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Voltammetric characteristics of miconazole and its cathodic stripping voltammetric determination

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ABSTRACT

Miconazole is reduced at mercury electrode above pH 6 involving organometallic compound formation, responsible for an anomalous polarographic behavior. The electrodic process presents a large contribution of the adsorption effects. The drug can be determined by cathodic stripping voltammetry from 8.0×10^{-8} to $1,5 \times 10^{-6}$ mol L^{-1} in Britton-Robinson buffer pH 8.0, when pre-accumulated for 30 s at an accumulation potential of 0 V. A relative standard deviation of 3.8% was obtained for ten measurements of 1.0×10^{-7} mol L^{-1} miconazole in B-R buffer pH 8.0 and a limit detection of $1,7 \times 10^{-8}$ mol L^{-1} was determined using 60 s of deposition time and scan rate of 100 mV s^{-1}. The proposed method is simple, precise and it was applied successfully for the determination of the miconazole in pure form and in commercial formulations, showing mean recoveries of 99.7–98.4%.

Key words: miconazole, voltammetry, electroanalysis, determination.

INTRODUCTION

Miconazole, 1-[2-(2,4-diclorofenil)-2-(2,4-diclorofenil)metoxietil-1H-imidazol, is an imidazole antifungal agent and antibacterial drug (Bennett 1996, Hoogeheide and Wycka 1982). The drug is administered locally or intravenously in cases of local or systemic mycotic infections. As a well established and useful drug it has generated significant analytical interest, several methods have been described for its determination in pharmaceutical formulations or biological fluids. The main methods employed are based on spectrophotometry (Cavrini et al. 1981, Goger and Gokcen 1999, Bonazzi et al. 1998, Kashaba et al. 2000, Erk and Altun 2001) and chromatography (Kobylinka et al. 1996, Indrayanto et al. 1999, Pietra et al.1996, Pietra et al. 1992, Cavrini et al. 1982). While all of these methods proved to be useful for certain studies, most of them are associated with specific procedures, requiring many steps and solvent extractions, lack of specificity and low molar extinction coefficient.

Electrochemical methods have shown remarkable advantage in analysis of drugs in pharmaceutical formulation (Smyth and Vos 1992). On the other hand, the voltammetric reduction of halogenated compounds is well known in the literature (Baizer and Lund 1985). However, only one study found in the literature has investigated the interaction of miconazole with some trace-elements (Willems et al. 1981) by means of polarographyc measurements. The stabilities constants with Mn, Fe, Co, Ni and Zn cations have been determined using the shiftting of $E_{1/2}$ (half-wave potential) produced in the metal reduction wave in the presence of miconazole. But,

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no work has been reported in the literature dealing with polarographic reduction of miconazole as well adsorptive stripping voltammetric determination of the drug.

The present work describes the electrochemical behavior of miconazole at mercury electrode in order to obtain an adsorptive stripping voltammetric method for determining the drug in aqueous solution and pharmaceutical formulations.

MATERIALS AND METHODS

Apparatus: Voltammetric experiments were performed with a Metrohm Polarecord E 506 linked to a compatible microcomputer, through a Microquimica interface. The multimode electrode Metrohm stand 663 VA was used in both the hanging mercury electrode (HMDE) and dropping mercury electrode (DME). The three electrode system was completed means of an Ag/AgCl (3 mol L^{-1} KCl) reference electrode and a glassy carbon auxiliary electrode.

Reagents: Suprapur grade reagents supplied by Merck and desmineralized water from a Milli-Q system (Milli-pore) were used in the preparation of all solutions. Britton-Robinson (B-R) buffer used as supporting electrolyte was prepared by mixing appropriate amounts of 0.2 mol L^{-1} sodium hydroxide to orthophosphoric acid, acetic acid and boric acid (0.04 mol L^{-1} in each) solution.

Procedure: Miconazole stock solution (1.0×10^{-2} or 1.0×10^{-4} mol L^{-1}) were prepared from the dried and pure substance (kindly supplied by Bayer S.A.) by dissolution in methanol. An aliquot of the miconazole standard solution to be investigated was added by micropipette to 20 mL of deaerated B-R buffer at the appropriate pH. The differential pulse mode was used with a pulse amplitude of 50 mV, a drop time of 0.8 s, unless stated otherwise. The cathodic stripping voltammograms were obtained using a step of accumulation at –0.2 V for 30 s by stirring unless otherwise stated. Following 15 s after stopping the stirring, a cathodic voltammogram was recorded, with a 100 mV s^{-1} scan rate in the linear scan mode.

Analysis of dosage forms by voltammetric method were carried out using a commercial spray of Vodol (nominally 10 mg in miconazole nitrate). An aliquot of this formulation after evaporation of the organic solvent under a stream of nitrogen was diluted with 10 mL of methanol. Aliquots of 20μL of this solution was transferred directly into the voltammetric cell containing 20 mL of phosphate buffer pH 8.0 and the voltammetric curve recorded as above procedure. For tablets, commercial samples of Daktarin were prepared in a simple way. A weighed quantity of the powder equivalent to 10 mg of the studied drug was dissolved into 10 mL of methanol and aliquots of 20μL of this stock solution was directly added to the voltammetric cell before electrochemical measurements.

Analysis of dosage forms by spectrophotometric method were carried out after complexation of miconazole with bromocresol green dye, following the procedure proposed in the literature by (Cavrini et al. 1981).

RESULTS AND DISCUSSION

Differential Pulse Polarography

Miconazole contains electroreducible carbon-chloride bonds that provide the basis for its voltammetric determination. In hydroalcoholic solution; 0.04 mol L^{-1} Britton-Robinson buffer/methanol (1:1), miconazole is readily reduced in the pH range 8.0-12.0, as is shown in Fig. 1. The cathodic peak located at relatively high negative electrode potential (pH = 8.0), Fig. 1, Curve B) shifts towards more negative values increasing the pH values up to -1.40 V at pH 12.0. The height of the peak decreases continuously above pH 8, being only about one-third of its original height at pH 12.0. Analyses of the shapes of the differential-pulse peaks have shown peak half-width values of about 91 mV, suggesting a reduction process involving one electron transfer (Bond 1980).

A linear dependence between log i_p versus log t was found for differential pulse polarograms obtained from 0.4 to 2.0 s with a slope of 1.44, showing

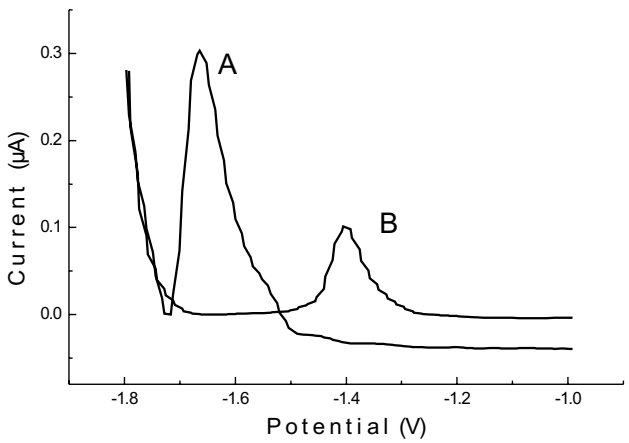

Fig. 1 – Differential pulse polarograms obtained for 5.0×10^{-4} mol L^{-1} of miconazole in pH 8.0 (Curve A) in pH 12.0 (Curve B).

that adsorption is involved in the electrode process (Zuman 1969). The above results were confirmed by means of the calibration curve obtained from 0.05 mM to 0.5 mM of miconazol. The relationship between ip versus concentration has shown a behavior unsuitable as analytical method. Although a linear relationship is obtained the curve does not cross the origin, following the equation: ip(μA)= –0.655 + 2465 C (C = concentration mol L^{-1}); R= 0.992, n=7. The recorded differential pulse polarographic are also distorted at higher concentrations than 2.0×10^{-4} mol L^{-1}, exhibiting anomalous baseline and non-symmetrical polarographic curves, indicating that strong adsorption are present in the electrodic process (Bond 1980).

This behavior is confirmed by cyclic voltammetric investigation. The reduction of 1.0×10^{-3} mol L^{-1} of miconazole solution in B-R buffer pH 8.0 shows a cathodic peak at -1.7V and an anodic peak resulting from re-oxidation of the reduction product at reverse potential scan. The difference between the cathodic and the anodic peak potential is almost zero, indicating the occurrence of a reduction process complicated by strong adsorption of reagent and product (Laviron 1974). The influence of scan rate (ν) on both peaks height was investigated from 10-500 mV s^{-1}. On plotting ip vs ν, a linear relationship was observed for both cathodic and anodic peak, which is indicative of an adsorption-controlled process involving the reagent and product generated. Multi cyclic voltammograms repeated at the same mercury drop, do not show any alteration on the height of the cathodic or anodic peak. These results confirm that the generated product on electrode surface is strongly adsorbed on mercury as a stable film, (Laviron 1974).

It is known from the literature, (Pereira et al. 2001, Baizer and Lund 1985), that the formation of organometallic compounds prior or after the electron transfer is often the preferred route of electroreduction of halogenated organic compounds on cathodes of mercury. Therefore, taking into consideration the polarographic results obtained, the overall course of the reduction of miconazole probably follows other imidazole compounds (Pereira et al. 2001, Baizer and Lund 1985), involving a reduction process where an organometallic reaction (eqn 2) could be competing with the reductive cleavage of the halide (eqn 1), as shown in Fig. 6. Hence, the direct participation of mercury on the electrodic pro-

cess explain all anomalous behavior observed in the polarographic experiments and the reversibility of the cyclic voltammograms in the first or successive scans. However, it is possible to conclude that differential pulse polarography or cyclic voltammetry can not be selected for analytical purposes.

Cathodic Stripping Voltammetry

The possibility of determining miconazole by stripping voltammetry was considered since the adsorption process detected in the electrochemical reduction could be used as an effective preconcentration step prior to the voltammetric reduction of the drug.

Linear voltammetric studies showed that miconazole is rapidly accumulated on an HMDE from a stirred solution, as shown the linear adsorptive stripping voltammograms obtained for 1.0×10^{-6} mol L^{-1} miconazole in B-R buffer pH 8.0 (Fig. 2). The height of the peak was shown to be directly proportional to the scan rate within the range $10 - 200$ mV s^{-1}, indicating that the reduction is that of an adsorbed species (Smyth and Vos 1992). On using a scan rate higher than 200 mV s^{-1} the peak shape was distorted, so a scan rate of 100 mV s^{-1} was used for further work.

In order to investigate the effect of pH values on the peak height and peak potential, the stripping voltammetric response was studied for 1.0×10^{-6} mol L^{-1} in B-R buffer between $7.0 - 12$. The peak potential is constant at pH < 8.0 and shifts linearly towards less negative values at higher pH values. But, the peak height decreases linearly with pH increasing as is shown in Fig. 3. So, a value of pH 8.0 was chosen as giving the best results.

The influence of deposition potential on the peak current of 1×10^{-6} mol L^{-1} miconazole was studied by changing potentials between 0 and -1.2 V. Taking into consideration that higher peak currents are obtained at an accumulation potential of 0 V, this value was chosen as best accumulation potential to pre-concentrate the drug.

The peak current is plotted as a function of accumulation time in Fig. 4. The peak current increases as the deposition time increases up to 60 s, and it is approximately constant after this time, indicating surface coverage.

The influence of miconazole concentration (pure sample) was studied from 8.3×10^{-8} to 1.5×10^{-6} mol L^{-1} using accumulation times of 30 s and 100 s, and the respective curves are shown in Fig. 5. The response was linear in all the range studied for 30 s of accumulation time, but the curve is linear only up to 4.2×10^{-7} mol L^{-1} when accumulation time of 100 s was used. An accumulation time of 30 s are recommended as optimum conditions for the determination of the drug in concentration above 4.2×10^{-7} mol L^{-1}.

Repetitive measurements of 1.0×10^{-7} mol L^{-1} miconazole in B-R buffer pH 8.0 using accumulation time and accumulation potential of 30 s and 0 V respectively, permitted the evaluation of the precision of the method. The experiment was repeated ten times, the relative standard deviation calculated for 1.0×10^{-7} mol L^{-1} was found to be 3.8%. A detection limit of 1.7×10^{-8} mol L^{-1} was determined using 60 s of deposition time and scan rate of 100 mV s^{-1}. In order to check the accuracy of the developed method, we carried out a recovery study (n=3) for samples containing 4.2×10^{-7} mol L^{-1}, an average recovery of 99% with a relative standard deviation of 1.6% was obtained.

The method was applied to some dosage forms containing miconazole nitrate, using the standard method addition. The results obtained for the commercial pharmaceutical formulations as Daktarin (Janssen Pharmaceutical Laboratory) and Vodol (Andromaco Laboratory), following a procedure described in the experimental part, are shown in Table I. The results are in good agreement with the namely in the label of the commercial sample exhibiting recovery of 99.7 and 98.4% for Daktarin and Vodol, respectively. The coefficient of variation of 1.7% for DAKTARIN and 1.6% for VODOL were obtained. The high recovery obtained in the experiment indicates the absence of interference from frequently excipients encountered in this kind of sample. The results (Table II) were compared with that obtained by applying a spectrophotometric method described

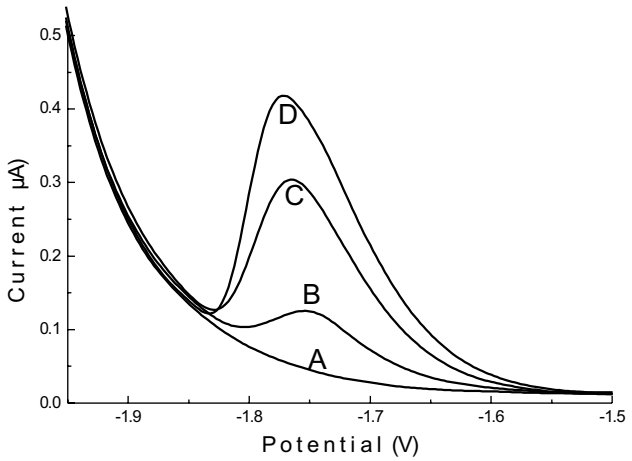

Fig. 2 – Cathodic Stripping voltammograms obtained for 1.0×10^{-6} mol L^{-1} of miconazole in B-R buffer pH 8.0. Accumulation potential (E_{ac}) = 0 V, Scan rate = 100 mV s^{-1}, using accumulation time (t_{ac}) of: Curve A = 0 s, curve B = 15 s, curve C = 30 s and curve D = 60 s.

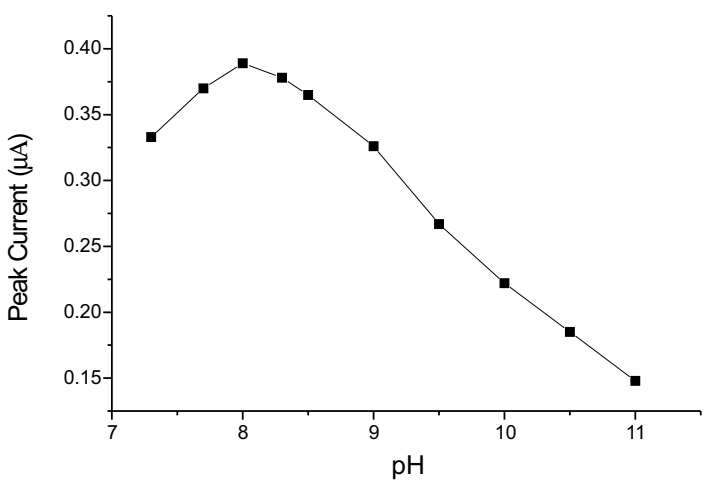

Fig. 3 – Influence of the solution of pH variation on peak current intensity obtained from cathodic stripping voltammograms of 1.0×10^{-6} mol L^{-1} miconazole. E_{ac} = 0 V, t_{ac} = 60 s and ν = 100 mV s^{-1}.

in the literature, (Cavrini et al. 1981). The results obtained for the same commercial sample nominally containing 1% of miconazole show a mean 100 and 99.0%, showing good agreement between both methods.

The proposed stripping voltammetric method proved to have an adequate precision and accuracy to carry out reliable analysis of miconazole. On the other hand, the voltammetric analysis has presented some advantages when compared with the spectrophotometric assay that usually requires derivatization reaction involving ion-pair formation, hydrolysis reaction, time consuming and presenting limited stability.

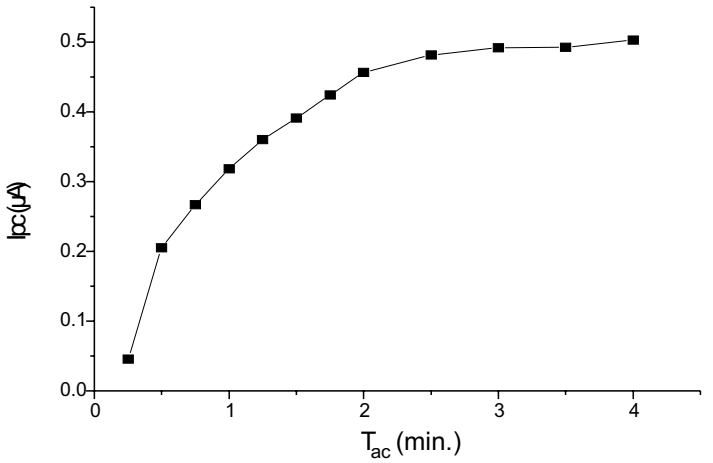

Fig. 4 – Influence of accumulation time on peak current intensity for 1×10^{-6} mol L^{-1} of miconazole in B-R buffer pH 8.0. E_{ac} = 0 V and ν = 100 mV s^{-1}.

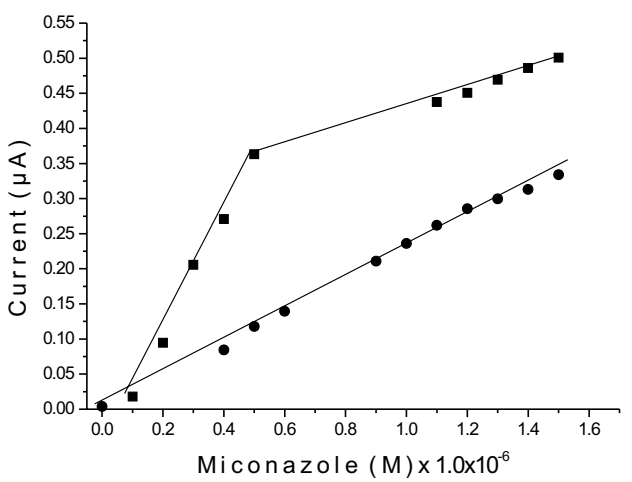

Fig. 5 – Calibration curves obtained for miconazole in B-R buffer pH 8.0. E_{ac}= 0 V, ν = 100mV s^{-1}, using accumulation time of 30 s (•) and 100 s (□).

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RESUMO

Miconazol é reduzido no eletrodo de mercúrio em valor de pH acima de 6,0 envolvendo formação de composto organometálico, responsável por um comportamento polarográfico anômalo. O processo eletródico apresenta uma larga contribuição de efeitos de adsorção. A droga pode ser determinada por voltametria de redissolução catódica de 8, 0×10^{-8} a 1, 5×10^{-6} mol L^{-1} em tampão Britton-Robinson pH 8,0 quando pré-acumulada por 30 s em potencial de acúmulo de 0 V. Um desvio padrão relativo de 3,8% foi obtido de 10 medidas de 1, 0×10^{-7} mol

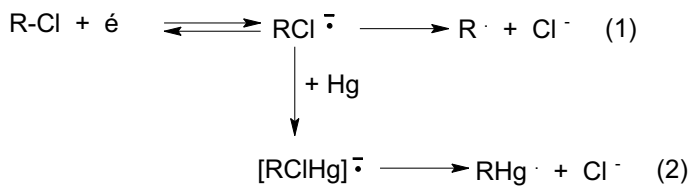

Fig. 6 – Reduction scheme of clotrimazole on mercury electrode.

TABLE I

Analysis of miconazole in pharmaceutical formulations by voltammetric method.

Samples	Label concentration (mol L^{-1})	Concentration found by the proposed method (mol L^{-1})	Comparison (%)±SD
Daktarin	2.0×10^{-7}	2.0×10^{-7}	100 ± 0.002
Daktarin	4.0×10^{-7}	4.0×10^{-7}	100 ± 0.002
Daktarin	1.0×10^{-6}	9.9×10^{-7}	99.1 ± 0.008
Vodol	6.0×10^{-7}	5.9×10^{-7}	98.6 ± 0.004
Vodol	8.0×10^{-7}	7.9×10^{-7}	98.4 ± 0.002
Vodol	1.0×10^{-6}	9.8×10^{-6}	98.1 ± 0.001

TABLE II

Analysis of miconazole in pharmaceutical formulations by spectrophotometric method (Cavrini et al. 1981).

Samples	Label concentration (mol L^{-1})	Concentration found by the official method (mol L^{-1})	Comparison (%)±SD
Daktarin	1.3×10^{-5}	1.3×10^{-5}	100 ± 0.002
Vodol	1.3×10^{-5}	1.2×10^{-5}	99.0 ± 0.003

L^{-1} de miconazol em tampão B-R pH 8,0 e um limite de detecção de $1,7 \times 10^{-8}$ mol L^{-1} foi determinado usando 60 s de tempo de deposição e velocidade de varredura de 100 mV s^{-1}. O método proposto é simples, preciso e foi aplicado com sucesso para a determinação de miconazol na forma pura e em formulações comerciais, mostrando médias de recuperação de $99,7 - 98,4\%$.

Palavras-chave: miconazol, voltametria, eletroanálise, determinação.

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