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ADSORPTIVE STRIPPING VOLTAMMETRIC DETERMINATION OF TRACE CLOMIPRAMINE HYDROCHLORIDE AT CARBON PASTE ELECTRODE

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Abstract

A highly adsorptive stripping procedure for trace determination of the antidepressant drug Clomipramine hydrochloride was described. The drug was accumulated on a carbon paste electrode and a well-defined oxidation peak was obtained in acetate buffer pH 5.0.The method was based on controlled adsorptive accumulation of the drug for 150 sec. at a carbon electrode followed by voltammetric measurement of the surface species. By anodic adsorptive linear sweep (LSV) and differential pulse voltammetry (DPV), the voltammetric response at carbon paste electrode yields a linear calibration graph from Clomipramine hydrochloride $4x10^{-9}$ to $2x10^{-8}$ mol L^{-1} and$4x10^{-11}$ to $2x10^{-10}$ mol dm^{3} for LSV and DPV , respectively. The voltammetric response is evaluated with respect to the pre-concentration potential and time, concentration dependence, detection limits, reproducibility and other variables. The method was applied for the determination of Clomipramine in diluted urine samples and in pharmaceutical preparations, the mean recovery was 101.06%.

Keywords: Clomipramine hydrochloride; carbon paste electrode; stripping voltammetry; differential pulse voltammetry; pharmaceutical

Introduction

Clomipramine hydrochloride (3-chloro-5-[3-dimethylamino)propyl]-10.11-dihydro5Hdibenz [b.f] azepinehydrochloride) (CLOMI) is a tricyclic antidepressants (TCAs) which commonly used for the treatment of depressive disorders owing their efficiency in elevating the mood of patients by interfering the reuptake of nor-epinephrine or serotonin [1] Pharmacological action of these drugs show high dependence on the structure. Tertiary amines are preferred in prescriptions since they are metabolized and excreted in the human body more rapidly than secondary amines [2]. (CLOMI) is official in current USP-27 [3] and Eur.Ph. [4]. Routine analysis methods for (TCAs) have been usually developed for the determination of the drugs in serum and plasma. Reversed-phase liquid chromatography [5-11] immune assay, including those based upon fluorescence polarization immune assay (FPIA) [12]. Anodic electro activity showing by (CLOMI) was studied at rotating disc electrodes [13]. Voltammetric measurements

of (TCAs) trimpramine, imipramine and desipramine were carried out using a glassy carbon and carbon past electrodes [14]. Adriana et-al [15] studied the use of betacyclodextrin to fabricate disposable electrochemical sensors for determination of TCAs drugs. Because of low levels of TCA's in the body fluids, highly sensitive techniques are required for their quantification. The present work describes the utility of differential pulse voltammetry at a carbon paste electrode for trace measurements of CLOMI, to fulfill the selectivity, speed, and simplicity.

Experimental

Apparatus

Voltammetric measurements were carried out using a computer driven AEW2 Analytical electrochemical workstation with ECProg 3. Electrochemistry software (Sycopel, England) in combination with C-2 stands with a three- electrode configuration; a carbon paste electrode (BAS Model MF-2010, 3 mm diameter) Working electrode, an Ag/AgCl/3M KCl (BAS Model MF-2063) reference electrode and platinum wire (BAS Model MW-1032) counter electrode. Microcal Origin (v.5.10) software was used for the transformation of the initial signal. A Cyberscan 500 digital (EUTECH Instruments, U.S.A) pH-meter with glass combination electrode used for the pH measurements .

Reagents

CLOMI (Purity 99.5%) and its pharmaceutical dosage form Anafranil labeled to contain 25 mg CLOMI per tablets were kindly provided by Novartes -Egypt.

The stock solution of CLOMI $1x10^{-3}$ mol dm^3 was prepared in water. Working standard solutions were then prepared daily by dilution with de-ionized water. Unless otherwise stated, acetate buffer solution (0.05M, pH 5.0) was used as supporting electrolytes. The working solutions for voltammetric investigations were prepared by dilution of the stock solution with selected supporting electrolyte. More dilute solution ($1x10^{-7}$ mol L^{-1}) was prepared daily just before use.

Procedure

Electrode preparation

The modified carbon paste electrode was prepared by hand mixing the carbon powder (graphite) (Measurements Ringsdorff Werker, Germany) with paraffin oil (Meark) in a mortar in the appropriate ratio (5:3). The paste was packed into the wall

of Teflon body. The electrode surface was smoothed using clean paper. The surface of the electrode activated by applying the potential (200-1200 mV).

Calibration

Voltammetric analysis was carried out in 5 ml of acetate buffer (0.05M, pH 5.0). The accumulation (usually open circuit condition) of CLOMI at the working electrode was carried for the selected time while the solution was stirred at 2000 rpm. The stirrer was then stopped, and after rest period (5 sec) , the drug was removed by stripping anodically using differential pulse voltammetry (DPV) was recorded with, pulse amplitude 50 mV, pulse width 50 ms, scan rate, 10 mV s^{-1}, between 0.4 and 1.2 V .

Aliquots of the standard drug were introduced and the adsorptive stripping cycle was repeated using a new electrode surface. The peak current was evaluated as the difference between each voltammogram and the background electrolyte voltammogram. All data were obtained at ambient temperature.

Tablets assay

Ten tablets of Anafranil ^{TM}, which contained a declared amount of 25 mg CLOMI, were crushed and powdered in a mortar. A weighed portion of the powder equivalent to about $1x10^{-3}$ mol $L^{-1}$of CLOMI was treated with water for 10 min in ultrasonic bath. Appropriate solutions were prepared by taking suitable aliquots of the clear supernatant liquor and diluting with the selected supporting electrolyte. Voltammograms were recorded as in calibration CLOMI Urine assay

For the determination of CLOMI in spiked urine samples, the pre-concentration / medium exchange/ voltammetry scheme were adopted. Urine (1ml) was mixed with (9.0 ml of acetate buffer (0.05M, pH 5.0), without any pre-treatment and transferred to the voltammetric cell. The differential voltammograms were recorded following optimized conditions: accumulation potential E_{acc} (open circuit concentration); accumulation time t_{acc} = 150 sec; Quantification was achieved by the standard addition method.

Results and discussion

As shown in Fig. (1-a), the analogous response without prior accumulation of CLOMI at carbon paste electrode in acetate solution of pH 5.0 . Fig. (1-b) displays a cyclic voltammogram (CV) for 2.5 $x10^{-5}$ mol L^{-1} at scan rate 100 mV s^{-1} CLOMI

recorded at carbon paste electrode in acetate buffer (0.05M, pH 5.0), after 150 sec. stirring at open circuit condition. In the forward scan, in large definite anodic peak, corresponding to the oxidation of the adsorbed drug, is observed at + 0.8V. No cathodic peaks are observed in the reverse sweep, which indicates that the CLOMI oxidation is irreversible process. The anodic peak may be attributed to the irreversible oxidation of nitrogen atom in the central ring of CLOMI [14].

The effect of scan rate (ν on stripping peak current (ip) was examined under the above conditions with a plot of ip versus logν giving a straight line with the scan range from 10 to 200 mV s^{-1}, which fitted the equation ip (μA) = (5.260±0.641) + (0.091±0.006) ν, where r = 0.9890, (r is the coefficient of variation).

The slope of 1.00 is expected for an ideal reaction of surface species [16]. Moreover, the peak potential (Ep) was shifted to more positive potentials when the scan rate was increased; this confirms the irreversibility of the oxidative process. Also, the effect of the potential scan rate (ν on the peak current ip, was studied after 150 sec. pre-concentration time, the relation showed that peak current was proportional to the increase of scan rate value at carbon past electrode. The peak stripping current is independent on accumulation potential, thus the adsorption stage was carried out at open circuit potential.

The effect of pH and the composition of the supporting electrolyte were evaluated for $2.5x10^{-5}$ mol L^{-1} of CLOMI solution following for 150 sec. accumulation at open circuit using differential voltammetry in various electrolytes, such as acetate, phosphate and Britton-Robinson buffers of different ionic strength in the range (0.04-0.20 molL^{-1}). Maximum size peaks were obtained with 0.05 mol dm^3 acetate buffer (pH 5.0); this electrolyte was used throughout this study. The dependence of the peak current developed in buffer solution pH 5.0 on accumulation time was investigated. As shown in Fig.2 , the plot of ip vs. t_{acc}. a full surface coverage is established after accumulation time. t_{acc} 150 sec. (ip =26.86 μA) . Thus, the accumulation time 150sec. of choice was be dictated by the sensitivity needed, which has been expected for a $2.5x10^{-5}$ mol L^{-1} CLOMI solution for times ranging from zero to 150 sec; as the pre-concentration period increases, there is a rapid increase in the well-defined oxidation peak at +0.8V.

The quantitative evaluation is based on the dependence of the peak current on CLOMI concentration under chosen conditions, the peak currents increased linearly with increasing amounts of CLOMI by differential pulse and linear sweep voltammetry. The data of the calibration and other parameters are listed in table (1)

The developed LSV and DPV techniques for CLOMI were applied to Anafraneyl™ tablets. The CLOMI content of commercially available tablets, prepared as described in experimental, was determined directly using LSV and DPV techniques. There is no need for any extraction procedure before voltammetric analysis. The recovery of CLOMI in tablets by using LSV, DPV techniques were 97.47% and 99.82% respectively. The results obtained statistically comparable with those given using official method [17]

The spontaneous interfacial process can be utilized as an effective pre-concentration step to the pulse Voltametric measurement; Fig. 3 shows differential pulse voltammograms obtained after successive standard additions of CLOMI, each addition was 2 $x10^{-7}$ mol L^{-1} increase in concentration; 150 sec. pre-concentration periods was used instead of 90 sec. (ip =26.30 μA) because it is higher in peak current and more stable. The peak current increases linearly with the concentration as shown in Fig.3 over the entire range examined, with a typical regression equation ip(μA) = (5.260 + 0.090) c (μg/ ml) r = 0.9894; slandard deviations for slope and intercept of the calibration curve were 0.641 and 0.005 , respectively.

The pre-concentration differential pulse voltammetric response to different concentrations of CLOMI in urine samples mixed with 9.0 ml acetate buffer (0.02 M, pH 5.0), after 150 sec. at open circuit conditions. The peak current was linearly related to the CLOMI concentration within the range (5 x 10^{-11} -7x10^{-11} molL^{-1}) per ml of urine, according to the regression equation:

ip (μA) = (1.296 + 0.286 c (μg /ml), r = 0.998;

standard deviations for slope and intercept of the calibration curve were 0.2862 and 0.0100 receptively.

Validation of the proposed analysis procedure

This was examined via evaluation of limit of detection LOD, limit of quantification LOQ, repeatability, recovery, selectivity and robustness. The LSV and DPV voltammograms of different concentrations of bulk CLOMI were recorded, following pre-concentration on to carbon paste electrode for different durations (10-150 sce.); four replicate measurements were carried out for each concentration.

The corresponding calibration graphs were linear over the concentration ranges reported in table 1. The LOD and LOQ were estimated as LOD= 3SB/b and LOQ= 10SB/b [18], where SB is the standard deviation of the blank and b is the slope of the calibration curve. The linearity of the calibration graph was validated by the high value of correlation coefficient (0.9989) and the small intercept (0.0100).

Accuracy and reputability

Applying the proposed method for analysis of dosage forms and urine validated the accuracy of the suggested procedure. The results obtained with the proposed method for analysis of CLOM I in dosage forms were compared with those obtained by (HPLC method) [17]. The chromatographic method and the proposed method resulted in an average recovery of (104.8%) with S.D (2.81) and (101%) with S.D (2.6) respectively. This indicates an excellent agreement between experimental and reported values, and there is no significance different between the proposed and HPLC method. The repeatability of the method was determined from multiplet , measurements at each of the studied sample (n=5).

Selectivity

The selectivity of the optimized procedure for assay of CLOMI was examined in the presence of some common excipients (usually present in formulations e.g. (starch, gelatin, lactose, talc and magnesium stearate.) no significance interference was observed. Also no interference from absorbable oxidizable components was observed. That is clear from the absence of peaks in voltammgrams recorded following accumulation from urine samples and medium exchange (Fig. 3 base line). The data, as well as that of previous studies [19-21], indicate that absorptive stripping measurements of oxidizable compounds at carbon electrode are less susceptible interferences. Moreover, the effect of uric acid, and some amino acids (glycine, alanine and glutamic acid), were studied at a concentration 10^{-4} $molL^{-1}$and had no effect on the electrode response.

The proposed method presents a sensitive, simple, accurate and precise procedures to determine trace CLMOI. Its main advantages over HPLC methods are its sensitivity, rapidity, no pre-treatment are needed, and low cost instrumentation.

Conclusion

The present work presents a highly sensitive voltammetric quantification of tricyclic antidepressant CLOMI; this can be successfully accomplished by coupling its adsorptive stripping voltammetry at carbon paste electrode, for determination of CLOMI at trace levels, because of its low detection limit. The proposed method is fast, rapid no pre-treatment or time consuming extraction steps was required and convenient recovery of the electrode allows it to use a single electrode for multiple determinations. Moreover, because of its very low limits of detection and quantitation the proposed method was successfully applied for the determination of CLOMI in a urine samples .

Table 1. Parameters of CLOMI calibration in acetate pH5.0 at a carbon paste electrode

Parameters	DPV	LSV
Linearity rang (mol L^{-1})	$4x10^{-11}$-$2x10^{-10}$	$4x10^{-9}$-$2x10^{-8}$
Slope (mA/ mol L^{-1})	0.641	0.256
Intercept/ MA	0.005	0.001
Correlation coefficient (r)	0.989	0.974
LOD/ (mol L^{-1})	$3x10^{-11}$	$3.5x10^{-9}$
LOQ (mol L^{-1})	$4.8x10^{-11}$	$4.6x10^{-9}$
RSD of slope	0.0186	0.105

Table 2. Application of the proposed voltammetric method to the determination of CLOMI in spiked human urine samples.

Added amount/μg ml^{-1}	Found	%Recovery
2.0	2.1	105
4.0	3.98	99.5
6.0	5.98	99.6
8.0	8.12	101.5
10.0	9.97	99.7
$\bar{x}$	-	101.06
$\pm$ S.D.	-	2.65

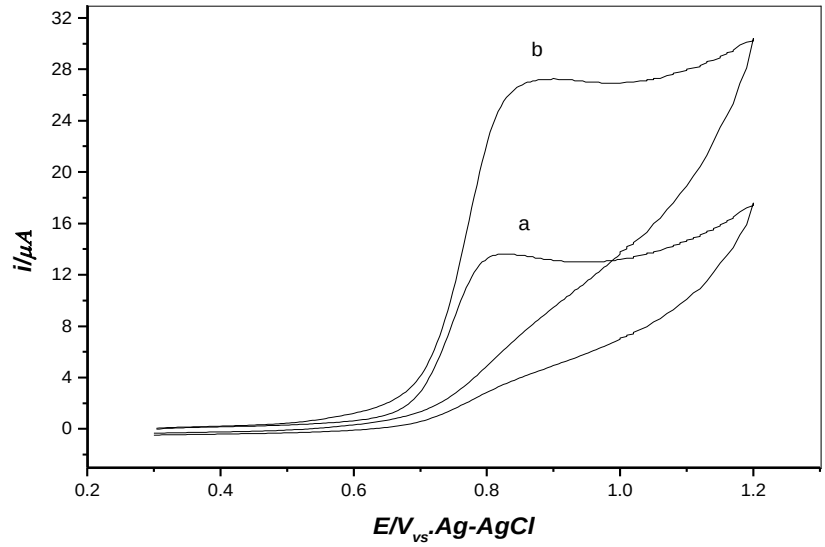
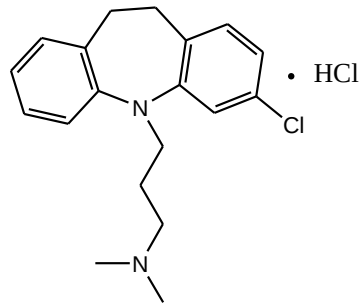


Fig. 1. Cyclic voltammogram for 5.0×10^{-5} M CLOMI (a) at zero time accumulation (b) at 150-s time accumulation in acetate buffer pH 5.0 at carbon paste electrode, scan rate = 100 mV s^{-}



Scheme (1)

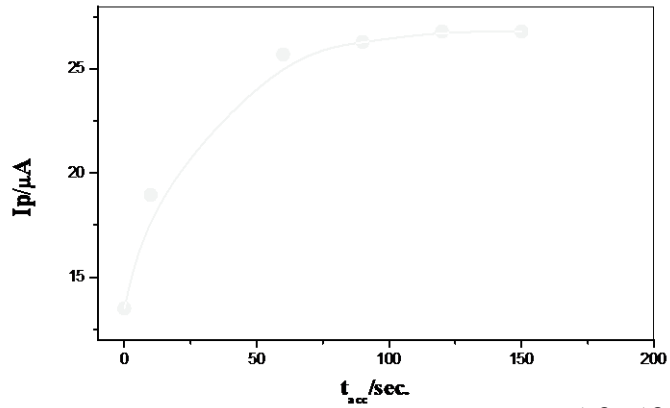


Fig. 2. Effect of the accumulation time on the peak current for 1.0×10^{-5} M CLOMI in acetate buffer (0.05M, pH5.0)

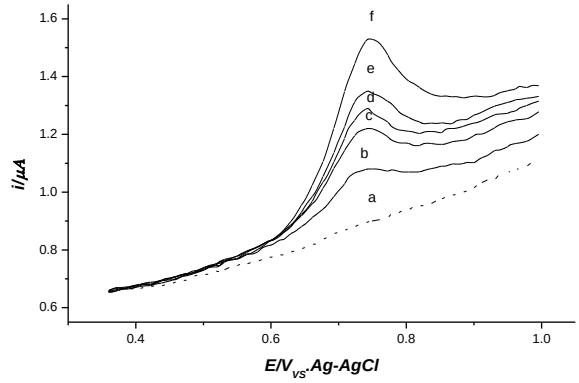


Fig.3. Anodic differential pulse voltammograms obtained for increasing concentration CLOMI (*b*) 2.0 (*c*) 4.0 (*d*) 6.0 (*e*) 8.0 and (*f*) 10.0 μg ml^{-1}. Inset is the calibration plot. Dotted lines represent the blank.

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