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HIGH PRESSURE LIQUID CHROMATOGRAPHIC DETERMINATION OF HALOPERIDOL STABILITY

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ABSTRACT

Haloperidol lacks stability when exposed to elevated temperatures and light. Current assay procedures described in the USP do not permit detection or quantitation of degradation products of haloperidol. An HPLC assay for the analysis of haloperidol and the detection of degradation products has been developed. The mobile phase consisted of 40:60 THF:water with 0.75% phosphoric acid. A microbondapak CN column was used to achieve the separation. Samples were injected using a fixed loop (200 microliter) injector and detection was by a fixed wavelength set at 254 nm. Using this mobile phase, haloperidol gave a retention time of 5.4 minutes. Samples of haloperidol treated with heat (60°C for 48 hours) gave peaks at 5.1 and 6.4 minutes as well as a haloperidol peak at 5.4 minutes. A standard curve of haloperidol concentrations was linear (r=0.99) over the range of 1 µg/ml to 100 µg/ml. The conversion of haloperidol to degradation products was noted after storage under conditions of elevated temperature, exposure to light, and as a function of pH.

INTRODUCTION

Haloperidol, a butryophenone used as an antipsychotic agent (1), is unstable when exposed to elevated temperatures and light (2). The

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current USP XX assays for this drug include titration of dissolved haloperidol powder with 0.05N perchloric acid or extraction of the drug from a dose form (i.e., oral solution, injection, tablets) with subsequent ultraviolet spectrophotometric analysis (3). Neither one of these assays permits the detection or quantification of haloperidol degradation products. A high-pressure liquid chromatography (HPLC) assay was developed which overcomes the problems associated with the USP assays (3). This HPLC assay has been modified slightly for the analysis of haloperidol and detection of degradation products in drug solutions exposed to elevated temperatures, light, and as a function of pH.

EXPERIMENTAL

Equipment: The chromatographic system consisted of a solvent delivery system[1], a syringe loading fixed loop sample injector[2], and a fixed wavelength detector[3]. The separation was performed on a 3.9 mm (id) x 30 cm column[4]. The chromatographic peaks were recorded using a strip chart recorder.

Mobile Phase: The mobile phase consisted of tetrahydrofuran[6] - water (40:60) with 0.75% phosphoric acid.

Standard and Sample Preparation: The standard solution was prepared by dissolving 20 mg of haloperidol[7] in a 200 ml volumetric flask with distilled water with the aid of phosphoric acid. The resulting solution has a pH of 2.3.

Standard solutions of pH 7 and pH 8 were obtainted by adjusting the original solution to the desired pH using 2M sodium hydroxide.

Storage Conditions: Five milliliter samples of the standard solutions were pipetted into glass culture tubes and capped. The solutions were stored in the dark at 25°C, 60°C, and 115°C. Samples were stored also

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[1]Model M6000a Waters Associates, Milford, MA

[2]Model 7120, Rheodyne Inc., Berkeley, CA

[3]Model 440, Waters Associates, Milford, MA

[4]uBondapakCN (reversed phase), Waters Associates, Milford, MA

[5]Model 300 series, Linear Instruments, Chicago, IL

[6]UV grade, Waters Associates, Milford, MA

[7]McNeil Pharmaceuticals, McN - Jr - 1625 Lot 7701128, Ft. Washington, PA

at 25°C in the light. Analysis of the sample solutions were performed at time 0, 6, 12, 24, 30, 36, 48, 120, 168, and 336 hours. Control solutions were stored at 25°C (light and dark), and 60°C, and 115°C in the dark with analysis as described above.

Analysis: The following chromatographic conditions were employed for the analysis: flow rate, 1 ml/min; detector wavelength, 254 nm; injector loop volume, 200 µl.

RESULTS AND DISCUSSION

Standard solutions of haloperidol assayed using the HPLC technique described gave a retention time of 5.4 minutes (Figure 1). A standard curve generated using the absorbance of the haloperidol

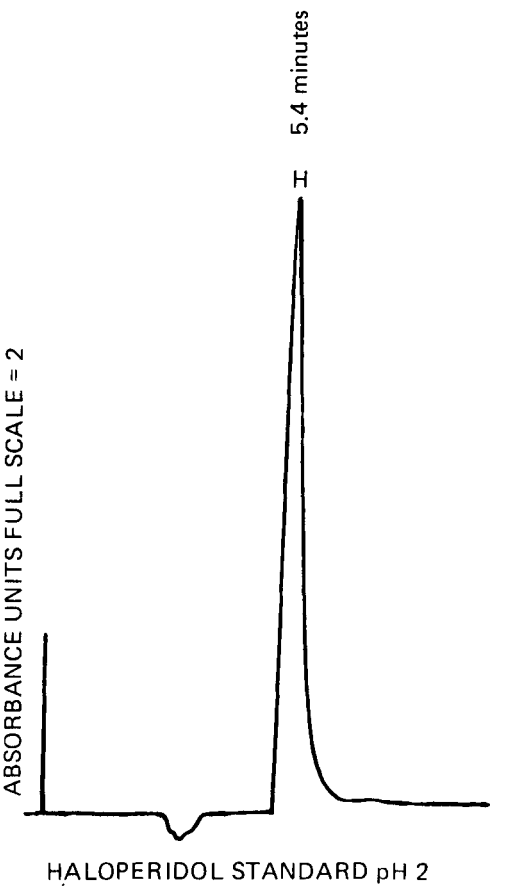

FIGURE 1: TYPICAL CHROMATOGRAM FOR HALOPENDOL STANDARD AT pH 2

TABLE 1

Extent of Haloperidol Degradation

Under Various Conditions

pH	CONDITION	TIME AND EXTENT OF DEGRADATION
	25°C Dark	none
2	25°C Light	some after 14 days
	60°C	after 24 hours; increasing with time
	115°C	after 6 hours; increasing with time
7,8	25°C Dark	none
	25°C Light	after 7 days; increasing with time
	60°C	after 48 hours
	115°C	after 6 hours; increasing with time

peak as a function of drug concentration was linear over the range of 1 µg/ml to 100 µg/ml (r=0.99, n=5).

Sample solutions of haloperidol were assayed similarly with differences from the standards noted in some cases. The appearance of new peaks either leading into or shouldering from the haloperidol peak were observed as degradation products of the drug. The extent of degradation was observed also with time (Table 1). Samples stored at 25°C in the dark for up to 14 days were unchanged under all pH conditions. Degradation was not apparent on a sensitive absorbance scale (0.2 units full scale). However, for those samples stored at 25°C in the light for 14 or 28 days, degradation was apparent at each pH. The greatest change occurred in those samples stored for 28 days at pH 7 where the appearance of two peaks was observed (Figure 2).

For those samples stored at 60°C, degradation of haloperidol was observed at each pH. Rapid degradation occurred for the drug at pH 2 with detection of a new peak after 24 hours. At 36 hours an additional peak was observed.

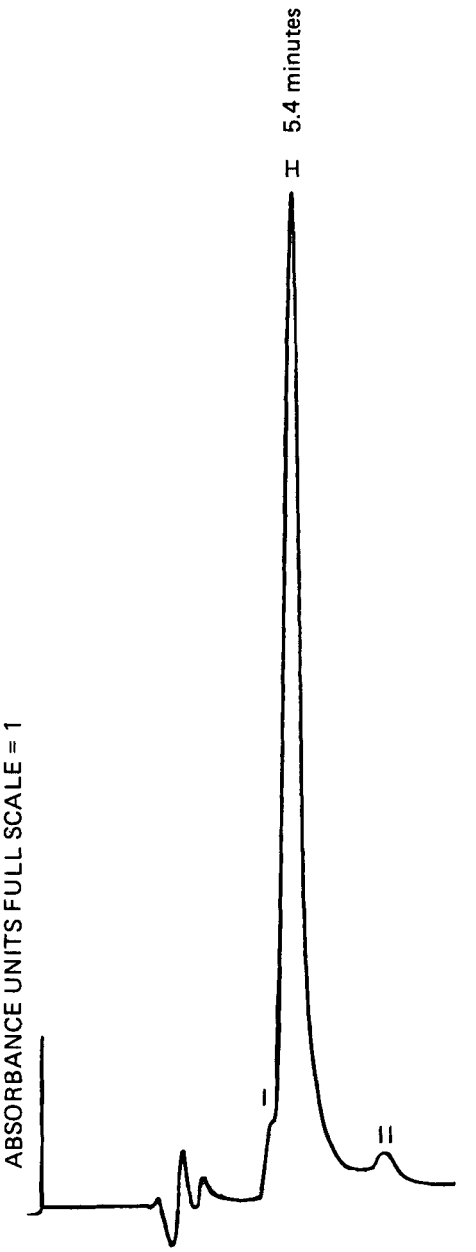

FIGURE 2: DETECTION OF HALOPERIDOL AND TWO ADDITIONAL PEAKS AT pH 7 STORED FOR 28 DAYS AT 25°C

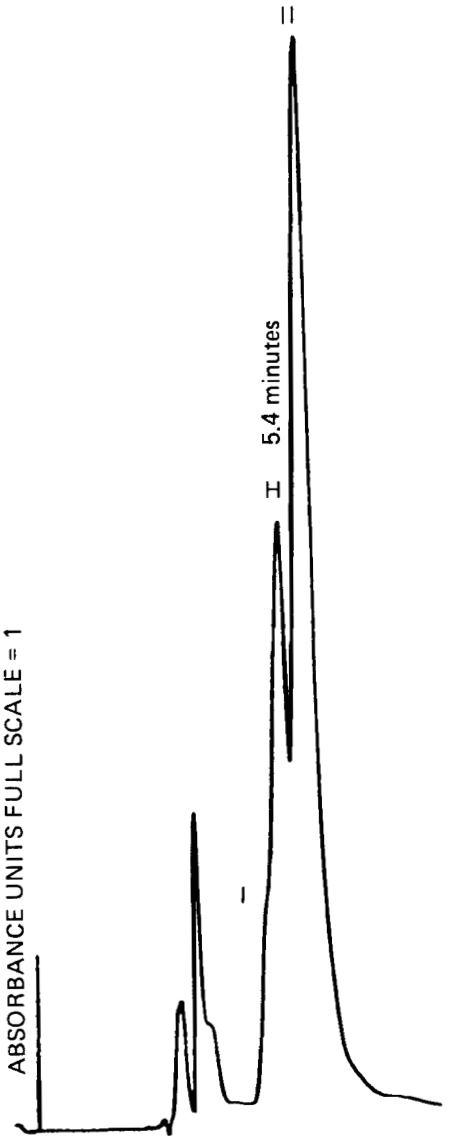

FIGURE 3: DETECTION OF HALOPERIDOL AND TWO ADDITIONAL PEAKS AT pH 2 STORED FOR 21 DAYS AT 115° C

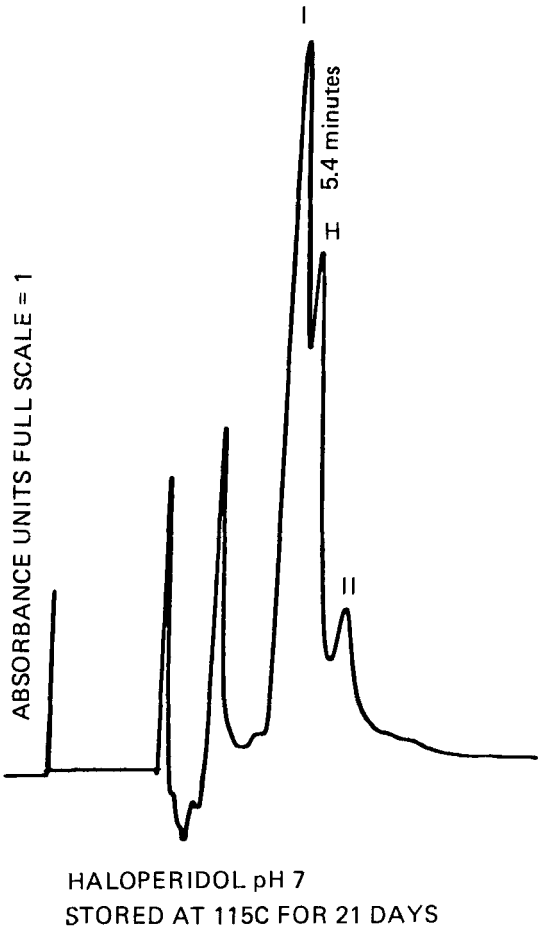

FIGURE 4: DETECTION OF HALOPERIDOL AND TWO ADDITIONAL PEAKS AT pH 7 STORED FOR 21 DAYS AT 115°C

The most rapid and dramatic evidence of haloperidol degradation was observed for samples stored at 115°C at each pH. After 6 hours a new peak was detected in samples stored at each pH and after 21 days two new peaks were noted as shown in Figures 3 and 4. In these cases the degradation peaks were larger than the haloperidol peak.

In conclusion, the HPLC assay described in this paper is suitable for determining the stability of heloperidol through the detection of additional peaks after storage under various condtions. Whereas haloperidol samples stored at 25°C were stable for at least

14 days except when exposed to light, extensive degradation of this drug was noted at temperatures above 60°C and at high pH.

REFERENCES

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2. C.A. Janicki, C.Y. Ko., "Analytical Profiles of Drug Substances; Academic Press, Inc., New York, NY, 1980, p. 341.

3. "The Unived States Pharmacopeia", 20th rev., United States Pharmacopeial Convention, Rockville, MD, 1980, p. 363.

4. D.S. Greene, Drug Dev. and Ind. Pharm., 5, 127 (1979).