



Electrochemical behavior of methocarbamol on platinum electrode by cyclic voltammetry

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Abstract

The electrochemical behavior of methocarbamol was investigated in semi organic media using a platinum electrode. A detailed study by cyclic voltammetry and potentiostatic electrolysis were carried out for better understanding of its anodic oxidation process. The effect of scan rate on current and potential showed that methocarbamol is electroactive with an irreversible peak located at $E_p = 1.44$ V /ECS and demonstrated that the electrode process was controlled by diffusion. Thus, the number of exchanged electrons during oxidation process, the standard redox potential and the standard rate constant were determined. In addition, the liquid chromatography–mass spectrometry and Fourier-transform infrared spectroscopy analysis of preparative electrolysis solution showed that guaifenesin is the major oxidation product of methocarbamol and permitted to propose its oxidative mechanical reaction. Furthermore, differential pulse voltammetry on platinum electrode permits the selective determination of methocarbamol. According to the XTP 90-210 standard the limit of detection and the limit of quantification were determined and are respectively equal to $0.4 \mu\text{g/mL}$ and $3.3 \mu\text{g/ mL}$.

1. Introduction

Methocarbamol (MET) also named 2-hydroxy-3-(2-methoxyphenoxy) propyl carbamate is a central muscle relaxant used to relax muscles and relieve pain and discomfort caused by strains, sprains, and other muscle injuries [1-5]. Methocarbamol is deriving of carbamate of guaifenesin and its chemical structure is represented in Figure 1. Several methods were reported in the literature proposing fast and reliable techniques for the determination of methocarbamol in different matrices such as chromatographic techniques [6-13]. To our knowledge, no electrochemical studies related to the anodic oxidation of methocarbamol was investigated. However, electrochemical methods have proved to be very sensitive for the determination of organic molecules that undergo oxidation and reduction reaction including drugs and related pharmaceuticals molecules [14-17]. Indeed, the advantage of electrochemical techniques is due to their simplicity, low cost and relatively short analysis time when compared to another technique's organic compounds [18-23]. For these reasons, the first part of this work aim to attend a deeper understanding of voltammetric behaviour of methocarbamol in aprotic medium using cyclic voltammetry. In the second part, results obtained from preparative electrolysis, after liquid chromatography mass spectrometry and FTIR analysis were performed in order to propose

a mechanistic scheme of its anodic oxidation and finally, an application of electrochemical study of methocarbamol by differential pulse voltammetry (DPV) was performed in order to highlight the applicability of this work.

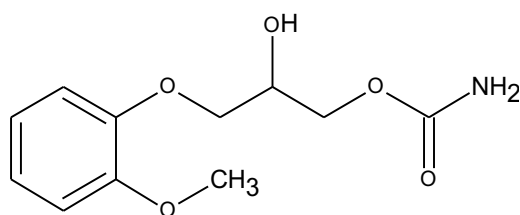


Figure. 1. Chemical structure of methocarbamol

2. Materials and Methods:

2.1. Electrochemical

The electrochemical measurements were made in semi-organic media (water/acetonitrile) in the presence of lithium perchlorate (LiClO_4) 0.1M as the supporting electrolyte. Volta lab 80 analyser purchased by radiometer was used to perform voltammetric study. The working electrode was a 2 mm diameter platinum disk. The exhaustive electrolyses were carried out at a constant potential located on the first wave using a PTJ 35-2 potentiostat and an IG5 integrator both from Tacussel. The separated cell was equipped with a platinum grid (4 cm^2) and a platinum wire respectively as the working and the auxiliary electrode. The reference was a saturated calomel electrode (SCE).

2.2. LC/MS analysis

The electrolysis solution was analysed using liquid chromatography equipped with a C-18 column type Symmetry® Waters ($150 \text{ mm} \times 4.6 \text{ mm}$ and $5 \mu\text{m}$ particle size) at 40°C . The mobile phase was 60 % acetonitrile, 40% phosphate buffer pH=8. The mass spectrometric analysis is performed with an Agilent 1100 MSD triple-quadrupole in the electrospray positive mode. Nitrogen is the nebulizer and the collision gas. The analysis parameters are fixed as follows: $T = 400^\circ\text{C}$; gas flow: 12 L/min; nebulizer gas pressure: 50 psi; capillary voltage: 5000 V; corona current: $4 \mu\text{A}$

2.3. Chemical

Methocarbamol (MET) also named 2-hydroxy-3-(2-methoxyphenoxy) propyl carbamate, lithium perchlorate, used as supporting electrolyte, and guaifenesin were purchased from Fluka. Acetonitrile and water with HPLC quality were purchased from Panreac.

3. Results and discussion

3.1 Voltammetric study of methocarbamol

To elucidate the electrode reaction of MET, a cyclic voltammogram at platinum electrode was recorded at 310^{-3}M concentration on semi organic medium. **Figure 2** exhibits one well defined anodic peak located at the potential ($E = 1.44 \text{ V/SCE}$) with no reduction peak in the reverse scan suggesting that the irreversible nature of electrode reaction.

3.1. Effect of scan rate variation

Relationship between peak current and scan rate can give us more information involving electrochemical oxidation mechanism. Thus, the voltammetric behaviour of MET at different scan rate between 20 to $100 \text{ mV}\cdot\text{s}^{-1}$ was studied. **Figure 3** illustrates all corresponding voltammograms.

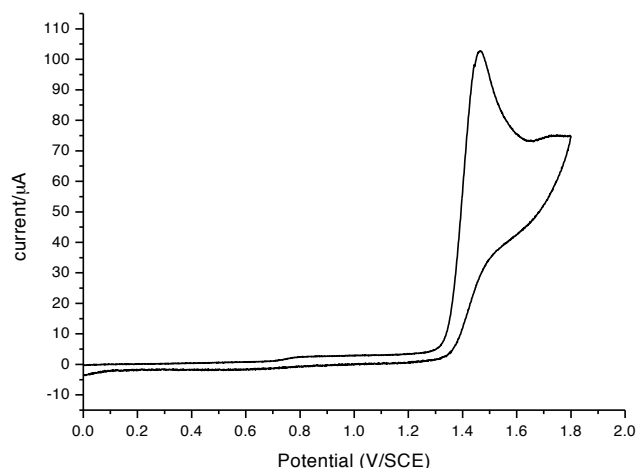


Figure 2. Oxidation voltammogram of methocarbamol in 50% ACN-50% water, LiClO₄(0.1M), C = 3 mM, $\nu = 100 \text{ mV} \cdot \text{s}^{-1}$, platinum disk ($\phi = 2 \text{ mm}$).

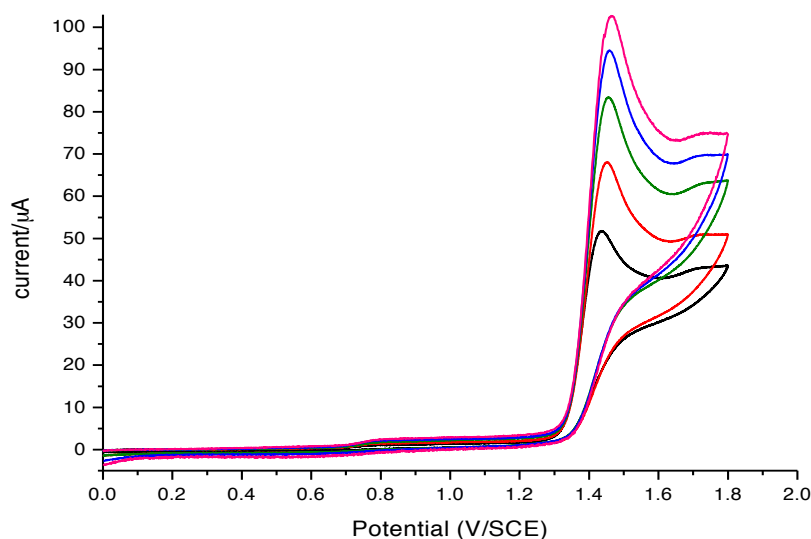


Figure 3. Oxidation voltammograms of MET in 50% ACN-50% water, LiClO₄ (0.1M), C = 3 mM, $\nu = 20, 40, 60, 80, 100 \text{ mV s}^{-1}$, platinum disk ($\phi = 2 \text{ mm}$).

The examination of [Figure 3](#) shows that when scan rate increase, current increase and the peak potential shift to more anodic values. The plot I_p as a function as $\nu^{1/2}$ was performed and illustrated in [Figure 4](#). Indeed, a good linear relationship between peak current and the square root of scan rate was obtained. The corresponding equation is $I_p = 9.33 \nu^{1/2} + 0.3002$ with $R^2 = 0.997$. The value of the slope equal to 0.933 was very close to the theoretically expected value obtained when the electrode process was controlled by diffusion [24-28]. Based on the literature, for an irreversible electrode process, the potential peak can be defined by the following equation:

$$E_p = E_0 + (2.0303RT/\alpha nF) \log (RTk_0/\alpha nF) + (2.303RT/\alpha nF) \log \nu$$

where α is the transfer coefficient, k_0 the standard rate constant of the reaction, n the number of electrons, ν the scan rate and E_0 is the standard redox potential, $T = 298 \text{ K}$, $R = 8.314 \text{ J mol}^{-1} \text{ K}^{-1}$ and $F = 96480 \text{ C} \cdot \text{mol}^{-1}$ [29-30]. Thus, $\alpha \cdot n$ value can be determined through the slope of curve of E_p as function as $\log \nu$ illustrated in [Figure 5](#).

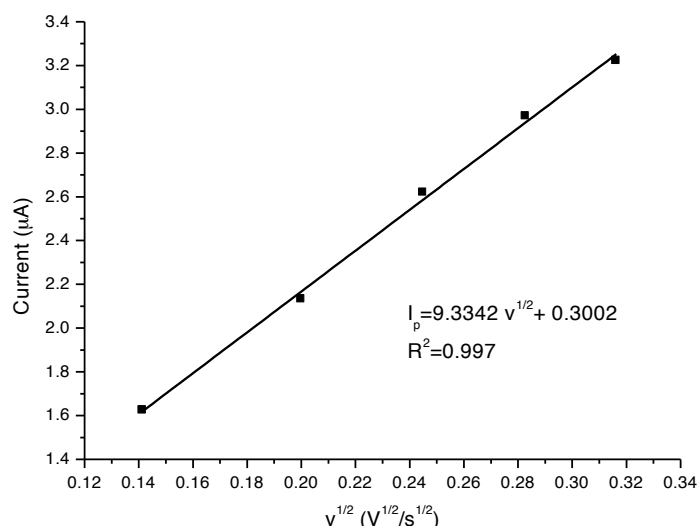


Figure 4. Dependence of peak current in the square root of scan rate or scan rate

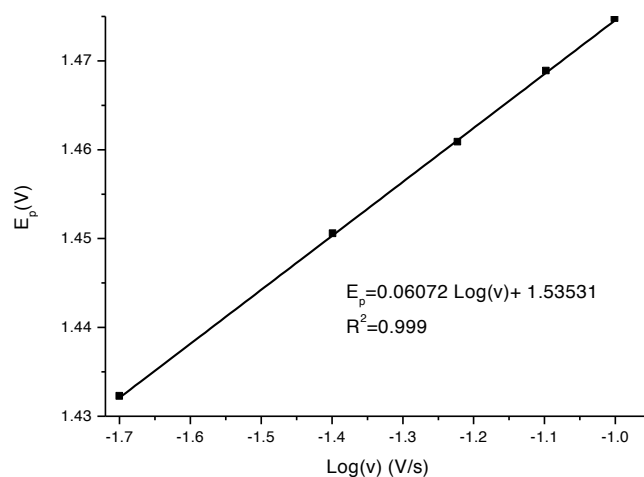


Figure 5. Linear relation between peak potential and logarithm of scan rate.

The examination of Figure 5 shows that the slope value is 0.06072 V and after equation 1 resolution αn was determined to be 0.974. Moreover, α is supposed to be 0.5 when total irreversibility electrode process was obtained [31-32]. Thus, the number of electron involving during the electrochemical oxidation was calculated to be $1.948 \approx 2$. The same result, concerning electronic stoichiometry, was obtained by comparison between the peak current and that related ferrocene, a reference compound which is characterized by a monoelectronic reversible peak and whose diffusion coefficient is comparable with the methocarbamol.

In the other hand, after determination of E_0 value obtained by extrapolation of the plot of E_p as a function as $\log v$ to vertical axis at $v=0$ from the interception of the above plot [33-34]. The value of standard rate constant k_0 was calculated to be 228 s^{-1} .

3.2. preparative electrolysis

To get more information about MET oxidation products, preparative electrolysis was conducted at a constant potential located on the first wave. Electrolysis was stopped after the passage of a quantity of electricity equal to $2F/\text{mol}$ to avoid the complication of the mechanism by possible reactions of products

formed. Liquid chromatography mass spectrophotometry and FTIR analysis were performed to identify electrolysis products.

Obtained results lead that the major oxidation product (P1) of MET is 3-(*o*-Methoxyphenoxy)-1,2-propanediol also named guaifenesin. In fact, the comparison between reference and electrolysis chromatograms indicate that the peak related to the MET was eluted at $t_R = 5.55$ min retention time disappear completely and a new peak appears at $t_R = 4.31$ min with high intensity. The P1 retention time suggests that this compound is more polar than MET in accordance with the retention mechanism on reversed phases [35]. This peak is probably due to the elimination of the carbamic acid. The proposed chemical structure was confirmed by the FTIR analysis. Indeed, the comparison between FTIR spectrum of reference and electrolysis solutions (Figure.6) shows that a wide and intense band located between $3200-3600\text{ cm}^{-1}$ appears in electrolysis solutions. This band can be attributed to the elongation of the OH bonds indicating an increase in the number of OH groups. We also noted that the band located around 1650 cm^{-1} becomes more intense. This result can be explaining, referred to the IR tables, as the elongation of the conjugated carbonyl functions.

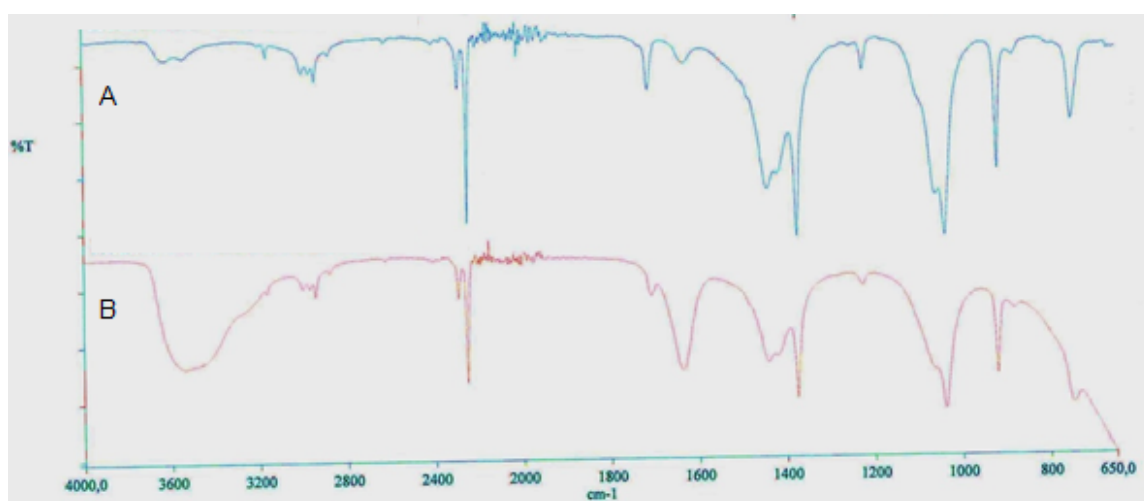


Figure 6. (A) FTIR spectra of methocarbamol and (B) FTIR spectra of electrolysis solution.

Finally, based on obtained results, the mechanistic scheme of methocarbamol oxidation on platinum electrode was proposed in Figure 7.

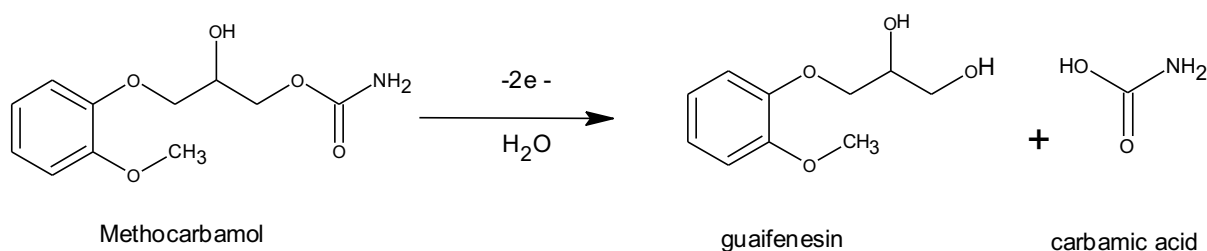


Figure 7. Mechanism of the anodic oxidation of Methocarbamol

3.3. Analytical application

In order to develop a voltammetric methodology for determining the drug, we selected the differential pulse voltammetry mode (DPV), since the peaks were sharper and better defined than those obtained by cyclic voltammetry, with lower background current. A typical DPV for methocarbamol concentration ranging between 10 and $60\text{ }\mu\text{g}\cdot\text{mL}^{-1}$ is reported on Figure. 8.

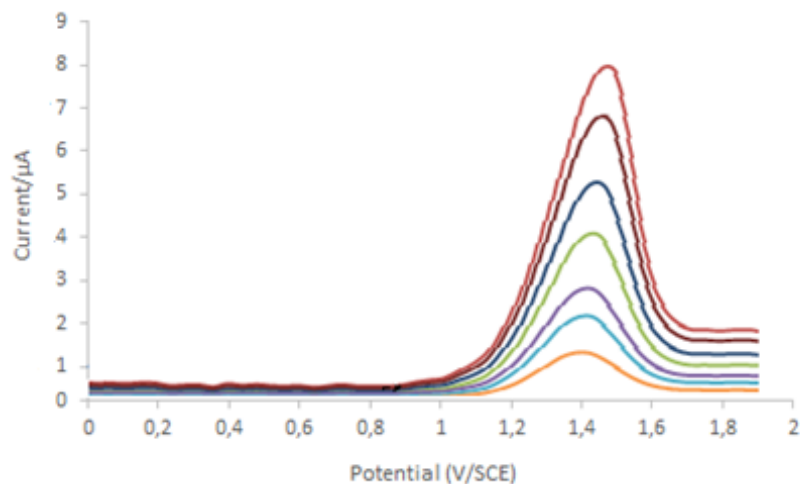


Figure 8. Differential pulse voltammograms of methocarbamol in 50% ACN-50% water, LiClO₄ (0.1M), platinum disk ($\phi = 2$ mm); scan rate: 5mVs^{-1} ; pulse amplitude = 50mV; pulse width: 20 ms. $C = 1 - 7 \mu\text{g/mL}$.

3.3.1. Linearity study

Linearity was evaluated by representing the variation of current with standard concentrations in semi organic media using DPV in Figure 9. Curve was represented by straight line equation $I_p = 0.1116 C - 0.08$, with $R^2 = 0.998$. The tests concerning the homogeneity of variances, the intercept, the existence of a significant slope led to the conclusion that the method is linear.

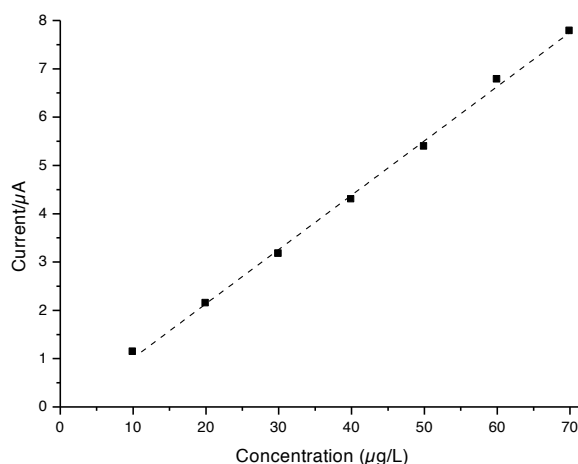


Figure 9. Linear relation between peak potential and concentration.

3.3.2. Limit of detection and limit of quantification

The limit of detection is the smallest amount or concentration of analyte in the sample that can be reliably distinguished from zero. In practice, this is the lowest concentration that can be detected, but not necessarily quantified. In our study, the limit of detection and the limit of quantification of methocarbamol using differential pulse voltammetry were determined and are respectively equal to $0.4 \mu\text{g/mL}$ and $3.3 \mu\text{g/mL}$. All results were obtained according to the XTP 90-210 standard.

3.3.3. Selectivity of DPV method

A mixture of methocarbamol and guaifenesin at the same concentration was prepared and then analyzed by differential pulse voltammetry (Figure 10). Examination of obtained voltammogram highlights evidence two well separated peaks: one located at a potential of 1.44 V / ECS corresponding to the MET

and the other located at $E = 0.9$ V / ECS relative to the guaifasein. This result proved that DPV technique is selective and can be used to determine MET in different matrices containing the guaifasein.

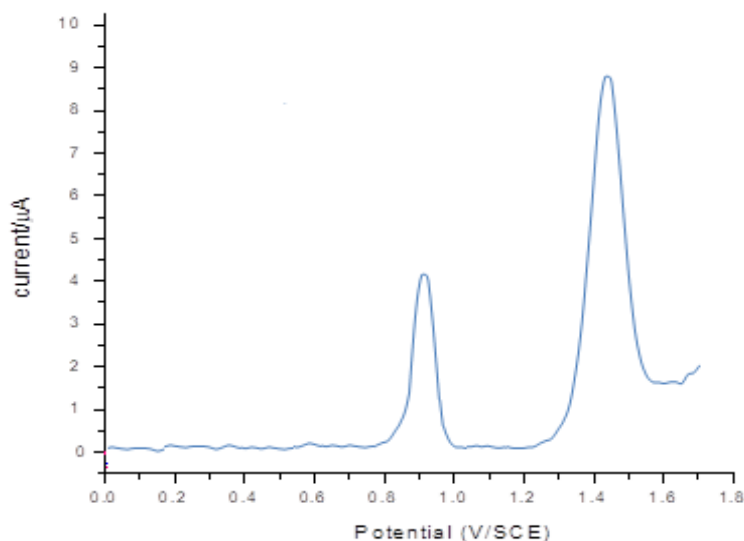


Figure 10. Differential pulse voltammogram of MET ($C = 60$ ppm) and guaifenesin $C = 60$ ppm) in 50% ACN-50% water, LiClO_4 (0.1M), platinum disk ($\phi = 2$ mm); scan rate: 5mVs^{-1} ; pulse amplitude = 50mV; pulse width: 20 ms.

Conclusion

The electrochemical behaviour of methocarbamol was investigated in semi organic media on platinum electrode. Cyclic voltammetry results indicate that methocarbamol is electroactive with an irreversible peak. The number of exchanged electrons during oxidation process, the standard redox potential and the standard rate constant were determined. A detailed study carried out by potentiostatic electrolysis shows that the major oxidation product is guaifenesin. Thus, a mechanistic scheme of methocarbamol oxidation on platinum electrode was proposed. Furthermore, this electrochemical study shows that differential pulse voltammetry is effective in the selective determination of methocarbamol in the presence of guaifasein. The corresponding limits of detection and quantification were determined according to the XTP 90-210 standard.

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