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Zero-crossing derivative spectrophotometry for the determination of haloperidol in presence of parabens

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Abstract

First derivative spectrophotometry with a zero-crossing technique of measurement is used for the quantitative determination of haloperidol in the presence of methylparaben and propylparaben, which is added as antimicrobial preservatives in pharmaceuticals. This technique permits the quantification of haloperidol in the presence of parabens, with closely overlapping spectral bands, and without any separation step. Linear calibration graphs of first derivative values (at 255.2 nm for haloperidol) versus concentration (in the range 4.0–20.0 μg ml^{-1}) were obtained with negligible intercepts. Relative standard deviation of 0.83% was obtained for intra-day precision and 1.86% for inter-day precision. The recovery of haloperidol in synthetic mixtures with parabens and in pharmaceutical dosage forms is also reported. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Haloperidol; Methylparaben; Propylparaben; Derivative spectrophotometry

1. Introduction

Haloperidol, a butyrophenone compound, is a neuroleptic used mainly for the symptomatic treatment of psychoses [1].

Methylhydroxybenzoate (methylparaben) and propylhydroxybenzoate (propylparaben) are added as preservatives in oral and injectable solutions of haloperidol.

Many methods have been reported for the assay of haloperidol in pharmaceutical preparations. Spectrophotometric methods usually involve extractions [2].

The interference of other chromophores such as phenolic preservatives can be a disadvantage; this interference can be overcome by chromatographic methods such as high performance liquid chromatography [3,4]. However, these methods require expensive equipment and considerable skill is necessary to operate them successfully.

In pharmaceutical analysis, Fell [5] has demonstrated the possibilities offered by derivative spectrophotometry. This technique has proven useful in the assay of single components in the presence of excipients [5,6] or degradation products [7,8] and in the analysis of two-component mixtures [9–11].

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This paper describes a direct method based on derivative spectrophotometry for the determination of haloperidol in the presence of methylparaben and propylparaben and its application to pharmaceutical preparations.

2. Materials and methods

2.1. Reagents and standard solutions

Haloperidol was purchased from Sigma Chimie (France). A 0.20 mg ml^{-1} haloperidol stock solution was prepared in methanol.

Methylparaben and propylparaben were purchased from Sigma Chimie (France). A 0.15 mg ml^{-1} methylparaben stock solution and a 0.03 mg ml^{-1} propylparaben stock solution were prepared in methanol.

Working standard solutions of haloperidol (4–20 μg ml^{-1}) containing methylparaben (1.5–15 μg ml^{-1}) and propylparaben (0.3–3 μg ml^{-1}) were obtained by dilution of the stock solutions with 0.1 M hydrochloric acid and mixing.

Injectable and oral solution dosage forms of Haldol (Janssen) were utilized and subjected to the general procedure.

2.2. Apparatus

All spectral measurements and treatment of data were carried out in 1 cm quartz cells using a Shimadzu UV 160A double beam recording spectrophotometer. This system permits derivative processing of spectra.

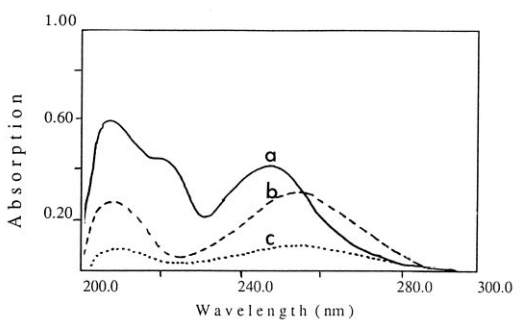

Fig. 1. Absorption spectra of (a) haloperidol (12 μg ml^{-1}); (b) methylparaben (3 μg ml^{-1}); and (c) propylparaben (0.9 μg ml^{-1}). The reference was 0.1 M HCl.

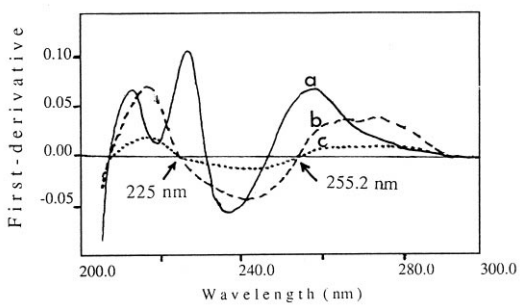

Fig. 2. First derivative spectra of (a) haloperidol (12 μg ml^{-1}); (b) methylparaben (3 μg ml^{-1}); and (c) propylparaben (0.9 μg ml^{-1}). The reference was 0.1 M HCl.

3. Results and discussion

3.1. Spectrophotometric measurements

Fig. 1 shows the absorption (zero-order) spectra of haloperidol, methylparaben and propylparaben.

The large overlap of the spectral bands of the three components at 200–300 nm prevents the formation from the total zero-order spectrum of any spectral future that could be used for analytical purposes.

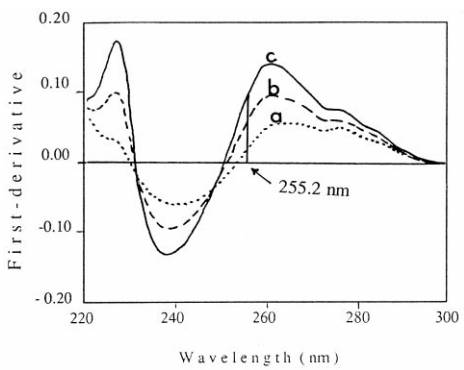

Fig. 3. First derivative mixtures of (a) methylparaben (3 μg ml^{-1}); (b) propylparaben (0.3 μg ml^{-1}); and (c) haloperidol (4, 12 and 20 μg $^{-1}$) in curves a, b and c, respectively). The reference was 0.1 M HCL.

Table 1
Statistical analysis of calibration graph in the determination of haloperidol (4–20 μg l^{-1}) by first derivative spectrophotometry at $\lambda = 255.2$ nm

Slope (10^3)	5.071
Intercept (10^3)	−0.3
Correlation coefficient	1.000
Standard deviation of the slope (10^4)	0.19
Standard deviation of the intercept (10^4)	2.58
Test of significance of the intercept ($P = 0.05$; df = 13)	$t_{experimental} = -1.161$, $t_{theoretical} = 2.16$
Test of significance of the slope ($P = 0.05$; $df_1 = 1$; $df_2 = 13$)	$F_{experimental} = 68\,354$, $F_{theoretical} = 4.67$

Number of samples, $n = 15$; level of significance, $P = 0.05$; df = degrees of freedom.

The first derivative spectra allowed the determination of haloperidol in presence of the two parabens. Fig. 2 shows the first derivative spectra of haloperidol, methylparaben and propylparaben; the zero-crossings of methylparaben occuring at 207.9–225 and 255.2 nm and those of propylparaben at 208.7–225 and 255.2 nm. At these zero-crossing points, it is possible to take derivative measurements of the mixture proportional to the haloperidol concentration only.

Among these wavelengths, we selected 255.2 nm as optimal for determination of haloperidol in mixture with the two parabens; the selected wavelength is common for the two parabens and do not show variation dependent on their concentration.

In Fig. 3, all curves which contain the same concentration of parabens, but three different concentrations of haloperidol (4, 12 and 20 μg ml^{-1}) converge to the abscissa value 247.6 and 231.2 nm corresponding to the zero-crossing wavelengths of haloperidol.

3.2. Calibration graphs and statistical analysis

3.2.1. Linearity

The calibration graph was constructed from the first derivative signals by measuring at 255.2 nm for standard samples containing between 4 and 20 μg ml^{-1} of haloperidol in presence of 3 μg ml^{-1} methylparaben and 0.3 μg ml^{-1} propylparaben.

The experiments showed that the height at 255.2 nm was proportional to the haloperidol concentration.

Table 1 shows the statistical analysis of the experimental data: the regression equation calculated from the calibration graph, along with standard deviations of the slope and the intercept of the ordinate. The high value of the correlation coefficient indicates the good linearity of the calibration graph. Test of significance of the experimental intercept showed that this did not differ significantly from the expected value of zero.

3.2.2. Accuracy and precision

The precision was ascertained by carrying out ten replicate determinations of mixtures of haloperidol (12 μg ml^{-1}), methylparaben (3 μg ml^{-1}) and propylparaben (0.3 μg ml^{-1}) during 3 days. Relative standard deviation of 0.83% was obtained for intra-day precision and 1.86% for inter-day precision.

Table 2
Recovery of haloperidol in synthetic mixtures with parabens by first derivative spectrophotometry

Theoretical concentration (μg ml^{-1})			Haloperidol	
Haloperidol	Methylparaben	Propylparaben	Found[a] (μg ml^{-1})	Recovery (%)
4.0	3.0	0.3	4.04	101.0
8.0	3.0	0.3	8.04	100.5
12.0	3.0	0.3	11.91	99.2
16.0	3.0	0.3	16.18	101.1
20.0	3.0	0.3	20.05	100.2

[a] Mean for six determinations.

Table 3
Determination of haloperidol in commercial injections and oral solutions

Formulation	Composition (mg ml^{-1})	Found[a] (mg ml^{-1})	Recovery (%)
HALDOL injection	Haloperidol (5.0) + methylparaben + propylparaben	5.017	100.3 ± 1.54
HALDOL oral solution 1	Haloperidol (2.0) + methylparaben + propylparaben	2.027	101.3 ± 1.65
HALDOL oral solution 2	Haloperidol (0.5) + methylparaben + propylparaben	0.502	100.4 ± 1.82

[a] Mean for six determinations.

The accuracy was tested by the determination of different concentrations of haloperidol in a mixture of methylparaben and propylparaben.

The results obtained (Table 2) for the recovery of haloperidol indicated that the accuracy was satisfactory.

3.3. Determination of haloperidol in injections and oral solutions

We applied the proposed method to the assay of haloperidol in injections and oral solutions of Haldol®, which contain parabens as preservatives. Six replicate analyses were performed. Satisfactory results (Table 3) were obtained for the recovery of haloperidol and were in good agreement with the claimed amounts.

4. Conclusion

In this work, the determination of haloperidol in the presence of two parabens was solved by applying the zero-crossing technique to first derivative spectra.

The proposed method was validated and applied to the determination of haloperidol in pharmaceutical solutions, confirming that first derivative spectrophotometry is a simple, rapid and selective technique.

References

[1] J.E.F. Reynolds (Ed.), Martindale, The Extra. Pharmacopoeia, 30th ed., 1993.
[2] British Pharmacopoeia, vol. 11, 1993, p. 937.
[3] Ph. Puig, J. Poey, P. Bourdon, Analysis 14 (1986) 242–246.
[4] J.E. Kountourellis, C.K. Markapoulou, J. Liq. Chromatogr. 14 (1991) 2969–2977.
[5] A.F. Fell, Proc. Anal. Div. Chem. 15 (1978) 260–267.
[6] J. Traveset, V. Such, R. Gouzalo, E. Gelpi, J. Pharm. Sci. 69 (1980) 629–633.
[7] A.G. Davidson, S.M. Hassan, J. Pharm. Sci. 73 (1984) 413–416.
[8] M.A. Korany, M. Bedair, H. Mahjoub, M.A. Elsayed, J. Assoc. Anal. Chem. 69 (1986) 608–611.
[9] K. Kitamura, R. Majima, Anal. Chem. 55 (1983) 54–56.
[10] A. Parra, M.D. Gomez, V. Rodenas, J. Carcia-Villanova, M.L. Lopez, J. Pharm. Biomed. Anal. 10 (1992) 525–528.
[11] B. Morelli, J. Pharm. Sci. 79 (1990) 261–265.