CROATICA CHEMICA ACTA
CCACAA **79** (4) 541–544 (2006)

ISSN-0011-1643
CCA-3122
Original Scientific Paper

Differential Pulse Polarographic Studies of Risperidone in Pharmaceutical Formulations

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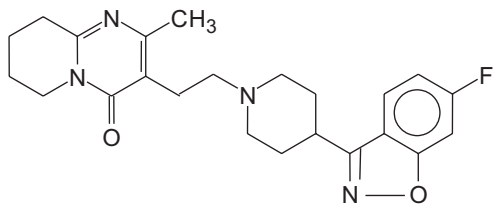
RECEIVED AUGUST 31, 2005; REVISED FEBRUARY 13, 2006; ACCEPTED FEBRUARY 28, 2006

A simple and rapid differential pulse polarographic method has been developed for trace determination of risperidone. A well-defined single peak with *E*p value of –1.54 V is obtained in Britton-Robinson buffer (pH = 8.0). The linearity is valid up to 5×10^{-5} mol/L (r = 0.9995) with minimum detection limit of 2×10^{-7} mol/L. Precision of the method developed is implied from the values of the relative mean deviation, standard deviation and coefficient of variation, which are 2.4 %, 0.016 % and 3.2 %, respectively. Commercial formulations of risperidone were analyzed by calibration and standard addition methods. Recovery experiments were found to be quantitative and the determined mass per tablet was obtained within ± 0.2 % of the expected value. The studies have shown that the method is simple, reproducible and accurate and can be used in the analysis of commercial formulations.

Keywords
differential pulse polarography
risperidone

INTRODUCTION

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*] pyrimidin-4-one is commonly known as risperidone and has the following structure.



Risperidone is an antipsychotic drug used for patients suffering from schizophrenia or other psychiatric diseases. It is also used for cases showing psychotic symptoms of depressive disorders.

The HPLC method is commonly used for the trace analysis of risperidone.[1,2] Liquid chromatographic separation with UV detection has been reported by Avenoso *et al.*[3] Other instrumental techniques used for the analysis of risperidone are capillary zone electrophoresis and first order derivative spectrophotometry.[4] Quantitative estimation of risperidone has been carried out in human plasma,[5] serum,[6] urine,[7] and human hair[3] by techniques such as HPLC and liquid chromatography combined with tandem mass spectrometry. Simultaneous determination of risperidone and its major metabolite 9-hydroxy risperidone was developed by Woestenborghs *et al.*[8] and applied to its determination in plasma, urine and animal tissue.

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Recently, Meng *et al.*[9] have reported an electrochemical method for risperidone determination. Electrochemical behavior of risperidone and the mechanism of electrode reactions have also been discussed. However, the detection limit obtained by this method was found to be lower compared to the known method. Also, the linear range was found to be much wider than the reported values. The developed method has also been applied to quantify the compound in commercial formulations.

EXPERIMENTAL

Apparatus

Differential pulse polarographic studies of risperidone were carried out with a Metrohm Polarecord E-506 Serie-03 connected to the Metrohm polarography stand E-505. The electrode assembly consisted of a dropping mercury electrode (DME) as working electrode, Ag/AgCl (sat. KCl) as reference electrode and a platinum auxiliary electrode. Nitrogen gas was used for deaeration. Mercury was purified by agitation for about 12 h in contact with 10 % nitric acid, followed by thorough washing with distilled water and further distillation under reduced pressure in a mercury distillation unit.

Reagents and Solutions

All chemicals used were of analytical reagent (AR) grade. Solutions were prepared in doubly distilled water. A standard solution of pure risperidone sample was prepared by dissolving 0.2 g of the substance in 50 mL of dimethyl formamide (DMF) and the volume was made up to 100 mL with doubly distilled water (DDW). The compound was insoluble in water but was found to be stable for about three weeks in a DMF-water mixture. In the present work, the solution was prepared afresh every seven days. A 0.1 % aqueous solution of Triton-X-100 was used to eliminate the polarographic maxima.

0.04 mol/L Britton-Robinson solution was used as base electrolyte while pH was adjusted (pH = 3.0–10.0) by adding an appropriate volume of 0.2 mol/L NaOH solution. The other buffer systems studied were acetate buffer (pH = 4.0–6.0), borate buffer (pH = 7.5–11.0), McIlavaine buffer (pH = 3.5–6.5), Clark-Lubs buffer (pH = 5.0–10.0) tetramethyl ammonium iodide (TMAI) and tetraethyl ammonium bromide (TEAB).[10]

General Procedure

To an aliquot containing 30 μg of risperidone 15 mL of the selected buffer (Britton-Robinson buffer pH = 8.0), 0.5 mL of 0.1 % Triton-X-100 was added and the total volume of the solution was made up to 25 mL. The solution was deaerated for 20 min with nitrogen. The polarograms were recorded with the recorder settings given below:

Starting potential	–0.6V	Paper speed	60 mm min^{-1}
Pulse amplitude	100 mV	Scan rate	6 mV s^{-1}
Drop time	2 s	Sensitivity	1×10^{-8} A / mm

In all cases a blank recording was first performed with the base electrolyte solution, and suitable blank correction was applied in the calculations if necessary. Experiments were repeated three times to ensure reproducibility of the results.

RESULTS AND DISCUSSION

Effect of pH

The polarograms of risperidone were recorded in different buffer systems. No peak was obtained in Britton-Robinson buffer from pH = 3.0 to 5.5. At pH greater than 6.0, initially a small unsymmetrical peak was observed. From pH = 7.5 to 8.5, the peak became symmetrical. At higher pH values (> 8.5), the peak became unsymmetrical again. The change in the *E*p value was from –1.48 to –1.63 V in the pH range 6.0 to 10.0. In acetate buffer, no peak was observed up to pH = 5.0 after which, at pH = 5.5 and 6.0, an unsymmetrical peak with *E*p value of –1.50 V and –1.52 V was recorded. In borate buffer, in the pH range 9.0 to 10.0, the *E*p value changed from –1.49 to –1.52 V while at other pH values no peak was obtained. In Mcllavaine buffer, from pH = 6.5 to 7.0, the *E*p value shifted from –1.40 to –1.45 V and at lower pH values no peak was observed. The shift in the *E*p value was from –1.45 to –1.55 V in the pH range 6.0 to 10.0 in Clark-Lubs buffer. No peak was obtained in TMAI or TEAB. Britton-Robinson buffer (pH = 8.0) was selected because it gave a narrow symmetrical peak.

Effect of pH on peak current and peak potential in Britton-Robinson buffer is shown in Figure 1.

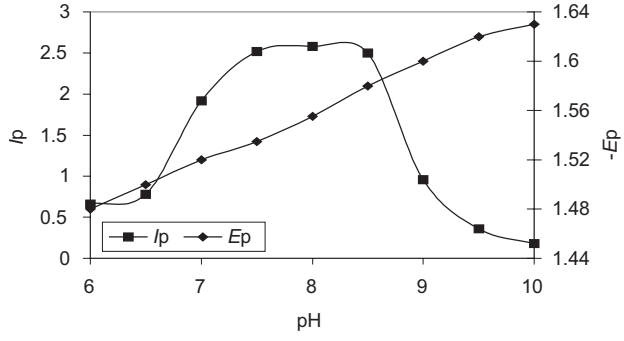

Figure 1. Effect of pH on peak current (*I*p) and peak potential (*E*p) for 2×10^{-6} mol/L RIS.

Effect of Maxima Suppressor

The effect of maxima suppressor was studied using Triton-X-100, gelatin and bromophenol blue. In the absence of maxima suppressor, the peak was highly un-

symmetrical. Addition of gelatin (0.1 %, 0.5 mL) and bromophenol blue (0.1 %, 0.5 mL) did not improve the symmetry of the peak either. With addition of 0.5 mL of 0.1 % Triton-X-100, a narrow, symmetrical peak was obtained. With every 0.5 mL addition of Triton-X-100 there was an about 8 % decrease in the diffusion current. Hence, 0.5 mL of 0.1 % Triton-X-100 was selected as the optimum concentration for further studies.

Other Parameters

Diffusion current increased linearly with an increase in the drop time of 0.4–2.0 s with an *I*p value of 0.17–0.45 μA. At drop times above 2 s, the increase was not linear. With an increase in pulse amplitude from 20 to 100 mV, the diffusion current showed a linear increase. Thus, the drop time of 2 s and pulse amplitude of 100 mV were selected for further studies.

Reversibility

A graph of E versus log $(I/I_d - I)$ from a DC polarogram showed that it was a diffusion controlled process. A series of DC polarograms were recorded at varying concentrations and $E_{1/4} - E_{3/4}$ was calculated; it was found to be greater than 56 mV. The value of the slope calculated from the graph of E versus $\log(I/I_d - I)$ was higher than 59.2 mV. In the differential pulse mode, the graph of *I*p versus $v^{1/2}$ (v = scan rate) did not pass through the origin, and the value of *E*p also showed a change with a change in drop time. This implied that the reaction taking place at the electrode was irreversible.[11,12]

Calibration and Validation

A linear calibration plot was obtained from 5.0×10^{-7} mol/L to 5.0×10^{-6} mol/L of risperidone with the equation of regression line y / μA = 0.016 + 0.15 x / μM and the coefficient of correlation 0.9995 indicating a high degree of current-concentration linearity in this range. The *E*p value obtained was in the range of –0.89 to –1.50 V, which is attributed to the reduction of keto (>C=O) group.[13] The lowest determinable limit of risperidone was found to be 2.0×10^{-7} mol/L.

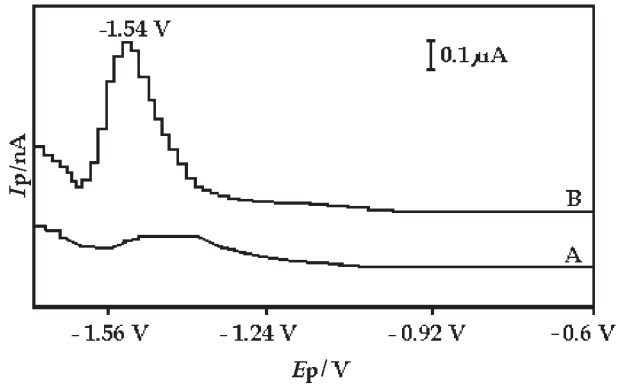

Figure 2. (A) Typical polarograms of Britton-Robinson buffer (pH = 8.0), and (B) after addition of 30 μg RIS.

The relative mean deviation (RMD), standard deviation (SD) and coefficient of variation (CV) were calculated for 10 repetitive recordings for 1.0×10^{-6} mol/L risperidone solution. These values were found to be 2.4 %, 0.016 % and 3.2 %, respectively.

A typical polarogram obtained under optimum conditions is shown in Figure 2. It clearly shows a distinct peak with peak potential –1.54 V.

Application

Utility of the method developed was observed by its application to the determination of risperidone in two commercial formulations, namely Risdone and Sizodone. Twenty tablets of the drug samples were weighed and finely powdered. Powder equivalent to 20 mg of RIS was weighed accurately and dissolved in 50 mL DMF. The solution was filtered and made up to 100 mL with doubly distilled water. Different aliquots of this solution were analyzed using the calibration curve and standard addition methods. The results obtained by these methods are shown in Table I.

TABLE I. Determination of risperidone in commercial formulations

Drug sample	Amount of risperidone /mg		
	Reported value	Observed values*	
		Calibration curve method	Standard addition method
Risdone	2.0	1.99 ± 0.03	2.005 ± 0.003
Sizodone	2.0	1.97 ± 0.02	1.99 ± 0.008

*Avg ± SD of 5 observations

Recovery Experiment

To determine the percentage recovery, a set quantity of risperidone sample solution was taken and three different (0.2, 0.4, 0.6 mg) levels of working standard ris-

peridone were added to it. At each level, the polarograms were recorded seven times and the amount of risperidone was computed using the formula:

$$\text{Percentage recovery} = \frac{N(\sum XY) - (\sum X)(\sum Y)}{N(\sum X^2) - (\sum X)^2} \times 100$$

where N is the number of observations, X is the amount of drug added and Y is the amount of drug obtained. The same procedure was adopted for both commercial samples of risperidone at two different initial concentrations. The average percentage recovery for Risdone was 99.91 % and for Sizodone 101.23 %.

CONCLUSION

An easy, simple and rapid DPP method is proposed for the study of risperidone. In Britton-Robinson buffer of pH = 8.0, it gives a narrow symmetrical peak, and the lowest determinable limit is 2.0×10^{-7} mol/L. The polarographic reduction is diffusion controlled and irreversible. The method can be applied to analyze commercial formulations. The mass of RIS present per tablet could be determined as well. Preparation of the sample solution using commercial formulations is also simple and no matrix effect was observed. The developed method is sensitive, convenient and can be used for routine analysis.

Acknowledgements. – The authors are grateful to the Alexander von Humboldt Foundation of Germany for the donation of the Metrohm Polarograph and to the Department of Pharmacy, Nagpur University, Nagpur, India, for providing the drug sample.

REFERENCES

1. O. V. Olesen and K. Linnet, *J. Chromatogr., B: Biomed. Sci. Appl.* **698** (1997) 209–216.
2. M. C. Price and D. W. Hoffman, *Therap. Drug Monit.* **19** (1997) 333–337.
3. A. Avenoso, G. Faccida, M. Salemi, and E. Spina, *J. Chromatogr., B: Biomed. Sci. Appl*. **746** (2000) 173–181.
4. X. Lui, C. Fu, L. Li, and X. Wang, *Zhongguo Yiyao Gongye Zazhi* **32** (2001) 174 –178.
5. M. Aravagiri, S. R. Marder, D. Wirshing, and W. C. Wirshing, *Pharmacopsychiatry* **31** (1998) 102–109.
6. M. Aravagiri and S. R. Marder, *J. Mass Spectrom*. **35** (2000) 718–724.
7. A. E. Balant-Gorgia and M. Gex-Fabry, *Therap. Drug Monit.* **21** (1999) 105–115.
8. R. Woestenborghs, W. Lorreyen, F. Van Rompaey, and J. Heykants, *J. Chromatogr., B: Biomed. Appl*. **583** (1992) 223–230.
9. Z. Meng, J. Zheng, and X. Zhu, *Acta Chim. Sinica,* **63** (2005) 827–833.
10. J. A. Dean, *Lange's handbook of chemistry*, 13th ed., McGraw Hill, New York, 1985, pp. 5–104.
11. Z. Galus, *Fundamentals of electrochemical analysis*, 1st ed., Ellis Horwood, England, 1976, p. 223.
12. A. K. Mishra and K. D. Gode, *Analyst* **110** (1985) 31–34.
13. G. Henze and R. Neeb, *Elektrochemische analtik,* 1st ed. Springer-Verlag, Berlin, Heidelberg, New York, 1986, p. 224.

SAŽETAK

Istraživanje risperidona u farmaceutskim pripravcima diferencijalnom pulsnom polarografijom

Christine Jeyaseelan, Ravin Jugade i Arun P. Joshi

Razvijena je brza i jednostavna metoda za analizu tragova risperidona korištenjem diferencijalne pulsne polarografije. U Britton-Robinsonovom puferu pH = 8,0 javlja se samo jedan, dobro definirani odziv s vršnim potencijalom jednakim –1,54 V. Za koncentracije risperidona manje od 5×10^{-5} mol/L ovisnost vršne struje o koncentraciji je linearna (r = 0,9995), a granica detekcije iznosi 2×10^{-7} mol/L risperidona. Preciznost metode procijenjena je korištenjem relativne srednje devijacije, standardne devijacije i koeficijenta varijacije, koje iznose 2,4 %, odnosno 0,016 i 3,2 %. Analizirani su komercijalni pripravci risperidona uporabom kalibracijskog pravca i metode standardnih dodataka. Rezultati analize pokazuju da se risperidon može kvantitativno određivati, a izmjerene koncentracije u skladu su sa nominalnim vrijednostima, uz pogrešku od ±2 %. Istraživanja su pokazala da je predložena metoda jednostavna, reproducibilna i točna i da se može koristiti za analizu komercijalnih pripravaka.