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Preconcentration and Voltammetric Study of Nicergoline at a Carbon Paste Electrode

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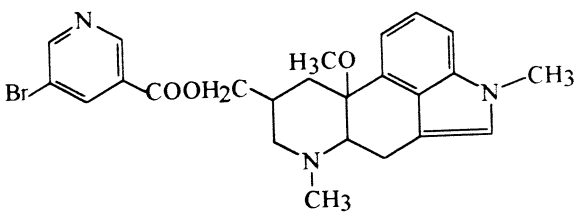
Abstract. The electrochemical oxidation of nicergoline is investigated using cyclic and differential pulse voltammetry at a carbon paste electrode. For the determination of nicergoline an adsorptive stripping procedure is proposed. The response is characterized with respect to pH, ionic strength, preconcentration time, accumulation potential, nicergoline concentration, reproducibility and other variables. By differential pulse voltammetry at a carbon paste electrode and pH 8.0, a linear calibration in the range 5×10^{-8} M to 1×10^{-7} M and a detection limit of 1×10^{-8} M are obtained. The preconcentration medium-exchange approach was used for a selective determination of nicergoline in urine. For dilute urine samples a detection limit of 5×10^{-8} M is obtained after 3 min of accumulation and medium-exchange. The procedure also is applied for the determination of nicergoline in dosage form.

Key words: nicergoline; stripping voltammetry; carbon paste electrode.



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Nicergoline I {10-Methoxy-1,6-dimethylergoline-8-methanol 5-bromo-3-pyridinecarboxylate (ester)} is a drug with vasodilatory properties due to its alpha-adrenergic blocking activity [1, 2]. The drug is useful in treating acute myocardial infarcts with diastolic hypertension [3]. Nicergoline is metabolized in vivo. The most important routes of chemical transformation in man appear to be hydrolysis of the ester linkage and N-demethylation. It is possible to determine this compound by direct or differential pulse polarography because of the presence of a reducable group in the molecule [4].

Chemically modified carbon paste electrodes have attracted the interest of several researchers during the past years [5–8]. As compared to other solid electrodes the main advantages of carbon paste electrodes arise from the lower residual current and noise, and the facts that they are cheap and easy to prepare and to replace. These electrodes have a wide range of applications, both when used as cathode or anode. Chemically modified electrodes, which display hydrophobic properties, can be used for the selective accumulation of lipophilic organic analyte at the electrode surface prior to voltammetric measurements. The preconcentration/medium exchange/voltammetry scheme advantageously can be used for the measurement of the accumulated analyte in the presence of non-accumulated species with similar redox potential in biological fluids without any need for sample pre-treatment. Hydrophobic CMEs have been used to determine a number of organic compunds, including promethazine [9], anti-inflammatory drugs [10], tricyclic antidepressants [11], antihypertensive drugs [12], ergot alkaloids [13], butylated hydroxyanisole [14], methylated indoles [15], phenanthrenequinone and oxoapomorphine [16], adriamycin [17] antitumor celiptim [18] and indomethacin [19].

While an electrochemical reduction of nicergoline already has been described [4], to the best of our knowledge, no work dealing with the electro-oxida-

tion of nicergoline has been reported. It was of interest to make use of the anodic behavior of the compound in view of the presence of electro-oxidizable groups, probably the indolic moiety. A preconcentration of nicergoline at the surface of carbon paste has been exploited for developing a new method for the determination of nicergoline at therapeutic concentrations in urine.

Experimental

Reagents

A stock solution of 1×10^{-3} M nicergoline (Pharmacia) daily was prepared in pure methanol. Britton-Robinson buffers (acetic, phosphoric and boric acids, all at 0.04 M and of which the pH was adjusted with NaOH) were used as supporting electrolytes. All solutions were prepared from AnalaR-grade reagents by using doubly distilled water.

Appartus

Differential pulse voltammograms were recorded with a SARGENT-WELCH model 4001 and cyclic voltammograms with an Oxford portable potentiostat, equipped with a Philips PM 8043 X-Y recorder. A three-electrode system was used and consisted of a carbon paste electrode (CPE) as working electrode, a Ag/AgCl (3 M KCl) electrode as reference electrode and a separation by a salt bridge. All potentials reported here are referred to the latter electrode and a glassy carbon electrode is used as counter electrode. The body of the working electrode was made of a PTFE sleeve (3.5 mm, i.d.), which is filled with carbon paste (Metrohm, 6.2801.000). A platinum wire embedded in the paste provided for the electrical connection.

The pH of the buffer solution was measured with a digital pH-meter with glass combination electrode (“SCHOTT Geräte”).

Procedure

In the adsorptive voltammetric measurements the analyte was accumulated at the electrode surface by stirring at $\sim$400 rpm with the aid of a magnetic stirrer using a stirring bar with a length of 1 cm, for a given time followed by a delay period of 15 s required to settle the solution and to decrease the background current. Subsequently, the cyclic (CV) or differential pulse voltammogram (DPV) was recorded in the anodic direction. As experimental settings utilized in DPV a pulse amplitude of 25 mV and a sweep rate of 1.0 V min^{-1} were used. The accumulation step was accomplished either at open circuit potential or at a potential range from -0.3 V to $+0.5$ V.

Determination in Tablets

Fifty tablets of Sermion®, which contained a declared amount of nicergoline (10 mg) were crushed and powdered in an agate mortar. A weighed portion of the powder equivalent to 0.0242 g of nicergoline was treated with methanol for 15 min. The solution and the methanol used for washing were made up to exactly 50 ml. An aliquot of 100 µl of the clear supernatant of this solution was transferred to the voltammetric cell, and the differential pulse voltammogram was recorded at the carbon paste electrode. The standard addition medthod was applied, and successive aliquots of 100 µl of (1×10^{-3}) nicergoline were added.

Detemination in Urine

For the determination of nicergoline in urine, the preconcentration/medium exchange/voltammetry scheme was adopted. Urine (1 ml) containing the drug was mixed with 18 ml of Britton-Robinson buffer having a pH of 8.0, and diluted to 20 ml with methanol. The solution was stirred at 400 rpm at open circuit conditions, and the carbon paste electrode was immersed in the solution for 60 s (preconcentration step). The electrode was then washed with water, dried, and placed in the measurement cell containing 20 ml of Britton-Robinson buffer at pH 8.0, Subsequently, the differential pulse voltammogram was recorded with a pulse amplitude of 25 mV and a sweep rate of 1.0 V min^{-1} between $+0.3$ V and 1.2 V. For electrode regeneration, the working electrode was transferred to a blank electrolyte solution and the series of cyclic scans was continued until a voltammogram corresponding to the residual current was obtained. The electrode was then ready for being used in a next measurement cycle. It has been noted that the same electrode surface could be used for more than 25 repetitive collection/measurement/cleaning clycles with no noticeable decrease of sensitivity or stability. Thereafter, the background current starts to increase, and a new surface paste was required. A thin layer of the surface was removed with a spatula and replaced with a fresh paste.

Results and Discussion

The anodic cyclic voltammogram for the oxidation of nicergoline in Britton-Robinson buffer having a pH of 8.0 at a carbon paste electrode are shown in Fig. 1. In the forward scan, a single anodic peak is observed, which corresponds to the oxidation of nicergoline, probably at the indolic moiety. In the reverse sweep

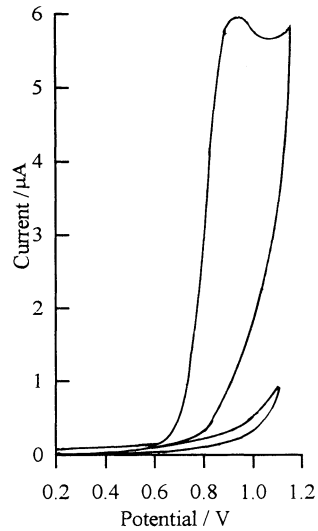

Fig. 1. Cyclic voltammogram for 2.5×10^{-5} M nicergoline in Britton-Robinson buffer at pH 8.0. Scan rate: 50 mV s^{-1}

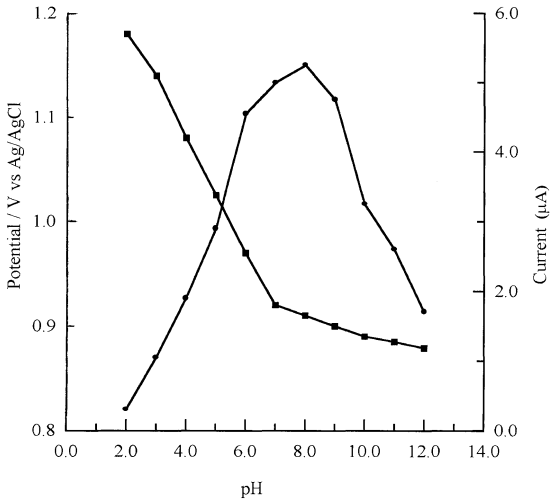

Fig. 2. Dependence of the peak potential and the peak current on the pH 2.5×10^{-5} M nicergoline, scan rate: 50 mV s^{-1}

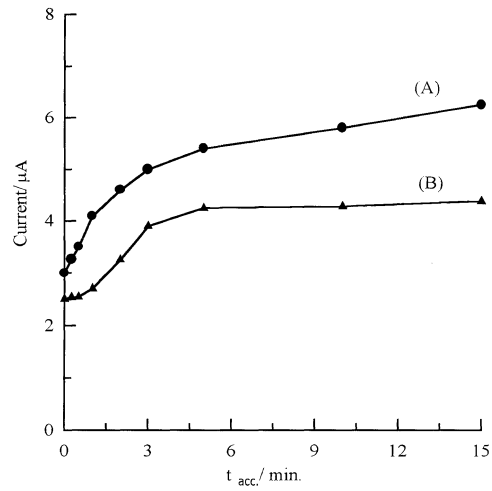

Fig. 3. Effect of the accumulation time on the peak current for (*A*) 2.5×10^{-5} M and (*B*) 1×10^{-5} M nicergoline. Other conditions as in Fig. 1

no cathodic peak is observed which indicates that the process is irreversible.

The effect of the potential scan rate v on the peak current i_p and the peak potential E_p was studied. Cyclic voltammetry at different scan rates v (5–200 mV s^{-1}) showed that the peak current i_p was proportional to the square root of the scan rate $v^{1/2}$ at the carbon paste electrode, which is expected for a diffusion-controlled process. This may be due to the diffusion of dissolved molecules from the oil layer to the graphite particle surface. Moreover, E_p shifted to more positive potentials when the scan rate increased, which confirms the irreversibility of the oxidative process.

The effect of the pH on the oxidation of nicergoline was studied over the pH range 2.0–12.0 by means of cyclic voltammetry. In all instances nicergoline undergoes one main irreversible oxidation process, which shifts towards less positive potentials as the pH increased (Fig. 2A). The plot of E_p vs. the pH exhibits two linear intervals with a break at a pH of approximately 7. In the pH range 2.0–7.0 a linear dependence is observed with a slope of approximately −60 mV per pH unit. At pH > 7.0 the process is nearly independent of the pH.

The peak current also depends on the pH. The plot of i_p vs. pH (Fig. 2B) shows that the maximum peak current was obtained at a pH of 8.0. This pH was selected for analytical puroposes.

Voltammograms recorded after stirring for a time showed an improved response at the carbon paste electrode. In Fig. 3 the dependence of the peak heights on the accumulation time for (A) 2.5×10^{-5} M and (B) 1×10^{-5} M nicergoline in a Britton-Robinson buffer of pH 8.0 is shown. The relation between the peak current and the accumulation time was linear for the case of short accumulation periods. After 5 min the rate of extraction decreased, but the extraction process went on for 30 min. The intersection of these graphs with the peak current axis may be attributed to the fact that the accumulation takes place during the equilibrium time or during the potential sweep. The current enhancement at the carbon paste electrode is attributed to preconcentration mainly by extraction.

The influence of the pH on the accumulation behavior of nicergoline at a carbon paste electrode in the case of Britton-Robinson buffers was evaluated buffers for the pH range of 2.0–12.0. The best accumulation is attained at pH 8.0, which was selected for the accumulation step. This pH value was also recommended for the measurement step.

The influence of the ionic strength on the efficiency of the accumulation for a 1×10^{-6} M nicergoline solution at the carbon paste electrode also was studied. The ionic strength was varied by changing the concentration of NaCl in the Britton-Robinson buffer of pH 8.0 from 0.001 to 0.05 M. The NaCl background solution concentrations were found to be of less significance for the degree of accumulation. The stripping peak remained almost constant. For this reason the ionic strength recommended for analytical purposes is given by the Britton-Robinson buffer (0.04 M).

Also at a potential range from -0.3 V to $+0.5$ V or at an open circuit potential the effect of accumulation potential was investigated. The extraction efficiency at the electrode surface was essentially found to depend on the accumulation potential. A significant decrease in the response at negative or positive accumulation potential was observed. Considering these data, circuit conditions were selected for further study.

The peak current for nicergoline as measured by the differential pulse mode was found to increase linarly with the concentration from 5×10^{-8} M to 1×10^{-7} M {C (μM) = 1.37 i_{pa} (μA−0.008, r = 0.987}. At a concentration of 1×10^{-7} M, a curvature of the calibration graph was observed. The curvature presumably indicates a saturation of the electrode surface [14]. A detection limit (3σ) of 1×10^{-8} M for nicergoline was obtained in the case of an accumulation period of 3 min. The relative standard deviation for the peak current at new surfaces was 4.5% and for the case of the same electrode after consecutive accumulation and cleaning step, it was 2.9% (n = 5).

A variation of the nicergoline concentration was found to have a slight influence on the peak potential. The peak potential shifted towards more negative values when the concentration is increased.

Analytical Application

For the analysis of Serminon® tablets in filtered solutions calibration by standard addition was applied. From five determinations a mean nicergoline content of 9.98 mg was obtained, which is in a good agreement with the declared value of 10 mg. The standard deviation obtained was 1.55%. A comparative polarographic analysis resulted in a mean value of 9.58 mg with a standard deviation of 0.064 [4]. The solutions of dissolved tablets were directly assayed by polarography. However, for the present method a separation of the excipients was required. It can be concluded that the voltammetric determination developed in this work is a good analytical alternative because the electrode is cheap and easy to prepare and to replace.

As shown in Fig. 4, a direct determination of nicergoline in a diluted urine sample is complicated by the large oxidation peak of blank urine. In contrast, after medium exchange, the peak of the urine components can be avoided.

In Fig. 5 the voltammetric response to successive standard additions of nicergoline to a urine sample is shown. The urine is diluted 20 times and a 3 min accumulation at open circuit conditions, as well as medium-exhchange were applied. The electrode response to the nicergoline concentration was linear within the range 1×10^{-7} M to 1×10^{-6} M and a detection limit of 5×10^{-8} M could be obtained by means of differential pulse voltammetry. The reproducibility of the total analytical process was determined from multiple measurements for each of the urine samples (n = 5) and an average relative standared deviation of 3.0% was obtained.

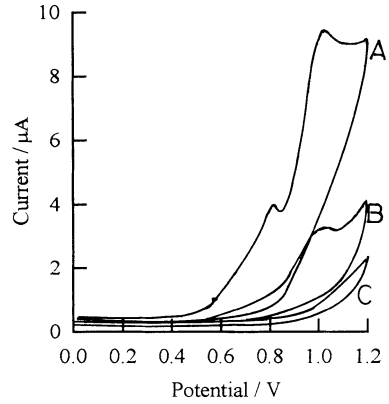

Fig. 4. (*A*) Cyclic voltammograms for 2.5×10^{-5} M M nicergoline in urine diluted 1:20 with Britton-Robinson buffer, (*B*) medium exchange after preconcentration from diluted urine $+2.5\times10^{-5}$ M at $t_{acc} = 3$ min and open circuit conditions, (*C*) medium exhcange and accumulation from diluted urine sample

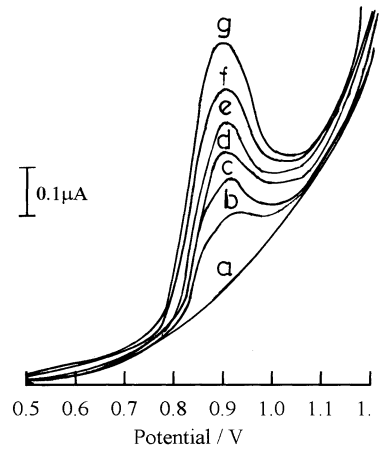

Fig. 5. Adsorptive differential pulse voltammograms obtained for the determination of nicergoline in urine samples after medium exchange: (*a*) blank; (*b*) urine spiked at a nicergoline level of 2×10^{-7} M; (*c, d, e, f and g*) sequential standard additions of 100 μl of a 1×10^{-4} M nicergoline solution

Conclusion

In the present study it was shown that adsorptive stripping voltammetry at a carbon paste electrode can be used to determine nicergoline at trace levels because of its low detection limit. Nicergoline can be effectively extracted from aqueous solutions or urine samples into the oil of the electrode with high selectivity and sensitivity. Moreover, the proposed method is fast and purging of the nicergoline solutions with nitrogen is not required. A rapid and convenient recovery of the electrode allows it to use a single electrode for multiple determinations. The detection limit found for nicergoline at the carbon paste electrode for urine samples after medium exhange is low enough to reach the levels expected in urine after applying therapeutic doses.

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