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ELECTROCHEMICAL BEHAVIOR OF MANIDIPINE AND ITS VOLTAMMETRIC DETERMINATION IN PHARMACEUTICAL FORMULATIONS

E. Sarala, V. Krishna Reddy, K. Madhusudhana Reddy, L. Kiran Babu, R. Chenna Krishna Reddy and Y. V. Rami Reddy *

Electroanalytical Laboratory, Department of Chemistry, Sri Venkateswara University, Tirupati - 517502, A.P., India

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Correspondence to Author:
Dr. Y.V. Rami Reddy

Professor of Chemistry,
Department of Chemistry,
Sri Venkateswara University,
Tirupati-517502, Andhra Pradesh, India.

E-mail:dryvrsvu@gmail.com

ABSTRACT: The electrochemical behavior of Manidipine is studied by employing cyclic voltammetry (CV) and Differential Pulse Polaro graphy (DPP) in universal buffers of PH ranging from 2.0 to 12.0. The kinetic parameters, such as transfer co-efficient, diffusion co-efficient, and heterogeneous forward rate constant values are evaluated by employing these techniques. Differential Pulse Polarography is employed for the estimation of Manidipine in selected pharmaceutical formulations.

INTRODUCTION: Manidipine is a calcium channel blocker (dihydropyridine type) that is used clinically as an antihypertensive [1-5]. Manidipine Dihydrochloride is used for antihypertension. It is chemically 1,4-dihyddro-2,6-dimethyl-4 (3-nitrophenyl)-3, 5-pyridine dicarboxylic acid 2-[4-(diphenyl methyl)]-1- Piperazinyl ethyl methyl ester hydrochloride [6]. A literature survey revealed a spectrophotometric [7] and few High Performance Thin Layer Chromatographic Method (HPLTC) for Manidipine Dihydrochloride determination in human biological fluids [8, 9]. However no high performance liquid chromatographic methods were found for Manidipine determination in bulk drug and formulations as a stability indicating assay method.

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The International Conference on Harmonization (ICH) guideline entitled "Stability testing of new drug substances and products" requires testing to be conducted to assess the inherent stability of the active substances and products" [10]. Test of susceptibility to oxidation, hydrolysis and photolytic degradation are required. An ideal stability indicating method is one that quantifies the drug and resolves its degradation products [11]. HPLC is becoming a routine analytical technique because of advantages [12-15] which includes the small amount of mobile phase required, the speed of the method and the possibility of analysis of several samples simultaneously unlike HPLC. It thus reduces analysis time and cost per analysis.

Very little attention has been paid on the polarographic determination of Manidipine. The purpose of this work is to establish the experimental conditions of the electrochemical behavior of Manidipine by D.C. Polarography, Cyclic Voltammetry, Differential Pulse Polarography (DPP) and the Determination of

Manidipine in Pharmaceutical Formulations by DPP.

MATERIALS AND METHODS:

Apparatus and conditions:

D.C. Polarography, Differential Pulse Polarography and Cyclic Voltammetric measurements were performed with Metrohm757 VA Computrace controlled by computer running electrochemical analysis. The experimentation includes three electrode assemblies Consists of Dropping Mercury Electrode (DME) and Hanging Mercury Drop Electrode (HMDE) as working electrodes, a saturated Ag/Agcl/ chloride reference electrode and a glassy carbon auxiliary electrode. pH measurements were carried out with Digital pH meter with ATC Probe (Hanna). All the measurements were made at room temperature.

Reagents and Solutions:

Universal buffers of pH 2.0 to 12.0 were prepared by using 0.2 M boric acid, 0.05 M citric acid and 0.1 M tri sodium orthophosphate. All the chemicals used were of analargrade and pure Manidipine was obtained from sigma Aldrich (India) and was used without further purification. A stock solution ($2X10^{-5}$M) of Manidipine was prepared in Dimethyl Formamide (DMF).

Procedure for studying the polarographic behavior:

A 0.5 ml volume of the stock solution of Manidipine was placed in the Polarographic cell and 9.5 ml of the appropriate buffer solution of selected pH was added and the solution was purged with oxygen free nitrogen for 10 min prior to each run.

Preparation of calibration graphs:

A stock solution of Manidipine ($2x10^{-5}$ M) was prepared in DMF and solutions containing various concentrations of the title compound in the range 10^{-3} - 10^{-8} M were obtained by dilution of the stock solution with the appropriate buffer of selected pH. The Polarograms of the final sample solutions were obtained after deaeration for 20 min. Graphs of measured diffution current were plotted against Manidipine concentrations. The lower detection limit (dl) was calculated using the following equation.

$$dl = 3\ Sd/m$$

Where Sd = Standard Deviation and
m= Slope of the Calibration plot

Analysis of pharmaceutical dosage forms:

Manidipine was available in tablet dosage forms. The tablet contains 20 mg of the drug. Ten tablets were weighed finally powdered and the average mass per tablet was determined. A portion of the finally ground sample equivalent to 25-30 mg of accurately weighed and transferred into a 100 ml calibrated flask containing 70 ml of DMF. The Contents of the flask were agitated for at least 15 min using a magnetic stirrer and then diluted to the mark with DMF. The solution was next filtered through a fine pure filter paper, discarding the first 20 ml of the filtrate.

A 5 ml aliquot of the clear filtrate was pipetted into a 50 ml calibrated flask and the solution again diluted to the mark with the respective buffer of selected pH.

A 10 ml volume of this solution was injected into a polarographic cell and polarograms were recorded after complete deaeration for 10 minutes at DME versus SCE.

After obtaining the polarograms, 1.0 ml of the standard solution ($2X10^{-5}$ M), of Manidipine was added to the cell, deaerated for 10 minutes and again polarograms were recorded under the same conditions. The wave heights H and h were measured are the mass of Manidipine per tablet was calculated using the following equation. Mass of

$$\text{Manidipine per tablet (mg)} = \frac{ahb \times 1000}{(1.10H - h)w}$$

Where a is the mass of Manidipine reference standard in 100 ml of standard solution (mg): b is the average mass of a tablet (g): w is the mass of sample (mg) taken for the polarographic determination: h is the wave height of Manidipine (µA) before standard additions, H is the wave height of Manidipine (µA) after standard additions. And 1.10 is the dilution factor.

RESULTS AND DISCUSSION:

Characterization of Wave/Peak:

Manidipine exhibits only one polarogrpahic wave/Peak throughout the pH range 2.0-12.0 in all the techniques the wave/peak is due to the reduction of nitro group to hydroxyl amine with four electron addition. Typical D.C. Polarogram is shown in **Fig. 1**.

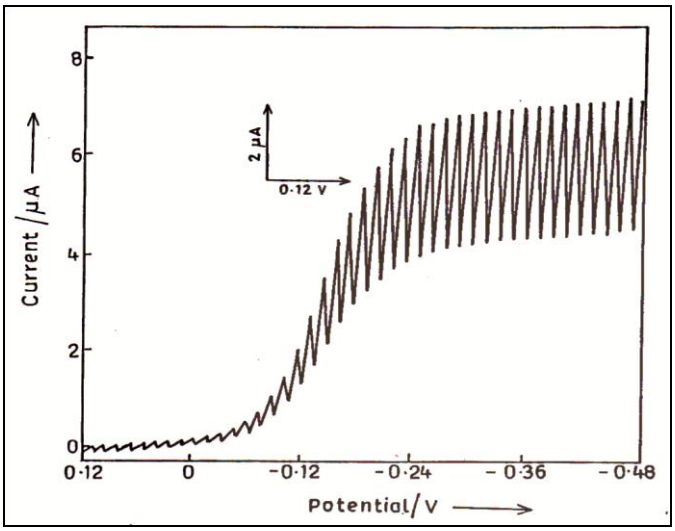

FIG.1: TYPICAL D.C. POLAROGRAM OF MANIDIPINE IN pH 2.0 CONCENTRATION = 2X10^{-5}M; DROP TIME =3 SEC

Experimental results show the well defined wave/peak of Manidipine obtained at pH 2.0. It was observed that with buffers of pH<2.0, the wave corresponding to the reduction of nitro group appeared at the start of the potential and therefore reduction wave/peak was well defined. Similarly with solutions of greater alkalinity (pH>8.0), further reduction of nitro group was not facilitated owing to the less availability of the protons.

Nature of the Electrode process:

The half-wave ($E_{1/2}$) and peak potential (Ep, Em and Es) values are observed to be linear functions of pH. As thepHof the buffer system is increased, the reduction potential is found to be shifted towards more negative values. The electrode process for Manidipine is found to be free from adsorption and currents are diffusion controlled in nature, which in confirmed through the linear plots of i_d Vs $h^{½}$ and i_m Vs $t^{2/3}$ passing through origin. When the concentration of the depolarizer is increased, the peak and half wave potentials are found to be shifted to more negative values. This phenomenon is characteristic of the irreversible process. The variation of peak potential with scan rate and absence of anodic peak in the reverse scan of cyclic voltammogram show the electrode process to be irreversible. Typical Differential Pulse Polarogram is shown in **Fig.2**.

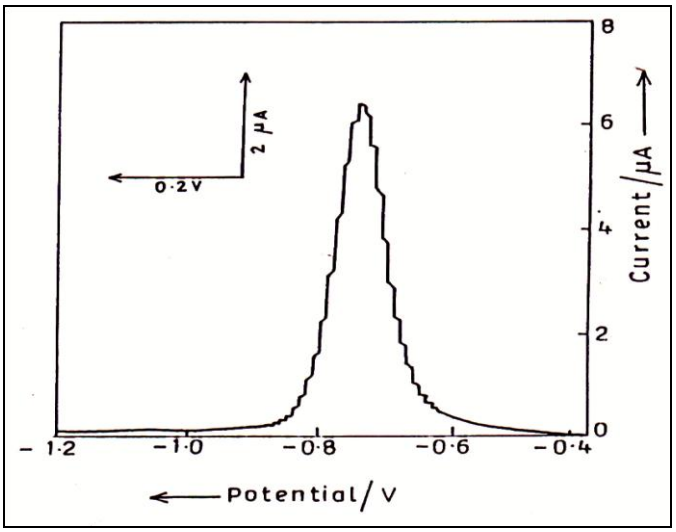

FIG. 2: TYPICAL DIFFERENTIAL PULSE POLAROGRAM OF MANIDIPINE IN pH 2.0; CONCENTRATION = 2X10^{-5} M; DROP TIME = 3 SEC

At higher pH values (pH > 10.00) a small anodic peak (a_1) is observed in the reverse scan of cyclic voltammogram. In the second scan another small cathodic peak at more positive potential than C_1 is observed. The anodic peak may be ascribed to the oxidation of (Hydroxylamine) reduced product at (C_1) and cathodic peak C_2 to the reduction of (nitroso derivative) oxidized product at a_1. The Typical Cyclic Voltammogram is shown in **Fig.3**.

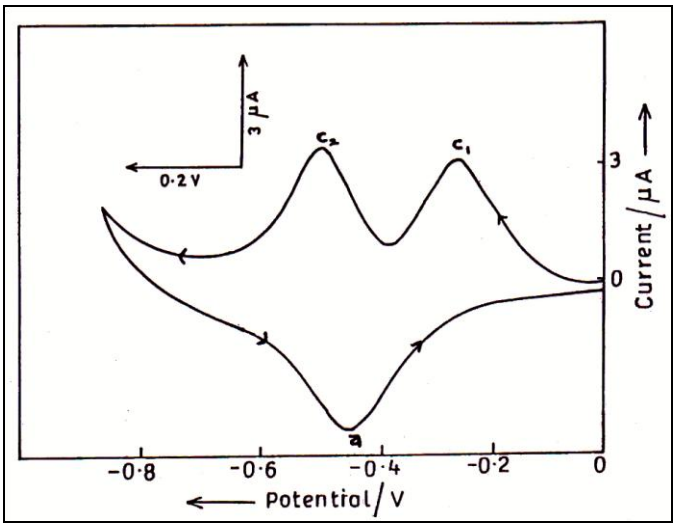

FIG.3: TYPICAL CYCLIC VOLTAMMOGRAM OF MANIDIPINE IN pH 2.0 CONCENTRATION = 2X10^{-5} M; SCAN RATE =45 Mvs^{-1}

Identification of the Product:

The technique of millicoulometry has been employed in the present investigation to evaluate the number of electrons involved in the reduction process.

From the comparison of the wave height observed, the number of electrons consumed in the overall reduction process of Manidipine is found to be four in acidic as well as basic media.

To isolate the reduction product, approximately 40 mg of the substance under investigation is dissolved in minimum amount of solvent DMF and required quantity of supporting electrolyte (pH 2.0) was added and placed in the cell. The applied potential was set at -0.26 v Vs SCE for Manidipine. During the electrolysis nitrogen gas was kept bubbling through the solution. When the current was lower than 1 mA the electrolysis was stopped and then 10 ml of water was added to the solution and extracted three times with 100 ml of ether. The ethereal extracts were dried with magnesium sulphate and evaporated. The isolated product was the characteristic peaks for hydroxyl amine group are obtained at the wave length of 2942.2, 3397.6 cm^{-1} in KBr.

Kinetic Data:

The various kinetic parameters of the electrode process such as diffusion coefficient transfer coefficient and heterogeneous forward rate constants for Manidipine from different techniques are reported in **Table 1** to **3**. The adsorption free nature of the electrode process is clearly evidenced from the nearly equal diffusion coefficient values obtained from all the techniques. The diffusion coefficient values gradually decrease which account for the decrease in diffusion current with increase in pH due to non availability of protons. The heterogeneous forward rate constant values are found to be high in acidic media indicating the proton involvement. The rate constant values are in general found to decrease with increase in pH which indicates, the electrode reduction tends to become more and more irreversible. The number of protons involved in the rate determining step is found to be one for nitro group reduction.

Electrode Mechanism:

The electro chemical reduction mechanism of Manidipine can be proposed as follows based on the above results.

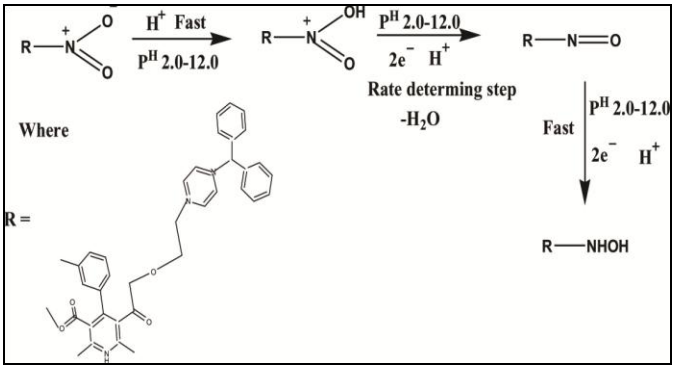

TABLE 1: TYPICAL D. C. POLAROGAPHIC DATA OF MANIDIPINE CONCENTRATION 2X10^{-5} M, DROP TIME: 3 SEC.

pH of the supporting Electrolyte	-E ½ / v	$\frac{id}{\mu A}$	∝ na	Dx10^6 Cm^{2}s^{-1}	K^{0}f,h Cms^{-1}
2.0	0.26	7.8	0.586	9.32	4.68x10^{-8}
4.0	0.34	7.2	0.594	6.84	8.46x10^{-10}
6.0	0.42	6.6	0.582	5.29	7.62x10^{-11}
8.0	0.48	5.4	0.584	4.22	6.28x10^{-12}
10.0	0.56	4.6	0.589	3.96	4.84x10^{-14}
12.0	0.64	3.8	0.586	2.88	3.42x10^{-15}

TABLE 2: TYPICAL CYCLIC VOLTAMMETRIC DATA OF MANIDIPINE CONCENTRATION 2X10^{-5} M, SCAN RATE: 45 Mvs^{-1}

pH of the supporting Electrolyte	-Ep / v	$\frac{ip}{\mu A}$	∝ na	Dx10^6 Cm^{2}s^{-1}	K^{0}f,h Cms^{-1}
2.0	0.26	7.2	0.785	9.326	3.46x10^{-7}
4.0	0.32	6.6	0.816	7.38	1.24x10^{-8}
6.0	0.42	5.2	0.794	6.26	7.44x10^{-10}
8.0	0.54	4.4	0.868	4.88	6.36x10^{-12}
10.0	0.64	3.6	0.809	4.56	5.64x10^{-13}
12.0	0.68	3.2	0.842	4.32	2.48x10^{-15}

TABLE 3: TYPICAL DIFFERENTIAL PULSE POLAROGRAPHIC DATA OF MANIDIPINE CONCENTRATION 2X10^{-5} M, DROP TIME: 3 SEC. PULSE AMPLITUDE 50 Mv.

P^H of the supporting Electrolyte	-Em / v	$\frac{im}{\mu A}$	$\propto$ na	$\frac{Dx10^6}{Cm^2S^{-1}}$	K^0f,h Cms^{-1}
2.0	0.26	8.4	0.32	9.34	$7.86x10^{-8}$
4.0	0.30	7.6	0.66	8.86	$6.18x10^{-9}$
6.0	0.36	7.2	0.78	8.26	$4.86x10^{-10}$
8.0	0.42	6.8	0.76	6.48	$3.28x10^{-11}$
10.0	0.46	5.6	0.68	5.62	$2.60x10^{-12}$
12.0	0.52	4.6	0.56	4.78	$4.52x10^{-14}$

Analysis:

In the present investigation, the experimental data of Differential Pulse Polarography is used to work out analytical procedure for the estimation of Manidipine in pharmaceutical formulations and biological media using both calibration and standard addition methods. The polarographic peak obtained in acidic media has been utilized in the analytical estimation of the Manidipine. The main nitro group reduction peak is useful in the DPP analysis of the drugs for the following reasons.

a) It occurs at small negative potentials, where a limited number or other polarographic reasons occur. Thus the determination of nitro group compounds enjoys a measure of selectivity in the field of polarographical analysis.

b) The peak height is relatively large because of four electron reduction. polarographic determination of nitro group containing drug more sensitive involving lower detection limit of 10^{-9} mole dm $^{-3}$.

c) The peak height is unaffected by the minor changes in p^H. For analytical purpose here pH 2.0 (or) 4.0 is used.

The peak currents of Manidipine are found to vary linearly with the concentration of the drug over the concentration range $1.0x10^{-5}$ – 2.0 X 10^{-9} mole dm^{-3} with the detection limit of 1.76 x 10^{-9} mole dm^{-3}. DPP is found to be more suitable at lower concentrations due to its high sensitivity and resolution.

Recommended Analytical procedure:

Standard solution ($2x10^{-5}$ M) is prepared by dissolving appropriate amount of the electro active species in DMF. A 10 ml of the solution (9 ml of supporting electrolyte +1 ml standard solution) is transferred into polarographic cell and polarogram recorded after completing the process. Deaeration for 10 minutes with nitrogen gas and after getting the polarogram, small increments (0.2 ml) of standard solutions are added and polarograms are recorded after each addition under the same experimental conditions. The concentration of the unknown sample solution is calculated by using the relevant equation given in Chapter-3. The optimum conditions for the estimation of Manidipine at pH 2.0 are found to be a drop time of 3 seconds. Pulse amplitude of 50 Mv and applied potential of – 0.26 v Vs. Ag/Agcl(s), cl^-. The relative standard deviation and correlation coefficient values for 10 replicates are 1.58% and 0.9888 respectively.

Manidipine in pharmaceutical formulations containing 245 mg in total tablet mass of approximately 250 mg has been analyzed in order to examine the applicability of the method. About 10 tablets were mixed uniformly and portions equivalent to 10, 20, 30 and 40 mg of compound were accurately weighed, dissolved in DMF and transferred into 25 ml calibrated flask. Aliquot of 0.5 ml clear supernatant liquid was made upto 10 ml with the supporting electrolyte (pH 2.0) and polarogram recorded. The amount of the compound in portion of the sample taken was estimated by reference to calibration plot. The recovery was found to be in the range of 98.40% to 99.80% and the assay results are given in **Table 4**.

For developing a faster and simple analytical procedure, we have study the effect of not degasifying the Manidipine solution with nitrogen gas before polarographic measurements. Our results indicated that previous puring was not required, because calibration plots were similar

without puring. However, the detection limit in this case was about $1.20X10^{-9}$ mole dm^{-3}. From the results it was concluded that puring of drug containing solution with nitrogen gas is not essential for the estimation of either the pure drug (or) dosage forms, reducing the measurement time nearly 10-15 minutes per run. The reliability of the method for the determination of Manidipine in urine was checked by using different spiked urine samples in conjunction with the standard addition method. Three different urine samples were spiked with standard in concentration range at which the unchanged drug is excreted. The recovery was found to be in the range of 97.25% to 99.83% with the relative standard deviation of 0.96%. The results are given in **Table 5**.

TABLE 4: DETERMINATION OF MANIDIPINE IN PHARMACEUTICAL FORMULATIONS BY DIFFERENTIAL PULSE POLAROGRAPHY. CONCENTRATION $2X10^{-5}$M, DROP TIME: 3 SEC. PULSE AMPLITUDE 50 Mv.

Sample (Tablet)	Labeled Amount(mg)	Amount Found(mg)	Recovery %	Standard Deviation
Manidipine	20	19.8	98.6	0.027
Manidipine	20	19.5	99.2	0.021
Manidipine	25	24.6	99.4	0.028

TABLE-5: DETERMINATION OF MANIDIPINE IN URINE SAMPLES BY DPP, CONCENTRATION: $2.0X10^{-5}$ M; DROP TIME: 3 SEC; PULSE AMPLITUDE: 50 Mv.

Sample	Labeled amount (ml)	Amount found (ml)	Recovery (%)	Standard Deviation	% RSD
1	2.0	1.96	98.24	0.8	2.4
2	4.0	3.94	98.60	0.6	1.8
3	6.0	5.96	99.46	0.4	1.2

Urine samples were obtained from the patients at a specific time intervals during single dosage administration. However it was observed that, after administration of single oral dose of 250 mg the drug concentration in urine increases until it reaches 12% of the initial dose at 4 hrs and then begins to decrease. Nearly 20-25% of a dose is excreted within 7 hrs. After 12 hrs, the polarographic signal disappears and the unchanged drug excreted below the method of detection of the method together with polarographically inactive Manidipine.

From the foregoing discussion, it has been demonstrated to be applicable to variety of samples including pharmaceutical formulations and biological matrices.

CONCLUSIONS: The work describes the voltammetric behavior of Manidipine based on the reduction of Nitro group at Dropping Mercury Electrode and Hanging Mercury Drop Electrode. Recovery results show that differential pulse polorogrophy was a simple, reliable and inexpensive method for the determination of Manidipine in formulations. The main advantage of the proposed method over the other one is that the recipients do not interfere and a separation procedure is not necessary.

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CONFLICT OF INTEREST: There exists no conflict of interest.

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