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Keyword:	Chlorpheniramine maleate; Oxidation; Voltammetric techniques; Anionic surfactant; Analytical applications

Electrochemical detection of chlorpheniramine maleate in the presence of an anionic surfactant and its analytical applications

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Abstract

Improvement of methods for the detection of an analyte at low concentration with high sensitivity has become an important point of interest. In reflection of this fact, an effort has been made to know the electrochemical behavior of chlorpheniramine maleate in the presence of an anionic surfactant. Voltammograms were obtained in the range of 6.0 - 11.2 pH and maximum peak current (Ip) was observed at pH 10.4. Various physico-chemical parameters such as, process on the surface of the electrode, which was found to be diffusion controlled, heterogeneous rate constant, number of electrons transferred and charge transfer coefficient were estimated. Square wave voltammetry of chlorpheniramine maleate at the modified electrode exhibited a linear calibration curve in the concentration range of 1.0-100 μM, with a limit of detection of 28 nM. The proposed technique was successfully used for the determination of chlorpheniramine maleate in pharmaceuticals as well as in biological samples.

Keywords: Chlorpheniramine maleate; Oxidation; Voltammetric techniques; Anionic surfactant; Analytical applications

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1. Introduction

Chlorpheniramine maleate (CPM) or 3- (4- chloro, phenyl)- n, n- dimethyl- 3- pyridin- 2- yl- propan- 1- amine (Scheme 1) is a familiar antihistamine drug. It has been used intensively for the treatment of common cold and allergic diseases both alone and in mixture with other drugs [1, 2]. The adverse effects include drowsiness, dizziness, confusion, constipation, anxiety, nausea, blurred vision, restlessness, decreased coordination, dry mouth, shallow breathing, hallucinations, irritability, problems with memory or concentration, tinnitus and trouble urinating.

"Here Scheme 1"

Owing to the importance, several analytical techniques have been suggested for the determination of CPM in drug formulations or in biological samples such as spectrophotometry [3], high–performance liquid chromatography (HPLC) [4-8], reversed phase high–performance liquid chromatography (RP-HPLC) [9, 10], liquid chromatography- mass spectroscopy (LC-MS) [11-13], chemiluminescence [14], electro generated chemiluminescence [15] and capillary electrophoresis [16]. As these methods are rather sophisticated, expensive, time consuming methods. Few attempts have also been made to use electroanalytical technique for the determination of CPM using carbon paste electrodes [17-19], modified glassy carbon electrode [20-22] and hanging mercury drop electrode [23]. However these methods have attracted much attention of researchers towards to their sensitivity for the determination of organic molecules, rapidity of analysis, inexpensive instrumentation and no complex sample pretreatment are also considered as eco-friendly [24, 25]. In addition application of electro analytical techniques includes the determination of electrode mechanisms. Redox properties of drugs can give insights into their metabolic fate or their in vivo redox processes or pharmaceutical activity [26].

In this paper we described the application of anionic surfactant, sodium dodecyl sulfate for the electrochemical analysis of CPM at glassy carbon electrode for the first time. Amphiphilic ions or molecules with polar head groups and long hydrocarbon tails are commonly known as surfactants. These are extensively used in many topical pharmaceutical and food products, cosmetics, antiseptics, shampoos, detergents, creams and lotions. There are a number of areas of application where surfactant adsorption is important. In the electrode process, surfactants can exert strong effect even in trace quantities. Adsorption at interfaces and aggregation into supramolecular structures are the two main helpful properties of surfactants in electrochemistry [27-31].

Therefore, present protocol uses a simple and sensitive method to detect chlorpheniramine maleate at glassy carbon electrode in the presence of an anionic surfactant sodium dodecyl sulfate. Moreover, cyclic and square wave voltammetric techniques have been used to estimate the electrochemical behavior of chlorpheniramine maleate (CPM). Further, the technique with good precision and accuracy was developed for the determination of chlorpheniramine maleate in tablet as well as in biological samples.

2. Experimental

2.1. Materials and Reagents

Electrochemical analyzer **(**CHI Company, D630, USA) was used to study the electrochemical activities of the drug under investigation at an ambient temperature of 25 ± 0.2 ^{0}C. A three electrode system consisting of glassy carbon electrode (GCE) as working electrode, platinum wire as counter electrode and Ag/AgCl (3M KCl) as reference electrode were used in a 10 ml single compartment. Chlorpheniramine maleate (CPM) (Sigma-Aldrich, USA) was used to prepare 1.0 mM stock solution in double distilled water. In this study, sodium dodecyl sulphate

(SDS), cetyltrimethyl ammonium bromide (CTAB) and triton-X from SD-Fine Chem Ltd. were used as anionic, cationic and neutral surfactants respectively. The phosphate buffer saline (PBS) solutions ranging 3.0 – 11.2 pH with ionic strength 0.2 M were prepared according to the literature [32]. pH of the solutions was measured by using pH meter (Elico Ltd., LI120, India). Double distilled water, analytical grade chemicals and reagents were used throughout the experiments.

2.2. Pretreatment of working electrode

Prior to use, the GCE was carefully polished using 0.3 micron Al_2O_3 slurry on a polishing cloth before each experiment. The GCE was first activated in phosphate buffer (pH 10.4) by cyclic voltammetric sweeps between 0.0 to 2.0 V until stable cyclic voltammograms were obtained. Then electrodes were transferred into another 10 ml of phosphate buffer (pH 10.4) containing proper amount of CPM.

Randles - Sevcik equation was used to calculate the active surface area of the electrode using cyclic voltammetric technique and $K_3Fe(CN)_6$ 1.0 mM as a probe at different scan rates in 0.1 M KCl as supporting electrolyte [33, 34]. At T = 298 K and for a reversible process the equation is as follows:

$$I_p = (2.69 \times 10^5)\, n^{3/2}\, A\, D_0^{1/2}\, \nu^{1/2}\, C_0^{*} \qquad (1)$$

In equation (1) I_P refers to the anodic peak current, n is the number of electron transferred during the electrode reaction = 1. A is the surface area of the electrode, D_0 is the diffusion coefficient i.e. 7.6×10^{-6} cm^2 s^{-1}, υ is the scan rate and C_0^{*} is the concentration of $K_3Fe(CN)_6$. The surface area of the electrode (A) was calculated from the slope of the plot of I_p vs. $\nu^{1/2}$. For the bare electrode, the area was found to be 0.042 cm^2 and for the modified electrode, the surface area was found to be 0.15 cm^2. Because of surfactant effect, the modified electrode surface area

increases. After activation the surfactant molecules adsorbed homogeneously over the whole electrode surface and make the surface more porous and sensible.

2.3. Procedures for pharmaceutical preparations

Ten pieces of CPM tablets were ground using mortar. Weight corresponding to stock solution was, taken in 100 ml calibrated flask and made to volume with double distilled water. After sonication for 10 minutes, required concentration of solution were prepared by diluting in buffer solution (pH = 10.4). By standard addition method, solution was analyzed. Recovery studies were performed using standard addition method. The content of the drug in tablet was determined by referring to the calibration graph or regression analysis.

2.4. Analysis of human urine and serum

Human urine was obtained from four healthy volunteers of similar sex and age. Aliquots were centrifuged at 7000 rpm for five minutes at room temperature (25 ± 0.1 ^{0}C). These urine samples were analyzed immediately or they were stored at low temperature until analysis.

Serum samples, obtained from healthy volunteers were stored frozen until assay. To achieve final concentration of 1.0 mM, an aliquot quantity of sample was fortified with CPM. 0.4 mL of acetonitrile was treated and the volume was completed to 3.0 mL with the same serum sample. To clear the protein residues in the mixture it was vortexed for one minute, then centrifuged for ten minutes at 4000 rpm. Analysis was carried out in pH=10.4 and quantification was performed by means of calibration plot method.

3. Results and discussion

3.1. Voltammetric behavior

Comparison of the electrochemical behavior of CPM in the absence and presence of anionic surfactant SDS was studied in pH= 10.4 (I = 0.2 M). The study evaluates that in the presence of SDS, the electro-oxidation behavior of chlorpheniramine maleate changes significantly. Due to, increase in electro-active area of the electrode, there was appreciable increase in the sensitivity and selectivity. In the existence of 5.0 μM SDS at glassy carbon electrode, as compared to bare, enhanced anodic peak was observed for CPM (Fig. 1). Voltammograms recorded on reversing the scan rate, absence of reduction peak indicative of the irreversibility of the process. Successive cyclic voltammogram sweeps shows decrease in the peak current due the adsorption of CPM or its oxidation product. Hence, the initial peak was been considered for analysis.

"Here Figure 1"

3.2. Influence of pH

Proton is always involved in the electrochemical reaction of an organic compound and exerts significant impact on the reaction speed. Therefore, the effects of solution pH on the electrode reaction of CPM recorded in the range pH 3.0 - 11.2 at a preferred scan rate of 0.05 Vs^{-1}Fig. 2. With increase in the solution pH, no peak was observed in the pH range 3.0 – 5.0. The potentials of the peaks were shifted to less positive values from pH 6.0 - 11.2. From the plot of peak potential as a function of pH (Fig. 2A), it is evident that the slope of, 62 mV/pH is of good agreement, and closer to the Nernstian value of 59.0 mV/pH for equal number of electrons and proton transfer [35] with linear equation: E_p= 0.062 pH + 1.341; R^2=0.939. The magnitude of peak current also depends on the pH of the solution (Fig. 2B). Maximum peak current was been obtained at pH 10.4 as observed from the plot of peak current as the function of pH.

"Here Figure2"

3.3. Influence of scan rate

Study of scan rate effect, play a crucial role in the investigation of many physico-chemical parameters. Peak current is proportional to applied voltammetric scan rate, which is analogous to the following equation; $I_p = 45.15\ \upsilon + 1.728$; $R^2 = 0.993$ (Fig. 3A). From the plot of log I_P as the function of log υ, it was signified as diffusion controlled electrode process, since its slope of 0.65, very close to theoretical value of 0.5 for diffusion controlled [36, 37] analogues to the equation; $\log I_p = 0.65 \log \upsilon + 1.527$; $R^2 = 0.987$ (Fig. 3B).

"Here Figure3"

Further from the plot of E_p versus log scan rate (Fig. 3C), it was been observed the peak potential shifted to positive value with increase in scan rate suggesting the irreversibility of the electrode process [38]. The relationship between peak potential and logarithm of scan rate is as follows: $E_p = 0.050 \log \nu + 0.730$; $R^2 = 0.987$. Considering the strong adsorption of the reactant and irreversibility of the electrode process, Laviron equation can be used [39].

$$Ep = E^0 + \left(\frac{2.303\ R\ T}{\alpha n F}\right) \log\left(\frac{RTk^0}{\alpha n F}\right) + \left(\frac{2.303\ R\ T}{\alpha n F}\right) \log\upsilon \qquad (2)$$

As per the above equation, linear plot for E_p as a function of log υ has been obtained. From the slope of the plot αn (α: transfer coefficient; n: number of electron transferred) was calculated to be 1.18. The intercept was used to find the k^0 (heterogeneous rate constant) value by deducing the value of E^0 from intercept of peak potential versus scan rate plot, by extrapolating the line to $\upsilon = 0$. Hence, value of k^0 and E^0 was been obtained to be $2.39 \times 10^3\ s^{-1}$ and 0.644 respectively. According to Bard and Faulkner [40], for an irreversible electrode reaction α was assumed to be

158 0.5, hence n was calculated to be two. Therefore, the number of proton and electrons
159 participating in the electrode reaction was been calculated to be two.

$$\alpha = \frac{47.7}{E_p - E_{p/2}} \text{ mV} \quad (3)$$

160

161 **3.4. Surfactant effect**

162 Surfactants consists a polar hydrophilic head on one side and an extended hydrophobic tail
163 on the other. Even in trace level these surface active molecules exert strong effect on the
164 electrode process [41]. The essential function of the surface active molecules is to reduce the
165 surface tension at the interface or at the surface and to allow easier spreading of molecules.
166 Adsorption of such substances at the electrode may inhibit the electrolytic process, bring about
167 the irregularity in the voltammograms, and cause a shift in the wave to more negative potentials.
168 Surfactants have common tendency of accumulation at interfaces. The potential, current and the
169 extent of reversibility of the electrode reaction was found to be dependent upon the nature and
170 concentration of the surfactant employed. The lack of affinity between the hydrophobic portion
171 of the surfactant and water leads to a repulsion of these substances from the water phase as a
172 consequence of oxidation of the microscopic CPM-water interface. Three types of surfactants viz
173 [sodium dodecyl sulphate (SDS) (anionic), cetyltrimethyl ammonium bromide (CTAB)
174 (cationic) and Triton x-100 (non-ionic)] were used in the present work to check the
175 electrocatalytic effect on CPM. Among these, the anionic surfactant, sodium dodecyl sulphate
176 (SDS) was showed excellent electrocatalytic activity for the investigation of CPM (Fig. 4). SDS
177 increases the polarity on the surface of glassy carbon electrode, which results in the enhancement
178 of current signals. It is well known that surfactants can be adsorbed on a hydrophobic surface to
179 form surfactant film, which may alter the over voltage of the electrode and influence the rate of

electron transfer. In the presence of SDS, the electrode surface may form a hydrophilic film with positive charge. This hydrophilic layer may increase the concentration of CPM on the electrode surface

"Here Figure 4"

3.5. Oxidation mechanism

The anodic peak on a forward scan indicating the oxidation of CPM and no peak was detected in the reverse scan. Therefore in this irreversible system, the result suggests two electron transfer process involved in the oxidation of chlorpheniramine maleate. The mechanism is shown in Scheme 2.

"Here Scheme 2"

4. Analytical applications

4.1. Validation of the analytical procedure

Quantitative analysis of CPM has been carried out in square wave voltammetric technique, since the peaks are sharper and better defined at lower concentration of CPM than those obtained by cyclic voltammetry, with a lower background current, resulting in improved resolution. Voltammograms with increasing concentration of CPM (Fig. 5) has been used to obtain the linear calibration curve in the range of 1.0 – 100 μM. The linear equation was:

$$I_p\ (\mu\ A) = 2.571\ C + 0.847\ (R^2 = 0.979;\ C \text{ is in } \mu M)$$

"Here Figure 5"

The adsorption of CPM or its oxidation product on the electrode surface diverge the linearity for more concentrated solution [42, 43]. Limit of detection (LOD) and limit of quantification (LOQ) were been calculated to be 0.028 μM and 0.096 μM, using following equation respectively [44].

$$LOD = 3\ S/m \quad (4)$$

$$LOQ = 10\ S/m \quad (5)$$

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 detection limits reported at different electrochemical methods for CPM is tabulated in the Table 1. This method was better as compared to other reported similar methods [17-23].

"Here Table 1"

4.2. Tablet Analysis

Commercially available tablets with standard addition method, was used for recovery studies. Calibration plot and similar condition used during calibration plot construction were employed for tablet analysis. The marked label and the results obtained were appreciable (Table 2).

"Here Table 2"

4.3. Effect of excipients

To evaluate the effect of excipients 0.1 mM CPM was used. The study shows that 100 folds of citric acid, gum acacia, oxalic acid, sucrose, and urea did not meddle with the voltammetric signal of CPM. The tolerance limit was less than ± 5%. The tolerance limit is defined as maximum concentration of the interfering substance that caused as error less than ± 5% for determination of CPM.

4.4. Analysis of human urine and serum samples

Samples of drug free urine was been spiked with a known amount of drug. The unknowns were analyzed using calibration plot. Easy assessment of CPM was possible only due to the simplicity of the method and no pre-extraction process for urine sample. Further, the results obtained from recovery studies showed good recoveries was found in the range of 94.6% to

99.5% with percentage of RSD 2.28 % (Table 3). In addition, from the results obtained it was easy indication for the applicability of the method for CPM determination from the real biological matrices. Previously, in section 2.4.we described the procedure for spiked human serum sample with the analyte. The recoveries in different samples were found to be in the range of 90.5% to 99.0% with 2.62 % of RSD.

"Here Table 3"

5. Conclusion

In the present study, an effective and efficient sensor for the electrochemical detection of chlorpheniramine maleate was developed by using glassy carbon electrode in the presence of sodium dodecyl sulfate at pH = 10.4. The obtained results illustrated that, the anionic surfactant sodium dodecyl sulfate can adsorb at the electrode surface through strong hydrophobic interaction and in the presence of sodium dodecyl sulfate, the voltammetric responses of chlorpheniramine maleate was facilitated. The electrode process was found to be diffusion controlled with two electron transfer. A sensitive and low detection limit of the proposed method is promising for the detection of chlorpheniramine maleate in pharmaceutical samples as well as in real samples.

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320

321 **Figure captions**

322 **Fig. 1.** Cyclic voltammograms of 1.0 mM CPM on glassy carbon electrode in pH 10.4,
323 phosphate buffer (I = 0.2 M) (a) blank, (b) pH 10.4 with SDS, (a1) CPM without SDS and
324 (b1) CPM with surfactant. (Scan rate: 0.05 Vs^{-1})

325 **Fig. 2.** Cyclic voltammograms obtained for 1.0 mM in buffer solution at (a) pH 6.0; (b) pH 7.0;
326 (c) pH 8.0; (d) pH 9.2; (e) pH 10.4; (f) pH 11.2. (Scan rate: 0.05 Vs^{-1}); **(A)** Influence of pH on
327 the peak potential E_P/V of CPM; **(B)** Variation of peak currents I_P/μA of CPM with pH.

328 **Fig. 3.** Cyclic voltammograms of 1.0 mM CPM in buffer solution of pH 10.4 (I = 0.2 M) at scan
329 rate of : (1) blank; (2) 0.005; (3) 0.008; (4) 0.01; (5) 0.03; (6) 0.05; (7) 0.08; (8) 0.12; (9) 0.15;
330 (10) 0.20; (11) 0.25; (12) 0.30; (13) 0.40; (14) 0.50 V s^{-1}; **(A)** Dependence of peak current
331 (I_P/μA) on the scan rate (υ/Vs^{-1}); **(B)** Plot of logarithm of peak current (log I_P/μA) versus
332 logarithm of scan rate (log υ/Vs^{-1}); **(C)** Plot of variation of peak potential (E_P/V) with logarithm
333 of scan rate (log υ/Vs^{-1}).

334 **Fig. 4.** Voltammetric behavior of 1.0 mM CPM with three types of surfactants.

335 **Fig. 5.** Square wave voltammograms with increasing concentrations of CPM in pH 10.4
336 phosphate buffer solution on glassy carbon electrode: (1) blank; (2) 1.0 x 10^{-6}; (3) 3.0 x 10^{-5}; (4)
337 4.0 x 10^{-5}; (5) 5.0 x 10^{-5}; (6) 6.0 x 10^{-5}; (7) 8.0 x 10^{-5};(8) 1.0 x 10^{-4}. **Inset:** Dependence of peak
338 current I_P/μA versus concentration (mM).

339 **Scheme 1.** Chemical structure of chlorpheniramine maleate [3-(4-chlorphenyl)-N, N-dimethyl-3-
340 pyridin-2-yl-propan-1-amine]

341 **Scheme 2.** Possible electrode reaction mechanism of chlorpheniramine maleate.

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348 **Table captions**

349 **Table. 1**. Comparison of linearity range and detection limits of chlorpheniramine maleate by
350 electroanalyticaltechniques.

351 **Table. 2.** Analysis of chlorpheniramine maleate in tablets by SWV and recovery studies.

352 **Table. 3.** Application of SWV for the determination of CPM in spiked human urine and blood.

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354

355

Tables

Table 1.

Method	Electrode	Linearity Range (µmol L^{-1})	LOD (µmol L^{-1})	Reference
Differential pulse voltammetry	SDS[a]/CPE[b]	1.0-800	1.7	17
Potentiometry	CPE-Ion exchanger	2.0-12000	0.51	18
Differential pulse voltammetry	CPE-Co[c] nanostructure	0.1-1.0	0.08	19
Cyclic voltammetry	Ru/Pty/GCE[d]	2.0-45	0.338	21
Differential pulse voltammetry	MWCNT/GCE[e]	5.0-500	1.63	22
Square wave voltammetry	HMDE[f]	0.98-9.75	0.984	23
Square wave voltammetry	SDS/GCE[g]	0.1-100	0.028	Current work

[a]Sodium dodecyl sulfate, [b]Carbon paste electrode; [c]Cobalt; [d]tris (2, 2'-bipyridyl) Ru (II) complex modified glassy carbon electrode, [e]Multiwalled carbon nanotube, [f]Hanging mercury drop electrode, [g]Glassy Carbon electrode

Table 2.

Labeled claim (mg)	100
Amount found (mg)*	98.6
RSD (%)	1.12
T-test of significant	0.49
F-test of significant	1.01
Bias (%)	-1.5
Added (mg)	1.0
Found (mg)	0.97
Recovered (mg)	97.2
RSD (%)	0.86
Bias (%)	-2.8

* Average of five determinations

Table 3.

Samples	Spiked (10^{-4} M)	Detected* (10^{-4} M)	Recovery (%)	RSD (%)
Urine sample 1	0.1	0.099	99.5	2.25
Urine sample 2	0.2	0.189	94.6	2.37
Urine sample 3	0.5	0.499	99.1	2.26
Blood sample 1	0.2	0.181	90.5	2.97
Blood sample 2	0.5	0.495	99.0	2.28

* Average of five determinations

Figures

Figure 1.

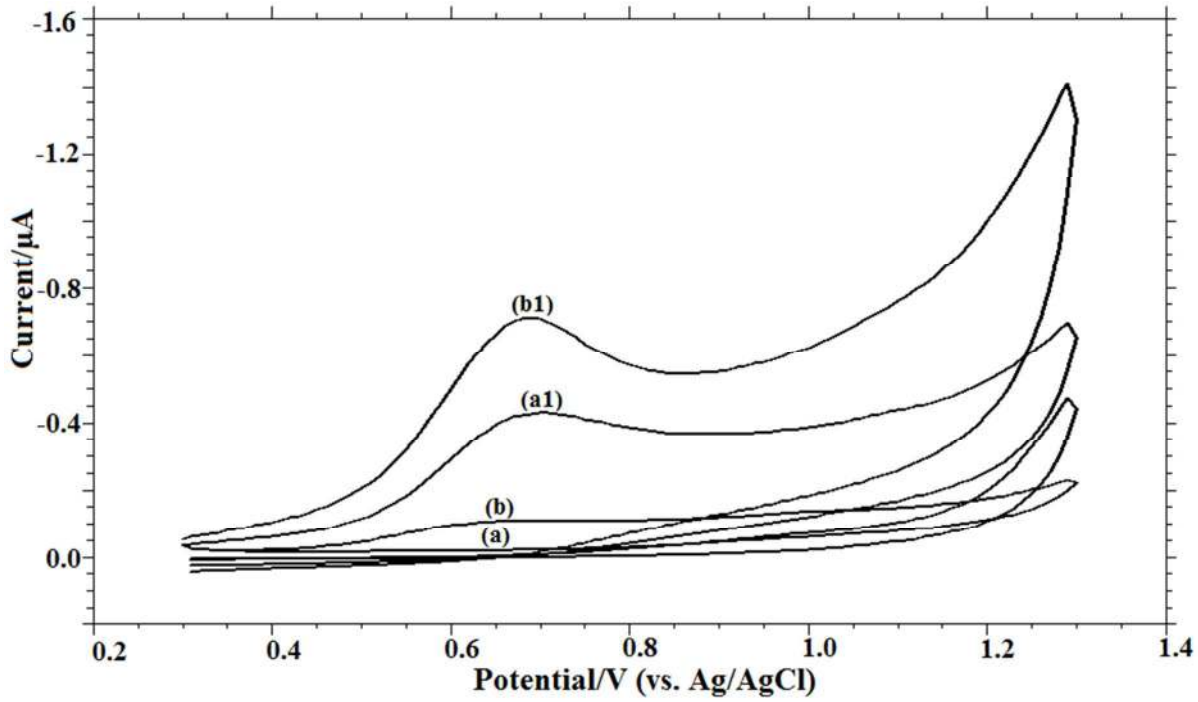


Figure 2.

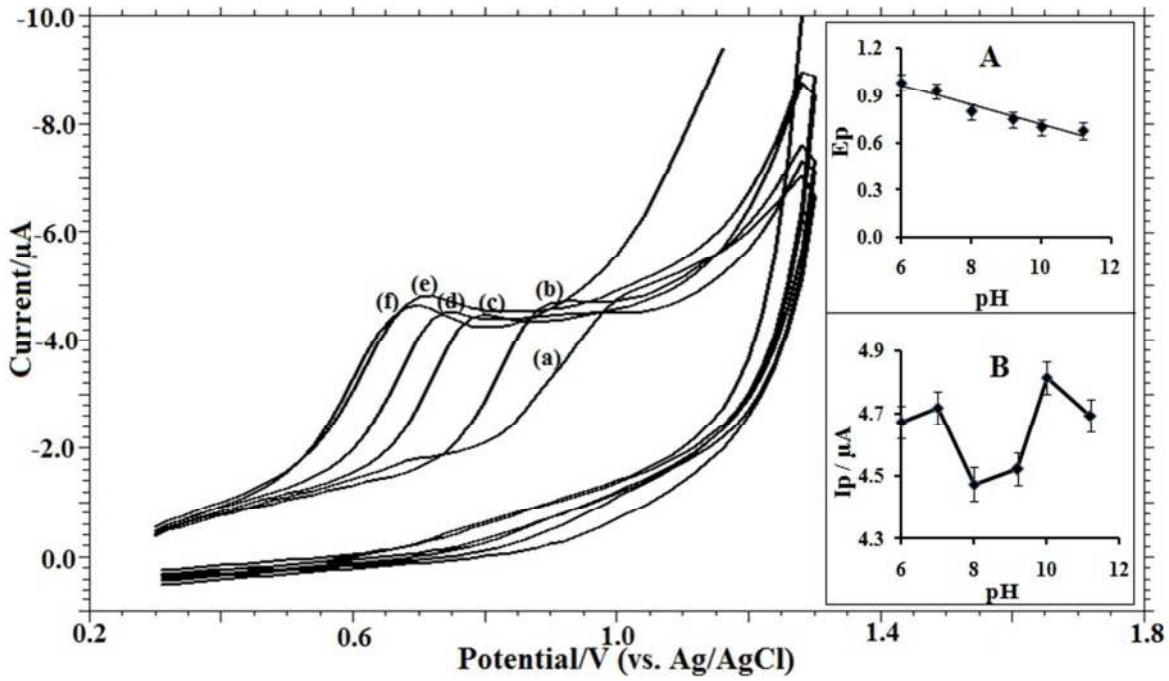


Figure 3.

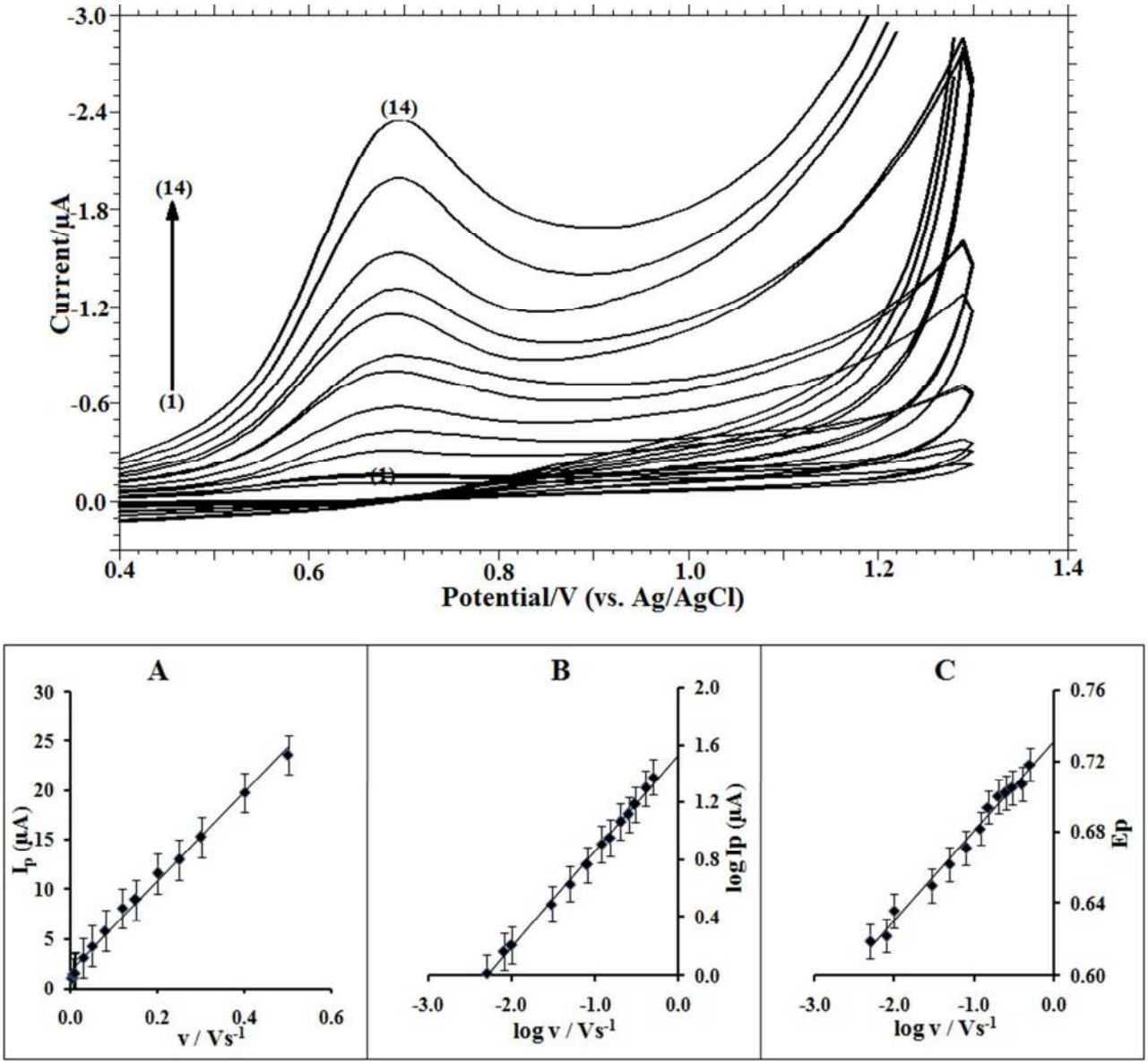

Current/μA
Potential/V (vs. Ag/AgCl)
(14)
(1)
A
B
C
Ip (μA)
v / Vs-1
log Ip (μA)
log v / Vs-1
Ep
log v / Vs-1

Figure 4.

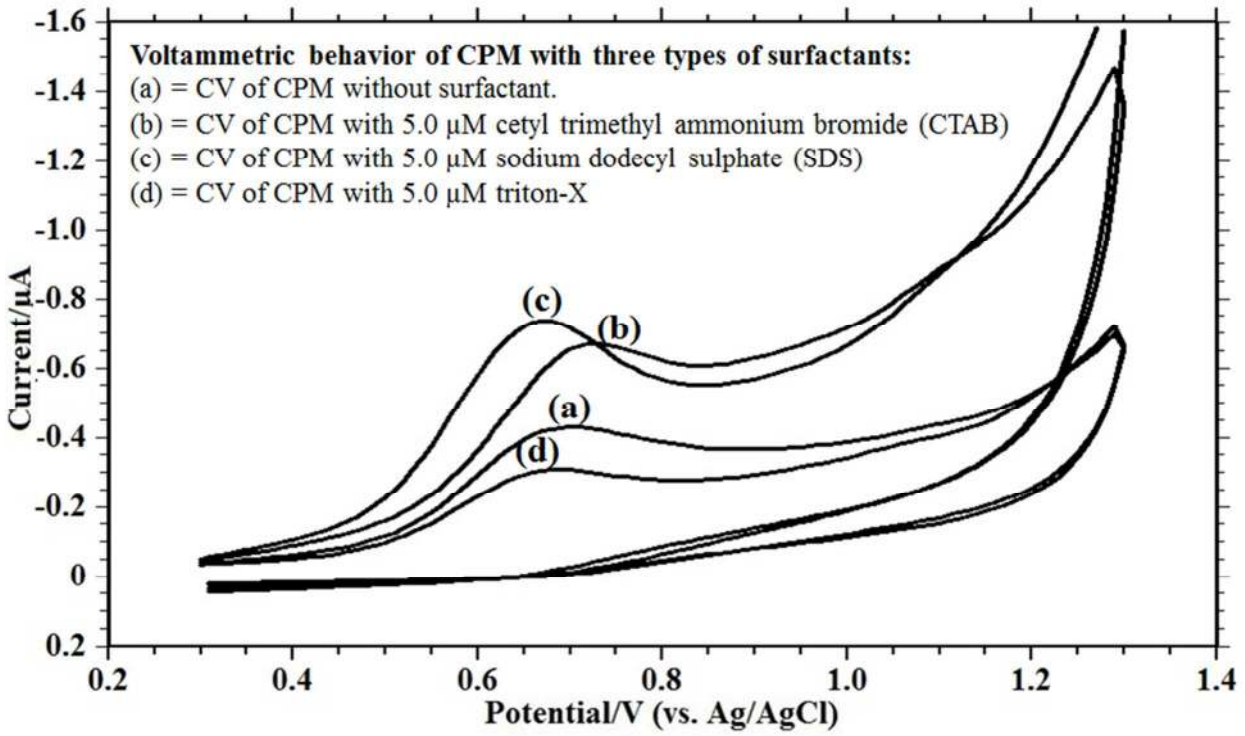
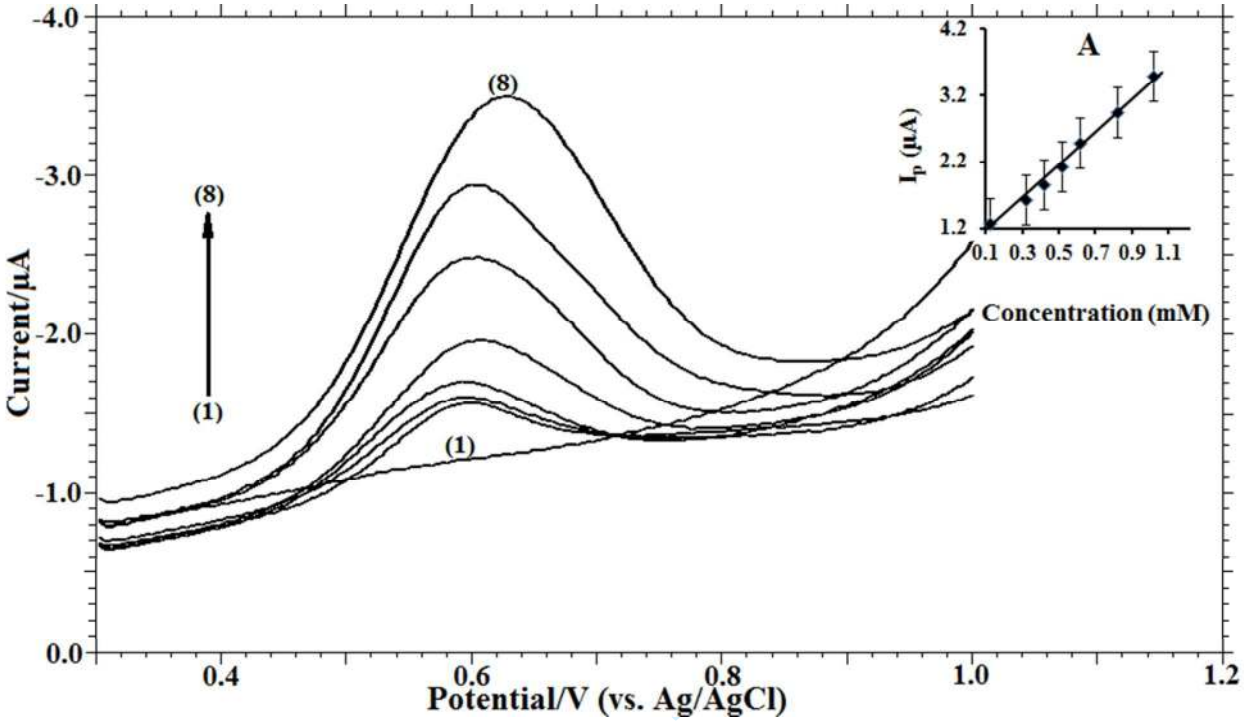
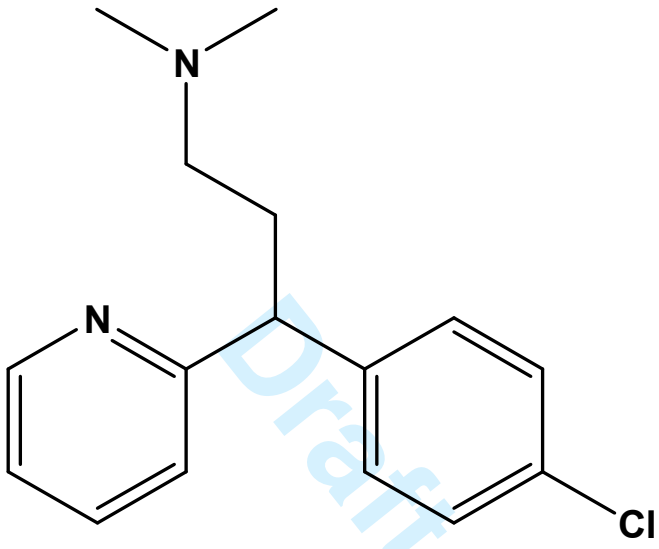

Voltammetric behavior of CPM with three types of surfactants:
(a) = CV of CPM without surfactant.
(b) = CV of CPM with 5.0 µM cetyl trimethyl ammonium bromide (CTAB)
(c) = CV of CPM with 5.0 µM sodium dodecyl sulphate (SDS)
(d) = CV of CPM with 5.0 µM triton-X
(a)
(b)
(c)
(d)
Current/µA
Potential/V (vs. Ag/AgCl)
-1.6
-1.4
-1.2
-1.0
-0.8
-0.6
-0.4
-0.2
0
0.2
0.2
0.4
0.6
0.8
1.0
1.2
1.4

Figure 5.


-4.0
-3.0
-2.0
-1.0
0.0
Current/μA
0.4
0.6
0.8
1.0
1.2
Potential/V (vs. Ag/AgCl)
(8)
(1)
(8)
(1)
A
4.2
3.2
2.2
1.2
I_p (μA)
0.1 0.3 0.5 0.7 0.9 1.1
Concentration (mM)

Scheme 1.



Scheme 2.