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Voltammetric behaviour of nifedipine

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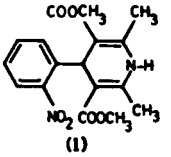
The electrochemical reduction behaviour of nifedipine has been studied by employing advanced electrochemical techniques in different supporting electrolytes. Analytical estimation of nifedipine in pharmaceutical formulations and in presence of some nitroimidazoles, employing differential pulse polarography is also discussed.

Nifedipine (I) [1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridine dicarboxilic acid dimethyl ester] is an active agent against coronary vascular resistance and increases coronary blood flow[1,2]. Nifedipine is a more potent vasodilator *in vivo* and *in vitro* than any other calcium channel blocker[3].



(I)

Polarography has been widely used to study the reduction mechanism of such compounds in order to understand the biological degradation of these nitro derivatives. These compounds are generally metabolised *in vivo* to the corresponding amines through nitroso and hydroxylamine intermediates. Nifedipine has been determined in different formulations by several workers[4-6] using different techniques. In the present investigation, the electrochemical techniques like DC polarography, cyclic voltammetry, chronoamperometry and chronopotentiometry have been used to elucidate the reduction mechanism and to work out analytical procedure for its estimation.

Materials and Methods

Nifedipine was supplied by Torrent Laboratories Pvt. Ltd., Ahmedabad. The purity of the sample was tested by thin layer chromatography and also by melting point determination. Other chemicals used were of AR grade. Polarographic assays were performed using a polarographic analyser Model 364. A dropping mercury electrode of flow rate 2.48055 mg/s was used as the working electrode and a saturated calomel electrode (SCE) as the reference electrode. Cyclic voltammetric, chronoamperometric and differential pulse polarographic experiments were carried out with a VA-Scanner 612. Hanging mercury drop electrode (HMDE) of area 0.04439 cm^2 and dropping mercury electrode of area 2.0323 cm^2 were employed as working electrodes and Ag/AgCl(s), Cl^- as the reference electrode. Chronopotentiograms were obtained by using a Beckman Electroscan-30 instrument; HMDE of area 0.0253 cm^2 and a molybdenum electrode were used as working and reference electrodes respectively. In all the cases platinum wire was used as an auxiliary electrode. All the experiments were carried out at $25 \pm 1°C$.

Nifedipine (173 mg) was dissolved in the minimum quantity of acetone and it was accurately diluted to 50 ml by adding acetone. From this stock solution, 1 ml was pipetted out into a 10 ml standard flask and to this was added 1 ml acetone and the solution diluted with the supporting electrolyte. The solution was deoxygenated by passing nitrogen gas for five minutes and then the polarogram was recorded. For the analysis of the sample in the form of tablets, about 100 mg or a complete tablet of fine powdered sample was dissolved in 250 ml of acetone by repeated extractions. Supporting electrolyte was used to prepare various desired concentrations of nifedipine solution from the standard solution prepared.

Results and Discussion

Under the experimental conditions described above, the electrochemical reduction of nifedipine (I) was found to depend on the *p*H of the supporting electrolyte. Only one cathodic wave/peak [0.71V vs SCE and 0.74V vs Ag/AgCl(s),Cl^- in phosphate buffer of *p*H 8.00] was obtained for the reduction of nitro group in nifedipine over the *p*H range studied in all the techniques employed except in Bates and Bower buffer of *p*H 12.50 where two waves/peaks were observed (Fig. 1). The waveheight (i_d) and peak height (i_p) were depend-

ent on mercury column height (h) and sweep rate (v) respectively and also on the *p*H of the supporting electrolyte. Half-wave potentials and peak potentials were found to be shifted towards more negative side with increase in *p*H. Addition of methanol, ethanol, DMF and actone was found to shift the half-wave potentials and peak potentials to more negative values. These were also found to be shifted towards more negative values with increase in solvent (acetone) concentration because of lower protonation, increase in viscosity of the medium and due to the possible adsorption of solvent molecules. $E_{1/2}$ and E_p values were found to be shifted towards more negative potentials with concentration which is quite understandable.

The linear plots of i_d vs $h^{1/2}$ and i_p vs $v^{1/2}$ passing through the origin, indicate the electrode process to be mainly diffusion-controlled and free from adsorption complications in all the supporting electrolytes except at *p*H 4.00. The plots of $i\tau^{1/2}$ vs i in chronopotentiometry also confirmed this. The dependence of half-wave potential on concentration and the absence of anodic peak in the reverse scan for C_1 (Fig. 1) in cyclic voltammetry as well as disobedience of Tomes' criterion confirm the electrode process to be irreversible. The change in the colour of the depolarizer solution from light yellow to dark yellow at higher *p*H was due to the formation of anions of nitro group[7,8].

Millicoulometry was employed in Clarks and Lubs buffer (*p*H 2.00), acetate buffer (*p*H 4.00) and in Bates and Bower buffer (*p*H 12.50) to find out the number of electrons in the electrode process. The results showed the number of electrons involved in the electrode process as six, four and four respectively. The products of controlled potential electrolysis (carried out at -1.0V, -1.3V and -1.7V vs SCE) in the above mentioned supporting electrolytes were indentified as amine and hydroxylamine[9]. This was also confirmed through UV spectra recorded before and after the controlled potential electrolysis[10]. The number of

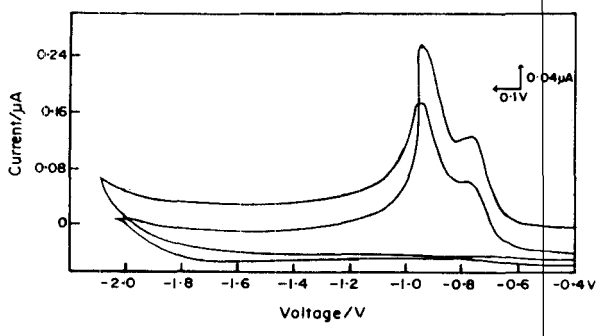


Fig. 1—Typical cyclic voltammogram of nifedipine in Bates and bower buffer of *p*H 12.50 [concentration : 0.5 m*M*, sweep rate : 80m V s^{-1}, solvent : 20% acetone].

protons involved in the rate determining step was evaluated to be one in the *p*H range 4.00-10.00.

A small anodic peak (a_1) was observed in the reverse scan in cyclic voltammetry in the *p*H range $2.00 < pH < 10.00$. In the second scan, another small cathodic peak (C_2) was observed at more positive potential than C_1. The anodic peak may be due to the imine or nitroso and the peak C_2 may be due to the reduction of oxidised imine or nitroso to hydroxylamine again. In Bates and Bower buffer of *p*H 12.50, two peaks were observed at peak potentials -0.73V and -0.95V vs Ag/AgCl(s),Cl^-. No other anodic or cathodic peaks were obtained even in subsequent sweeps indicating that the oxidation of hydroxylamine does not occur in the reverse scan in this medium.

On the basis of the above results of the present investigations as well as the literature data, the following Schemes I, II and III may be proposed for the electrochemical reduction of nifedipine in different ranges of *p*H:

(*I*) *In acid media, i.e.,* *p*H 2.00

The nitro group of nifedipine is reduced probably in a $6e^-$, $6H^+$ step to amino group.

(*II*) *In the range* $4.00 < pH < 10.00$

Nifedipine is reduced to the corresponding hydroxylamine in a four-electron single step reduction. The formed hydroxylamine cannot undergo imine intermediate rearrangement because of reduced availability of protons[11].

(*III*) *In Bates and Bower buffer, i.e.,* *p*H 12.50

Nifedipine is reduced in a two-step two-electron reduction leading to the formation of corresponding hydroxylamine. In DC polarography the second wave was found to merge with that due to hydrogen evolution. The first wave/peak has been attributed to the corresponding two-electron reduction to $R-NO_2^{2-}$. The second wave/peak observed with two-electron addition may probably be due to further reduction of $R-NO_2^{2-}$ to the corresponding hydroxylamine[12].

The analytical method is based on the results obtained and uses differential pulse polarography at DME. The polarograms were recorded over the applied potential -0.1V to -1.0V (pulse amplitude : 50 mV, drop time: 2 sec). The concentration range studied was 0.5×10^{-3} *M* to 0.5×10^{-7} *M* for pure samples. Pharmaceutical samples could be estimated down to 0.5×10^{-6}*M* concentrations. Weak adsorption complications involved in acetate buffer of *p*H 4.00, presence of second wave/peak in Bates and Bower buffer of *p*H 12:50 and comparatively ill-defined wave/peak obtained in Clarks and Lubs buffer of *p*H

2.00 suggested that neutral media be used for the estimation of nifedipine where satisfactory results were obtained. The lower detection limit was found to be 0.2×10^{-7} *M*. Estimation of nifedipine in different pharmaceutical formulations and in presence of nitroimidazoles was possible using differential pulse polarography. The relative standard deviations were found to be less than 2%. The correlation coefficient was found to be 0.9931 (from 20 replications). The reduction potentials of nitroimidazoles were found to be widely different from those of nifedipine which makes simultaneous determination possible.

Acknowledgement

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