Asian Journal of Chemistry; Vol. 24, No. 2 (2012), 895-898

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Simultaneous Determination of Haloperidol and Isopropamide Iodide in Pharmaceutical Dosage Forms by High Performance Liquid Chromatography-Diode Array Detection

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(*Received*: 27 April 2011; *Accepted*: 21 October 2011) AJC-10554

A specific, simple, sensitive and precise high performance liquid chromatography with diode array detection (HPLC-DAD) was developed for the assay of haloperidol and isopropamide iodide. Good chromatographic separation was achieved using a C_{18} (150 mm × 4.6 mm, 5 µm) column, mobile phase being methanol: phosphate buffer 50 mM (60:40 v/v) at pH 4.0 ± 0.2 and a flow rate of 1.5 mL/min. The peak was detected at 254 nm. The detector response were linear at concentrations over the range 10-1000 µg/mL and 2.0-1000 µg/mL for isopropamide iodide and haloperidol with percent relative standard deviation (RSD %) ≤ 4.8 and 4.1 %, respectively. The limits of quantification (LOQ) were at 3.67 and 0.018 µg/mL and the limits of detection (LOD) were at 1.21 and 0.0059 µg/mL for isopropamide iodide and haloperidol, respectively. The proposed method was successfully applied with high accuracy and good precision for the determination of isopropamide iodide and haloperidol in a various pharmaceutical formulations tablets with no interference from the excipients.

Key Words: Isopropamide iodide and haloperidol, Pharmaceutical formulations, HPLC-DAD.

INTRODUCTION

Haloperidol, 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4fluorophenyl)-1-butanone, $C_{21}H_{23}NO_2ClF$ (357.9 g/mol), Fig. 1(a), a major tranquilizer, is used in the treatment of schizophrenia, mania and neurological disorders with hyperkinesias[1]. A number of methods have been reported for its quantitation in dosage forms. They include acidimetric titration in non aqueous medium[2,3], NMR[4], colourimetry, conductometry and spectrophotometry[5-8], fluorimetry[9], polarography and voltammetry[10-12], GC and HPLC[13-17].

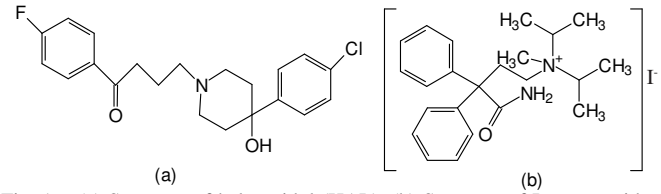

Fig. 1. (a) Structure of haloperidol (HAL), (b) Structure of Isopropamide iodide (ISPI)

Isopropamide iodide, γ-(aminocarbonyl)-*N*-methyl-*N,N-bis*(1-methylethyl)-γ- phenylbenzenepropanaminium iodide (ISPI), $C_{23}H_{33}N_2OI$ (480.43 g/mol), Fig. 1(b), is a antispasmodic and antisecretory effect on the gastrointestinal tract. The official method for the determination of (isopropamide iodide) is non aqueous titration with perchloric acid[3]. Various spectrophotometric methods have been reported for the determination of (isopropamide iodide) by measurement of the UV absorption at 225 nm, ion pair formation with methyl orange and charge transfer complexation with iodine. The binary mixture of trifluoperazine (TFP) and isopropamide iodide is used for their antiemetic and antispasmodic effect. The spectrophotometric derivative ratio method has been reported for their simultaneous determination in two component mixture. Only one method has been reported for simultaneous determination of this mixture based on measurement of second derivative spectrophotometric values at 248-264 nm in methanolic solution for trifluoperazine and 232 nm in 0.1 N sodium hydroxide after chloroformic extraction procedure for isopropamide iodide with linearity range of 2.5-12.5 µg mL^{-1} for trifluoperazine and 20-80 µg mL^{-1} for isopropamide iodide. Second derivative ultraviolet spectrophotometry for the simultaneous determination of trifluoperazine hydrochloride and isopropamide iodide in binary mixture[18-23]. The official method for determination of isopropamide iodide in tablet is ion exchange chromatographic spectrophotometric read out procedure, HPLC method using CROWN PAK column has been reported for the simultaneous determination of isopropamide iodide and phenylpropanolamine HCl in capsule[24-26].

EXPERIMENTAL

The high performance liquid chromatography system consisted of an LC-10AD pump, a column oven (model CTO-10AS), a diode array detector (SPDM10A), an autosampler SIL-10AD and a controller module SCL-10A (all from Shimadzu) coupled to a personal computer running the software Shimadzu Class VP for data acquisition.

Pharmaceutical drugs of haloperidol and isopropamide iodide were supplied by Gemini (India). The commercial pharmaceuticals Pal-Vesal (each tablet contents: 2.0 mg isopropamide iodide + 0.300 mg haloperidol) manufactured by Future Pharmaceutical Industries Company (Syria), Isodol (each tablet contents: 2.0 mg isopropamide iodide + 0.300 mg haloperidol) and Hayadol 0.5 (each tablet contents: 0.500 mg haloperidol) manufactured by Ibn Hayian Pharmaceutical Industries Company (Syria) and Halomid 0.5 (each tablet contents: 0.500 mg haloperidol) manufactured by Medico Labs (Syria). Methanol, sodium hydroxide, phosphoric acid, potassium dihydrogen phosphate (HPLC-grade) were purchased from Merck, Germany. Water was purified with a reverse osmosis system coupled to an ion exchange unit (Gehaka, Brazil). All other chemicals used were of analytical reagent grade.

Mopile phase: The mobile phase consisted of potassium dihydrogen phosphate 0.05 M (pH 4.0 ± 0.2): methanol (40:60 v/v). The phosphate buffer pH was adjusted with 1 M phosphoric acid or 1 M sodium hydroxide.

Stock standards of haloperidol: 400 mg/100 mL solutions were prepared by accurately dissolving measured amounts of haloperidol in mobile phase. During the experiments, this solution was found to be stable for several weeks if kept in the dark and at room temperature. Working standards were prepared daily by diluting different volumes of stock solution (0.025, 0.050, 0.10, 0.25, 0.50, 1.00, 1.50, 2.50, 5.0, 7.5, 15 and 25 mL) to 100 mL with mobile phase (these solutions content 1.0, 2.0, 4.0, 10, 20, 40, 60, 100, 200, 300, 600 and 1000 μg/mL of haloperidol).

Stock standards of isopropamide iodide: 400 mg/100 mL solutions were prepared by accurately dissolving measured amounts of isopropamide iodide in mobile phase. During the experiments, this solution was found to be stable for several weeks if kept in the dark and at room temperature. Working standards were prepared daily by diluting different volumes of stock solution (0.20, 0.25, 0.50, 1.00, 1.50, 2.50, 5.0, 7.5, 15 and 25 mL) to 100 mL with mobile phase (these solutions content 8, 10, 20, 40, 60, 100, 200, 300, 600 and 1000 μg/mL of isopropamide iodide).

Sample preparation: Twenty tablets of pharmaceutical formulations (Pal-Vesal, Isodol, Hayadol 0.5 and Halomid 0.5) tablets were weighed and ground to a fine powder. A quantity equivalent to ten tablets were weighed, dissolved in mobile phase, transferred to a 100 mL volumetric flask and diluted to the mark with mobile phase (these solutions content: 20 mg isopropamide iodide + 3 mg haloperidol in 100 mL *i.e.* 200 μg/mL isopropamide iodide + 30 μg/mL or 5.0 mg haloperidol in 100 mL *i.e.* 50 μg/mL).

Stock standards of Mixtures (isopropamide iodide & haloperidol): Three stock standards of mixture were prepared daily by diluting different volumes of stock solutions of isopropamide iodide and haloperidol as the follows: 3.75 mL of isopropamide iodide + 0.50 mL of haloperidol, 5.00 mL of isopropamide iodide + 0.75 mL of haloperidol and 6.25 mL of isopropamide iodide + 1.50 mL of haloperidol to 100 mL with mobile phase (these three solutions content 150 μg/mL of isopropamide iodide + 20 μg/mL of haloperidol, 200 μg/mL of isopropamide iodide + 30 μg/mL of haloperidol and 250 μg/mL of isopropamide iodide + 60 μg/mL of haloperidol, respectively).

Procedure: Separation was achieved at 30 ºC using a Shimpak C_{18} column (150 mm × 4.6 mm; 5 μm). The flow rate was set at 1.5 mL/min and a discrete channel on the diode array detector configured to acquire data at 254 nm. 20 μL of samples were introduced using the autosampler and the injection.

RESULTS AND DISCUSSION

The procedure for the simultaneous analysis of haloperidol (HAL) and isopropamide iodide (ISPI) using high performance liquid chromatography with diode array detection (HPLC-DAD) has been developed. In order to avoid derivatization of compounds, our goal is to develop a simple HPLC assay to be used in routine control of these drugs in Pal-Vesal and Isodol F.C. Tablets. Therefore, this work was focused on optimization of the conditions for the simple and rapid, as well as low cost and no time consuming analysis, including a selection of the proper column or mobile phase to obtain satisfactory results. To obtain satisfactory resolution and to avoid peak tailing of compounds, an optimization of the proposed method was carried out using the different mobile phases. The use of mobile phase methanol and potassium dihydrogen phosphate 0.05 M (pH 4.0 ± 0.2) gave symmetrical peaks. Mobile phases of various compositions of methanol and water were also tested. The best results were obtained using the mobile phase of potassium dihydrogen phosphate 0.05 M (pH 4.0 ± 0.2 adjusted with phosphoric acid or sodium hydroxide): methanol (60:40 v/v). The most reproductive results were obtained with a C_{18} column (150 mm × 4.6 mm; 5 μm) and DAD detector. The detection was performed at 254 nm in sensitivity range 0.01 AUFS. Typical chromatograms obtained are illustrated in Fig. 2. The retention times were 2.398 min for isopropamide iodide and 8.956 min for haloperidol. System suitability tests were performed and chromatographic parameters calculated from experimental data are given in Table-1. The validity of the liquid chromatographic assay was established through a study of linearity, sensitivity, intra-day and inter-day precision, accuracy and reproducibility. The linearity was established with a series of working solutions prepared by diluting the stock solution with mobile phase to the final concentrations. Each concentration was injected in triplicate and the mean value of peak area was taken for the calibration curve. A linear response in peak area ratios was observed over the concentration range 10-1000 μg/mL and 2.0-1000 μg/mL for isopropamide iodide and haloperidol respectively. The mean of five different calibration graphs yielded the following equations: y = 1.3078C - 1.3684, r = 0.9999 and y = 44.508C + 20.406, r = 0.9998 for isopropamide iodide and haloperidol respectively. The limits of quantification [LOQ = 10(SD/slope)][27,28] were found to be 3.67 μg/mL for isopropamide iodide and 0.018 μg/mL for

TABLE-1
CHROMATOGRAPHIC PARAMETERS OBTAINED IN HPLC-DAD ASSAY OF ISOPROPAMIDE IODIDE AND HALOPERIDOL

Parameters	Isopropamide iodide	Haloperidol
Buffer pH	4.0 ± 0.2	
Mobile phase	Methanol: phosphate buffer 50 mM (60:40 v/v)	
Flow rate	1.5 mL/min	
Column	C_{18} (150 mm × 4.6 mm, 5 µm)	
λ_{max} (nm)	254	
Range of concentration (µg/mL)	10–1000	2.0–1000
Retention time (t_R) (min)	2.398	8.994
Linear regression* equation	Y = 1.3078 C–1.3684	Y = 44.508 C + 20.406
Slope	1.3078	44.508
Intercept	–1.3684	+ 20.406
Correlation coefficient (r)	r = 0.9999	r = 0.9998
Range of error	± 4.8 %	± 4.1 %
LOQ (µg/mL)	3.67	0.018
LOD (µg/mL)	1.21	0.0059

*With respect to Y = mC + b, where C is the concentration (µg/mL), m is slop and Y is Area

haloperidol and the limits of detection [LOD = 3.3 (SD/slope)][27,28] were found to be 1.21 µg/mL for isopropamide iodide and 0.0059 µg/mL for haloperidol. The intra-day precision of the method was determined by preparing the standards of isopropamide iodide and haloperidol at five different concentrations and values for each compound were determined by 5 repeated analyses. Inter-day precision was checked with the same concentrations as intra-day assay and the determination of each compound was repeated day by day during 5 days, the results are given in Tables 2 and 3. The accuracy of HPLC method was confirmed by determining the

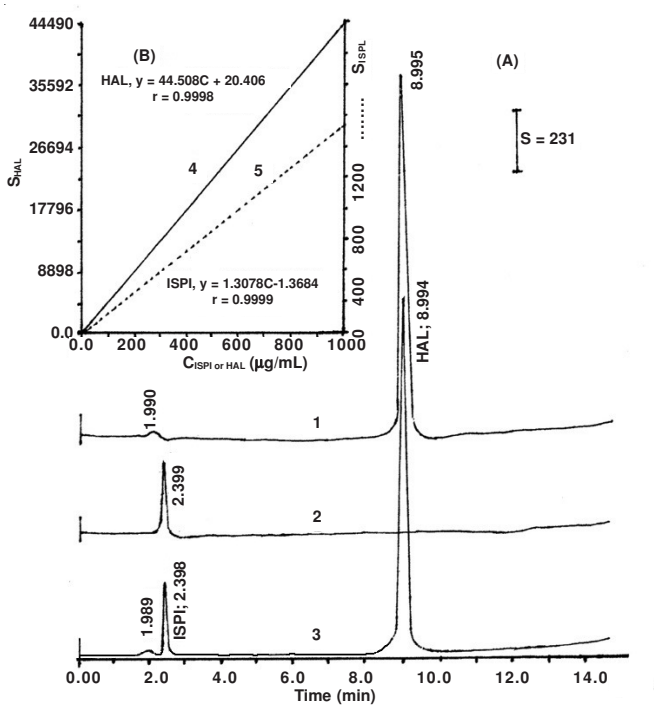

Fig. 2. (A) HPLC-DAD chromatograms of isopropamide iodide and haloperidol: 1- 200 µg/mL of isopropamide iodide (t_R: 2.398 min); 2- 30 µg/mL of haloperidol (t_R: 8.994 min) ; 3- mixture of 200 µg/mL of isopropamide iodide and 30 µg/mL of haloperidol; (B) Standard curves of haloperidol (4) and isopropamide iodide (5) [Column C_{18} (150 mm × 4.6 mm, 5 µm), mobile phase being methanol: phosphate buffer 50 mM (60:40 v/v) at pH 4.0 ± 0.2 a flow rate 1.5 mL/min, λ_{max} 254 nm]

TABLE-2
DETERMINATION OF ISOPROPAMIDE IODIDE IN DIFFERENT PREPERD STANDARDS USING HPLC–DAD

Taken (µg/mL)	Found* (µg/mL)	SD (µg/mL)	RSD (%)	Recovery (%)	Confidence limit (µg/mL)
10.0	9.9	0.48	4.8	99.0	9.9 ± 0.59
20.0	20.1	0.89	4.4	100.5	20.1 ± 1.10
30.0	30.0	1.05	3.5	100.0	30.0 ± 1.30
50.0	50.5	1.62	3.2	101.0	50.5 ± 2.01
80.0	81.2	2.44	3.0	101.5	81.2 ± 3.02
100	103	2.9	2.8	103.0	103 ± 3.6
200	205	5.1	2.5	102.5	205 ± 6.3
500	500	10.0	2.0	100.0	500 ± 12.4
800	800	12.8	1.6	100.0	800 ± 15.9
1000	1012	13.4	1.3	101.2	1012 ± 16.6

*n = 5, t = 2.776 (95 %)

TABLE-3
DETERMINATION OF HALOPERIDOL IN DIFFERENT PREPERD STANDARDS USING HPLC–DAD

Taken (µg/mL)	Found* (µg/mL)	SD (µg/mL)	RSD (%)	Recovery (%)	Confidence limit (µg/mL)
2.00	1.96	0.08	4.1	98.0	1.96 ± 0.099
5.00	5.00	0.17	3.5	100.0	5.00 ± 0.217
10.0	10.3	0.31	3.0	103.0	10.3 ± 0.384
20.0	20.0	0.54	2.7	100.0	20.0 ± 0.67
30.0	30.2	0.72	2.4	100.7	30.2 ± 0.89
60.0	59.9	1.3	2.2	99.8	59.9 ± 1.61
100	100	2.0	2.0	100.0	100 ± 2.5
300	305	5.5	1.8	101.7	305 ± 6.8
500	508	8.1	1.6	101.6	508 ± 10.1
800	792	9.5	1.2	99.0	792 ± 11.8
1000	1010	10.5	1.0	101.0	1010 ± 13.0

*n = 5, t = 2.776 (95 %)

high recovery values for isopropamide iodide (99.0-103 %) and haloperidol (98.0-103.0 %). The recoveries are obtained by determination of these drugs in standard dosages contain different per cents of active substances.

Application: The applicability of the method for the simultaneous determination of isopropamide iodide and haloperidol was verified by the determination of these compounds

TABLE-4
DETERMINATION OF ISOPROPAMIDE IODIDE AND HALOPERIDOL IN PHARMACEUTICALS: PAL-VESAL, ISODOLE, HAYADOL 0.5 AND HALOMID 0.5 TABLETS

Pharmaceuticals	Drug	Company	Taken (m, mg/tab)	Found (*m, mg/tab)	RSD (%)	Recovery (%)
Pal-vesal	ISPI	Future	2.000	2.040	2.5	102.0
	HAL		0.300	0.312	1.8	104.0
Isodole	ISPI	Ibn hayian	2.000	2.060	2.3	103.0
	HAL		0.300	0.298	2.0	99.33
Hayadol 0.5	HAL	Ibn hayian	0.500	0.504	1.7	100.8
Halomid 0.5	HAL	Medico labs	0.500	0.510	1.7	102.0

* n = 10

in pharmaceuticals: Pal-Vesal, Isodole, Hayadol 0.5 and Halomid 0.5 tablets. The high recovery (99.33-104.0 %) and RSD values within 1.8-2.5 % confirm the suitability of the proposed method for the routine determination of these compounds in tablets (Table-4).

Conclusion

High performance liquid chromatography with diode array detection (HPLC-DAD) was used to develop a method for the simultaneous determination of haloperidol and isopropamide. The proposed method is simple, rapid and sensitive and therefore suitable for the routine analysis of haloperidol and isopropamide iodide in tablets.

ACKNOWLEDGEMENTS

The authors acknowledged the Department Toxicology Chemical, Charité, Berlin, Germany and Companies of Future of Pharmaceutical, Ibn Hayian Pharmaceutical Industries and Medico Labs, Syria for technical assistance.

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