ELECTROCHEMICAL BEHAVIOUR OF NIFEDIPINE AND NITRENDIPINE IN CHLOROFORM AND CHLOROFORM-ISOPROPANOL MIXTURE☆

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ABSTRACT: *The electrochemical behaviour of nifedipine (I), nitrendipine(II) and their photodegradation products has been studied by employing electrochemical techniques in chloroform and in 1:4 mixture of chloroform-isopropanol using piperidinium perchlorate (PPC) as supporting electrolyte. It has been shown that I and II undergo in a 4e, $4H^+$ irreversible reduction reaction, while the reduction product, phenylhydroxylamine, is oxidized in a 2e, $2H^+$ reversible process to an unstable nitrosophenyl compound. Photodegradation of I and II by sunlight produces a nitrosophenyl derivative which is reversibly reduced to the corresponding unstable phenylhydroxylamine. No significant change is observed in electrochemical properties of drugs by passing from chloroform to chloroform-isopropanol mixture. The possibility of analysis of I and II by dp polarography is also verified.*

KEY WORDS: *Nifedipine, Nitrendipine, Chloroform, Polarography, Cyclic voltammetry.*

INTRODUCTION

Nifedipine or dimethyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridine-carboxylate (Scheme 1) is a well known drug used as a calcium slow channel blocker in the treatment of cardio-vascular diseases [1]. It is also reported to act by reducing cardiac work and myocardial oxygen demand, and by reducing peripheral resistance and heart load [2]. Nitrendipine or ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridine-carboxylate (Scheme 1) is also reported as an antihypertensive agent [3], but is not introduced in U.S. Pharmacopoeia till 1995.

The presence of a nitro group in the structure of these compounds gives rise to important electronic and pharmacodynamic characteristics [4]. Several

☆ *Dedicated to Professor Abbas Shafiee on the occasion of his 60th birthday.*

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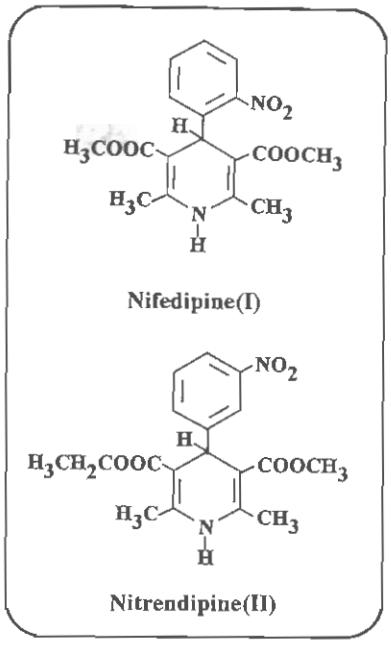


Scheme 1

authors have studied the electrochemical properties of nifedipine and nitrendipine in order to elucidate the reduction mechanism [5,8] or to develop a sensitive electroanalytical method for its quantitation [7,11]. The solvents used in these investigations were always the mixtures of water and an organic liquid such as ethanol or acetone because of the insolubility of nifedipine and nitrendipine in water. However, chloroform, known as one of the best solvents of nifedipine [2], has not been used in such studies. We have previously reported that chloroform or a 4:1 mixture of chloroform-isopropanol are the prefered solvents for extraction of some drugs including 1,4-dihydropyridine calcium antagonists from pharmaceutical preparations and are the valuable media for their electrochemical studies [12,16].

In this paper, we will describe the electrochemical behaviour of nifedipine, nitrendipine and their photodegradation products in chloroform and in a 4:1 mixture of chloroform-isopropanol using different techniques like dc and dp polarography, cyclic voltammetry and controlled potential coulometry with the objective of clarifying the reduction mechanism of drugs and to reveal the possibility of their electroanalytical determinations in these media.

EXPERIMENTAL

Reagents and Chemicals

Sample of nifedipine was provided from Anonyma Materie Syntetiche Afini S.P.A. (Italy) and was used as received. Nitrendipine was synthesized and purified as described before [17]. The stock solutions were prepared by dissolving the necessary amount of drugs in 100 mL absolute ethanol in a volumetric flask to obtain a 0.010 M solution. Other diluted solutions were prepared by diluting the stock one just before use. All solutions were kept and assayed in darkness to avoid the photodegradation of solute. The solvents used in electrochemical investigations were chloroform or a 4:1 mixture of chloroform-isopropanol, both pro-analysis grade from E.Merck. These solvents were used without further purification. Piperidinium perchlorate (PPC), was prepared by published procedure [15] and used as supporting electrolyte. In the case of pure chloroform, piperidine(P) is added to increase the solubility of PPC.

Instrumentation

A Polarecord 626+663 VA Stand, from Metrohm (Switzerland), was used to plot dc, ac and dp polarograms. A function generator from Metrohm, (VA Scanner E 612), connected to polarecord 626 as potentiostat was used for cyclic voltammetry and voltammograms were recorded by an X-Y Hewlett-Packard 3310A recorder. All experiments were carried out in a water-jacketed cell from Metrohm at a thermostated temperature of 15±0.1°C and covered by black covering sheet to avoid the photochemical transformation of drug to the corresponding nitrosophenylpyridine derivatives [18]. Controlled potential coulometry was achieved in a pool mercury electrode using an EG & G model 176 PAR galvanostat. The reference/potentiostat- AgI in electrode was Ag 0.05M tetrabutylammonium iodide + 0.50M tetrabutylammonium perchlorate solution in chloroform. Dissolved oxygen was removed from the solution by bubling 99.999% nitrogen through the cell for at least 20 minutes. The evaporation of solutions during the experiments was avoided by passing the nitrogen through a gas-washing vessel located before the cell and containing the solvent used in the experiment.

RESULTS AND DISCUSSION

Electrochemical behaviour of nifedipine in pure chloroform

a) Polarography

Dc tast polarography of a 5×10^{-4}M solution of nifedipine in chloroform and in the presence of 0.5 M PPC+0.15M P as supporting electrolyte exhibits a well shaped reduction wave (Fig. 1A). The plot of $\log[(i_d - i)/i]$ against E_{dme} gives a straight line with a slope of 0.084 V. Considering the number of transferred electrons, (4e per molecule, see coulometry), it can simply be cocluded that the electrode reaction is totally irreversible with an estimated value of 0.64 for $\alpha\, n_\alpha$ [19]:

$$\alpha\, n_\alpha = 0.0542/\text{slope} = 0.542/0.084 \simeq 0.64$$

where, α and n_α are the transfer coefficient and the number of electrons involved in the rate determining step of overal reaction respectively. As the value of n_α must obviously be integral, and in the most cases it is most probably 1[19], so a value of 0.64 can be suggested for α . The use of Tomes criterion reported for a totally irreversible cathodic wave [20] yields similar results:

$$E_{3/4} - E_{1/4} = 0.0517/\alpha\, n_\alpha$$

The calculated value of $E_{3/4}$-$E_{1/4}$ is 0.080 V from polarogram shown in Fig. 1A, hence $\alpha\, n_\alpha$ becomes 0.64. In this conditions, ac polarography shows no signal because of total irreversibility of electrode process [21]. However, differential pulse (dp) polarography exhibits a well shaped peak (Fig. 1B). The electrode process corresponds to the irreversible reduction of nitrobenzene ring incorporated in the nifedipine structure and thus can be treated as totally irreversible electrode reaction [20]. The irreversible reduction of nitrobenzene in aqueous solutions is attributed mainly to a series of protonations and electron transfers following the first electron addition[22]. Admitting the validity of this approach in chloroform, it seems plausible to assume that in our case (in the presence of sufficient quantity of PPC as proton donor), the irreversibility observed arises from electron transfer than the protonations and the overal rate of reduction process is ultimately determined by a one electron step. In such conditions, the

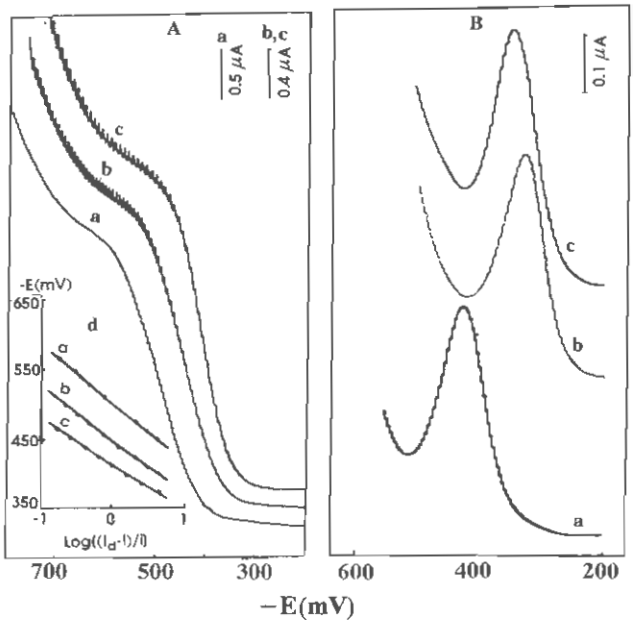


Fig. 1: A-dc tast(a) and dc(b and c) polarograms of a 5×10^{-4}M solution of a) nifedipine in chloroform, b) nifedipine in a 4:1 mixture of chloroform-isopropanol, and c) nitrendipine in chloroform. Supporting electrolyte: 0.50M PPC+0.15 M P for a and c, 0.25M PPC for b. d) E-log[(i_d-i)/i] plots for a, b and c. B-dp polarograms of a 10^{-5}M solution of a) nifedipine in chloroform, b) nitrendipine in chloroform, c) nitrendipine in a 4:1 mixture of chloroform-isopropanol. Supporting electrolyte: 0.50M PPC+ 0.15M P for a and b., 0.25M PPC for c. t_{drop}= 2s., ΔE=-50mV.

general kinetic treatment of totally irreversible reactions can be used for estimation of $\alpha\, n_\alpha$ by means of the following equation:

$$\lambda = K^{*}(\tau/D)^{1/2} \cdot \exp[(-\alpha\, n_\alpha F/RT)(E-E^{*\prime})]$$

$$\log\lambda = \log K^{*}(\tau/D)^{1/2} + (\alpha\, n_\alpha F/2.303RT)E^{*\prime} -$$

$$(\alpha\, n_\alpha\, F/2.303RT)E$$

where $\lambda = K_f(\tau/D)^{1/2}$ and is easily obtained by referring the $i/i_d = F_1(\lambda)$ values on the $F_1(\lambda)$ versus $\log\lambda$ working curve in reference [20]. i/i_d parameters are measured at some potentials on the rising portion of a sampled current (tast) polarogram. A plot of $\log\lambda$ against E gives a straight line which the slope allows the estimation of $\alpha\, n_\alpha$. A linear plot indicates that only one rate determining step can be considered.

Table 1: Polarographic and voltammetric data of nifedipine and nitrendipine

Solvent	Substrate	Polarographic data							Voltammetric data[c]			
		dc						dp				
		$E_{1/2}$[d]	$E_{3/4}-E_{1/4}$	dE/dlog[(i_d-i)/i]	αn_α	α	n_α	E_p	$E_{p(C_1)}$	$E_{p(C_2)}$	$E_{p(A_2)}$	ΔE_p
Chloroform[a]	Nifedipine	-499	84	84	0.64	0.64	1	-420	-542	+14	+170	156
	Nitrendipine	-416	64	66	0.83	0.83	1	-338	-484	+63	+142	79
Chloroform-isopropanol[b] (4:1)	Nifedipine	-456	84	84	0.64	0.64	1	-412	-639	-52*	+315	367
	Nitrendipine	-438	86	85	0.64	0.64	1	-347	-544	-24*	+308	332

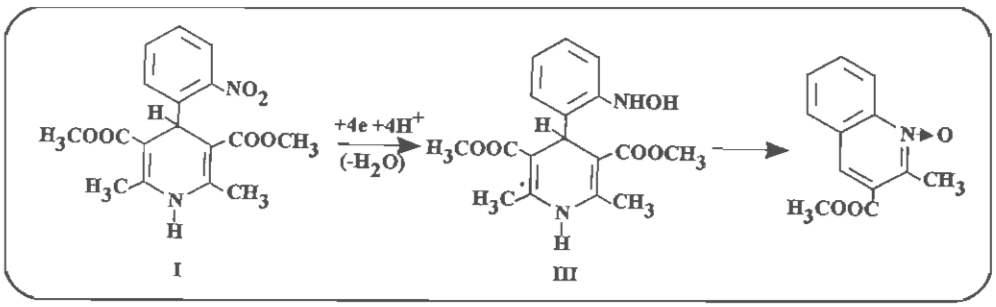
Supporting electrolyte: a) 0.50M PPC + 0.15M P, b) 0.25M PPC. c) Data obtained for v= 100mVs^{-1}, d) The potentials are in mV/ref
** Data corrected for 100mVs^{-1}*

The analysis of polarogram(a) shown in Fig. 1A by this method gives a value of 0.60 for αn_α which is in agreement with the 0.64 value. The polarographic data were collected in Table 1.

b) Cyclic voltammetry

Cyclic voltammetry of nifedipine in pure chloroform and in the presence of 0.5M PPC + 0.15M P was carried out in the potentials ranging from +0.300 to −0.700 V/ref. By sweeping the potential in cathodic direction and at low scan rates, a well shaped cathodic peak, C_1, appears; whereas, in the reverse scan, a small anodic peak, A_2, is seen at positive potentials (Fig. 2A). When the range of sweeping potential is limited between +0.300 to −0.300V/ref., the anodic peak A_2 is not observed. Thus, it can be concluded that this peak arises from the reduction product of nifedipine. On the other hand by increasing the scan rates the general aspect of the cyclic voltammograms remains unchanged and the $I_{p.(A_2)}/I_{p.(C_1)}$ ratio also slightly increases; reaching a fixed value of 0.5 for v>600 mVs^{-1} (Fig. 3a). This suggestes that the number of electrons involved in C_1 peak process is double of those transferred in A_2 peak reaction and the later one cannot be considered as the counterpart of C_1 peak. Thus, it can be accepted that nifedipine is reduced within an irreversible process. Moreover, the plot of current function, $(I_p/v^{1/2})$, as a function of scan rate (v) for peak C_1 shows that it decreases slowly at first and then remains constant (Fig. 3b). In addition, C_1 peak potential is shifted by about $30/\alpha n_\alpha = 47$ mV in the negative direction for a tenfold increase in v [23]. These results promote us to propose an E_iC_i mechanism for the reduction of nifedipine in chloroform and to write the electrode process as follows considering the previously reported results in protic medium [6] (Scheme 2).

On the other hand, when the potential is sweeped in the positive direction from −0.700 to +0.300V/ref., only the anodic A_2 peak appears at all scan rates,



Scheme 2

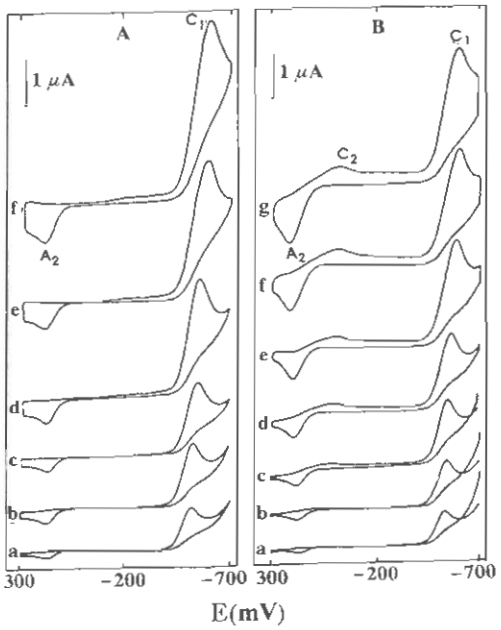


Fig. 2: Cyclic voltammograms of nifedipine ($5\times10M^{-4}$) in chloroform at scan rates: a) 20, b) 50, c) 100, d) 200, e) 400, f) 600 and g) 800 mVs^{-1}. Forward scan: A) from +300 to -700 mV/ref. in cathodic direction, B) from -700 to +300 mV in anodic direction. Supporting electrolyte: 0.50M PPC + 0.15M P.

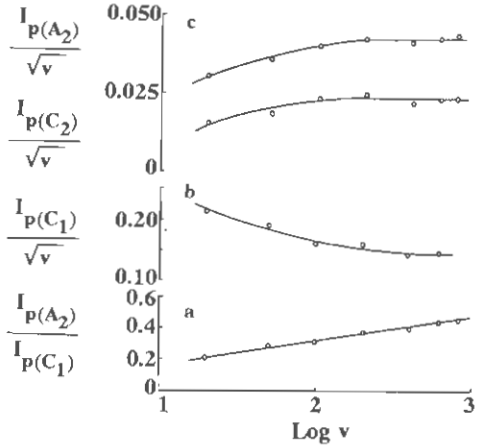
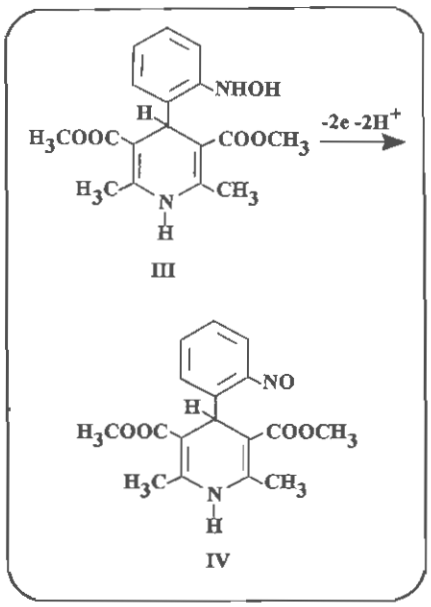


Fig. 3: a) plot of $I_{p(A_2)}/I_{p(C_1)}$ versus log v for cyclic voltammograms shown in Fig. 2B, b) plot of $I_{p(c_1)}/V^{1/2}$ versus log v for cyclic voltammograms shown in Fig. 2A, c) plot of $I_{p(A_2)}/v^{1/2}$ and $I_{p(C_2)}/v^{1/2}$ versus log v for cyclic voltammograms shown in 2B.

whilst at the reverse scan, in addition to the cathodic C_1 peak the cathodic counterpart of A_2 peak, i.e. C_2 peak, is also observed; the height of which increases significantly with increasing v (Fig. 2B). The variation of current functions as a function of v for A_2 and C_2 peaks are also represented in Fig. 3. From this figure, it can be seen that for these two peaks, the current functions increase slightly at first and then become independent of v. Finally, a value of 0.5 for peak current ratio ($I_{p(A_2)}/I_{p(C_1)}$) in high scan rates indicates that the A_2 peak arises from a 2e process. Hence, the electrode processes due to the A_2 and C_2 peaks can be presented as Scheme 3 according to the previously reported results [6].



Scheme 3

The product **IV** is unstable in the presence of proton donors because of its participation in an rearrangement process and converting to the electroinactive products [24]. Table 1 contains the data derived from cyclic voltammetry.

c) Cyclic voltammetry of nifedipine after exposure to the sunlight

It has been reported that nifedipine is converted into 4′-(2′-nitrosophenyl) pyridine homologue under visible light [25]. In order to investigate the effect of photodegradation of nifedipine, a 5×10^{-4}M solution of drug in chloroform was exposed to sunlight for 6 hours and then cyclic voltammetry was performed as above. The resulting voltammogram illustrated in Fig. 4 shows a nearly complete elimination of C_1 peak and the appearance of one cathodic and corresponding anodic peak at potentials very close to those

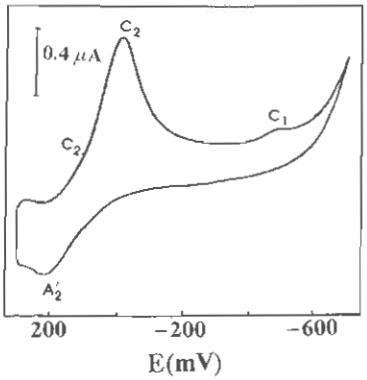


Fig. 4: Cyclic voltammogram of a 5×10^{-4} M solution of nifedipine in chloroform after exposure to sunlight for 6 hours. Supporting electrolyte: 0.50M PPC+0.15M P. Scan rate: 400 mVs^{-1}.

of C_2 and A_2 peaks. Cyclic voltammetry at various scan rates exhibits further informations about the electrode process. The current function for peak C'_2 decreases slightly by increasing the sweeping rate, while the peak current ratio ($I_{p(A'_2)}/I_{p(C'_2)}$) increases with increasing the scan rate. A decrease at the beginning of peak current ratio curve may be due to the effect of an internal transformation of **V** to **III**. A small shoulder observed in the beginning of peak C'_2 may also be corresponds to the reduction of a minor quantity of **III** produced from **V**. Assuming the quasi-reversibility of electrode process (since $\Delta E_p = E_{p.c} - E_{p.a} = 156$ mV$>59/n \simeq 30$ mV.), $E_{p.c}$ shifts also negatively with increasing v by about $30/\alpha n$ mV. for a tenfold increase in v. These criteria promote us to propose an E_qC_i mechanism for electrode process, which is illustrated by Scheme 4 according to previous observations [6].

d) Controlled potential coulometry of nifedipine in chloroform

Controlled potential coulometry of nifedipine was implemented in chloroform containing a known quantity of drug and 0.5 M PPC. The potential of a pool mercury electrode used as cathode was fixed at −550 mV/ref. The cyclic voltammograms recorded at different stages of operation are shown in Fig. 5. The number of transferred electrons was found 4e per molecule of nifedipine.

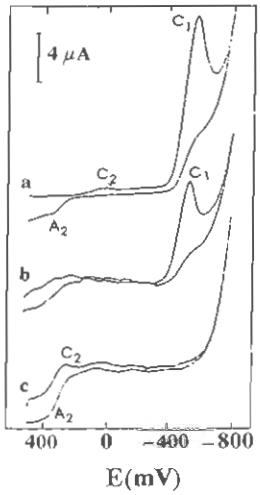


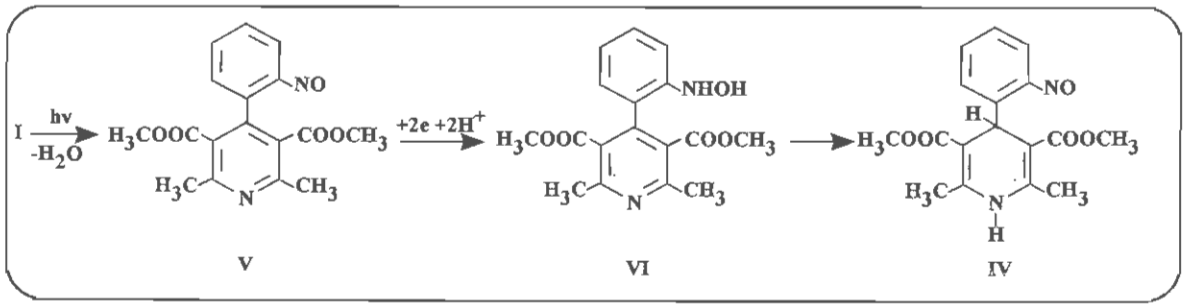
Fig. 5: Cyclic voltammograms obtained at the a) beginning, b) midway and c) end of coulometry of 0.44 mmole nifedipine in chloroform. Supporting electrolyte: 0.50M PPC + 0.15M P. Scan rate: 100mVs^{-1}

Electrochemical behaviour of nitrendipine in chloroform

Dc, ac and dp polarography of nitrendipine in pure chloroform and in the presence of 0.5M PPC + 0.15M P as supporting electrolyte exhibits the results similar to that of nifedipine (Fig. 1A and B). The mere difference corresponds to the fact that nitrendipine is reduced at less negative potentials and shows a lesser irreversibility than the nifedipine. Cyclic voltammetry of nitrendipine in pure chloroform produces the voltammograms shown in Fig. 6. The voltammetric results are also in accordance with those of polarography and confirm the more reactivity of nitrendipine in comparison with nifedipine (see Table 1). This might be attributed to the effect of nitro group position on benzene ring [10].

Electrochemical properties of nifedipine and nitrendipine in a 4:1 mixture of chloroform-isopropanol

The need for use of a 4:1 mixture of chloroform-isopropanol as solvent has already been discussed [12]. Indeed, the extraction of drugs from biological media (serum, plasma, whole blood and urine) requires the use of a protein denaturing agent such as isopropanol. Moreover, the electrochemical studies in such



Scheme 4

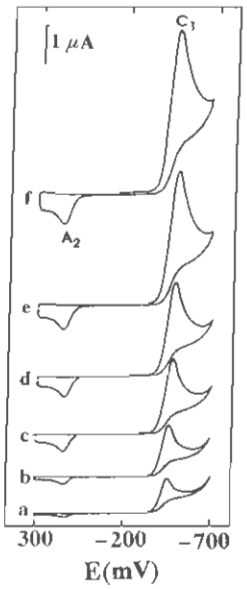


Fig. 6: Cyclic voltammograms of nitrendipine ($5\times10^{-4}M$) in chloroform at scan rates: a) 20, b) 50, c) 100, d) 200, e) 400, and f) 600 mVs^{-1}. Initial potential: +300mV/ref., switching potential: -700mV/ref. Supporting electrolyte: 0.50M PPC + 0.15M P.

a solvent mixture will be allowed to develop the electroanalytical methods for drug assay in biological samples. The polarographic and voltammetric data obtained for nifedipine and nitrendipine in the above mixture and in the presence of 0.25M PPC as supporting electrolyte are collected in Table 1. The comparison of polarographic data indicates that by passing from chloroform to chloroform-isopropanol mixture, the reduction of drugs shift towards more negative potentials without any significant change in the reversibility of the process. However, cyclic voltammetric data show a noteworthy change in the reversibility of nitrosophenyl to phenylhydroxylamine system (C_2/A_2 peak) which is manifested by an increase in ΔE_p .

The increase in the irreversibility of the electrode processes is probably provided from the reduced time window of cyclic voltammetry towards polarography. Figs. 1 and 8 show the polarograms and cyclic voltammograms obtained for nifedipine and nitrendipine in chloroform-isopropanol mixture respectively.

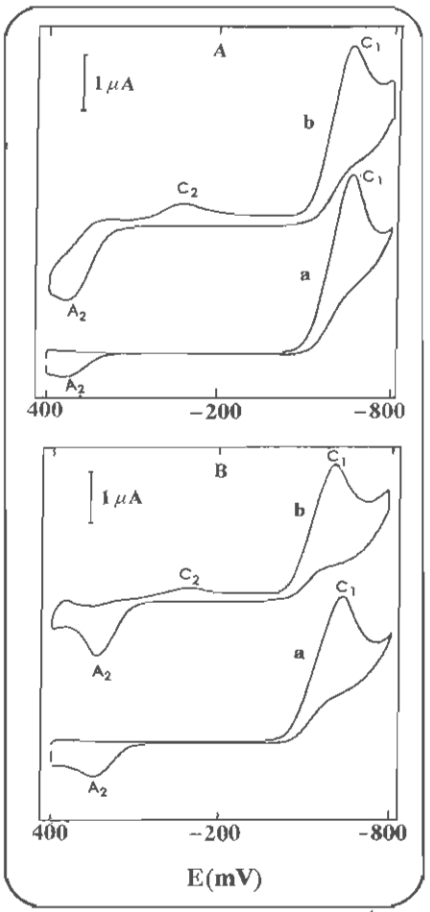


Fig. 7: Cyclic voltammograms of a $5\times10M^{-4}$ solution of A) nifedipine, B) nitrendipine in a 4:1 mixture of chloroform-isopropanol. Sweeping from a) +400mV/ref. in cathodic direction, b) -800mV/ref. in anodic direction. Scan rate: 400mVs^{-1}. Supporting electrolyte: 0.25M PPC.

Analytical aspect

The above studies indicate that nifedipine and nitrendipine are reduced in both chloroform and chloroform-isopropanol media within a 4e, $4H^+$ processes. Differential pulse polarography exhibits the well shaped peaks for both compounds and in both solvents (Fig. 1). The peaks currents are diffusion controlled and vary linearly with concentrations. Moreover, the extraction of drugs from pharmaceutical preparations (capsule and tablet) by chloroform or from spiked biological fluids by a 4:1 mixture of chloroform-isopropanol is carried out with a good yield (>99%) [26]. Hence, a method based on dp polarography can be developed for quantitation of these drugs in biological samples.

CONCLUSION

Investigation of electrochemical properties of nifedipine and nitrendipine in chloroform and chloroform-isopropanol mixture provides valuable informations about the mechanism of electrode reactions. On the base of these results, it is found that the processes are approximately similar to those in the protic media if PPC is used as supporting electrolyte. Moreover, it is possible to develop various electroanalytical methods such as linear sweep voltammetry (L.S.V.) and polarography (dc and dp) for the analysis of drugs and their photodegradation products in pharmaceutical and biological samples.

Received, 24th December 1996; Accepted, 27th October 1997

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