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Short communication

Differential-pulse polarography determination of pipamperone in pharmaceutical formulations

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Abstract

The electrochemical reduction of pipamperone has been carried out in aqueous solution in KNO_3 (0.1 mol l^{-1}) by differential-pulse polarography (DPP). Pipamperone exhibits a well-defined irreversible reduction peak at −1.3 V/ref. The influence of pH on the reduction of pipamperone was studied in Britton–Robinson buffer (pH range 2–10). A method for the analysis of pipamperone in KNO_3 (0.1 mol l^{-1}), which allows quantification over the range 1.6×10^{-5}–2.0×10^{-4} mol l^{-1}, was proposed and successfully applied to the determination of pipamperone in tablets with mean recovery and relative standard deviation (R.S.D.) of 100.35 and 0.49%, respectively.

Keywords: Pipamperone; Butyrophenone; DPP; Pharmaceutical formulation

1. Introduction

The butyrophenones are a class of drugs employed in the treatment of psychiatric diseases. There is an extensive literature concerning the pharmacology and properties of these drugs and a number of studies relating to their chemistry have been published [1].

The analysis of drugs belonging to the butyrophenone family has been performed by different methods. Spectrofluorimetric methods were successfully applied to the analysis of benperidol, azoperone and fluorisone with detection limit of 5×10^{-2} μg ml^{-1} [2]. Chromatographic methods have been also applied to the analysis of butyrophenone drugs. GC with electron capture detector was used for the analysis of haloperidol and the developed method was used for determining the distribution and metabolism of this drug in rats [3]. HPLC was applied to the analysis of antipsychotic flupentixol and haloperidol in human plasma with detection limit of 0.1 μg for haloperidol [4].

Pipamperone (1′-[4-(4-fluorophenyl)-4-oxobutyl]-[1,4′-bipiperidine]-4′-carboxamide), the structure of which is given below (Fig. 1), is a member of the butyrophenone group. It is a widely used tranquilizer, particularly in the treatment of schi-

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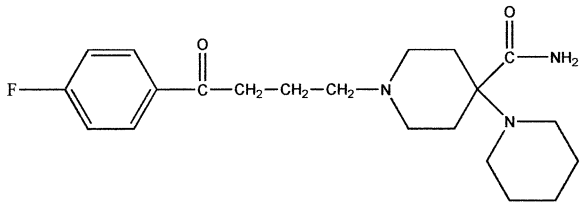


Fig. 1. Structure of pipamperone.

zophrenic patients. There is a considerable interest in sufficiently sensitive and inexpensive methods for the quantification of this drug. A survey of literature revealed that the determination of pipamperone in different media has been carried out using various methods like fluorescence after conversion into strongly fluorescing derivatives by the action of sulfuric acid on their aqueous or alcoholic solution [2] and by chromatographic methods such as HPLC [5–7], HPLC-thermospray-tandem MS [8,9], GC [10,11].

Electrochemical methods, such as differential-pulse polarography (DPP), anodic stripping voltammetry (ASV) and differential-pulse voltammetry (DPV), have been widely applied for the determination of pharmaceuticals. In general, these methods offer high sensitivity, low limit of determination, easy operation, and sometimes the use of simple instrumentation.

The polarographic behavior of butyrophenones, benperidol, droperidol, spiperone, azoperone [12] and haloperidol [13] at mercury electrodes were reported. It was reported that all those drugs exhibited an irreversible reduction mechanism involving two electrons and consuming two hydrogen atoms.

Up to date, no electroanalytical data concerning pipamperone are available in the literature.

In the present study, the electrochemical behavior of pipamperone has been studied at mercury electrodes using various polarographic techniques. A differential-pulse polarographic method was developed for the determination of pipamperone in tablets.

2. Experimental

2.1. Reagents and materials

Pipamperone base (99% purity) was kindly donated by Janssen-Pharmaceutica (Belgium) and was used as received. Capsules containing pipamperone (Dipiperon, Janssen-Cilag) labeled to contain 48 mg of pipamperone dichlorhydrate corresponding to 40 mg of pipamperone base were obtained from commercial sources. A KNO_3 (0.1 mol l^{-1}) solution was prepared in distilled water and used as supporting electrolyte. A stock solution of pipamperone (1×10^{-3} mol l^{-1}) was prepared in KNO_3 (0.1 mol l^{-1}).

Britton–Robinson buffer (0.04 mol l^{-1}) in the pH range 2–10 was used as supporting electrolyte when studying the influence of pH. The pH was adjusted to the desired value by adding the required volume of a 5 mol l^{-1} NaOH solution.

All reagents used were purchased from Prolabo (France) and were of analytical grade.

2.2. Apparatus

Standard three-electrode potentiostatic circuitry was used, employing a POL 150 model system (Radiometer Analytical), utilizing the standard cell provided. The counter electrode was a platinum wire, and the reference electrode was an Ag | AgCl electrode (4 mol l^{-1} KCl containing saturated AgCl). All potentials are given versus the Ag | AgCl reference. The working electrode for direct-current polarography (DCP) and DPP was dropping mercury electrode. A hanging mercury drop electrode (HMDE) was used for voltammetric studies. The system was controlled by Volta-Master software (Radiometer Analytical). A PHM 210 pH meter (Radiometer Copenhagen) equipped with an InLab 413 pH electrode (Mettler Toledo) was used for pH measurements. An automatic pipettor (Gilson, France) was used for adding drug samples.

2.3. Procedures

2.3.1. Recommended procedure

For the polarographic determination of pipamperone, the following procedure was proposed. The polarographic cell was poured with 5 ml of KNO_3 (0.1 mol l^{-1}). A stream of nitrogen was bubbled for 3 min and the blank polarogram was recorded at a pulse amplitude of −50 mV with a scan rate of 10 mV s^{-1}.

The drug sample was then added using an automatic pipettor so that the final pipamperone concentration was between 1.6×10^{-5} and 2.0×10^{-4} mol l^{-1}. Solutions were purged with nitrogen and polarograms recorded with the same conditions as the blank.

2.3.2. Analysis of tablets

Ten tablets (Dipiperon, 40 mg of pipamperone base) were selected at random, thoroughly ground and mixed. An amount equivalent to a single tablet was transferred to a 100 ml volumetric flask and dissolved in 50 ml of KNO_3 (0.1 mol l^{-1}), sonicated for 5 min and then completed to the mark with KNO_3 (0.1 mol l^{-1}). After the non-dissolved excipients have settled down, then an aliquot of the clear supernatant liquor was transferred into a polarographic cell containing 5 ml of KNO_3 (0.1 mol l^{-1}) to yield a concentration of 2.0×10^{-4} mol l^{-1} pipamperone. After purging with pure nitrogen, the differential pulse polarogram was subsequently recorded employing a scan rate of 10 mV s^{-1} and a pulse amplitude of −50 mV. The content of the drug was determined referring to regression equation. The standard addition method was also used to test the influence of other excipients present in tablets. No significant differences were observed between the two approaches, denoting the absence of interferences.

3. Discussion

3.1. Differential-pulse polarography

In general, pH is one of the variables that commonly and strongly influences the shapes of voltammograms, and it is important to investigate the effects of pH on electrochemical systems.

Fig. 2 illustrates the peak potential of a 2×10^{-4} mol l^{-1} pipamperone over the pH range 2–10 in Britton–Robinson buffer. The peak shifts to a more negative potential as pH increases. The slope of the curve Ep–pH is 40.9 mV per unit pH, indicating process involving the protons in the electrode reaction [14]. The half-peak width in DPP mode, $W_{1/2}$, is given approximately by $W_{1/2} = (3.52RT)/nF \approx (90/n)$ (mV) [15]. Values of $W_{1/2}$ at different pH are reported in Table 1 and suggest that the number of electrons transferred is probably 2.

Fig. 3 shows the influence of pH on peak height. The absolute value of I_p passes through a maximum at pH 4, then decreases and remains nearly constant for pH > 7.

The DPP of pipamperone in KNO_3 (0.1 mol l^{-1}) was also recorded and shows a well developed peak. In this work, the KNO_3 (0.1 mol l^{-1}) was selected as a suitable analytical medium because the sensitivity for pipamperone was relatively high. The choice of this medium permits also to avoid laborious buffer preparations, which may be detrimental to the simplicity of the method.

3.2. Direct-current polarography

Direct-current (DC) polarogram of pipamperone in Britton–Robinson buffer at different pH

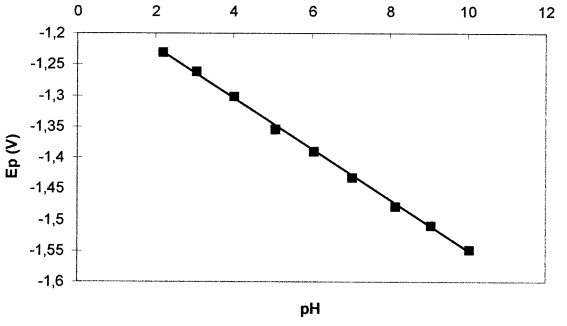


Fig. 2. Peak potential, Ep, of a 2×10^{-4} mol l^{-1} pipamperone solution in Britton–Robinson buffer (pH 2.1; 3; 4; 5; 6; 7; 8.1; 9; 10). Scan rate 10 mV s^{-1}, pulse amplitude −50 mV.

Table 1
Effect of pH on the development of the polarographic waves of pipamperone

pH	$-E_{1/2}$	$\Delta E_{1/2}/\Delta$pH	$W_{1/2}$ (mV)	αn	Z (H^+)
2.16	1.257		70	1.18	
3.03	1.273	18.3	70	1.31	0.75
4	1.323	51.5	70	1.20	0.83
5.05	1.352	27.6	82	1.25	1.05
6.03	1.4	48.9	84	1.01	0.61
7.03	1.44	40	94	0.98	0.69
8.14	1.478	34	88	1.12	0.77
9.04	1.535	63	80	1.11	0.63
10.04	1.583	48	84	0.96	0.63

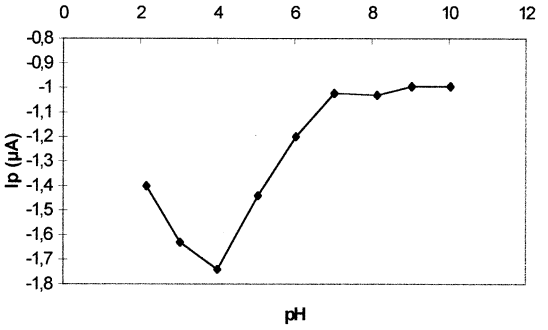


Fig. 3. Peak height, Ip, of a 2×10^{-4} mol l^{-1} pipamperone solution in Britton–Robinson buffer (pH 2.1; 3; 4; 5; 6; 7; 8.1; 9; 10). Scan rate 10 mV s^{-1}, pulse amplitude −50 mV.

was also recorded. Reduction of the studied compound at the DME was found to be pH dependent as the $E_{1/2}$ values were shifted to more negative values upon increasing pH. A plot of $E_{1/2}$ versus pH gave a straight line with a slope of −41.6 mV per unit pH. The relation between $E_{1/2}$ values and the pH of solution is represented by the following equation:

$$E_{1/2} = -0.04\ \text{pH} - 1.15 \quad (r = 0.992).$$

The number of protons, Z, consumed in the electrode reaction is given by the following equation:

$$\frac{\Delta E_{1/2}}{\Delta \text{pH}} = \frac{0.059Z}{\alpha n},$$

where α is the transfer coefficient. The value of αn was calculated after performing a logarithmic analysis of the following equation:

$$E = E_{1/2} + \frac{0.059}{\alpha n} \log \frac{(i_d - i)}{i},$$

where i_d is the diffusion current.

Logarithmic analysis of the reduction waves obtained in Britton–Robinson buffer of different pH values resulted in straight lines. The αn values were calculated using the treatment of Meites and Israel [16]. The results are shown in Table 1. Assuming that the rate determining step involves the transfer of two electrons (a free radical, one-electron transfer is not likely to occur), the values of the slopes suggest that the reduction process is irreversible in nature.

3.3. Cyclic voltammetry

To elucidate further the electrode reaction of pipamperone, a cyclic voltammogram at HMDE was recorded. As shown in Fig. 4, the cyclic voltammogram of a 3.38×10^{-4} mol l^{-1} pipamperone in KNO_3 (0.1 mol l^{-1}) exhibits a single cathodic peak, with no peak on the reverse scan, indicating the irreversible nature of the electrode reaction. The study of the influence of scan rate shows that the peak current changes linearly with scan rate (n) according to the equation $I_p = Av^x$. The x values 1.0 and 0.5 are expected for adsorption-controlled and diffusion-controlled reaction [17]. The regression of log I_p versus log v gave a slope value of 0.33 indicating that the reduction current is of diffusional nature. On the other hand, as scan rate was increased from 10 to 250 mV s^{-1}, the peak potential shifted towards more negative potential as expected for an irreversible reduction process [18].

3.4. Reaction mechanism

Taking into account the results of the pH effect, logarithmic analysis, cyclic voltammetry studies, a reduction pathway for pipamperone at mercury electrode can be suggested. It can be concluded that, only the carbonyl group is involved in the reduction process according to the following equation.

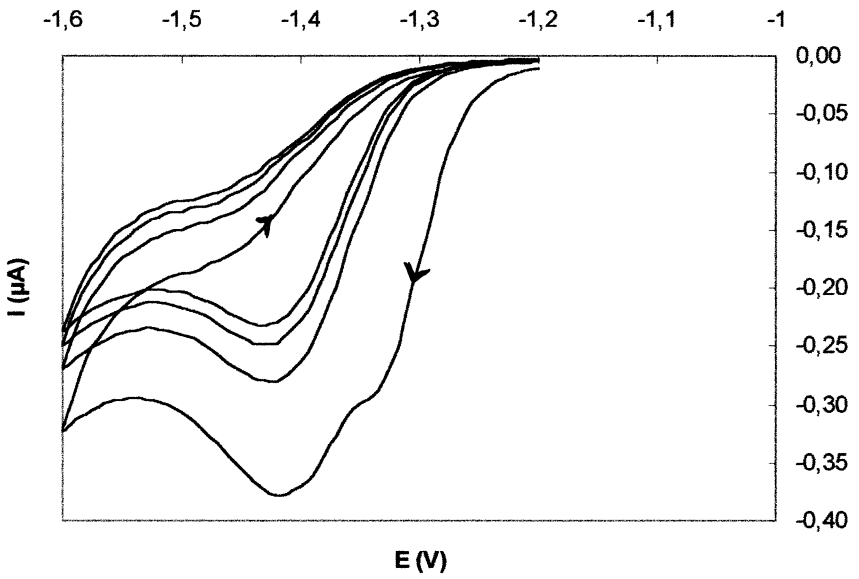
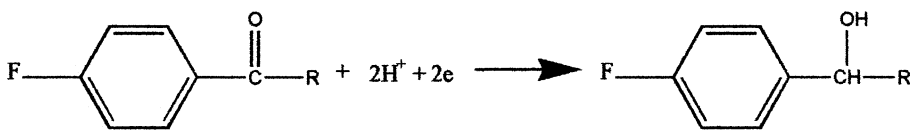


Fig. 4. Cyclic-voltammogram at a Hanging Mercury Drop Electrode (HMDE) of a 3.38×10^{-4} mol l^{-1}. Pipamperone solution in KNO_3 (0.1 mol l^{-1}). Scan rate, 100 mV s^{-1}; number of cycles, 4.



This reaction mechanism is similar to that observed for haloperidol [13] and benperidol, droperidol, spiperone and azoperone [12], with the major difference that no adsorption phenomenon occurs. As pointed by Vire et al. [12], lateral substitution does not influence the carbonyl reduction process. This fact is specific to the butyrophenone family and is substantially different from that observed for aromatic ketones [19–22].

3.5. Analytical application

The influence of pipamperone concentration on the peak current in KNO_3 (0.1 mol l^{-1}) using DPP (pulse height: −50 mV and scan rate 10 mV s^{-1}) is shown in Fig. 5. A linear range was observed for concentrations between 1.6×10^{-5} and 2.0×10^{-4} mol l^{-1}. The variation of peak current (I_p) with pipamperone concentration (mol l^{-1}) was represented by a straight line equation I_p (nA) = $26.94 + 3.66 \times 10^6$ C, $r = 0.994$ ($n = 5$), where r is the correlation coefficient and n is the number of points. Statistical evaluation of the data [23] were performed through determination of the standard deviation (S.D.) of the residuals ($S_{x/y} = 32.50$), S.D. of the intercept ($S_a = 23.23$) and S.D. of the slope ($S_b = 214\,043$). The small figures obtained refer to the high precision of the method. The percent recovery (%R) was found to equal 99.1–101.3% with relative standard deviation (R.S.D.) 0.24–0.39%. The detection limit (3×10^{-6} mol l^{-1}) of pipamperone was calculated using the equation LD = (3 S.D.)/a, where, S.D. is the standard deviation of the blank and a is the slope of the calibration curve.

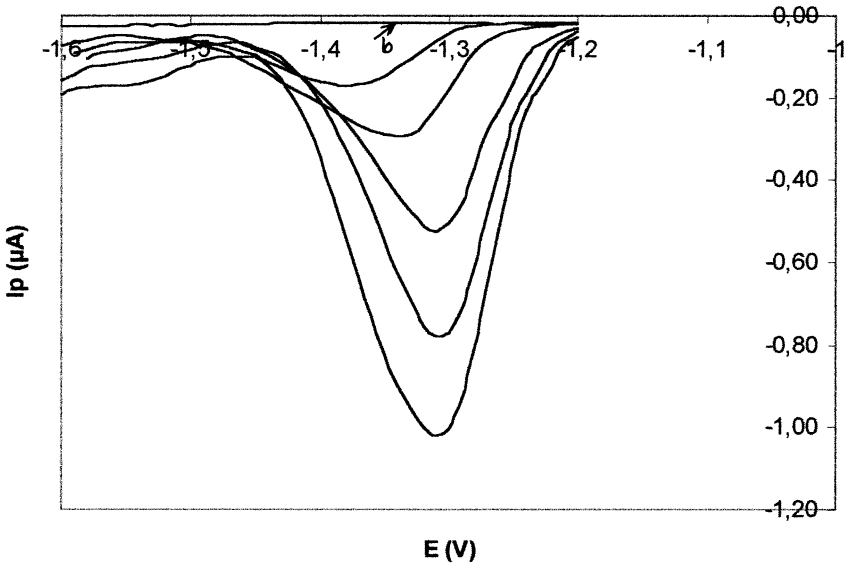


Fig. 5. DPP of pipamperone in KNO_3 (0.1 M), concentration range 1.6×10^{-5}–2×10^{-4}; scan rate, 10 mV s^{-1}, pulse amplitude, −50 mV (b = blank).

The proposed analysis procedure was successfully applied for the assay of pipamperone in pharmaceutical formulation (Dipiperon, 40 mg of pipamperone base). Five determinations of six different samples of the drug gave an average pipamperone content of 40.14 mg corresponding to a mean recovery of 100.35%. The R.S.D. was 0.48%.

4. Conclusion

Based on the above results, we consider that the developed method is a good technique for application to the determination of pipamperone with adequate reproducibility and recovery. Chromatographic methods for the determination of pipamperone need expensive equipment and materials, and also include time-consuming extraction steps to eliminate the excipients. The described method is a direct method for the determination of pipamperone and does not include any extraction process. Polarography is a considerable time saver when compared with HPLC and the overall cost of analysis is lower than that of a chromatographic method. Most spectrophotometric methods include complex reactions, which cause contamination and loss of substance.

In conclusion, the proposed method is precise, accurate, sensitive, rapid, cheap, easy to use and might be preferred to other published methods.

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