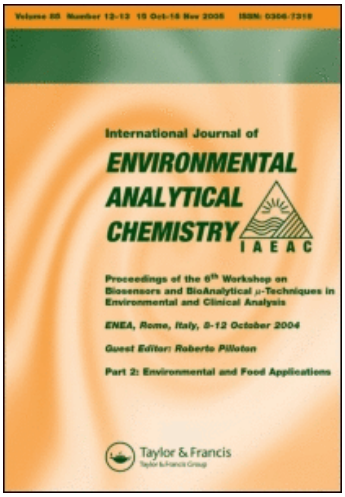

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Polarographic Determination of Butorphanol Tartrate

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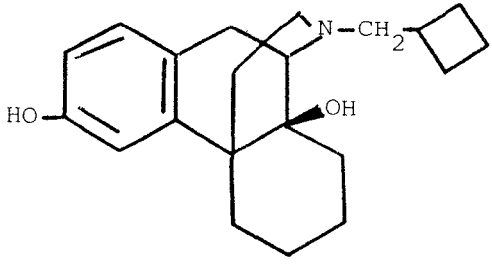
A new indirect polarographic method is proposed for the determination of butorphanol tartrate in the injectable solution form (Stadol$^{(R)}$). Direct-current polarography and differential pulse polarography (DPP) were applied for the study of authentic butorphanol and its injectable solution form in alkaline medium after nitration with 1 M potassium nitrite in presence of 1 M hydrochloric acid. The standard addition method was employed for the evaluation of the results and the mean percentage found for the injectable solution form was 99.2 ± 1.0.

KEY WORDS: Butorphanol tartrate, direct current polarography, differential pulse polarography, nitration procedure.

INTRODUCTION

Butorphanol, levo-N-cyclobutylmethyl-6, 10a-β-dihydroxy-1,2, 3,9,10, 10a-hexahydro-(4H)-10, 4a-iminoethano-phenanthrene, is a narcotic agonist-antagonist with potent analgesic activity comparable to that of morphine and meperidine.[1-10]



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The published methods[11] of detection and quantitative determination of butorphanol are based mainly on gas–liquid chromatographic techniques.

The work in this report describes a sensitive polarographic method proposed for the determination of the drug. Being a phenol with unsubstituted ortho- positions, butorphanol can be nitrated to give an ortho-nitrophenol derivative which can be readily reduced[12] at the dropping mercury electrode (DME). The nitration procedure adopted is the same as that for morphine since the structures of the two compounds are very similar

Aparatus, materials and reagents

(a) Metrohm Polarecord assembly (unit 626) consisted of three electrodes, namely a silver–silver chloride reference electrode, a platinum auxiliary electrode and the DME. The polarograph stand was model E505. The DME was a fine capillary fitted with a drop controller supplying a steady stream of mercury droplets at the frequency of $0.5\,sec^{-1}$ and a flow of approximately $3\,mg\,sec^{-1}$.

(b) Butorphanol tartrate:Authentic butorphanol powder (Lot: G9 × 22) and the injectable solution form (Stadol$^{(R)}$) 1 ml-Vials ($1\,mg\,ml^{-1}$) × Lot: C9JO4, were kindly received from Bristol Laboratories, Biological Research, Division of Bristol Myers Co., Syracuse, New York, U.S.A.

(c) Gelatin solution (maxima suppressor): 0.1% w/v freshly prepared in 1 M HCl.

Potassium nitrite (1 M), hydrochloric acid (1 M) and potassium hydroxide (20% w/v) were all prepared from analytical grade chemicals.

Standard Butorphanol Solution: Prepared as $1\,mg\,ml^{-1}$ in 1 M HCl.

Procedure

Carefully empty three vials of Stadol$^{(R)}$. Pipette 1 ml into the polarographic vessel, add 2 ml 1 M HCl followed by 6 ml of 1 M potassium nitrite. Mix, allow the solution to stand for 10 minutes and add 9 ml of 20% w/v potassium hydroxide followed by 3 ml of

0.1% w/v gelatin solution. Complete to 30 ml with distilled water. Deaerate for 10 min with a stream of nitrogen [$W(N_2) = 0.9999$] and polarograph the solution according to the set of polarographic parameters in Table I.

TABLE I

Polarographic parameters for the proposed method.

Mode	:	Differential pulse polarography (DPP)
Initial potential	:	−0.45 V
'drop/S	:	0.5
Sensitivity	:	5 nAmm^{-1}
Sweep rate	:	−5 mV sec^{-1}
Modulation amplitude	:	50 mV

Measure the total peak heights from the baseline.

Standard additions (spikes)

Add 2 ml 1 M potassium nitrite to 5 ml of the authentic butorphanol standard solution. Mix and allow to stand for 10 minutes. Add 3 ml potassium hydroxide (20% w/v). Add a known aliquot portion from this solution to the polarographed sample solution and repeat polarographing according to the parameters set in Table I. Measure the total peak heights and calculate the concentration of butorphanol tartrate (C_u) in the sample solution using the following expression.[13]

$$C_u = \frac{h_1 C_s V_s}{h_2 v_s + (h_2 - h_1) V_u}$$

where

h_1 = Peak height for sample,
h_2 = Peak height for sample and spike,
v_s = Volume of standard solution used for spike,
V_u = Volume of sample taken before spiking,
C_s = Concentration of standard used to spike,
C_u = Concentration of unknown in the sample.

RESULTS AND DISCUSSION

Butorphanol tartrate, being a phenol with free ortho-positions is readily nitrated to yield the corresponding nitro-derivative which is amenable to reduction at the DME under the appropriate applied potential.[12] The similarity of the structure of butorphanol to that of morphine indicates that a similar electroactive nitroderivative[14] can be produced with characteristics suitable for polarographic quantitative work. A typical cathodic wave recorded in the d.c. mode for the nitroderivative in the alkaline medium is shown in Figure 1. The wave consists of two irresolvable steps indicating a two-phase

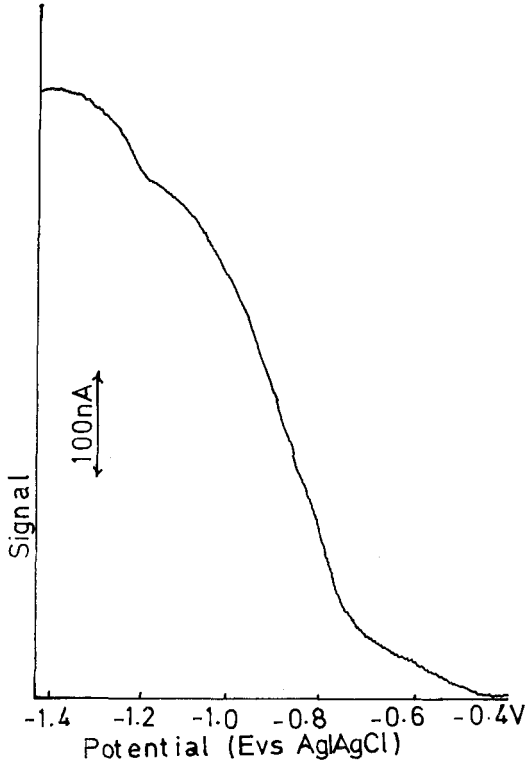

FIGURE 1 DC-Polarogram of butorphanol tartrate (1 mg/30 ml) in an alkaline medium. Damping = 2.

reduction reaction at the DME. This is confirmed by the two peaks obtained in the differential pulse polarogram (Figure 2).

Polarography in the d.c. mode was used to check the relation between the square root of the mercury height (corrected for the back (pressure) and the limiting current of a solution of 1 mg/30 ml butorphanol tartrate. The linearity found suggests that the current (i) is diffusion controlled.

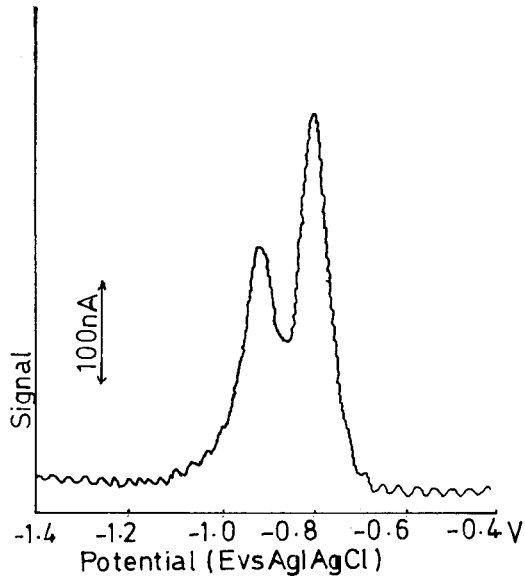

FIGURE 2 Typical differential pulse polarogram (DP50) of butorphanol tartrate in alkaline medium. Damping = 2.

The logarithmic plot, $\log((i_L - i)/i)$ vs E, where i_L is the limiting current and E is the applied potential, calculated with values from d.c. polarogram of 1 mg/30 ml solution of nitrated butorphanol tartrate, was linear within experimental error. The number of electrons (n), involved in the reduction process calculated from the slope was 5.4. It is probable that the nitroderivative of butorphanol tartrate undergoes a 6-electron reduction to yield the corresponding amine. Further, the differential pulse polarogram (Figure 2) suggests

that the reduction occurs in two phases. The second peak height is approximately 1/3 of the total peak heights indicating that two electrons (out of 6) are probably involved in the second phase of the reduction process.

To establish the linearity for the standard additions method, a series of standard solutions of authentic butorphanol tartrate was polarographed after nitration. A calibration curve was obtained showing linearity between total peak height and concentration over the range 0.5 mg/30 ml to 4.0 mg/30 ml.

Table II summarises the results of analysis of butorphanol injectable solution (Stadol$^{(R)}$) using the proposed method. The mean percentage found is 99.2 with a standard deviation of $\pm 1.0\%$.

TABLE II

Proposed polarographic determination of butorphanol tartrate.

Claimed amount of butorphanol tartrate injectable (Stadol$^{(R)}$) (mg/30 ml)	Added amount of authentic butorphanol tartrate (mg/30 ml)	Percentage found
0.5	0.5	98.9
1.0	1.0	98.5
1.5	0.5	100.7
2.0	1.0	100.1
1.0	2.0	99.0
2.0	2.0	98.1
		Mean percentage = 99.2
		Standard deviation = $\pm 1.0\%$

[a]Total volume of polarographic vessel is 30 ml.

Acknowledgement

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