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RESEARCH ARTICLE

Spectrophotometric Determination of Haloperidol in Pure Form and Pharmaceutical Formulation using Calcon and Amido Black

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ABSTRACT:

Two simple, rapid and sensitive spectrophotometric methods have been developed for determination of Haloperidol (HP) in pure form and pharmaceutical formulations. A good sensitive colour reaction has been developed, based on the fact that Haloperidol (HP) reacts with a Calcon (Cal) or Amido Black (AB), to form an ion-association complex in acidic buffer solution, giving pink color with Calcon and blue color with Amido Black, the absorbance of chloroform extracted complexes were measured at 531 nm and 626 nm respectively. The effects of analytical parameters on the reported systems were investigated. The complexation reactions were extremely rapid at room temperature and the absorption values remain unchanged up to 72 h. Beer's law was obeyed in the concentration ranges of 1.20 – 33.83 µg .ml-1 and 0.752 -30.00 µg. ml-1, detection limits were 0.142 and 0.085 µg.ml-1 and the molar absorptivity coefficients were 2 1817 and 2 3230 l .mol-1.cm-1 for Cal and A.B respectively. Recoveries were between 99.35–101.67% for HP-Cal and between 98.67–100.87% for HP-AB complexes. The two methods were successfully applied for the determination of commercially available haloperidol in pure and in pharmaceutical formulations (tablets and dropes) without interference from its excipients. Statistical comparison of the results of the proposed method with those of the reference method shows excellent agreement and indicates no significant difference in accuracy and precision.

KEYWORDS: Haloperidol, calcon, amido black, ion-association complex, spectrophotometry.

INTRODUCTION:

Haloperidol (HP), $C_{21}H_{23}ClFNO_2$ 1-Butanone, 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl] -1-(4-fluorophenyl)- 4– [4- p-Chlorophenyl)-4-hydroxypiperidino] -4'-fluorobutyrophenone. Haloperidol (HP) a major tranquilizer, is a neuroleptic used in clinical medicine mainly for treatment of schizophrenia, mania and neurological disorders with hyperkinesias [1].

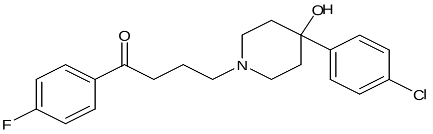

Fig 1: Chemical structure of Haloperidol

Several analytical methods have been reported for assay of haloperidol including acidimetric titration in non-aqueous medium[2], UV-spectrophotomet [3-4], HPLC with MS detection[5], capillary electrophoresis[6], derivative spectrophotometry[7], fluorimetry[8], colorimetry[9-12], H-nuclear magnetic resonance [13], ^{19}F NMR spectroscopy[14], gas chromatography (GC) with electron-capture detection[15,17], liquid chromatography (LC) with electrochemical detection[18,19], high performance thin-layer chromatography[20-22], and voltammetry [23].

Most of the reported methods did not allow the rapid quantification and identification of haloperidol in a one single run since most of these methods necessitate samples pretreatment prior to analysis of the drug. Besides, most of these methods require expensive equipment and considerable skill to operate them successfully.

Research Highlights

The proposed methods depend on the formation of ion-association complexes between the Haloperidol (HP) and Calcon (Cal) or Amido Black (AB) that are useful in the Extractive spectrophotometric determination of HP in pure form and were successfully applied for the determination of HP in pharmaceutical dosage forms with average recovery of 99.35–101.67% for Cal and between 98.67–100.80% for AB with RSD less than 3.85% and 4.12% respectively.

MATERIALS AND METHODS:

Apparatus:

Measurements were made on a Jasco V-650 model spectrophotometer UV-VIS (Japan Spectroscopic Co. L td., Tokyo) with a scanning speed of 400 nm/min and a bandwidth of 2.0 nm, equipped with 10 mm matched quartz cells. All absorption spectra were made for electronic spectral measurements between (190-1100 nm). The pH measurements were made with Crison pH meter Model GLP21, Spain.

Materials and reagents:

Haloperidol bulk substance was supplied from Sigma (USA). Calcon from BDH, Amido Black from Serva, the pharmaceutical formulation tablets were supplied from local market in Syria. All solvents were Spectroscopic grade from SCP (Surchem product Ltd , England).

Stock standard solution of HP (0.001 mol) was prepared by dissolving 37.59 mg (considering the purity) of drug in 5 ml of Methanol and 5 ml (0,1 N) HCl and diluted to 100 ml in volumetric flask. The standard solution was prepared by dilution of the stock standard solution with double distilled water to reach concentration (0.0002 mol) of HP. This solution was stored in well-closed vessels, the solution is stable up to 1month in refrigerator. Solutions of reagents (Calcon and Amido Black) were prepared with a concentration of (0.001 mol) by dissolving suitable weight of the reagent in double distilled water and diluted to 100 ml in volumetric flasks separately.

Procedure for the assay of bulk sample:

Aliquots of the standard HP solutions were transferred into a series of 50 ml funnels. 3.5 ml of Briton buffer (pH=2.4 for Cal and AB) and 3 ml of reagent were added and diluted to 20 ml using double distilled water and mixed well. The amount of 10 ml of chloroform was added with three portions and the mixture was shaken well. The absorption of the separated chloroform layer was measured at a maximum wavelength 531 nm, 626 nm for the complexes HP-Cal and HP-AB respectively, against the reagent blank. The standard calibration plot was prepared to calculate the amount of the analyzed drug in bulk samples. Into a series of 50 ml separating funnels, 3.5 ml of buffer and 3 ml of dye solution were placed. An appropriate volume of 0.001 mol standard drug solution was added to each funnel and mixed well, Q.s to 20 ml of distilled water was added to each funnel . The funnels were shaken vigorously with 10 ml chloroform for 2 min, then allowed to stand for clear separation of the two phases. The separated organic phase was transferred to a 10 ml volumetric flasks , The color is stable for at least 72 h up to 25 ±2°C (room temperature).

Procedure for formulations

The contents of twenty tablets of HP drugs were weighed and powdered, and an amount equivalent to 5 mg of the drug was dissolved in 5 ml of methanol and 5 ml (0,1 N) HCl and diluted to 100 ml and filtered and suitable aliquot was analyzed using the procedure described earlier .

RESULTS AND DISCUSSION:

Preliminary investigations have shown that HP reacts with Cal and AB in suitable buffer to give chloroform-soluble ion-association complexes. The optimum reaction conditions for quantitative determination of the ion-association complexes are established via a number of preliminary experiments.

Effect of pH

The effect of pH was studied by extracting the colored complexes in the presence of various buffers such as Briton, Acetate and phosphate. It was observed that the maximum color intensity and constant absorbance were found in Briton buffer of pH=2.4 for HP-Cal system and HP-A.B system using 3.5 ml of buffer (Fig.2).

Effect of Amount of dye

The optimum volume of the reagent necessary for the assay of drugs was studied. 3 ml of (0.001 mol) Cal and AB were sufficient for complete color development for HP- dye complex.

Extraction Solvent

Several organic solvents (chloroform, ether, dichloromethane and carbon tetrachloride) were examined for their ability to extract HP-Dye ion-association complexes. The chloroform was found to be the most suitable solvent for quantitative extraction of the complexes.

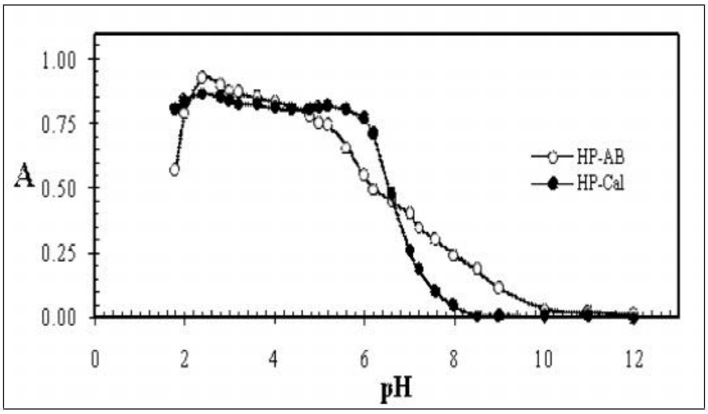

Fig.2. : Effect of the pH on absorption of HP-dye complexes
HP-Cal Complex at λ_{max} = 531 nm , HP- AB complex at λ_{max} = 626 nm

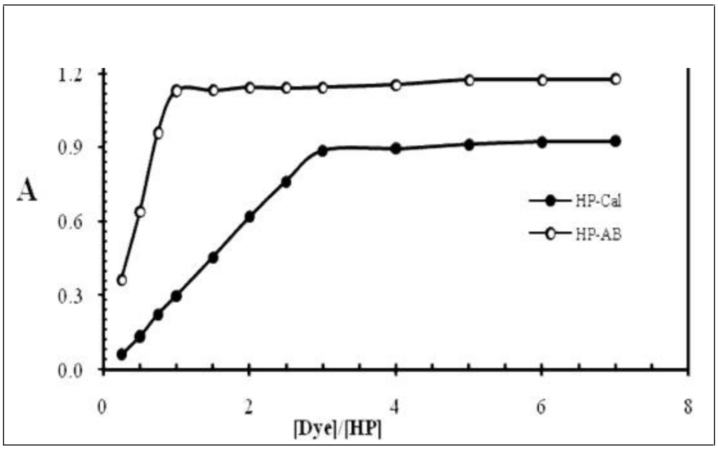

Fig. 3. Molar ratio plots for HP-Dye.

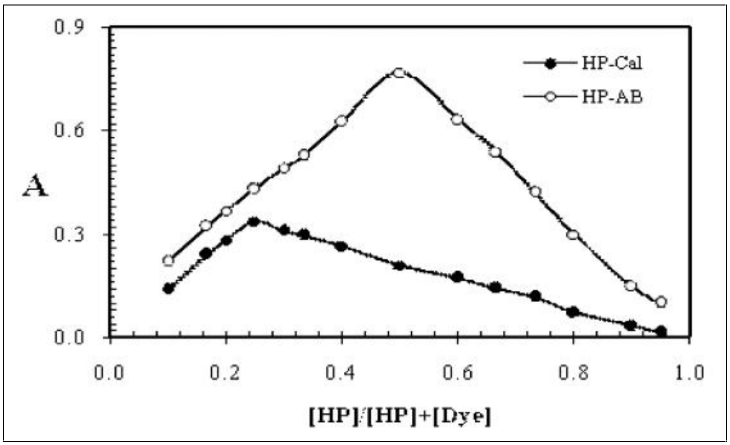

Fig. 4. Continuous Variations plots for HP-Dye

Molar Ratios Determination of HP-Dye complexes:

The molar ratio of the drug to dye in each of the colored complexes was determined using the molar ratio [24] and continuous variation [25] methods. The ratio of HP to each of the reagents Cal and AB was 1:3 for HP: Cal complex and 1:1 for HP:AB complex (Fig.3 and Fig.4).

Linearity and range:

The Beer's law limits, molar absorptivity, linear regression equation, correlation coefficient and detection limits determined for each method are given in Table (1). A linear relationship was found between the absorbance at λ_{max} and the concentration of the drug in the ranges 1.20– 33.83 and 0.752 -30.00 µg/ml for HP-Cal method and HP-AB method, respectively. (Fig.5 and Fig.6). The graphs show negligible intercept and are described by the regression equation, A= mC + b (where A is the absorbance of 1 cm layer, m is the slope, b is the intercept and C is the concentration of the measured solution in µg.ml^{-1}) obtained by the least-squares method[26]. The high molar absorptivities of the resulting colored complexes indicate the high sensitivity of the methods (2 1817 and 2 3230 l .mol^{-1}.cm^{-1} for HP-Cal. and HP-AB respectively.

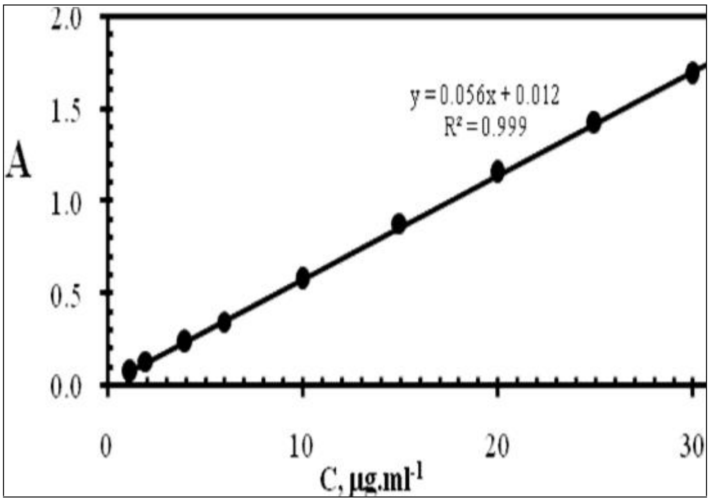

Fig. 5. Calibration plot of HP using Cal.

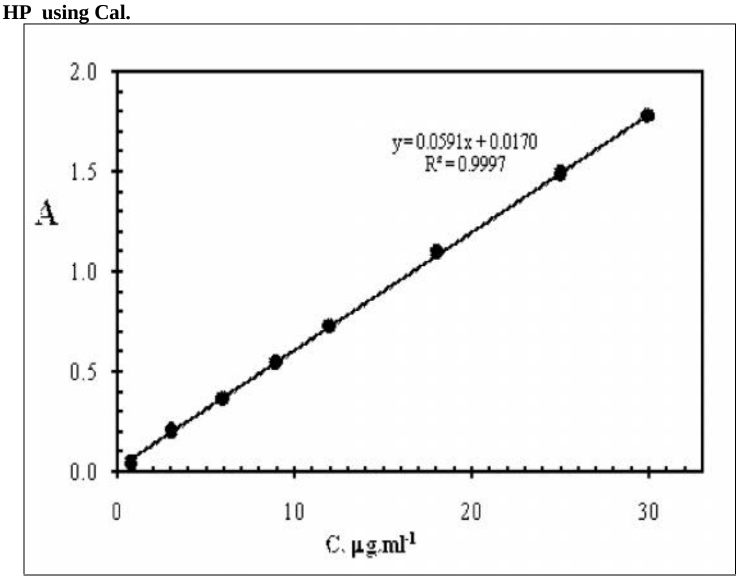

Fig. 6. Calibration plot of HP using AB.

Table 1. Spectral characteristics of HP-dye complexes

Parameters	Extraction method	
	HP-Cal	HP-AB
pH of Buffer	2.4	2.4
λ_{max} (nm)	531	626
Stoichiometric relationship	1:3	1:1
Beer's law limit (µg. ml^{-1})	1.2-33.83	0.752-30,00
Molar absorptivity (l.mol^{-1}.cm^{-1})	2 1817	2 3230
Linear Regression equation	A= 0.056C + 0.012	A= 0.059C + 0.017
Correlation coefficient, r	0.9997	0.999
LOD (µg.ml^{-1})	0.142	0.085
Range of Error	±3.85%	±4.12%

Table 2. Evaluation of precision and accuracy of the proposed methods for determination of HP in pure form.

Dye	HP, μg. ml^{-1}			RSD%	Recovery%	Confidence limit
	Taken	Found*	SD			
Cal	1.20	1.22	0.049	3.85	101.67	1.22±0.060
	3.00	2.95	0.110	3.56	98.33	2.95±0.135
	6.00	6.08	0.187	2.96	101.33	6.08±0.230
	10.00	9.89	0.281	2.71	98.90	9.89±0.347
	15.00	14.86	0.394	2.53	99.07	14.86±0.486
	20.00	19.81	0.481	2.32	99.05	19.81±0.594
	25.00	25.23	0.537	2.03	100.92	25.23±0.663
	30.00	30.26	0.596	1.88	100.87	30.26±0.736
	33.83	33.61	0.620	1.76	99.35	33.61±0.765
AB	0.75	0.74	0.032	4.12	98.67	1.328±0.040
	3.00	3.04	0.094	3.09	101.33	2.507±0.116
	6.00	5.91	0.143	2.80	99.50	5.044±0.177
	9.00	8.87	0.198	2.56	98.56	9.835±0.244
	12.00	12.15	0.253	2.34	101.25	14.76±0.312
	18.00	17.85	0.374	2.15	99.17	20.33±0.462
	25.00	24.78	0.482	1.82	99.12	25.16±0.595
	30.00	30.26	0.536	1.77	100.80	28.16±0.662

Average of five determinations.

Accuracy and Precision:

The results obtained are summarized in Table (2). The low values of relative standard deviation (RSD) indicate good precision and reproducibility of the methods. The average percent recoveries obtained were 98.33–101.67% for HP-Cal and 98.56–101.33% for HP-AB complexes, indicating good accuracy of the methods.

Table 3 shows the comparison of the performance of the proposed method with other existing methods for the determination of haloperidol in pharmaceutical preparations. The existing spectrophotometric methods are tedious[4] and time consuming[4,9]. The derivative spectrophotometric method [21] has acceptable linear range with higher RSD values. The HPLC, HPTLC[20-22,19] FNMR [14] methods are sensitive with good linear range. The RSD values for these methods are also higher. In addition, all analytical laboratories cannot afford to keep these instrumentations owing to high cost. In comparison, the proposed method is simple and sensitive employing only a cheaper reagent, and the use of Cal and AB methods were successfully applied for the determination of commercially available haloperidol in pure and in pharmaceutical formulations (tablets and drops) without interference from its excipients having in mind that calcon have not been used to determine the active components concentration in pharmaceutical forms. Hence, this research is considered one of its kind using calcon.

Application to the pharmaceutical dosage forms

The proposed methods have been successfully applied for the determination of Haloperidol in pharmaceutical preparations (table 4). The ingredients in the tablet did not interfere with the experiments.

Table 3. Comparison of the proposed method with existing methods for determination of haloperidol

Techniques/ Methods/reagents	λ_{max} (nm)	Linear range (μg. ml^{-1})	Molar absorptivity (l. mol^{-1}. cm^{-1})	LOD (μg. ml^{-1})	Recovery (%)	RSD (%)	Remark	Ref
Spectrophotomety								
$[Cr(CNS)_6]^{3-}$	329	0.15-1.14	1 4600	-	-	-	Precipitate were formed, then they were dissolved in appropriate solvents	4
$[BiI_6]^{3-}$	489	0.21-1.57	2 8500	-	-	-		4
Picric acid	422	0.06-0.91	8 5700	-	-	-		4
Chloranilic acid	576	95.60- 215.14	-	-	100.41	1.17	60 min required	9
Methanol-HCl (9:1)	245	2.50-12.50	-	-	100.28	0.25	immediate	27
First derivative Spectrophotometry with base line to peak technique	253	4.56-22.82	-	0.87	96.0-106.3	2.20	-	28
HPTLC	-	10-100 ng μL^{-1}	-	0.89 ng μl^{-1}	97.76-100.33	< 4.5	-	20
19F NMR	-	60-600	-	1.40	96.0-103.0	< 8	-	14
Cal	531	1.20-33.83	2 1817	0.142	99.35-101.67	3.85	immediate	This work
AB	626	0.752-30.00	2 3230	0.085	98.67-100.80	4.12	immediate	

Table (4): results of the estimation of Haloperidol in tablets and drops

Formulation	Claim (mg/tab)	Cal method			AB method		
		Content determined[a] (mg/tab)	RSD %	Recovery %	Content determined[a] (mg/tab)	RSD%	Recovery %
Paldol tab	5	5.07	1.76	101.40	5.05	1.81	101.20
	10	10.11	1.69	101.10	9.92	1.34	99.10
Doperidol tab	5	4.95	1.73	99.00	5.05	1.75	101.00
	10	10.10	1.66	101.00	9.93	1.41	99.30
Doperidol drops	2mg/1ml	2.03	2.04	101.50	1.97	2.22	98.50
Hayadol	0.5	0.51	2.33	102.00	0.51	2.35	102.30
	1.5	2.11	1.48	99.00	1.49	2.21	99.00
	5	1.79	5.06	101.2	5.04	1.79	101.2

a: tablets from different manufacturers, b: Average of five determinations.

CONCLUSION:

The proposed methods (Cal and AB) can be used for determination of Haloperidol in pure and Pharmaceutical Formulation. The methods are rapid, simple and they have great sensitivity and accuracy. Proposed methods make use of simple reagents which an ordinary analytical laboratory can afford. Methods are sufficiently sensitive to permit determination even down to 1.20 µg ml^{-1} for Calcon and 0.752 µg ml^{-1} for Amido Black . The proposed methods are suitable for routine determination of Haloperidol in its formulations. The commonly used additives do not interfere with the assay procedures.

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