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Short communication

# Polarographic determination of propranolol in pharmaceutical formulation

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**Abstract**

Propranolol was reacted with nitric acid to give nitropropranolol and was then measured in Britton–Robinson solutions in the pH range 2.0–12.0 by differential-pulse polarography. Nitropropranolol gave rise to a well-resolved differential-pulse polarographic peak at pH 2.0. A linear calibration graph in the range $5.0 \times 10^{-7}$–$5.0 \times 10^{-5}$ M and a detection limit of 5 nM was obtained. The relative standard deviation was 1.95% ($n = 10$) at $5 \times 10^{-6}$ M. The effect of common exceipient on the peak height was evaluated. The method was applied for the determination of the drug in the tablet dosage form. © 2002 Published by Elsevier Science B.V.

*Keywords:* Propranolol; Drug analysis; Polarography; Nitrated propranolol

## 1. Introduction

Propranolol (1-isopropylamino-3-(1-naphthyloxy)-2-propranolol; Fig. 1a) is a β-adrenergic blocking drug that has wide application for the treatment of cardiac arrhythmia, sinus tachycardia, angina pectoris and hypertension. It has also been suggested for use for a number of other conditions including a dysfunction labour and anxiety [1].

Propranolol has been determined in pharmaceutical preparations by a range of methods, such as colorimetric analysis [2,3], spectrophotometry [4,5], spectroflourimetry [6,7], potentiometric analysis [8], conductometric titration [9], thin-layer chromatography [10] and high-performance chromatography [11,12]. Few papers have been published already with the delay of voltammetric determinations of propranolol at platinum electrodes in sulfuric acid. Yet the number of electroanalytical methods for the analysis of propranolol are available in the literature. The voltammetric method is sensitive, quite, rapid and can be used as an alternative for the widely used (HPLC) monitoring of drugs. This makes the determination of propranolol by voltammetric methods a new approach.

Functionalization polarography, which means the conversion of a polarography inactive compound into an active one, is achieved by the

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introduction of an electroactive group through chemical reactions. The reaction should occur rapidly and with a yield of about 100%. The nitration procedure as a derivatization method was applied successfully for the determination of a wide variety of drugs, which lack functional groups amenable to electroanalytical methods [13–18].

Propranolol is not electroreducible at a mercury electrode as can be deduced from its structure. In the present paper we tried a nitration procedure in order to convert the drug into an electroactive nitrated derivative amenable to electrochemical reduction at the mercury electrode.

## 2. Experimental

### 2.1. Reagents

All reagents were of analytical pure grade. All solutions were prepared with Ultra-pure water. Propranolol hydrochloride was obtained from Zeneca Pharmaceutical company. Britton–Robinson buffers (0.04 M, pH 2.0–12.0) were used as supporting electrolytes.

The exact composition of the tablet was given. Each tablet was labeled to contain 10 mg propranolol hydrochloride, 79 mg lactose, 3.39 mg calcium carboxymethyl cellulose, 0.71 mg gelatine and 1.9 mg magnesium sterate.

### 2.2. Apparatus

Differential-polarographic measurements were made by means of 394 electrochemical trace analyzer and PAR 303A static mercury drop electrode. The static mercury drop electrode mode was used. The counter and the reference electrodes were platinum and a saturated silver–silver chloride electrode, respectively.

### 2.3. Procedure

The drug was dissolved in de-ionized water to give a $10^{-2}$ M solution. The drug solution (1 ml) was pipetted into 1ml concentrated nitric acid contained in a test tube and the combined solution was sonicated for 60 s. The solution was then made up to 25 ml in a calibrated flask. A suitable aliquot was transferred into a polarographic cell, deoxygenated for 10 min with nitrogen gas and then the polarograms were recorded. The time of nitration was studied; no significant increase in the signal was observed when the nitration time was increased beyond 60 s. Spectrophotometric measurements were carried out with a Perkin–Elmer model 551 spectrophotometer using 1 cm quartz cell. The spectra were recorded between 200 and 400 nm, and quantitative sample measurements were made at 375 nm.

### 2.4. Tablets assay

Ten tablets of the pharmaceutical formulation were thoroughly ground until a fine powder was obtained. An amount of the powder, nominally corresponding to 20 mg of propranolol, was accurately weighed, dissolved in de-ionized water and 1 ml of concentrated nitric acid was added. The solution was sonicated and then made up to 25 ml with water. A suitable aliquot was taken from this solution in order to obtain a propranolol concentration in the cell within the calibration curve range. The same solutions as for the polarographic measurements were filtered of, diluted with de-ionized water and measured with spectrophotometer at 375 nm.

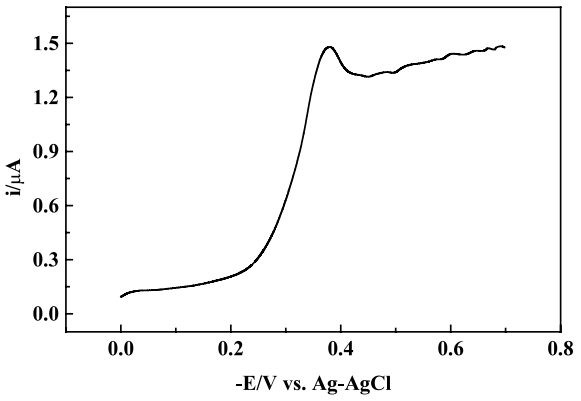


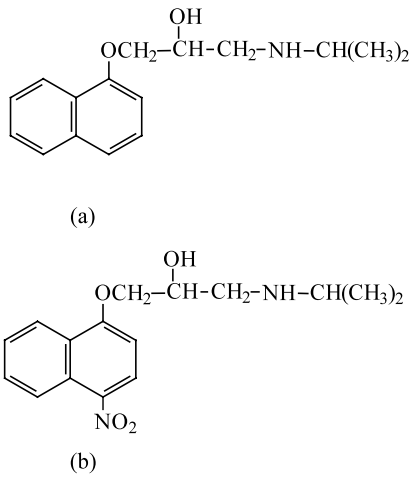

Fig. 1. Sampled dc polarograms of $5.0 \times 10^{-5}$ M nitrated propranolol in Britton–Robinson buffer at pH 2.0.

### 2.5. Synthesis and isolation of nitropropranolol

About 1.0 g of propranolol with 1.0 ml of concentrated nitric acid in a test tube was sonicated for 60 s. A yellow solid was precipitated. The precipitate was filtered of and dried into powder. The powder was analyzed in 1% potassium bromide pellets by Bruker Vector 22 IR spectrophotometer.

## 3. Results and discussion

Propranolol is not electroreducible at the mercury electrode as evidenced by the absence of polarographic signal in the available potential range. Consequently, we tried a derivatization method in order to transform the drug into an electroactive moiety, in this case a nitration procedure. According to the nitration procedure, only one wave (Fig. 1) is observed, which corresponds to the reduction of the aromatic nitro group. In addition, by following the limiting current of this wave, it is clear that the reaction occurs immediately after the addition of nitric acid to the drug with a yield of about 100%. In order to confirm the nitration procedure and identify the nitrated derivative we have used IR spectroscopy. We have confirmed that the nitration occurs by comparison of IR spectrum of propranolol with that of nitroderivative. The latter shows two bands at 1530 and 1300 $cm^{-1}$ which do not appear in the propranolol IR spectrum. These bands are characteristic of a nitro group in a *p*-position to a substituent with electron donating properties in an aromatic compound [19]. In accordance with the molecular orbital picture of naphthalene with α-substituent with electron-donating properties, the incoming substituent generally enter at 4-position (Scheme 1b). Consequently, the wave observed in acidic media may be attributed to a single six-electron irreversible reduction step of the nitro group to amine, since the *p*-alkoxy substituent in nitrated propranolol promotes the loss of water from the hydroxylamine derivative to form the easily reducible quinoid intermediate [20]. The nitropropranolol was stable and no current change was observed over the analysis time.




Scheme 1. Structural formulae of the (a) propranolol and the (b) nitropropranolol derivative.

The nature, pH and concentration of the supporting electrolyte all influence the voltametric response various supporting electrolysis, such as HOAc–NaOAc, $KH_2PO_4$–$K_2HPO_4$ and Britton–Robinson buffer solution were tested. It was found that Britton–Robinson buffer solution pH 2.0 resulted in the highest signal. This pH value was also recommended for the polargraphic determination of propranolol. The peak current of $5 \times 10^{-7}$ M was carried out in acidic buffer at pH 2.0 in different ionic strengths, 0.01, 0.05 and 0.1 M. The enhancement of peak current is decreased on increasing ionic strength. The method seems to be selective sine the addition of excipent did not interfere.

The effect of pH on peak current and peak potential was studied for $1 \times 10^{-5}$ M propranolol in a Britton–Robinson buffer over the pH range 2.0–12.0 by means of DP polarography. As can be seen from Fig. 2), the peak potential was shifted cathodically, showing a linear dependence between 2.0 and 11.0, implying the involvement of protons in the electrode process. The peak current remains practically constant over all the pH range. At pH 2.0, a single, well-resolved peak is observed at $-0.275$ (curve a, Fig. 3). This pH was recommended for analytical purposes.

Cyclic voltammograms obtained for $5.0 \times 10^{-5}$ M propranolol solution in Britton–Robinson

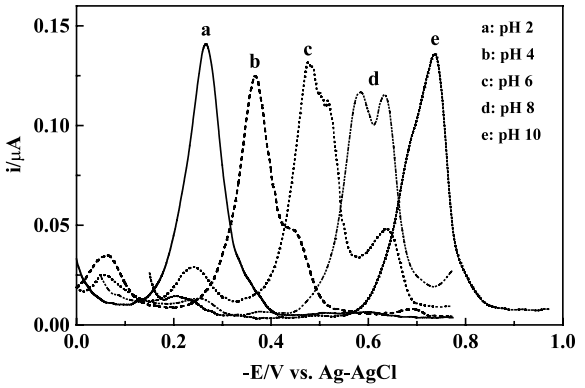



Fig. 2. Effect of pH on the DP polarographic peak of $1.0 \times 10^{-5}$ M nitrated propranolol in Britton–Robinson buffer.

buffer at pH 2.0 is shown in (Fig. 3). The cathodic peak due to the reduction of the nitrated propranolol can be clearly seen. On the reverse scan, there is no anodic peak in the voltammogram. On varying the potential scan rate, the cathodic peak current increased linearly with scan rate. These characteristics are typical of an irreversible reduction process of an adsorbed species.

### 3.1. Quantitative analysis

Typical calibration graph is shown in (Fig. 4);

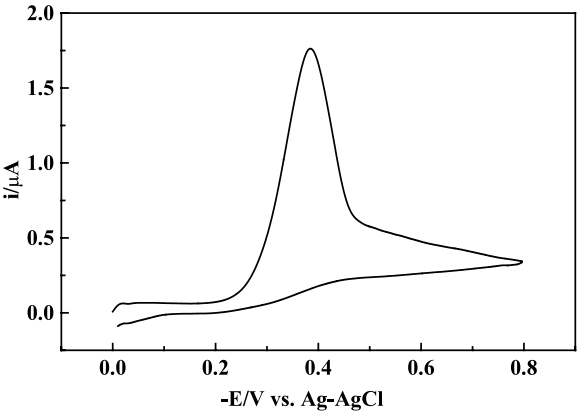



Fig. 3. Cyclic voltammograms of $5.0 \times 10^{-5}$ M nitrated propranolol in Britton–Robinson Buffer at pH 2.0.

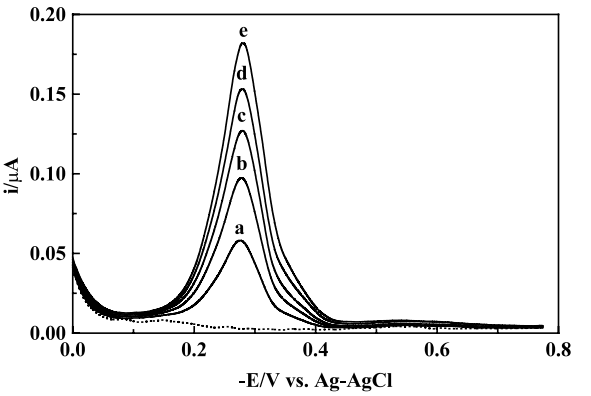



Fig. 4. DP polarograms of different concentrations of nitrated propranolol in Britton–Robinson at pH 2.0. Scan rate = 5 mV $s^{-1}$ and pulse amplitude = 25 mV. (a) 2.5; (b) 5.0; (c) 7.5; (d) 10.0; and (e) 12.5 μM.

the peak current of nitrated propranolol increases linearly with concentration in the range $5.0 \times 10^{-7}$–$5.0 \times 10^{-5}$ M. At concentration higher than $5.0 \times 10^{-4}$ M, a curvature of the calibration graph is observed. This curvature presumably indicates that a limiting value of the amount of the nitro-propranolol has been attained under the prescribed conditions. Further increases in concentration were not accompanied with an increase in amount of nitro-propranolol at the electrode owing to surface saturation, and peak current remained constant. The calibration curve is described by the following regression equation:

$$i_p\ (\mu A) = 0.033 \pm (0.0044) + 0.012 \pm (0.0053)C\ (\mu M);\quad r = 0.996,\ n = 10$$

where $i_p$ is the peak current and $C$ is the propranolol concentration). The detection limit calculated as $dl = 3s_I/m$, where, $s_I$ is the standard deviation of the intercept and $m$ is the slope, was $1.0 \times 10^{-7}$ M.

The precision data, expressed as RSD% value, was determined on $5.0 \times 10^{-6}$ M propranolol standard solution and was 1.95%. Addition of pure propranolol to sample of Inderal tablets at five different concentrations for the determination of the recovery studies leads to the follow-

Table 1
Comparison of DDP with UV standard for the determination of propranolol in some pharmaceutical preparations

| Drug | Trade name and source | Nominal content (mg/tablet) | Recovery (%)[a] [21] | |
|---|---|---|---|---|
| | | | DDP method | UV standard method |
| Propranolol | Inderal (Cairo Pharm. Co.) | 40 | $102.2 \pm 1.9$ | $101.0 \pm 1.3$ |
| | | 10 | $100.5 \pm 1.1$ | $101.0 \pm 1.4$ |

[a] Average of five measurements.

ing results: mean recovery is 99.7% with a mean RSD% of 2.1%.

The quality control assays of propranolol in Inderal tablets (10 mg/tablet), expressed as percentage of the label claim, gave results, which were near to 100% with relative standard deviation less than 3.0%. Furthermore, to obtain comparative results an UV spectrophotometric method was also developed. Nitro-propranolol shows a relatively strong UV adsorption maximum with higher absorbance at 375 nm. The Britton–Robinson buffer (pH 2.0) was chosen in order to employ the same medium as that used in the differential pulse polarographic method. The maximum exhibits a linear relation between absorbance and drug concentration between $1.0 \times 10^{-5}$ and $1.0 \times 10^{-4}$ M. The curve is described by the regression equation:

$$A = 6.30 \pm 0.21 \times 10^{-3} + 4.20 \pm 1.17 \times 10^{3} C \text{ (M)}; \quad r = 0.997,\ n = 10$$

where $A$ is the absorbance of nitro derivative at 375 nm and $C$ is the propranolol concentration. The results of the recovery assay (99.8% recovery, 2.7% RSD) and quality control assay (10 mg, 3.1%, RSD) are in accordance with the polarographic results Table 1.

The results obtained by both methods were statistically compared and no significant differences between the two methods regarding accuracy and precision as revealed by the $t$-test and $F$-test, respectively. The principle advantage of the polarographic method over the spectrophotometric one is that the excipients do not interfere and consequently no filtration procedure is necessary.

## 4. Conclusion

This study has provided a satisfactory method for the determination of propranolol based on the nitration of the drug followed by differential-pulse polarography of the nitro derivative. The proposed polarographic method is recommended as a useful tool for the analysis of propranolol in pharmaceutical form. Although it is indirect method, it is not time consuming as the derivatization process is rapid and the nitration had gone to completion (100%) immediately after the addition of nitric acid to the drug. The method describe herein is suitable for the determination of propranolol in tablet dosage form. The excepients present in formulation did not interfere with the assay at the same time, the analytical results confirm that the proposed method after accuracy and precision with the added advantage of the low cost, speed and simplicity.

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