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# Electroanalytical characteristics of piribedil and its differential pulse and square wave voltammetric determination in pharmaceuticals and human serum

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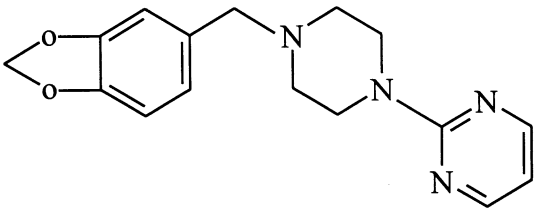
**Abstract**

The electrochemical oxidative behavior of piribedil (PR) was described. It was investigated by cyclic, linear sweep, differential pulse (DPV) and square wave (SWV) voltammetric techniques. The redox behavior of PR was found irreversible. Different parameters were tested to optimize the conditions for the determination of PR. The dependence of intensities of currents and potential on pH, concentration, scan rate, nature of the buffer was investigated. Two sensitive methods for the measurement of PR were described. For analytical purposes, a very well resolved diffusion controlled voltammetric peak was obtained in 0.1 M $H_2SO_4$ and pH 5.7 acetate buffer. The determination peaks are obtained at 1.27 and 0.95 V for differential pulse and 1.29 and 0.97 V for SWV in 0.1 M $H_2SO_4$ and pH 5.7 acetate buffer, respectively. The linear response was obtained in the ranges of $2 \times 10^{-6}$–$1 \times 10^{-3}$ M in 0.1 M $H_2SO_4$ and $2 \times 10^{-6}$–$8 \times 10^{-4}$ M in pH 5.7 acetate buffer for both techniques. The proposed techniques were successfully applied to the determination of PR in tablet dosage forms and human serum. Excipients did not interfere in the determination. The necessary statistical validation reveals that the proposed methods are free from significant systematic errors.


*Keywords:* Piribedil; Voltammetry; Determination; Human serum; Pharmaceuticals

## 1. Introduction

Piribedil (PR) is a non-ergot dopamine agonist and has been tried in the treatment of parkinsonism and in depression. In some countries it is used in the treatment of circulatory disorders. PR is an alkoxybenzyl-4-(2-pyrimidinyl) piperazine derivatives. PR may be more effective in reducing tremor than in improving other aspects of Parkinson's disease, but its parkinsonian efficacy is considerably less than that of levodopa [1,2].



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There have been few reports for the determination of PR in biological media or in pharmaceutical dosage forms including spectrophotometry [3,4], high-performance liquid chromatography [5,6], gas-chromatography [7], gas-chromatography-mass spectrometry [8] and ion selective electrodes [9].

The reported literature methods require solid phase extraction or expensive reagents and equipments, which are not economically feasible for routine use in pharmacokinetic and pharmaceutical studies.

There is no written information concerning electrochemical studies, oxidation mechanism and analytical assay from pharmaceuticals or biological media using by voltammetric techniques.

The electroanalytical techniques have been shown to be excellent for the determination of pharmaceutical compounds in different matrices. Many of the active constituents of formulations, in contrast to excipients, can be readily oxidized. The selectivity of this method is normally excellent because the analyte can be readily identified by its voltammetric peak potential. The advance in experimental electrochemical techniques in the field of analysis of drugs is due to their simplicity, low cost and relatively short analysis time when compared with the other techniques [10–15]. The use of carbon based electrodes, especially glassy carbon electrode, for electroanalytical measurements has increased in recent years because of their applicability to the determination of active compounds that undergo oxidation reactions, a matter of great importance in the field of clinical and pharmaceutical analysis. Voltammetric techniques are most suitable to investigate the redox properties of drugs. This can give insights into its metabolic fate or their in-vivo redox processes or pharmaceutical activity [16,17].

The main objectives of this work were to investigate the electrooxidative behavior of PR in aqueous media and its determination possibilities at glassy carbon electrode using differential pulse (DPV) and square wave (SWV) voltammetry. The proposed voltammetric techniques were applied to the quantitation of PR in pharmaceutical formulation and human serum without the necessity of sample pre-treatment. These techniques allow researchers to save time and decrease cost compared with already published methods.

## 2. Experimental

### 2.1. Apparatus

The cyclic, linear sweep, DPV and SWV experiments at a stationary electrode were performed using a BAS 100W Electrochemical analyzer. A three-electrode cell system incorporating the glassy carbon disc electrode as working electrode: a Ag/AgCl (3 M KCl) reference electrode and platinum-wire auxiliary electrode were also used. Before each experiments the glassy carbon electrode was polished manually with alumina ($\phi = 0.01$ μm) in the presence of bidistilled water on a smooth polishing cloth.

DPV conditions were: pulse amplitude, 50 mV; pulse width 50 ms; scan rate, 20 mV $s^{-1}$ and SWV conditions were: pulse amplitude, 25 mV; frequency, 15 Hz; potential step 4 mV.

### 2.2. Reagents

PR and its pharmaceutical dosage forms were kindly provided by Servier Pharm. Ind. (Istanbul, Turkey).

PR stock solutions were prepared daily by direct dissolution in methanol. The solutions under voltammetric investigations were prepared by dilution of the stock solution in the presence of methanol (20%; v/v). 0.1 M $H_2SO_4$, 0.2 M phosphate buffer pH 2.03–11.0, 0.04 M Britton–Robinson buffer pH 2.06–11.04 and 0.2 M acetate buffer pH 3.5–5.7 were used for the supporting electrolytes.

All solutions were protected from light and were used within 24 h in order to avoid decomposition.

### 2.3. Tablet assay procedure

Ten tablets of Trivastal retard® each one containing 50 mg of PR were crushed in a glass mortar. An adequate amount of this powder corresponding to a stock solution of approxi-

mately $1 \times 10^{-3}$ M was accurately weighed and transferred into a 50 ml calibrated flask and complated to the volume with methanol. The contents of the flask were sonicated for 10 min to effect complete dissolution. Appropriate solutions were prepared by taking suitable aliquots of the clear supernatant liquor and diluting with the selected supporting electrolyte. Voltammograms were recorded as in pure PR.

### 2.4. Recovery experiments from tablets

To study the accuracy, reproducibility, precision and to check the interference from excipients used in the formulation of the above methods, recovery experiments were carried out. In order to know whether the excipients show any interference with the analysis, known amounts of the pure drug were added to the different pre-analyzed formulations of PR and the mixtures were analyzed by the proposed methods. After five repeated experiments, the recoveries were calculated for both methods.

### 2.5. Recovery studies in spiked human serum samples

Serum samples, obtained from healthy individuals (after obtaining their written consent) were stored frozen until assay. After gentle, thawing aliquots of serum were spiked with PR dissolved in methanol to achieve final concentration of $10^{-3}$ M and treated with 500 μl acetonitrile as serum protein precipitating agent, then the volume was completed to 2 ml with the same serum sample. The tubes were vortexed for 5 min at 1500 rpm and then centrifuged for 10 min at $5000 \times g$ for getting rid of protein residues. The supernatant was taken carefully. Appropriate volumes at this solution were analyzed in the voltammetric cell containing selected supporting electrolyte. Voltammograms were recorded as in pure PR.

## 3. Results and discussion

PR appears to be an electroactive compound. The drug is capable to be oxidable. PR was subjected to a voltammetric study in DPV and SWV modes, and to cyclic and linear sweep voltammetric study with the aim of characterizing its electrochemical oxidation behavior. PR was electrochemically oxidized in a broad pH range using a glassy carbon disc electrode, producing a rather complex signal at high anodic potential. The cyclic, linear sweep, DPV and SWV voltammetric behavior of $2 \times 10^{-4}$ M PR was examined with varying pH over a wide range of values from acidic (0.1 M $H_2SO_4$) to alkaline (pH 11.04) in different buffer systems. The electrochemical behavior of PR at this electrode over the pH range 1.8–11.04 yielded one main irreversible oxidation process. The presence secondary process was observed in all pH value except in 0.1 M $H_2SO_4$ (Fig. 1a and b).

Cyclic voltammetric measurements performed on $2 \times 10^{-4}$ M PR solutions in the presence of 20% methanol show an irreversible nature of the oxidation peak in the range of scan rates comprised of between 5 and 1000 mV $s^{-1}$ and in the entire pH range investigated. As shown in Fig. 1, no cathodic peak was observed and the first peak was easily measurable. Hence, all subsequent work was based on the measurement of the magnitude of this step.

The peak potential of PR moves to more positive potentials with increasing pH. A 86 mV positive shift in the peak potential was observed, which confirmes the irreversibility of the process, with the simultaneous increase in peak current when the scan rate was increased. Scan rate studies were then carried out assess whether the processes on glassy carbon electrode were under diffusion or adsorption control. Voltammograms obtained for $2 \times 10^{-4}$ M PR solution for increasing scan rates showed that a linear relationship exists between the peak current and square root of the scan rate in the range 5–1000 mV $s^{-1}$, indicating that the process is diffusion control. The equation is noted below:

$$i_p(\mu A) = 1.104 v^{1/2}(\text{mV s}^{-1}) - 1.12$$

$$r = 0.998, \quad n = 10$$

A plot of logarithm of peak current versus logarithm of scan rate gave a straight-line. The

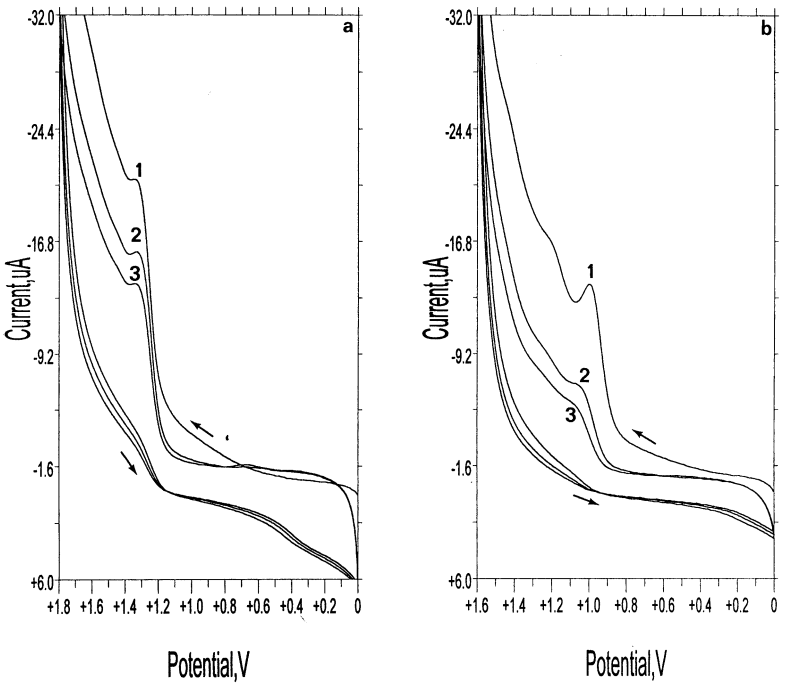


Fig. 1. Repetitive cyclic voltammograms of $2 \times 10^{-4}$ M PR solutions in 0.1 M $H_2SO_4$ (a) and pH 5.7 acetate buffer (b). Scan rate 100 mV $s^{-1}$. The number indicate the number of scans.

obtained slope is very close to the theoretical value of 0.5, which is expected for an ideal reaction of solution species [18], so in this case the process had an diffusive component. The equation obtained is:

$$\log i_p(\mu A) = 0.54 \log\ v(\text{mV s}^{-1}) - 0.09$$
$$r = 0.999,\ \ n = 10$$

Various electrolytes, such as sulfuric acid, Britton–Robinson, acetate and phosphate buffer were examined. The best results with respected to signal enhancement accompanied by sharper response (Fig. 1b, Figs. 2 and 3) was obtained with sulfuric acid and acetate buffer at pH 5.7. These supporting electrolytes were chosen for the subsequent experiments.

Tafel plot was obtained with a scan rate of 5 mV $s^{-1}$ beginning from a steady-state potential in 0.1 M $H_2SO_4$ and pH 5.7 acetate buffer and from the slope of the linear part $\alpha n$ was found to be 0.22 and 0.45, respectively.

The variation of peak intensity and peak potential with pH for a $2 \times 10^{-4}$ M PR solution were studied by cyclic, DPV and SWV techniques between pH 1.8 and 11.04. The peak potential versus pH plots of DPV were similar to that obtained by cyclic and SWV. For this reason, only DPV data were given as Fig. 3. The plot $E_p$ versus pH showed two different regions (Fig. 3a). The first one appeared between pH 1.8 and 7.0. In this region, the peak potential shifted to less positive potential values according to the equation:

$$E_p(\text{V}) = 1.42 - 8.78 \times 10^{-2}\ \text{pH} \quad (r = 0.982)$$

For higher pH values $E_p$ was practically pH independent, following the equation:

$$E_p(\text{V}) = 0.86 - 1.70 \times 10^{-3}\ \text{pH}$$

The pH-independent zone above pH 7 means that there are no proton transfer steps before the electron transfer rate-determining step. These two linear regions intersect at about pH 7, which is supposed to correspond to the $pK_a$ value of the piperazine moiety [19]. This can be explained by changes in protonation of acid–base functions in

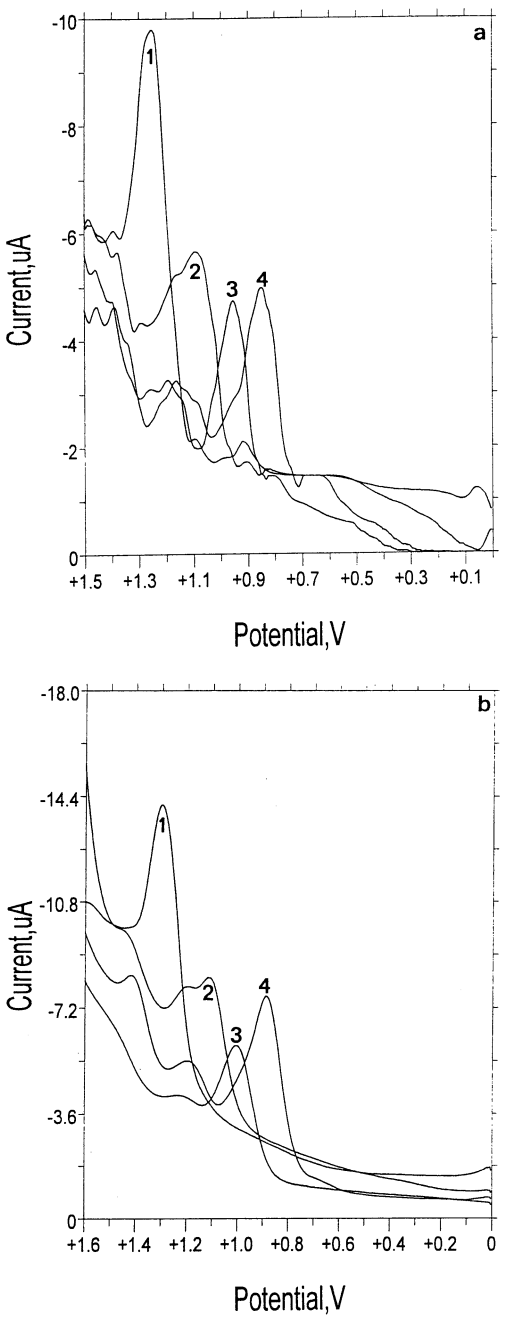


Fig. 2. Differential pulse (a) and square wave (b) voltammograms of $2 \times 10^{-4}$ M PR in different buffer system (1) 0.1 M $H_2SO_4$; (2) Acetate buffer at pH 3.5; (3) Britton–Robinson buffer at pH 5.12; (4) Phosphate buffer at pH 7.52.

the molecule. The effect of the solution pH on the peak enhancement is also shown in Fig. 3b. As the peak currents are higher at pH 1.8 (0.1 M $H_2SO_4$) and at pH 5.7 (acetate buffer), these values were chosen as the working pHs and supporting electrolytes.

The study on trazodone and nefazodone, which have piperazine moiety like PR were realized by cyclic, DPV and SWV at the glassy carbon electrode, as a function of pH in order to identify the oxidation process of PR.

Taking into account that the voltammograms of trazodone and nefazodone closely match the voltammograms of PR, we may postulate that the oxidation steps of PR are located on the piperazine moiety which represents a typical redox system with two electron oxidation process in acidic and basic media. We may assume that when the aliphatic nitrogen of the piperazine ring, distal to the pyrimidine moiety of the molecule, is protonated, oxidation occurs on the proximal nitrogen. This mechanism and all of obtained results are in agreement with reported data concerning anodic voltammetry of trazodone and nefazodone at glassy carbon electrode [19,20].

### 3.1. Quantitative determination

In order to develop a voltammetric methodology for determining PR, DPV and SWV modes were selected, since the peaks were sharper and better-defined at lower concentration of PR than those obtained by cyclic and linear sweep voltammetry, with a lower background current, resulting in improved resolution. Supporting electrolytes and pH values were chosen as 0.1 M $H_2SO_4$ at pH 1.8 and acetate buffer at pH 5.7 for PR determination. The maximum response and higher resolution of DPV and SWV peaks of the investigated compounds can be obtained with these supporting electrolytes at these pH values.

The influence of different percentages of methanol, in the solvent was evaluated and it was found that for 0.1 M $H_2SO_4$ and acetate buffer (pH 5.7), in the presence of 20% methanol (v/v), led to the best improvement of peak definition and height. These supporting electrolytes were chosen for the subsequent experiments. According to the ob-

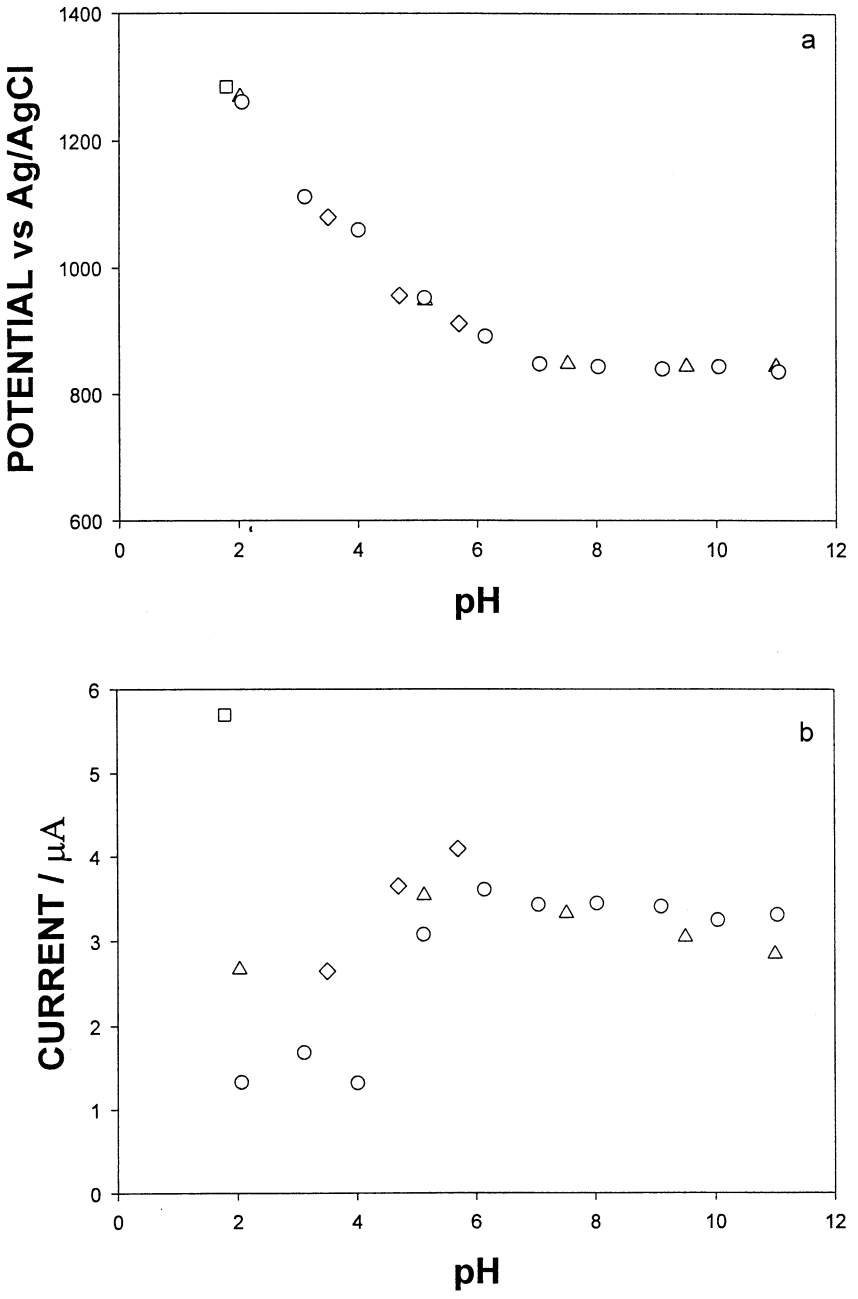


Fig. 3. Effect of pH on PR peak potential (a) and peak current (b); PR concentration $2 \times 10^{-4}$ M. (□) 0.1 M $H_2SO_4$; (○) Britton–Robinson buffer; (△) Phosphate buffer (◇) Acetate buffer.

tained results, it is possible to apply DPV and SWV techniques to the quantitative analysis of PR. The quantitative evaluation is based on the dependence of the peak current on PR concentration. The peak currents increased linearly with increasing amounts of PR by DPV and SWV.

Using the optimum conditions described in Section 2, linear calibration curves were obtained

Table 1
Regression data of the calibration lines for quantitative determination of PR in 0.1 M $H_2SO_4$ and acetate buffer at pH 5.7 (20% methanol) using DPV and SWV

| | 0.1 M $H_2SO_4$ | | Acetate buffer pH 5.7 | |
|---|---|---|---|---|
| | DPV | SWV | DPV | SWV |
| Working electrode potential (V) (vs. Ag/AgCl) | 1.27 | 1.29 | 0.95 | 0.97 |
| Linearity range (M) | $2 \times 10^{-6}$–$1 \times 10^{-3}$ | $2 \times 10^{-6}$–$1 \times 10^{-3}$ | $2 \times 10^{-6}$–$8 \times 10^{-4}$ | $2 \times 10^{-6}$–$8 \times 10^{-4}$ |
| Number of data points | 15 | 15 | 14 | 14 |
| Slope (μA $M^{-1}$) | $1.83 \times 10^4$ | $2.55 \times 10^4$ | $1.91 \times 10^4$ | $2.04 \times 10^4$ |
| Intercept (μA) | 0.22 | 0.38 | 0.06 | 0.15 |
| Correlation coefficient | 0.999 | 0.999 | 0.999 | 0.999 |
| R.S.D.% of slope | 0.93 | 1.02 | 0.21 | 0.36 |
| R.S.D.% of intercept | 0.60 | 0.66 | 0.83 | 0.24 |
| LOD | $5.6 \times 10^{-7}$ | $2.75 \times 10^{-7}$ | $1.01 \times 10^{-7}$ | $6.1 \times 10^{-8}$ |
| LOQ | $1.88 \times 10^{-6}$ | $9.18 \times 10^{-7}$ | $3.38 \times 10^{-7}$ | $2.1 \times 10^{-7}$ |
| Repeatability of peak current (R.S.D.%) | 0.43 | 0.89 | 0.96 | 0.61 |
| Repeatability of peak potential (R.S.D.%) | 0.36 | 0.58 | 0.77 | 0.87 |
| Reproducibility of peak current (R.S.D.%) | 0.45 | 0.90 | 0.81 | 0.66 |
| Reproducibility of peak potential (R.S.D.%) | 0.42 | 1.02 | 0.92 | 0.62 |

for PR in the range of $2 \times 10^{-6}$–$1 \times 10^{-3}$ M for DPV and SWV in 0.1 M $H_2SO_4$ and $2 \times 10^{-6}$–$8 \times 10^{-4}$ M for DPV and SWV in pH 5.7 acetate buffer. The characteristics of calibration plots were shown in Table 1. The limit of detection (LOD) and quantification (LOQ) were also shown in Table 1. The LOD and LOQ were calculated on the peak current using the following equations:

$$\mathrm{LOD} = 3s/m \quad \mathrm{LOQ} = 10s/m$$

where $s$, the noise estimate, is the standard deviation of the peak currents (five runs) of the sample, $m$ is the slope of the calibration curve.

All solutions are freshly prepared to ensure stability of analyte in solutions. However, for stability indicating, sample solutions recorded after 4 days did not show any appreciable change in assay values.

The repeatability and reproducibility of peak potentials and peak currents were tested by repeating five experiments on $6 \times 10^{-5}$ M PR for both techniques. The results are given in Table 1.

### 3.2. Application to analysis of pharmaceuticals

On the basis of the above results, DPV and SWV methods were applied to the direct determination of PR in tablets, using the related calibration equations without sample preparation and after an adequate dilutions (Table 2).

The proposed methods could be applied with great success to PR assay in tablet dosage forms without any interferences. The mean results for five determinations are very close to the declared value of 50.0 mg in all supporting electrolytes and both techniques; the confidence limits were calculated for a significance level of 0.05.

Table 2
Results from commercial tablet dosage forms and mean recoveries obtained for five determinations of PR in spiked Trivastal retard® tablets

| | 0.1 M $H_2SO_4$ | | Acetate buffer at 5.7 | |
|---|---|---|---|---|
| | DPV | SWV | DPV | SWV |
| Labelled claim (mg) | 50.0 | 50.0 | 50.0 | 50.0 |
| Amount found [a] (mg) | 50.37 | 50.16 | 50.06 | 49.83 |
| R.S.D.% | 1.07 | 1.04 | 0.84 | 0.34 |
| 95% confidence limit | 0.68 | 0.65 | 0.52 | 0.21 |
| Added (mg) | 5.0 | 5.0 | 5.0 | 5.0 |
| Found (mg) | 4.99 | 4.98 | 5.03 | 5.00 |
| Recovered [a] | 99.89 | 99.63 | 100.6 | 99.9 |
| R.S.D.% of recovery | 0.65 | 0.91 | 0.55 | 0.46 |

[a] Each value is the mean of five experiments.

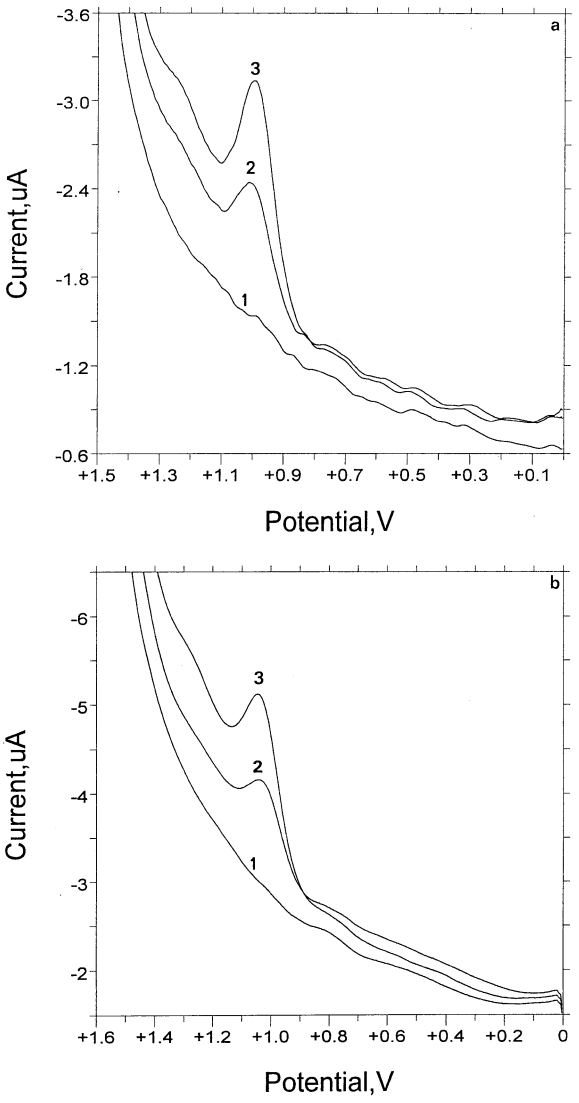


Fig. 4. Differential pulse (a) and square wave (b) voltammograms obtained for the determination of PR in spiked human serum samples (1) blank serum extract; (2) extract containing $2 \times 10^{-5}$ M; (3) extract containing $4 \times 10^{-5}$ M.

As far as we know, there is no official method in any pharmacopoeias related to pharmaceutical dosage forms or bulk drugs of PR. For this reason, in order to check the accuracy, precision and selectivity of the developed method, we have also carried out a recovery study (Table 2). For the recovery studies, the standard addition method was used. Moreover, in order to know whether the excipients in the tablets show any interference with the analysis and the accuracy of the proposed methods were evaluated by recovery tests after addition of known amounts of pure drug to various pre-analyzed formulations of PR (Table 2). The results of Table 2 demonstrate the validity of the proposed techniques for the determination of PR in tablet dosage forms. According to the recovery results, the proposed techniques are sufficiently accurate and precise in order to be applied to pharmaceutical dosage forms.

### 3.3. PR determination in spiked serum samples

In order to check, the possibility of applying the proposed methods for the determination of PR in spiked human serum samples was also tested. The determination of PR in spiked human serum could be achieved adopting the DPV and SWV modes in pH 5.7 acetate buffer. The oxidation potential is obtained at high positive potential with 0.1 M $H_2SO_4$. We could not obtained good results in serum samples when 0.1 M $H_2SO_4$ used as supporting electrolyte. On the other hand, in acetate buffer at pH 5.7, good results were obtained.

Analysis of drugs from serum samples usually requires extensive time-consuming sample preparation, use of expensive organic solvents and other chemicals.

Serum samples were spiked with PR to achieve final concentrations of $2 \times 10^{-5}$, $4 \times 10^{-5}$, $6 \times 10^{-5}$ M. In our proposed techniques, the serum proteins were precipitated by the addition of acetonitrile, which is centrifuged at 5000 rpm and the supernatant is diluted with the supporting electrolyte (acetate buffer at pH 5.7 in the presence of 20% methanol) and analyzed.

For the determination of PR in spiked serum samples, three replicate samples at three different levels of PR were run through the procedure (Table 3). Fig. 4 shows typical DPV and SWV curves of PR in serum samples. The amount of PR in human serum samples was calculated from related linear regression equations. The proposed techniques were successfully applied to spiked human serum samples. The methods were opti-

Table 3
Application of the proposed method to the determination of PR in spiked human serum using DPV and SWV modes

| Technique | PR added (M) | $N$ | PR found (M) | Average recovery (%) | R.S.D.% |
|---|---|---|---|---|---|
| DPV | $2 \times 10^{-5}$ | 3 | $1.98 \times 10^{-5}$ | 99.41 | 0.95 |
| | $4 \times 10^{-5}$ | 3 | $3.99 \times 10^{-5}$ | 99.76 | 0.79 |
| | $6 \times 10^{-5}$ | 3 | $5.97 \times 10^{-5}$ | 99.59 | 0.67 |
| SWV | $2 \times 10^{-5}$ | 3 | $1.99 \times 10^{-5}$ | 99.26 | 0.40 |
| | $4 \times 10^{-5}$ | 3 | $3.995 \times 10^{-5}$ | 99.64 | 0.53 |
| | $6 \times 10^{-5}$ | 3 | $5.99 \times 10^{-5}$ | 99.77 | 0.23 |

mized and justified by the sufficiently accurate and precise percentage recoveries (Table 3).

## 4. Conclusion

This work shows that the PR can be determined by using voltammetric techniques on the basis of its oxidation process over the glassy carbon electrode. This voltammetric behavior provides a useful tool for PR detection and determination at low levels of concentration in serum samples. The described DPV and SWV procedures allow simple, highly sensitive, accurate, fast response and low cost quantitative method for determination of PR in the pharmaceutical dosage forms and human serum samples. These techniques can be readily adopted to routine bioanalytical analysis. As can be seen the DPV and SWV methods can be applied to for the PR determination in commercial tablet dosage forms with very good results, and a faster analysis can be the direct measure from the related calibration equation from DPV and SWV methods because it is sensitive enough and there were no interferences in the analysis of the tablet excipients. This paper is not intended to be a study of the pharmacodynamic properties of PR, since only healthy volunteers were used for the sample collection and results may be of no significance. It only shows that the possibility of monitoring this compound makes the method useful for pharmacokinetic and pharmacodynamic purposes.

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