ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
29 (2002) 239–245

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

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Derivative spectrophotometric determination of droperidol in presence of parabens

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Received 17 September 2000; received in revised form 23 January 2002; accepted 10 February 2002

Abstract

We have developed a fast and accurate method for the determination of droperidol in the presence of methylparaben and propylparaben using derivative spectrophotometry. The first derivative amplitudes at 255.2 nm were selected for the assay. Calibration graph follows Beer's law in the range of 5–35 μg ml^{-1}. The coefficient of variation (CV) for intra-day and inter-day precision were less than 1.0 and 2.0%, respectively. The method was applied in the quality control of commercial oral and injection solutions and proved to be suitable for routine analysis.

Keywords: Droperidol; Neuroleptic; Derivative spectrophotometry

1. Introduction

Droperidol, 1-[1-[4-(4-fluorophenyl)-4-oxobutyl]-1,2,3,6tetrahydropyridin-4-yl]-2,3 dihydro-1H-benzimidazol-2-one, a neuroleptic drug, is widely used in psychiatry and anesthesiology. Various methods have been reported in the literature for its determination. These include UV spectrophotometry [1], colorimetry [2], fluorimetry [3,4], voltammetry [5–7], gas chromatography [8–10] and high performance liquid chromatography [11–16]. However, no derivative spectroscopic studies on droperidol are available.

This paper introduces a direct method using derivative UV spectrophotometry for the determination of droperidol in the presence of methylparaben and propylparaben. The method was applied to pharmaceutical preparations. The advantage of the proposed technique is the speed, selectivity and ease of performing the assay.

2. Experimental

2.1. Apparatus

Absorption spectra and measurements were performed in 1 cm quartz cells using a shimadzu UV-160 recording double beam UV-visible spectrophotometer capable of taking first to fourth order derivative spectra. The pH values were measured with a SCHOTT CG 825 pH meter.

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0731-7085/02/$ - see front matter
PII: S0731-7085(02)00095-X

2.2. Reagents and solutions

All solvents and reagents were of analytical reagent grade. Droperidol was donated by Janssen Pharmaceutica (Beerse, Belgium). In order to prepare droperidol stock solution (100 μg ml^{-1}), 10 mg were accurately weighed, dissolved in 3 ml methanol and completed to 100 ml with a diluting solution consisting on an acidified water adjusted to pH 3.4 by using aqueous lactic acid solution (1%). Both methyl parahydroxybenzoate (methylparaben) and propyl parahydroxybenzoate (propylparaben) were donated by Pharmaghreb Laboratories (Tunisia). A total of 50 μg ml^{-1} methylparaben stock solution and a 5 μg ml^{-1} propylparaben stock solution were prepared in the same manner as droperidol. Two sets of working standard solutions of droperidol (5–35 μg ml^{-1}) were prepared by dilution of stock solution in the diluent (described previously). One set contained droperidol only (standard solution: ST) while the other contained a constant amount of methylparaben (0.5 μg ml^{-1}) and propylparaben (0.05 μg ml^{-1}) in addition to droperidol (reconstituted solution formulation: RSF). Injectable and oral solution dosage forms of Droleptan were obtained from Janssen and were subjected to the general procedure.

2.3. Validation parameters

Linearity, accuracy and precision were determined according to the statistical method of validation described previously [17]. The percentage recovery of the droperidol was computed from the regression equation.

3. Results and discussion

3.1. Spectrophotometric measurements

The absorption (zero-order) spectra of droperidol, methylparaben and propylparaben in the 200–350 nm wavelength region are reported in Fig. 1. The large overlap of the spectral bands of the three components prevents determination of droperidol by direct absorbance measurements of the total zero-order spectrum. Fig. 2 shows that the zero crossing points occur at 217.8, 225.2 and 255.2 for methylparaben and at 217.4, 225 and 255.2 nm for propylparaben. At these wavelengths it is possible to take derivative measurements of the mixture proportional to the droperidol concentration only. Thus, the wavelength at 255.2 nm was selected as optimal for the quantification of droperidol with the key entry $N = 2$ (a kind of smoothing factor) since this

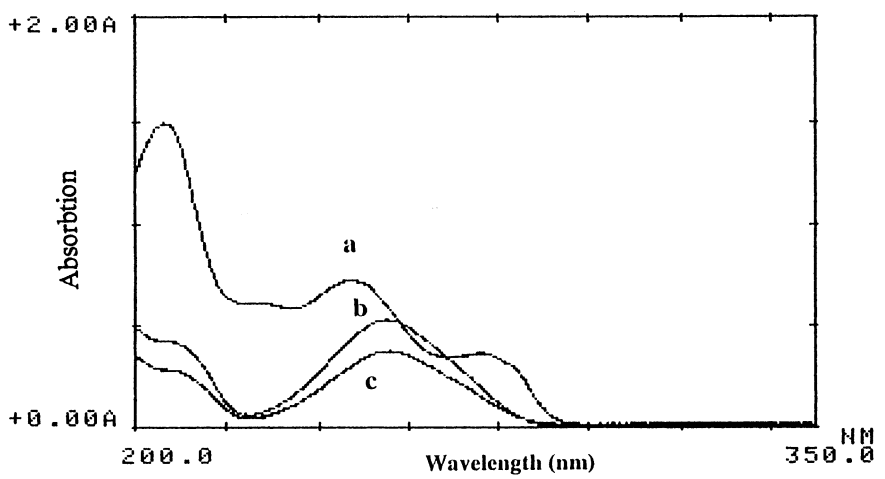

Fig. 1. Absorbtion spectra of (a) droperidol (20 μg ml^{-1}), (b) methylparaben (5 μg ml^{-1}) and (c) propylparaben (2 μg ml^{-1}). The reference was acidified water adjusted to pH 3.40 with lactic acid solution (1%).

Table 1
Statistical study of linearity

Type of solution tested Range of concentration	Standard solution (ST) 5–35 μg ml^{-1}				Reconstituted solution formulation (RSF) 5–35 μg ml^{-1}			
	D0	D1	D2	Mean	D0	D1	D2	Mean
Slope	5.007×10^{-3}	5.002×10^{-3}	5.193×10^{-3}	5.067×10^{-3} (RSD = 2.14%)	5.086×10^{-3}	5.014×10^{-3}	5.179×10^{-3}	5.093×10^{-3} (RSD = 1.62%)
Intercept	1.143×10^{-3}	-7.143×10^{-3}	-5.286×10^{-3}	-3.762×10^{-3}	-5.714×10^{-4}	1.286×10^{-3}	4.286×10^{-3}	1.667×10^{-3}
Correlation coefficient.	0.9998	0.9997	0.9999	–	0.9991	0.9998	0.9998	–
Comparison of slope (t test)	$t = 0.3252$ (ns)				Theoretical value t (0.05, 4) = 2.776			
Comparison of intercept (t test)	$t = 2.1265$ (ns)				Theoretical value t (0.05, 4) = 2.776			

t (0.05, 4) = 2.776
ns, not significant.

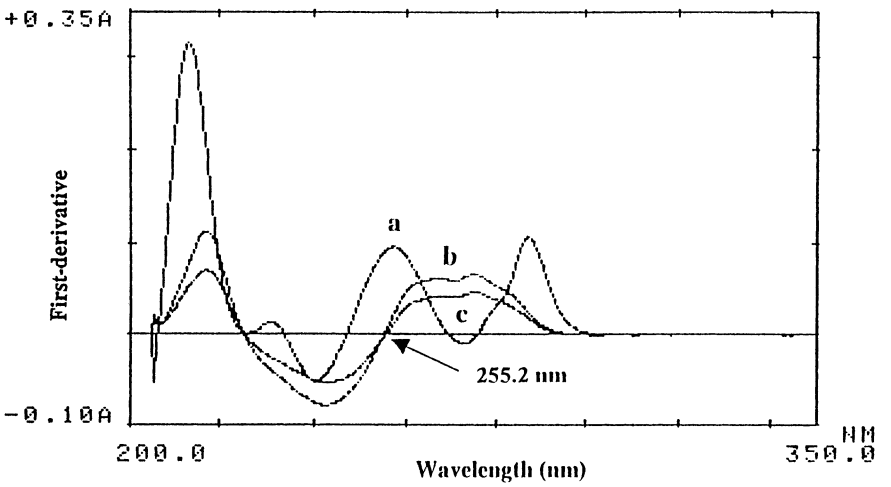

Fig. 2. First derivative mixtures of (a) droperidol (20 μg ml^{-1}), (b) methylparaben (5 μg ml^{-1}) and (c) propylparaben (2 μg ml^{-1}). The reference was acidified water adjusted to pH 3.40 with lactic acid solution (1%).

Table 2
Precision of the method

	Repeatability $n = 8$ within 1 day			Reproducibility $n = 24$ within 3 days		
Concentration of droperidol (μg ml^{-1})	10	20	30	10	20	30
Amount found (μg ml^{-1})	9.90	20.12	30.10	9.66	20.26	30.40
RSD (%)	1.00	0.48	0.33	2.00	1.60	0.95

wavelength is common for the two parabens and does not show interference by adding high amounts of methylparaben or propylparaben to a known concentration of droperidol solution.

3.2. Calibration curve and statistical analysis

The linearity of the method was established from first derivative spectra by measuring the

Table 3
Accuracy/recovery of droperidol in synthetic mixtures with parabens by first derivative spectrophotometry

Amount added (μg ml^{-1})			Droperidol		
Droperidol	Methylparaben	Propylparaben	Found* (μg ml^{-1})	Recovery (%)	RSD (%)
5.0	0.5	0.05	5.09	101.9	1.14
10.0	0.5	0.05	9.81	98.0	1.34
15.0	0.5	0.05	14.98	99.8	0.80
20.0	0.5	0.05	20.02	100.1	1.51
25.0	0.5	0.05	25.06	100.2	0.80
30.0	0.5	0.05	30.29	100.9	1.40
35.0	0.5	0.05	34.74	99.2	1.08

* Mean for three determinations.

Table 4
Determination of droperidol in commercial formulations

Formulation	Composition (mg ml^{-1})	Derivative spectrophotometric method			HPLC (USP method)			Statistical study (Student test)	
		Found* (mg ml^{-1})	Recovery (%)	RSD (%)	Found* (mg ml^{-1})	Recovery (%)	RSD (%)	Theoretical value	Calculated values
Droleptan injection	Droperidol (5)	5.20	104.0	1.92	5.01	100.2	1.36		2.6 (ns)
Droleptan Oral solution 1	Droperidol (20), methylparaben (0.5) and propylparaben (0.05)	20.25	101.3	0.60	20.20	101.0	1.55	t (0.05, 4) = 2.776	0.26 (ns)
Droleptan Oral solution 2	Droperidol (20), methylparaben (0.5) and propylparaben (0.05)	20.40	102.0	0.60	20.02	100.1	1.10		2.41 (ns)

* Mean of three determinations.
ns: not significant.

absorbance at 255.2 nm ($N = 2$) of standard at seven concentration levels in the range listed in Table 1. The experiments showed that the absorbance was proportional to droperidol concentration. The obtained results are summarized in Table 1. The linearity of the calibration graph and the adherence of the method to Beer's law are validated by the high value of the correlation coefficient and by the value of the intercept on ordinate, which is close to zero. In addition data of slope and intercept obtained for standard solution (ST) and reconstituted solution (RSF) were statistically comparable. Furthermore no interference from parabens were observed.

3.3. Accuracy and precision

The precision of the method was assessed by carrying out eight replicate determinations of three concentrations of droperidol solutions, (10, 20, 30 μg ml^{-1}) to a constant amount of methylparaben (0.5 μg ml^{-1}) and propyl paraben (0.05 μg ml^{-1}) for 3 consecutive days (Table 2). The coefficient of variation for intra-day and inter-day were less than 2%. Thus, it was concluded that there was no significant difference for the assay which was tested within day and between days. The accuracy of the method was demonstrated by spiking samples of droperidol solutions prepared in our laboratory such that their composition was similar to those of the formulations found on the market, with known amounts of the active ingredients in presence of parabens. Satisfactory recoveries (Table 3) were obtained and no significant differences were observed between the amount of droperidol added and the amount found which indicated the accuracy of the method.

3.4. Sensitivity

The detection (DL) and quantification limits (QL) were calculated by using equations given in the International Conference on Harmonisation (ICH) guideline [18]:

$$\mathrm{DL} = \frac{3.3\sigma}{S} \quad \text{and} \quad \mathrm{QL} = \frac{10\sigma}{S}$$

where σ is the noise estimate and is the S.D. of the three blank responses and S is the slope of calibration curve of the droperidol. In this condition the DL and the QL found are 0.30 and 0.91 μg ml^{-1}, respectively.

3.5. Marketed products analysis

The proposed method was compared to the HPLC method of the USP [19] for the determination of the drug in injectable form and in oral solution of Droleptan. The oral formulation contains parabens as preservatives. The results reported in Table 4 were in good agreement with the label values, indicating that the excipients did not interfere with the analysis. In addition, comparison between the two methods based on the t test shows no significant difference.

4. Conclusion

Precise, economical, simple and rapid, since no treatment of the sample is required before the analysis, the proposed method could be applied successfully to the droperidol assay in pharmaceutical formulations without the interference of parabens.

Acknowledgements

The authors thank Professor S. Ben Rejeb (faculté des Sciences, Tunis) for his helpful discussion.

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