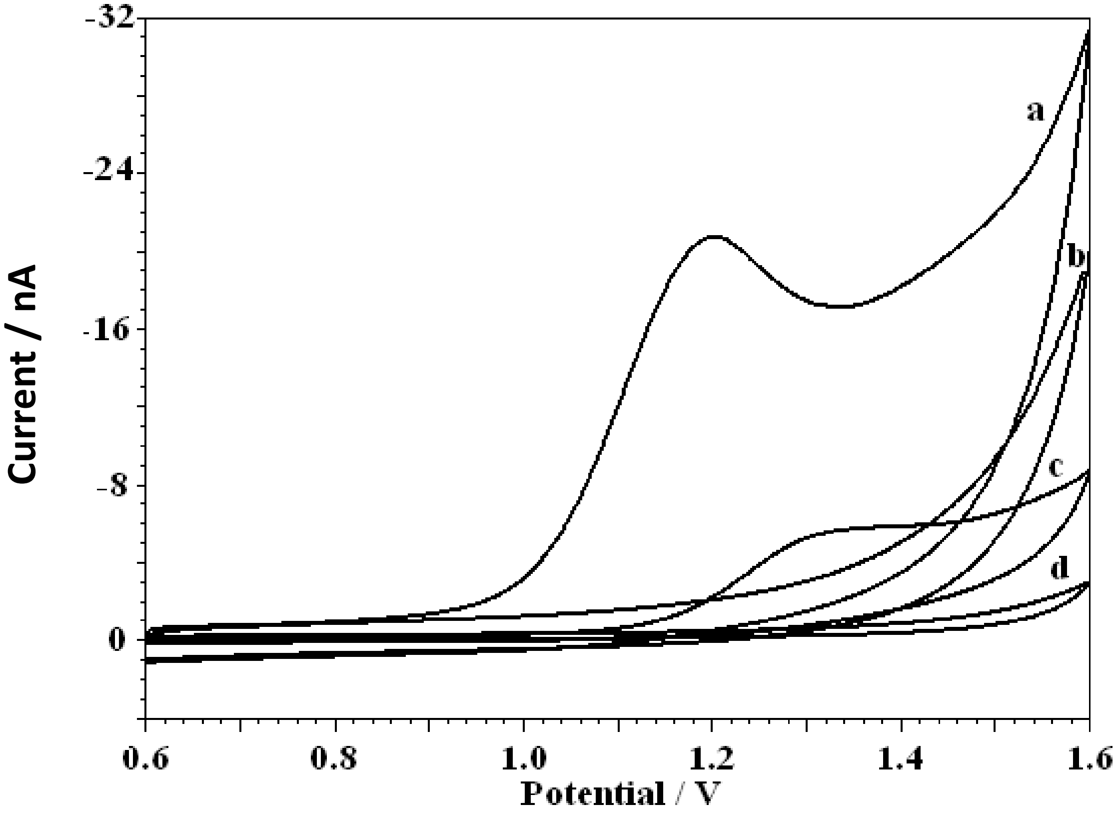
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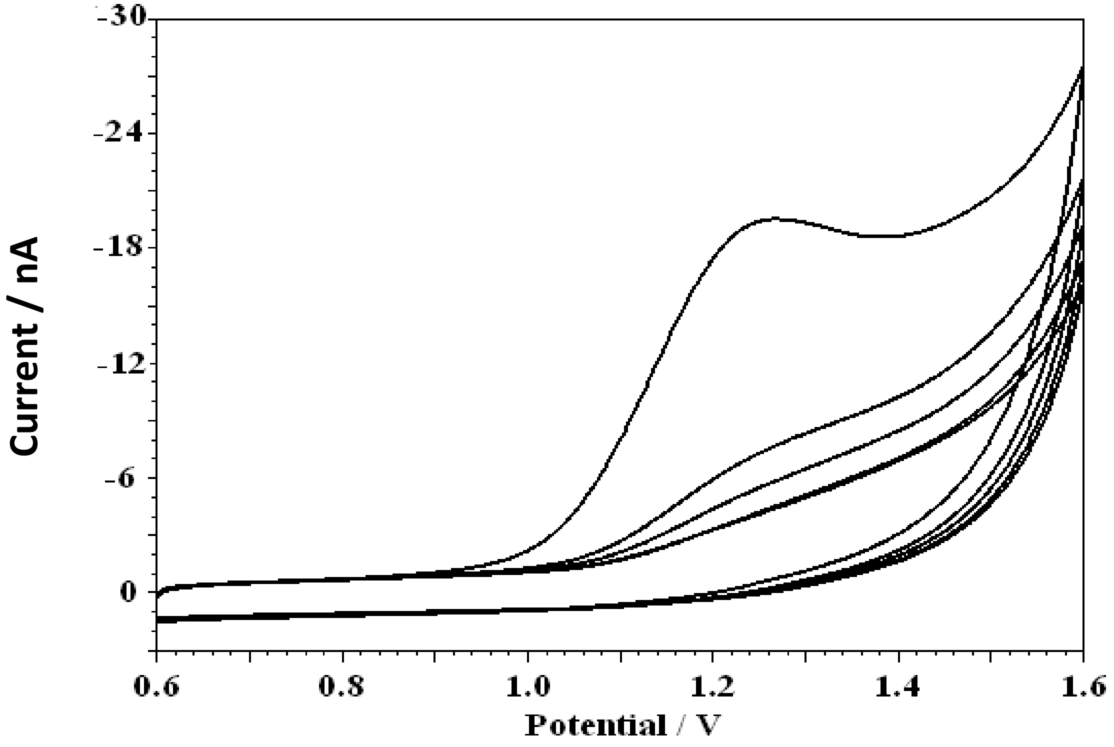
Fig. 2.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Potential / V

Fig. 3.

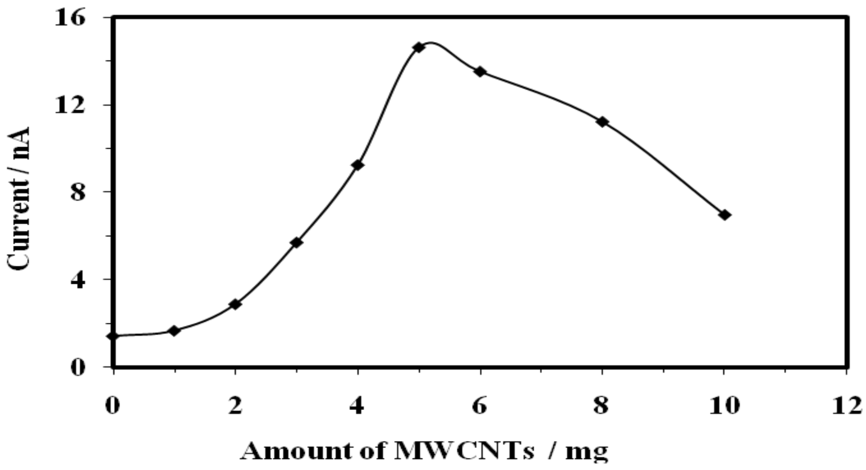
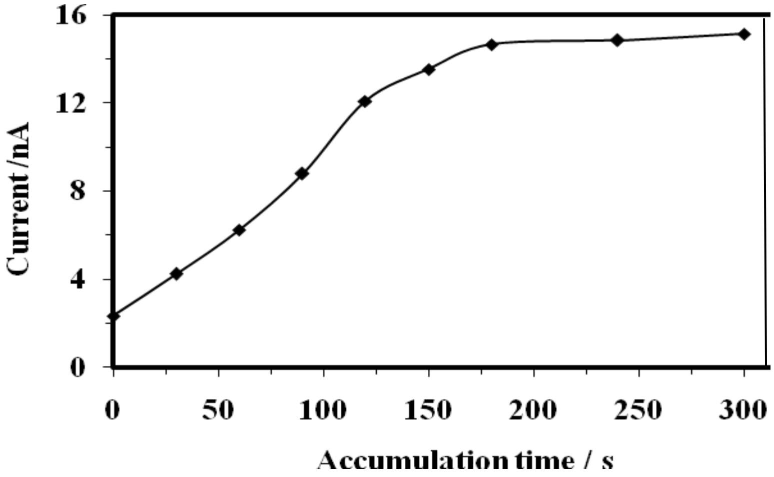


Fig. 4



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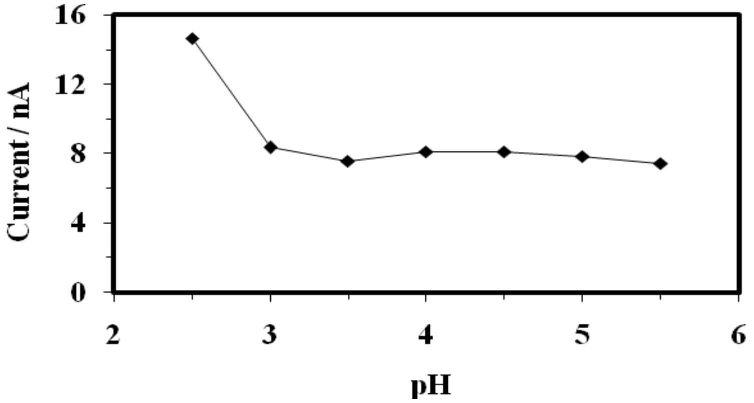

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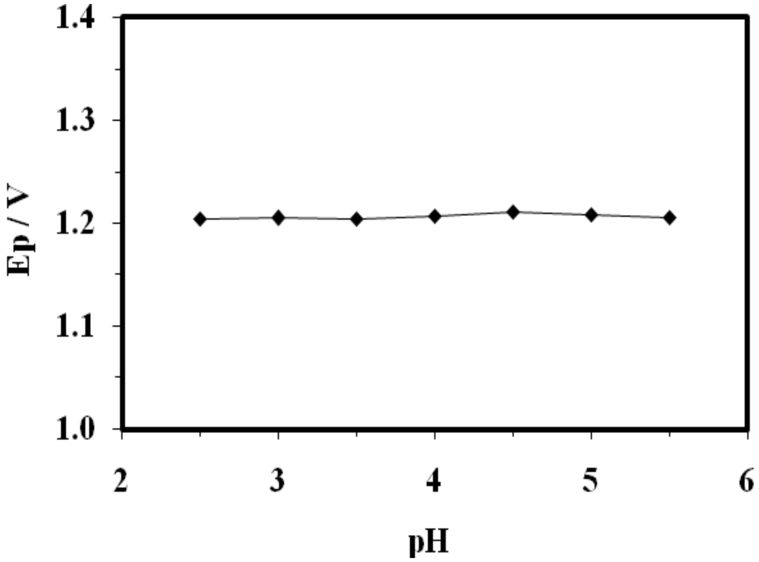
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Fig. 7.

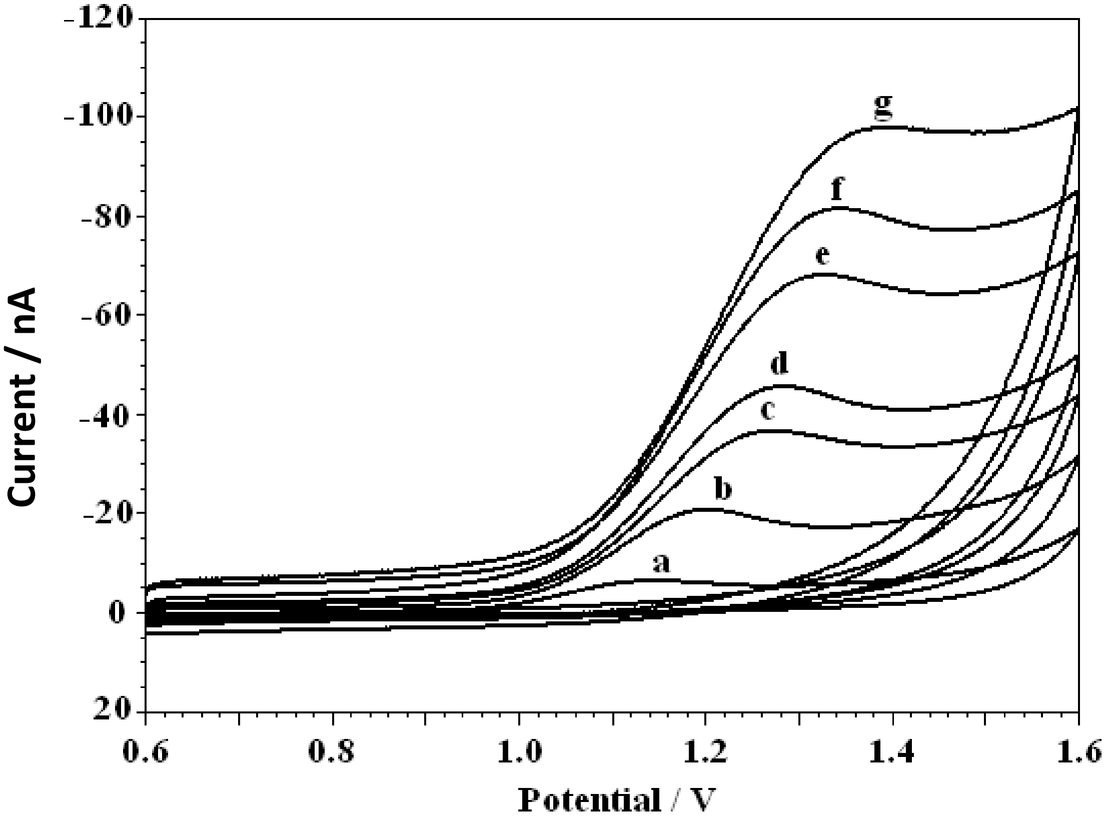
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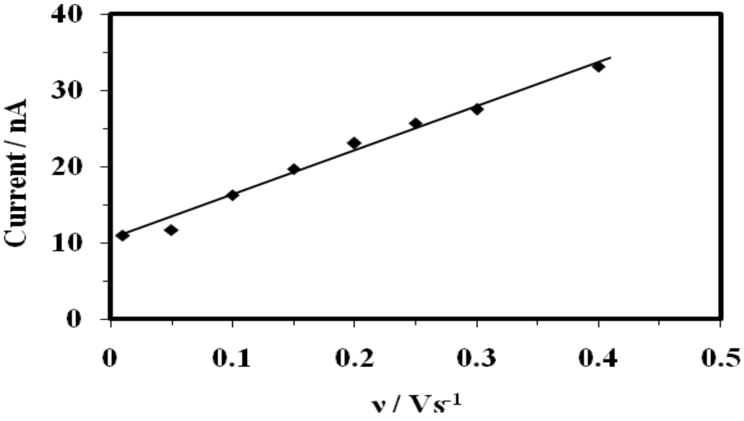
Fig. 8.



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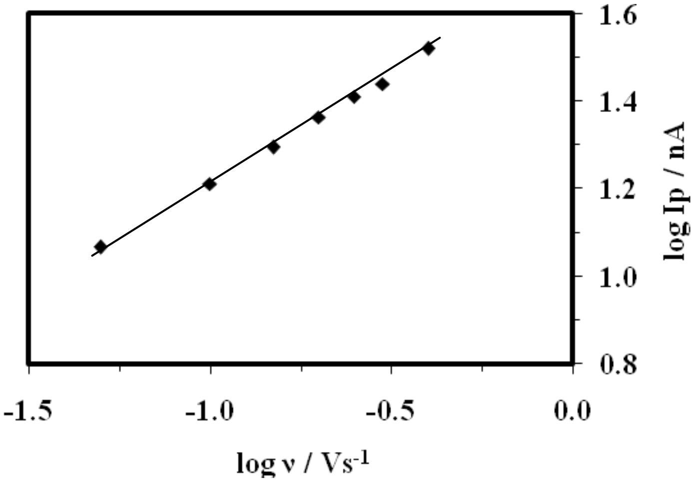

Fig. 10

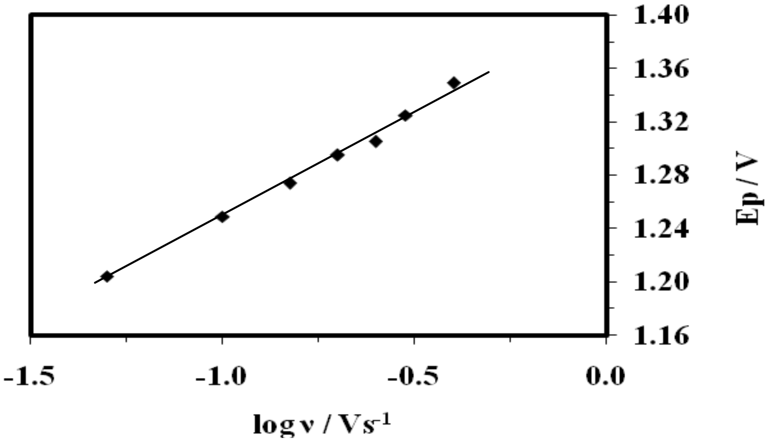

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Fig. 11.

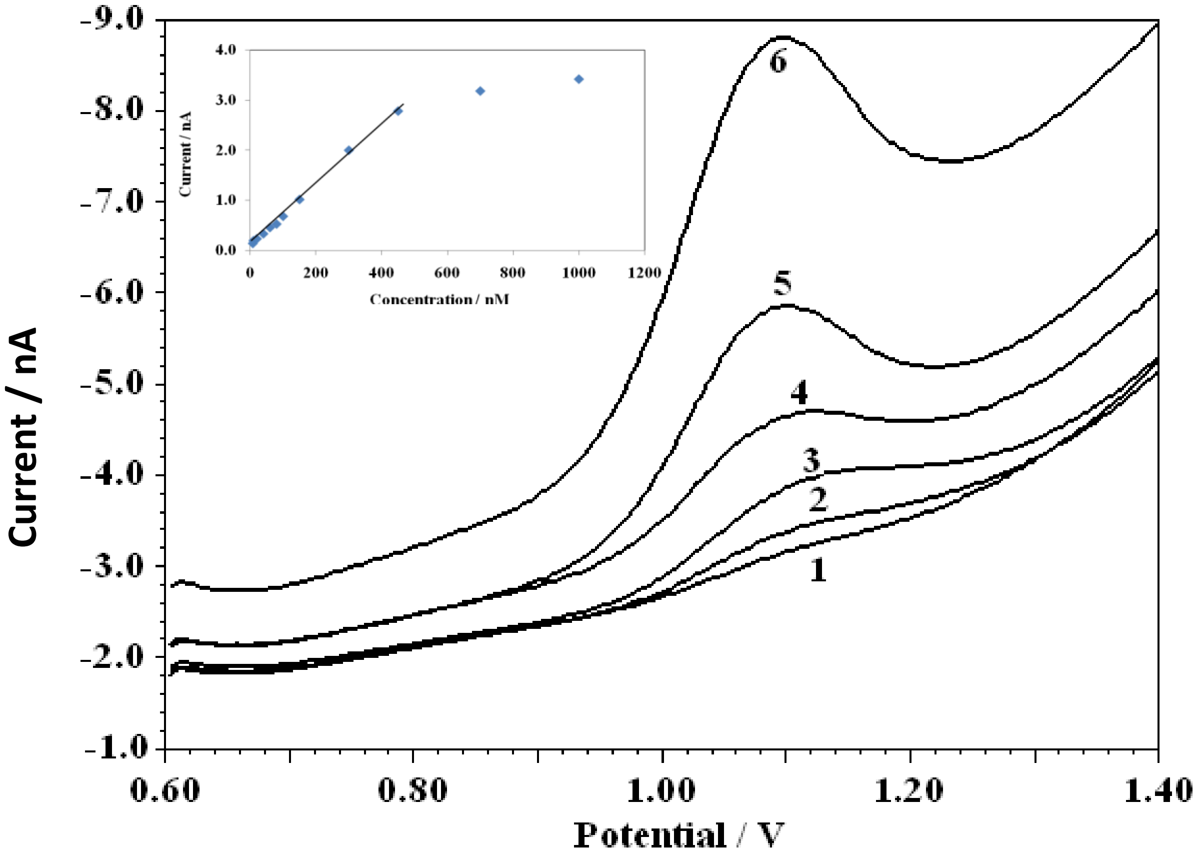

Fig. 12.

Table 1

Comparative studies for CNR in Vertigil and Vergo tablets by proposed and literature methods and mean recoveries in spiked tablets.

	AdSV[a] [13]	Vertigil[b]	Vergo[c]
Labelled claim (mg)	25.0	20.0	25.0
Amount found (mg)[d]	24.82	19.67	24.86
R.S.D. (%)	1.65	2.03	1.34
Added (mg)	-----	10.0	10.0
Found (mg)	-----	9.91	9.89
Recovered (%)[e]	-----	99.1	98.9
(%) of recovery in R.S.D.	-----	1.35	0.94

[a] Adoptive stripping voltammetry. [b] Cipla Co. [c] Alkem Pentacare Co. [d] Each value is the mean of five experiments.

[e] Recovery value is the mean of five experiments.

Table 2

Determination of CNR in urine samples

Urine	Spiked (10^{-9} M)	Found (10^{-9} M)[a]	Recovery (%)
Sample 1	10.0	9.87	98.7
Sample 2	20.0	20.1	100.5
Sample 3	100.0	99.8	99.8
Sample 4	200.0	201.2	100.6

[a] Average of five determinations