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^{1}H-NUCLEAR MAGNETIC RESONANCE SPECTROSCOPIC DETERMINATION OF HALOPERIDOL IN TABLETS

John W. Turczan and Cesar A. Lau-Cam*

Food and Drug Administration
New York Regional Laboratory
850 Third Avenue, Brooklyn, New York 11232

ABSTRACT

A ^{1}H-nuclear magnetic resonance spectroscopic method was developed for the assay of haloperidol in commercial tablets. Dimethylsulfoxide-d_6 and 1,4-dinitrobenzene were used as the solvent and the internal standard, respectively. Recovery values of haloperidol (mean $\pm$ SD) from synthetic formulations were 99.8 $\pm$ 0.86% (CV = 0.86%, n = 10) by the proposed method, and 99.6 $\pm$ 0.80% (CV = 0.80%, n = 3) by the titrimetric method of USP XXI. Assay results for commercial 10 and 20 mg tablets agreed closely with those obtained by the compendial spectrophotometric method.

*Present address: St. John's University, College of Pharmacy and Allied Health Professions, Jamaica, New York 11439.

INTRODUCTION

Haloperidol is a potent antipsychotic, with pharmacological effects similar to the phenothiazines, and an effective antiemetic (1). Chemically it is a butyrophenone compound designated as 4-[4-(p-chlorophenyl)-4-hydroxypiperidino]-4-4'-fluorobutyrophenone. Haloperidol has been quantitatively determined in pharmaceutical samples by UV absorption spectrophotometry (2-4), colorimetry (5-10), acidimetric titration in nonaqueous medium (2), fluorometry (11), polarography (12), cyclic voltammetry (13), and HPLC (14-16). Compendial assay methods for the drug substance and its dosage forms are based on a nonaqueous titration (17) and UV spectrophotometry (17), respectively.

This report describes the application of ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectroscopy to the assay of haloperidol in tablets. In contrast to other techniques, ^{1}H-NMR offers the possibility of identifying the analyte in the test sample with a minimum of reagents and procedural steps, while providing the required specificity and reliability.

EXPERIMENTAL

Apparatus - All spectra were recorded using a Varian EM-390 NMR spectrometer operating at 90 MHz, with an ambient probe temperature of 30°C, a sweep time of 5 min, and a sweep width of 10 ppm (Varian Instrument Group, Sunnyvale, CA).

Materials and Reagents - Haloperidol tablets of two strengths were obtained from commercial sources. The sample of haloperidol

was a USP Reference Standard (United States Pharmacopeial Convention, Inc., Rockville, MD). The internal standard was 1,4-dinitrobenzene (DNB), m.p. 173.5°C, purified by sublimation (Caution: DNB is a highly toxic substance and extreme care must be exercised in its handling) (Aldrich Chemical Co., Milwaukee, WI). The reference standard was tetramethylsilane (TMS), 99.9+ %, NMR grade (Aldrich Chemical Co.). Dimethylsulfoxide-d_6 (DMSO-d_6), 99.5 atom % D, was used as the NMR solvent (Merck Sharp & Dohme Canada Ltd., Montreal, Canada).

Procedure - Weigh and finely powder not less than 20 tablets. Transfer an accurately weighed portion of powder, equivalent to about 40-50 mg of haloperidol, to a 15 ml graduated glass-stoppered centrifuge tube. Add about 30-40 mg of DNB, accurately weighed, and fill the tube with DMSO-d_6 to the 2 ml mark. Effect solution with the aid of a vortex mixer, keeping the solution from coming in contact with the stopper, and centrifuge. Transfer about 0.5 ml of the supernatant to an analytical NMR sample tube that contains 1 or 2 drops of TMS. Record the spectrum using a spin rate that will produce no interfering spinning side bands in the spectral regions 7.1-7.7 ppm and 8.2-8.9 ppm. Integrate the singlet at 8.5 ppm, and the multiplet centered at 7.4 ppm, at least five times each. Obtain the average integral values and calculate the quantity of haloperidol, in mg per tablet, from the following equation: $(A_U/A_S) \times (EW_U/EW_S) \times C \times (T/W)$, where A_U = the average integral value of the resonance signal of haloperidol

centered at 7.4 ppm; A_S = the average integral value of the resonance signal of DNB at 8.5 ppm; EW_U = the formula weight of haloperidol divided by the number of absorbing protons, i.e. 375.87/6 = 62.645; EW_S = the formula weight of DNB divided by the number of absorbing protons, i.e., 168.11/4 = 42.0275; C = the weight of DNB taken for the analysis, mg; T = the average tablet weight, mg; and W = the weight of sample taken for the analysis, mg.

RESULTS AND DISCUSSION

DMSO-d_6 was chosen as the NMR solvent because it easily and quantitatively dissolved the haloperidol present in commercial tablets without removing any interfering materials. A possible limitation to the use of this solvent might be an impurity which produces a multiplet centered at about 2.6 ppm that partially overlaps with the resonance signals of haloperidol in the 2.2-2.8 ppm spectral region. Fortunately, the analyte also exhibited a well resolved signal further downfield, which was found to be satisfactory for quantitative work. DNB, the internal standard, was completely soluble in DMSO-d_6 and its four phenyl protons produced a strong resonance signal at the convenient downfield position of 8.5 ppm.

Figure 1 is the 90 MHz ^{1}H-NMR spectrum of a mixture of haloperidol and its internal standard. The chemical assignments and multiplicities of the resonance signals of haloperidol are given

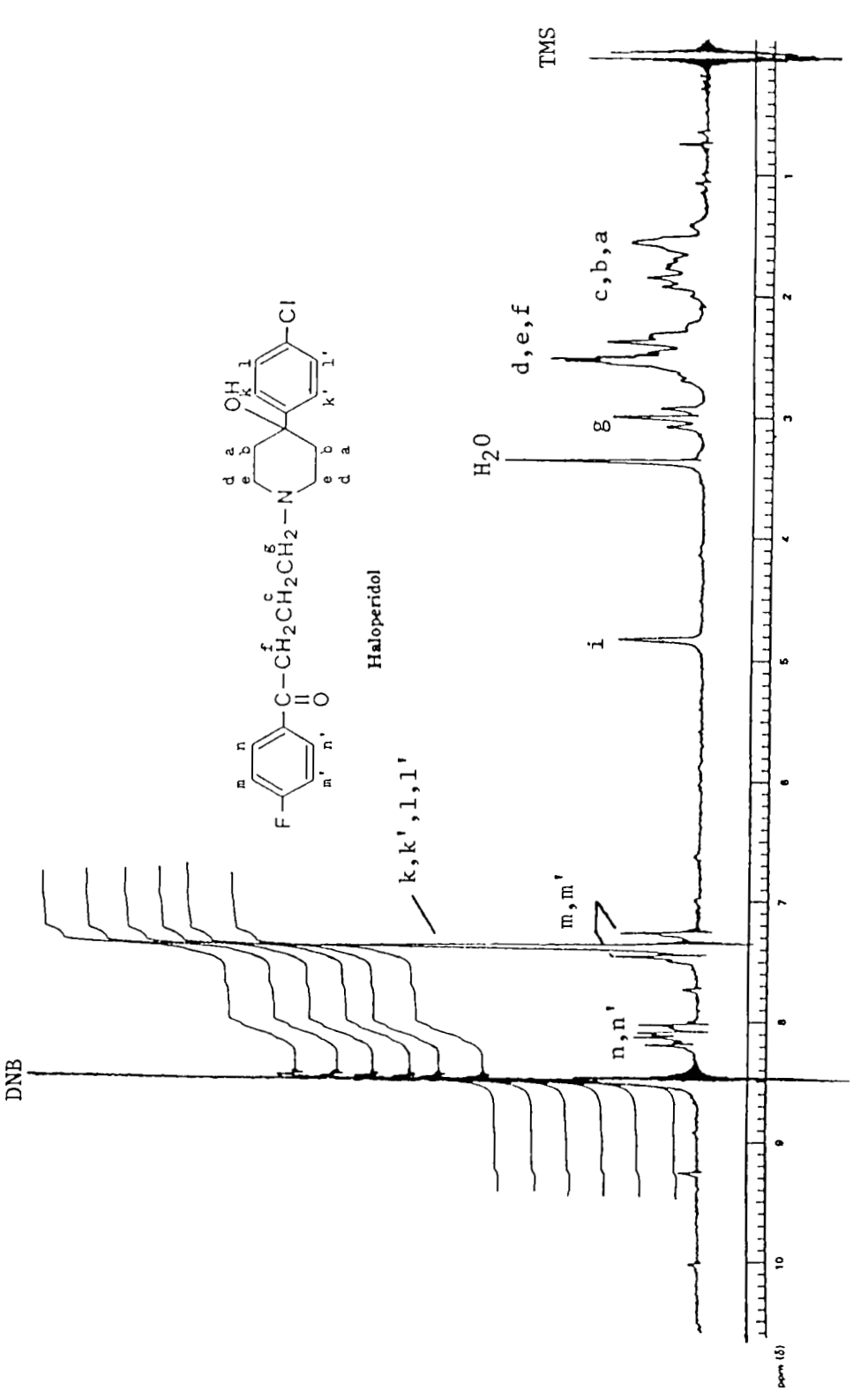

Figure 1. 90 MHz ^{1}H-NMR spectra of haloperidol and 1,4-dinitrobenzene, the internal standard, in DMSO-d_6 solution.

Table 1 - ^{1}H-NMR Spectral Assignments for Haloperidol

Proton identification[a]	Chemical shift, ppm (δ)	Multiplicity
a, b, c	1.4 - 2.2	multiplet
d, e, f	2.2 - 2.8	multiplet
g	3.02	triplet
h	4.83	singlet
i, i', j, j'	7.35	singlet
k, k'	7.31	multiplet
l, l'	8.11	multiplet

[a]For location of protons see Figure 1. DMSO-d_6 contained an impurity absorbing at 2.6 ppm. Moisture absorbed at 3.35 ppm.

Table 2 - Analysis of Synthetic Mixtures by ^{1}H-NMR Spectroscopy and USP XXI Titrimetric Method

Mixture No.	DNB added, mg	Haloperidol Added, mg	Haloperidol Found, mg	Haloperidol Recovery, %
1	18.9	34.0	34.2	100.6
2	39.8	50.0	50.2	100.4
3	41.1	48.2	47.8	99.0
4	36.0	40.9	40.6	99.3
5	20.9	20.2	20.0	99.1
6	55.6	60.1	59.7	99.3
7	60.1	59.9	60.4	100.8
8	20.2	13.1	12.9	99.1
9	54.7	20.0	20.2	101.1
10	41.7	40.0	39.6	98.9
Mean				99.8
Range				98.9 - 101.1
SD				0.86
CV, %				0.86
USP XXI titrimetric method:				
Mean (n = 3)				99.6
SD				0.80
CV, %				0.80

Table 3 - Analysis of Haloperidol Tablets by ^{1}H-NMR Spectroscopy and USP XXI Spectrophotometric Method

Sample No.	Amount declared, mg/tablet	Amount found, mg/tablet	Amount found, % of declared
1	20	19.90	99.50
2	20	19.80	99.00
3	20	19.80	99.00
4	20	19.90	99.50
5	20	19.70	98.50
6	20	20.22	101.00
7	20	19.80	99.00
Mean			99.35
SD			0.84
USP XXI method:			
Mean (n = 3)			99.40
SD			0.26
8	10	10.07	100.70
9	10	9.89	98.90
10	10	9.90	99.00
11	10	9.88	98.80
Mean			99.35
SD			0.90
USP XXI method:			
Mean (n = 3)			99.56
SD			0.61

in Table 1, and are in agreement with the data reported by Janicki and Ko (18). The resonance signal of relevance to the assay corresponds to the multiplet centered at about 7.4 ppm, which arises from the overlapping of the singlet for the k, k', l, and l' protons with the multiplet due to the m and m' protons.

The accuracy and precision of the proposed method was assessed on the basis of the analysis of a set of synthetic mixtures containing known quantities of haloperidol and DNB. The mean recovery value (99.8%, n = 10) compared very well with that obtained by the titrimetric method of USP XXI (99.6%, n = 3). The coefficient of variation (CV) for the proposed method was less than 1%. Varying the proportion of internal standard to analyte over the range shown in Table 2 had no significant effect on the accuracy and precision of the proposed method. The assay of commercial 10 and 20 mg tablets of haloperidol yielded the results presented in Table 3. The mean assay values for these tablets showed good agreement with those obtained by the spectrophotometric assay method of USP XXI.

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