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Sensitive anodic voltammetric determination of methylergometrine maleate in bulk and pharmaceutical dosage forms using differential pulse voltammetry

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ABSTRACT

The voltammetric oxidation behavior of methylergometrine maleate (MM) was investigated applying differential pulse voltammetry (DPV) at three different electrodes; pencil graphite (PGE), carbon paste (CPE) and glassy carbon (GCE) electrodes. Cyclic voltammetric analyses were performed to optimize the voltammetric conditions. MM cyclic voltammogram showed a well-defined anodic peak at around 740–780 mV using Britton Robinson buffer at pH 5.0 for PGE and GCE, and pH 6.0 for CPE. The oxidation process was shown to be completely irreversible and diffusion-controlled. Based on this study, a sensitive quantitative method was proposed for determination of MM in its pure and pharmaceutical dosage forms. Various experimental conditions were examined and optimized; including pH, type of supporting electrolyte, accumulation time, scan rate and electrode material. The results obtained were linear over the concentration ranges 0.10–1.00, 0.08–0.36 and 0.50–5.50 μg/mL with a square of correlation coefficient (R^2) 0.9996, 0.9995 and 0.9994 at PGE, CPE and GCE, respectively. The method showed a minimum detectability (LOD) of 0.02, 0.008 and 0.14 μg/mL and a limit of quantitation (LOQ) of 0.06, 0.02 and 0.42 μg/mL at PGE, CPE and GCE, respectively. The method was validated and compared with the reference valid method. It revealed good accuracy and reproducible results. The anticipated voltammetric procedure has the advantage of being simple, precise, inexpensive and highly sensitive.

1. Introduction

Methylergometrine maleate (MM) [(8S)-N-[(1S)-1-(hydroxy methyl)propyl]-6-methyl 9,10-dihyddroergoline-8-carboxamide monomaleate] (Fig. 1) is a smooth muscle constrictor that mostly acts on the uterus. It is official in [1–3]. MM has more powerful action on the uterus than most other ergot alkaloids. Its main action is the production of intense contractions, which at higher doses are sustained. Its action is also more prolonged than that of oxytocin. MM is used in the active management of the third stage of labor, and to prevent or treat postpartum or postbortal hemorrhage caused by uterine atony; by maintaining uterine contraction and tone, blood vessels in the uterine wall are compressed, and blood flow reduced [4].

Several methods for analysis of the cited drug have been reported. The British, European and the Unites States pharmacopeias recommend the liquid chromatography technique with UV detection [1–3]. Literature review also revealed other techniques. These included: spectrofluorimetry [5,6], spectrophotometry [6], thin layer chromatography (TLC) [7], high performance liquid chromatography (HPLC) [8–11], and radioimmunoassay [12].

To the best of our knowledge, no methods were found in the literature based on the electrochemical redox properties of MM. Thus, in the presented work, the voltammetric oxidation behavior of MM at PGE, CPE and GCE was studied using CV and DPV, and the optimum conditions for the quantification analysis were determined. The electroanalytical technique provided the advantage of simplicity, high sensitivity, low cost, relatively short analysis time and direct analysis, without any derivatization, extraction or clean-up steps. [13,14].

2. Experimental

2.1. Apparatus

All voltammetric experiments were carried out using a Metrohm computrace voltammetric analyzer model 797 VA with

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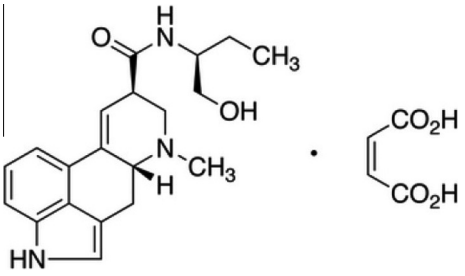

Fig. 1. Structure of methylergometrine maleate.

Software Version 1.0 (Metrohm, Switzerland) for voltammetric analysis equipped with three-electrodes: a working electrode, Ag/AgCl (3 ML-1 KCl) electrode as reference electrode and a platinum electrode as auxiliary electrode. The pH measurements were carried out using digital pH-meter Metrohm.

2.2. Working electrodes

Experiments were performed on three different electrodes:

(a) *Glassy carbon electrode* (*GCE*)*:* mini glassy carbon disk electrode of active area: 2.8 mm, for ELCD 641/656. To improve the sensitivity and resolution of the voltammetric peaks, the GCE was polished manually with 0.5 μm alumina powder on a smooth polishing cloth prior to each electrochemical measurement. Then, it was thoroughly rinsed with methanol and double distilled water, and gently dried with a tissue paper.
(b) *Carbon paste electrode* (*CPE*)*:* the carbon paste was prepared by mixing of 0.5 g graphite powder (particle dimension 20 μm, Sigma–Aldrich, Egypt) with 0.3 mL of paraffin oil in a mortar with a pestle. A portion of composite carbon paste was packed into the hole of the insulin syringe body with diameter 3.0 mm which contain copper wire contacted the apparatus and the tip of the electrode was polished with a weighing paper until it had a shiny appearance.
(c) *Pencil graphite electrode* (*PGE*)*:* rotring HB pencil leads with length of 60 mm and a diameter of 0.5 mm were employed. Electrical contact with the lead was achieved by soldering a metallic wire to the metallic part fixing the lead inside the pencil. The electrode was polished using a cloth felt pad with 0.05 m alumina slurry.

Whenever necessary, the electrodes' surfaces were polished using a weighing paper.

2.3. Materials

All chemicals used were of analytical grade.

- MM (99.80%) was kindly supplied by the National Organization for Drug Control and Research (NODCAR) (Cairo, Egypt).
- Pharmaceutical dosage forms; Methergin® tablets and ampoules (Novartis Pharmaceuticals Corporation, Egypt) containing 0.125 mg MM/tablet and 0.2 mg/mL ampoule, were purchased from the local market.
- 0.04 M Britton Robinson buffer solutions were prepared over the pH range 2.0–11.0 [15].
- Double distilled water was used throughout all experiments.

2.4. Standard solutions

A stock standard solution of MM (100.0 μg/mL) was prepared by dissolving 10.0 mg pure MM in double distilled water and the volume was completed to 100 mL using the same solvent. Working solution (10.0 μg/mL) was prepared by transferring 10 mL of stock solution into a 100 mL measuring flask and completing to the mark with double distilled water.

2.5. General procedure

Appropriate aliquots of MM working solution (10.0 μg/mL) were transferred into a 10 mL volumetric flask and completed to the mark with 0.04 M BR buffer (pH 5.0 at PGE and GCE and pH 6.0 at CPE) to cover the final concentration ranges 0.10–1.00, 0.08–0.36 and 0.50–5.50 μg/mL at PGE, CPE and GCE respectively. The solution was then transferred to the voltammetric cell and de-aerated by pure nitrogen gas at 1 atmosphere for 2 min. The pre-concentration time was 10 s at applied potential (E_{app}) +100 mV with continuous stirring at speed of 2000 rpm at room temperature. The stirrer was stopped and the solution was allowed to rest for 10 s, then voltammograms were recorded using scan rate "υ" = 100 mV/s, voltage step (V) = 0.0065 applying CV, while a pulse amplitude (V) = 0.05, scan rate "υ" = 100 mV/s, voltage step time = 0.065 s, voltage step (V) = 0.0065 and pulse time = 0.04 s when using DPV. Scan was done over an oxidation potential range from +100 to +1000 mV. The mean of triplicate measurements of content in the sample were calculated using the obtained regression equations.

2.6. Pharmaceutical dosage forms assay procedure

(a) *Assay for ampoule:* a solution of 10.0 μg/mL was prepared by transferring a 0.5 mL aliquot of the ampoule solution into a 10 mL measuring flask, and diluting to the mark with double distilled water. Further dilutions were made by transferring different aliquots into a 10 mL volumetric flask and completing to the mark with the supporting electrolyte. The procedure was then completed as described above.
(b) *Assay for tablet:* 20 tablets of Methergin® were accurately weighed and finely powdered. A weighed portion of this powder equivalent to 1000 μg of MM was transferred into a 100 mL calibrated flask and completed to the volume with double distilled water to obtain a final concentration of 10.0 μg/mL. The content of the flask was sonicated for 15 min to achieve complete dissolution. The solution was then centrifuged and different concentrations were prepared by transferring suitable aliquots of the supernatant solution into a 10 mL volumetric flask and completing to the mark with the supporting electrolyte. The procedure was then completed as described above.

3. Results and discussion

The voltammetric behavior of MM was studied at three different electrodes; PGE, CPE and GCE, using Britton-Robinson BR buffer solution as supporting electrolyte. Different chemical and electrochemical parameters were thoroughly investigated to study the voltammetric behavior of MM.

Applying CV technique, MM showed a prominent anodic peak at a potential around 740–780 mV with no peak on the reverse scan, suggesting the completely irreversible nature of the electrode reaction as depicted by the cyclic voltammograms given in Fig. 2.

3.1. Effect of type and pH of supporting electrolyte

The influence of the type of supporting electrolyte on the peak current was examined using CV. The composition of the supporting electrolyte was evaluated in various electrolytes, such as acetate, phosphate and Britton–Robinson (BR) buffers. It was observed that