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ELECTROCHEMICAL DETERMINATION OF CARBOPLATINUM

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ABSTRACT

This study is related to the electrochemical determination of carboplatinum. The main problem associated with the electrochemical examination of this compound is its slow rate of reaction. Therefore the main goal of this study was to find the appropriate electrocatalysis which may accelerate the rate of reaction. The compound was examined by the use of modified carbon paste (MCPE), modified glassy carbon (MGCE) and platinized platinum (Ptz/Pt) electrodes. Among these, MCPE electrode showed to be the most effective electrocatalyst. The results indicated that the compound could be quantitatively determined in the concentration range of 9.0×10^{-5} and 8.0×10^{-4} M with Ptz/Pt and 9.0×10^{-5} and 9.0×10^{-4} M with modified carbon paste electrodes.

1. INTRODUCTION

Carboplatinum is a second generation Pt(II) complex [1,2], a derivative of Cisplatinum Generic discovered by Barnett Rosenberg, used in cancer therapy with relatively few side effects. Pure carboplatinum used as flacon and applied to patients in serum solution. It is generally used in treatment of epithelium origined ovary cancer[3], non- small cell lung cancer[4] and brain and neck tumors [5] where the other treatment modalities are not very successful. The platinum complexes employed for this purpose are [cis-diamino(1,1- cyclobutano dicarboxylate) Pt(II)] (carboplatinum, CBDCA) and [cis-dichloride diamino Pt (II)] (cis-platinium, cis-DDP)[6]. The investigation of voltammetric behaviour of the carboplatinum, was carried out in comparison with its prototype cisplatinum [7-9]. In literature the investigation of carboplatinum and cisplatinum, which have a similar structure, were carried out by the use of spectroscopic [10], chromatographic [11] and electrochemical methods [12-20]. The center of the structure of carboplatinum is the Pt(II) complex. This complex has a square planar geometry [21] and the organic group is attached to this complex with 90^0 angle. That is why the compound is sterically hindered to reach the electrode surface and does not give any reaction on many electrodes. That is the prime reason that the studies related to the electrochemical behavior of this complex are limited. Although there are some

studies related to the electrochemical reduction of carboplatinum, its electrooxidation is not explored in detail.

This study is concerned with electrooxidation of carboplatinum under different conditions. The electroxidation of carboplatinum, which is highly slow and not observed by many workers under their working conditions, was observed to be accelerated on polymer modified carbon paste, platinized platinum and modified glassy carbon electrodes.

This study also shows that carboplatinum can be determined by voltammetric method which is very simple, rapid and unexpensive.

2.1. EXPERIMENTAL

Apparatus

The experiments were carried out by the use of Tacussel PRG-3 three electrode polarographic system. All the chemicals were analytical grade and the solutions were prepared with doubly distilled water. The electrodes used in the study were as follows:

2.1.1.Working Electrodes

2.1.1.1.Pt electrode :

A Pt wire with the diameter of 1 mm and the length of 14.8 mm was used.

2.1.1.2.Glassy carbon electrode:

The glassy carbon electrodes employed during the study were manufactured by Tacussel company (XM-540) with the diameter of 3 mm and the modified electrode with the length of 4.2 mm and non-modified electrode with the length of 9.4 mm.

2.1.1.3.Carbon paste electrode:

The carbon paste electrode was prepared in our laboratory. It has a diameter of 3.25 mm and surface area of 8.29 mm^2.

2.1.2. Preparation and Pretreatment of the Working Electrodes :

The reference and counter electrodes were saturated calomel and platinum were respectively. All the potentials in the text were given vs. standard hydrogen

electrode. The carbon paste was prepared by homogeneus mixture of 0.8 g graphite powder and 1 ml nujol (mineral oil). It was put in a pyrex tube open from both ends using a spatula. The electrical contact was obtained by the use of a copper wire.

2.1.2.1. Modified carbon paste electrode:

The modified carbon paste electrode was also prepared in our laboratory. The dimension of the electrode was the same of those of unmodified carbon paste electrode described above. The electrode was prepared by mixing homogenously graphite powder and certain amount of modifying polymer of poly-4-vinlypyridine and adding 1 ml of nujol to obtain a homogenous mixture. The mixture was put in a Pyrex tube open from both ends as described above. The electrical contact was obtained by the use of a copper wire.

2.1.2.2 Pretreatment of the carbon paste electrode :

The electrodes were not subjected to any pretreatment process, they were only washed with conductivity (doubly distilled) water and dried with filter paper throughout the study.

2.1.2.3. Preparation and pretreatment of the modified glassy carbon electrode :

Our previous studies [22] showed that the glassy carbon electrode could be activated for many reactions for a period of a month by application of following steps :
Step I : Application of high frequency square wave (350 Hz); Step II : Application of high frequency (3500 Hz) triangular waves between -6 V and +6 V; Step III : Application of 1.50 V for 5 min. and -1.0 V for 2-3 s in 0.1 M KNO_3 .These steps were repeated until reproducible voltammetric curves were obtained. After that the electrode was subjected only to Step III prior to each experiment.

2.1.2.4. Preparation and pretreatment of the platinized platinum (Ptz/Pt) electrode :

A Pt electrode was washed with hot HNO_3 and then with conductivity water. The electrode was subjected to a potential of 1.75 V (SHE) in 1N H_2SO_4 for five minutes and then kept at 400mV(SHE) till the current dropped down to 0 μA to complete the electrochemical pretreatment .

The electrode was then washed with conductivity water and placed in hexacholoroplatinic acid [$H_2(PtCl_6)$] solution and subjected to a potential of 0.25 V(SHE) for 30 minutes in order to cover the electrode with Pt black. The electrode was washed with conductivity water again and kept at oxygen and hydrogen evolution potentials for five minutes in 1N Na_2SO_4. The Ptz/Pt electrode thus prepared was subjected to the following procedure before each experiment.

The electrode was kept at 1.42V (SHE) in 1N H_2SO_4 for two minutes and potential was dropped down to 0.01 V. The electrode was then subjected to a consecutive scan at a scan rate of 10 mV/s between 0.0 and 1.42V till the reproducible curves were obtained. The electrode was washed with conductivity water after the experiments and short circuited with a calomel electrode through a micro ampermeter between them till the next experiment.

2.1.3. References and Counter Electrodes:

The reference and counter electrodes were saturated calomel and platinum were respectively. All the potentials in the text were given vs. standard hydrogen electrode

2.1.4. Method

The test were performed by cyclic voltammetry and linear sweep voltammetry. Proper results were obtained at scan rate of $10mVs^{-1}$, at higher scan rates the shapes of the curves were not convinient for quantitative evaluation. At lower scan rate the current was lower.

3. RESULTS AND DISCUSSION

The electrochemical behaviour of carboplatinum on Ptz/Pt electrode :

The supporting electrolyte used with Ptz /Pt electrode was 1M Na_2SO_4 including 1M Cl^- ions, the pH of which was $6.0x10^{-2}$ M. A stock solution of the compound was prepared using this supporting electrolyte. The cyclic voltammograms were taken between -0.5 V and 1.2 V at a scan rate of 10 mVs^{-1} in $2x10^{-4}$ M carboplatinum solution. With this scan rate good results were obtained in the concentration range of $9x10^{-5}$-$8x10^{-4}$ M from the analytical view point. The hydrogen region is apparent at 0,0 V (Figure 1). The oxidation of the compound investigated occurs at about 0.45 V. Oxygen evolution potential shifts to 1.0 V in a solution with pH 6. On the reverse part of the curve only the peak specific to the reduction of the surface oxides of the Pt electrode was observed. As the concentration of the compound increases, hydrogen peaks at the anodic branch were

observed to get smaller as regards to those observed in supporting electrolyte. Meanwhile the current in the double layer region increases. This is attributed to the decrease the hydrogen adsorption as a result of coverage of the electrode surface with the compound investigated. Two other anodic steps at about 0.65 and 0.85 V were observed. With concentrated solution one observes a peak related to the reduction of the compound at about 0.3 V. When anodic current values at 0.85 V were plotted against the concentration a linear relationship between $9x10^{-5}$ and $8x10^{-4}$ M were obtained.The regression analysis data listed in Table 1 showed that the quantitative analysis of this drug could be made by this method.

The electrochemical behaviour of carboplatinum by the use of modified glassy carbon electrode :

The electrochemical behavior of carboplatinum was also investigated by the use of glassy carbon electrode modified as mentioned above. Voltammograms were taken at a scan rate of 10 mVs^{-1}. The supporting electrolyte employed during the experiments was 1 N $NaClO_4$ which is highly inert for the carboplatinum and gives a good pH range for solubility. The pH of the working medium was kept at pH 6 which was constantly monitored by a pH meter. The voltammetric curves were recorded between 0.25 and 1.6 V (Figure 2). Carboplatinum starts to oxidize arround 0.45 V. There appears some peaks at about 0.75, 0.95 and 1.35 V related to the first and second oxidation steps and oxygen evolution respectively. The plot of current values at 0.95 V against the concentration gives a line in the concentration range of $8x10^{-5}$ and 10^{-3} M. Table 1 gives the regression analysis data. The experimental results obtained in anodic direction with the use of modified glassy carbon electrode revealed that there is no need to add Cl^- in to $NaClO_4$ solution. However the regression analysis data shows that sensitive analysis can not be made by this electrode.

The investigation of the electrochemical behaviour of carboplatinum using poly (4-vinyl pyridine) modified carbon paste electrode :

The supporting electrolyte employed for the anodic polarization was 0.1 M Na_2SO_4. Concentrated NaCl was added to the experimental solution in order to make the Cl^- concentration 1M. The oxidation curve of the modified carbon paste electrode was recorded in the supporting electrolyte between -0.5 and 1.1 V (Figure 3). The sharp increase in current at 1 V corresponds to oxygen evolution. The fact that the modification of the carbon paste electrode with by poly (4-vinylpyridine) increases the sensitivity of the electrode against carboplatinum was proven by the comparison of the curves obtained using modified electrode with those obtained using normal carbon paste electrode. The investigation of the curves in the anodic direction revealed that there is an anodic peak at about 0,5 V corresponding to the oxidation of carboplatinum. The linear regression analysis of the peak current-

concentration relationship is given in Table 1. These data show that the compound can be quantitatively analyzed between 9.0×10^{-5} M and 9×10^{-4} M using this modified carbon paste electrode. On the reverse scan two reduction peaks were observed at about ˉ0.1 and 0.8 V related to the hydrogen and carboplatinum respectively.

The electrochemical reactions of carboplatinum is based upon highly slow electrode processes. The investigation of the anodic and cathodic electrochemical reactions showed that it was necessary to improve the electrochemical activity of the drug. The data obtained with modified and non-modified electrodes showed that the reaction is very slow on the latter. There is a significant activation overpotential on non-modified electrodes. Therefore it is necessary to decrease this overpotential in order to increase the rate of electrode reaction.

The significant activation overpotential and therefore the lower rate in the reaction of carboplatinum seem to stem from the difficulty of electron transfer to electrode. One of the methods to overcome this dilemma is to modify the electrode surface. Also the supporting electrolyte and pH have an important role on the electroactivity of the drug. The electrochemical behavior of the drug was investigated by the use of a supporting electrolyte such as $NaClO_4$ and Na_2SO_4 which gives no complex with the drug and a pH value suitable for stability of the compound [23]. It was reported that the reduction of carboplatinum upon mercury electrode was difficult [12]. It was also stated that the half wave potential of Pt (II) complex drugs shifts to more positive values depending upon the concentration of chloride ions in the supporting electrolyte [13]. The addition of chloride ions makes the polarographic peaks much more measurable [14].

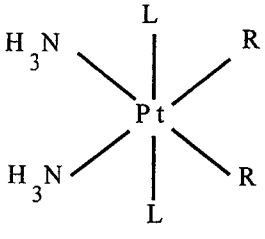
The oxidation and reduction of Pt (II) complex drugs are dependent upon the structure of the coordinated ligands [24]. The square planar structure of carboplatinum [21] and the fact that the organic group attached to the center of the structure makes an angle of 90^0 creates steric hindrance and makes it difficult for the molecule to reach the surface of the electrode.

Our studies carried out with carboplatinum with the use of Pt and carbon electrodes revealed that the surfaces of these unmodified electrodes show no reactivity towards the compound and there needed certain modifications upon the surface of the electrode. Some workers emphasized the catalytic effect of Pt particules formed on the electrode surfaces after multiple scans and the role of the adsorbed chloride ions on the electrooxidation kinetics of Pt (II) complexes [24].

In this study the platinum electrode was covered with platinum black so the catalytic effect was observed at the first scan. The relation between the Pt (II) complex and the chloride ion in the investigation of Pt (II) complexes with carbon

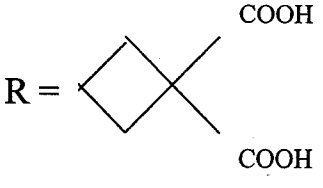
paste electrode is also the case for the electroreduction and oxidation of the cisplatinum on the same electrode. There are three different structures possible based on the chloride concentration employed [25], as follows:

For chloride concentrations of 10^{-4}-10^{-3} M the following oxidation product (I) probably exists

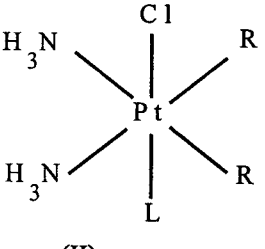


(I)

$L = H_2O$ or OH^-

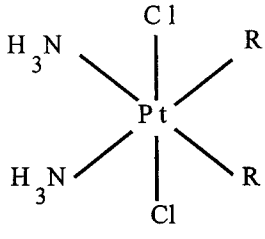


For chloride concentrations of 10^{-3}-10^{-2} M the following oxidation product (II) may be present



(II)

For chloride concentrations of 10^{-2}-1.0 M the following oxidation product (III) may occur



(III)

These oxidation products form by the addition of chloride ions at different concentrations in to media, containing sulfate or perchlorate ions with no complexation capacity, as a result of a single step two electron transfer reaction . The reduction of these three oxidation products of carboplatinum gives cathodic peaks. Carboplatinum has irreversible redox behaviour on Pt electrode as stated in literature[15, 25]. The capacity of chloride ions added to the media to bind to the Pt (II) complex structure improves this irreversible behaviour to a certain extent. On Pt electrode as on carbon paste electrode there is no reduction phenomena observed. Also on Ptz/Pt electrode the reaction seemed to be irreversible ,on modified glassy carbon electrode also the reaction took place irreversibly.

In conclusion the oxidation phenomenon of carboplatinum was found to be accelerated on Ptz/Pt, modified glassy carbon and polymer modified carbon paste electrodes. It was also found that the compound can be quantitatively determined by the use of modified carbon paste and Ptz/Pt electrodes.

ÖZET

Bu çalışmada karboplatinin elektrokimyasal tayini yapılmıştır. Bu bileşiğin elektrokimyasal araştırılmasında, başlıca problem reaksiyonun yavaş hızda oluşmasıdır. Bu nedenle çalışmamızın amacı reaksiyon hızını artırabilecek uygun elektroktalitik etkiyi bulmak oldu. Bu bileşiğin elektrokimyasal araştırması modifiye karbon pasta (MCPE), modifiye camsı karbon (MGCE) ve platinlenmiş platin (Ptz/Pt) elektrotları kullanılarak yapıldı. Bunların arasında en etkin elektrokatalitik etki MCPE elektrodu ile görüldü. Bu araştırmanın sonuçları bileşiğin 9.0 x 10^{-5} ve 8.0 x 10^{-4} M konsantrasyon aralığında Ptz/Pt ile ve 9.0 x 10^{-5} ve 9.0 x 10^{-4} M konsantasyon aralığında modifiye karbon pasta elektrodu ile kantitatif olarak tayin edilebileceğini gösterdi.

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Table 1. The regression analysis data of the relation between the concentration of carboplatinum and the peak current on different electrodes .

Electrodes	Lower limit of the concentration c/ (mol/L)	Upper limit of the concentration c/ (mol/L)	Linear relationship	Correlation coefficient (r)	St.error of Slope	St. error of intercept	LOD (mol/L)
Ptz/Pt	9.0×10^{-5}	8.0×10^{-4}	$y=1.35 \times 10^{5} x + 3.89$	0.999	3739.4	1.79	2.4×10^{-5}
MGCE	8.0×10^{-5}	1.0×10^{-3}	$y=3.61 \times 10^{4} x + 7.43$	0.987	2966.0	1.52	2.1×10^{-5}
MCPE	9.0×10^{-5}	9.0×10^{-4}	$y=3.45 \times 10^{4} x + 1.40$	0.999	1010.7	0.53	2.2×10^{-5}

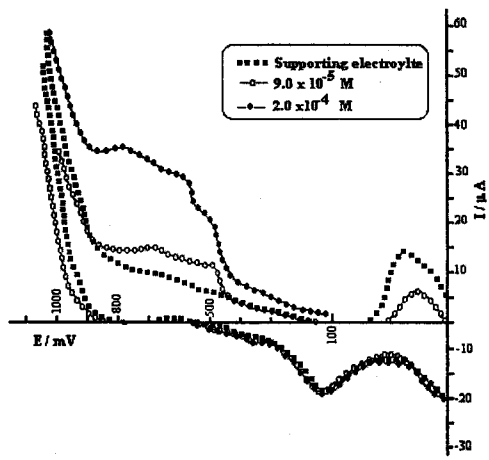

Figure 1. The voltammograms of carboplatinum solutions taken by the use of Ptz/Pt electrode

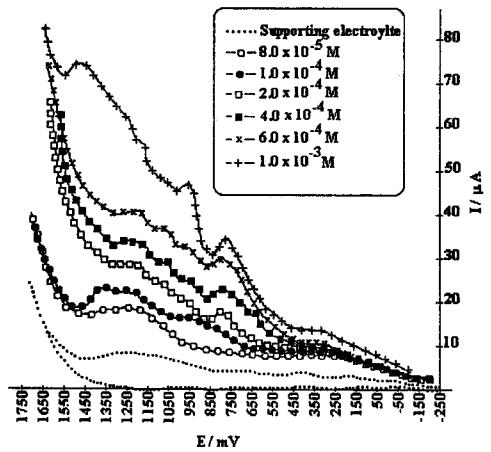

Figure 2. The voltammograms of carboplatinum solutions recorded with modified glassy carbon electrode (MGCE) .

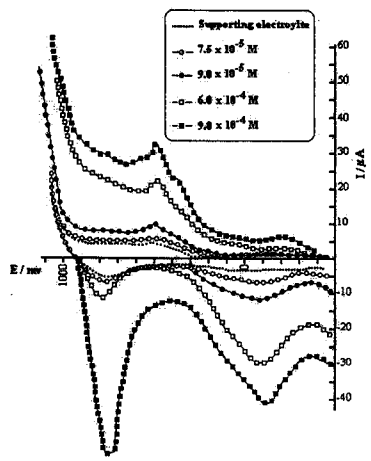

Figure 3. The voltammograms of carboplatinum solutions at different concentration recorded on modified carbon paste electrode (MCPE)