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Role of Alkaloidal Precipitants for the Assay of Aripiprazole Hydrochloride in Bulk and Pharmaceutical Formulations

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Simple spectrophotometric methods (**A-C**) for the assay of aripiprazole (APZ) based on the formation of its complex with alkaloidal precipitants are described. Aripiprazole under quantitative precipitation in the form of molecular complexes with iodine (method **A**), ammonium molybdate (method **B**) or phosphomolybdic acid (method **C**) when used in excess. In addition to precipitation reactions, colour reactions have also been combined to estimate aripiprazole. They are based on the colour formation with either unreacted precipitant of the filtrate (I_2) or released precipitant from the molecular complex (method **B** or **C**) with chromogenic reagent such as P-N-methyl amino phenol sulphate-sulphanilic acid (method **A**), potassium thiocyanate (method **B**), cobalt nitrate Co(II)-disodium salt of ethylene diamine tetra acetic acid complex (method **C**).

Key Words: Assay, Alkaloidal precipitants, Aripiprazole hydrochloride.

INTRODUCTION

Alkaloids are detected with the aid of group of reactions due to their chemical properties, structure and presence of functional groups. These reactions are based on the ability of the alkaloid to yield insoluble complexes mainly with acetone, I_2 and PMA and hence these reagents are named as alkaloidal precipitants[1]. The precipitate is ascribed due to the formation of a molecular complex resulting from the interaction of the unshared electron on nitrogen in amine with an unoccupied molecular orbital of the alkaloidal precipitant molecule. Aripiprazole is a new antidepressant agent and chemically it is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril, literature survey reveals that UV spectrophotometic[1-8] HPLC[9-26] and LC-MS[27-30] methods were reported for the determination of aripiprazole in its formulation and in biological fluids. The aim of the present work is to provide simple and sensitive visible spectrophotometric method, for the estimation of aripiprazole in bulk form and formulations. The effects in this accord resulted to develop the present methods. Aripiprazole furnish precipitates with alkaloidal precipitants given above, since it contains the nitrogen containing groups (tertiary amino groups). In addition to precipitation reactions colour reactions have also been combined to estimate aripiprazole. They are based on the chemical reaction with either released alkaloidal precipitant from the precipitated with acetone or unreacted precipitant in the filtrate (I_2 or TA) with chromogenic reagents such as potassium thiocyanate (for acetone) PMAP-SA (for I_2) or PMAP- Cr (VI) for (for TA). The results are statistically validated.

EXPERIMENTAL

Spectral and absorbance measurements were made on Systronics UV- Visible spectrophotometer 117 with 10 mm matched quartz cells.

All the chemicals and reagents used were analytical grade and the solutions were freshly prepared. Aqueous solution of I_2 (0.089 %) in 0.83 % of potassium iodide (KI), PMAP (2 %), SAc (0.4%), hydrochloric acid (HCl) (1M) for method **A**; acetone (2 %), PTC (10 %), conc. HCl (used as it is) for method **B**; PMA (4 %) Co(II) (3 %), DETA (4 %) for method **C**, 0.01 M HCl for methods **B** and **C** were prepared in triple distilled water. A 1 mg/mL solution was prepared by dissolving 100 mg of pure aripiprazole in 100 mLof distilled water and this stock solution was diluted stepwise with distilled water to obtain the working standard solution of concentrations 200 µg/mL for method **A** and **C**, 400 µg/mL for method **B**, respectively.

Recomeended procedures

Method A: Aliquots of working standard solution (1.0-3.0 mL, 200 µg/mL) were delivered into a series of centrifuge

tubes and the volume in each tube was adjusted to 3 mLwith distilled water. Then 2 mL each of 1M HCl and I_2 were added successively and centrifuged for 5 min. The precipitate was collected by filtration and subsequently washed with 2 mL distilled water. The filtrate and washings were collected in 25 mL graduated test tubes. Then 3 mL of PMAP solution and 2 mL SAc solution were added successively and the volume was made up to the mark with distilled water. The absorbance was measured during next 30 min. at 520 nm against distilled water. A blank experiment was also carried out omitting the drug. The decrease in absorbance and in turn drug concentration was obtained by subtracting the absorbance of the test solution from blank. The amount of drug was calculated from calibration graph.

Method B: Aliquots of working standard solution (1.0-3.0 mL, 400 µg/mL) were delivered into a series of centrifuge tubes and the volume in each tube was adjusted to 3.0 mLwith 0.01 M HCl. Then 1.0 mL of acetone was added and centrifuged for 5 min. The precipitate was collected by filtration followed by washing with 50% alcohol until it is free from the reagent. The precipitate in each tube was dissolved in 5.0 mL of acetone and transferred into 25.0 mL graduated tube. The 5 mL of conc. HCl and 3 mL PTC solution were successively added and kept aside for 30 min and then volume in each tube was made up to the mark with distilled water. The absorbance was measured at 480 nm against a similar reagent blank. The amount of drug aripiprazole was calculated form the calibration graph.

Method C: Aliquots of working standard solution (1-3 mL, 200 µg/mL) were delivered into a series of centrifuge tubes and volume in each tube was adjusted to 3.0 mL with 0.01 M HCl. The 2 mL PMA was added and centrifuged for 5 min. the precipitate was collected by filtration followed by washing with distilled water until it is free from the reagent. The precipitate in each tube was dissolved in 5 mL of acetone and transferred into 25 mL graduated tubes. 1 mL each of Co (II) and EDTA solutions of were successively added and the tubes were heated for 15 min. at 60 ºC in water bath. The tubes were cooled and the solution of each tube was made upto the mark with distilled water. The absorbance was measured at 840 nm against a similar reagent blank. The amount of drug was calculated from its calibration graph.

RESULTS AND DISCUSSION

The optimum conditions for the colour development of methods (**A**, **B** and **C**) were established by varying the parameters one at a time keeping the others fixed and observing the effect produced on the absorbance of the coloured species.

The optical characteristics such as Beer's law limits; molar absorptivity and Sandell's sensitivity for each method (**A-C**) are given in Table-1. The precision of each method to the drug was found by measuring the absorbance of six separate samples containing known amounts of drug and the results obtained are incorporated in Table-1. Regression analysis using the method of least squares was made to evaluate the slope (b), intercept (a), correlation coefficient (r) and standard error of estimation (S_e) for each system and is presented in Table-1.

TABLE-1
OPTICAL CHARACTERISTICS, PRECISION AND ACCURACY OF THE PROPOSED METHODS FOR ARIPIPRAZOLE

Parameters	Method A	Method B	Method C
λ_{max} (nm)	520	480	840
Beer's Law limits (µg/mL)	4-30	10-60	4-30
Molar absorptivity ($L\ mol^{-1}\ cm^{-1}$)	1.00×10^4	3.43×10^3	9.08×0^3
Sandell's sensitivity (µg/cm^2/ 0.001 absorbance unit)	0.045	0.131	0.049
Regression equation y=a+ bc*			
Slope (b)	0.0223	0.0076	0.0201
Intercept (a)	0.0004	0.0014	0.0016
Correlation coefficient (r)	0.9998	0.9997	0.9999
Relative standard deviation (%)**	0.4182	0.4262	0.0014
% Range of error ** (0.05 level confidence limit)	0.350	0.356	0.433

*Y = a + bc, where c is the concentration in µg/mL.
**From six determinations.

The accuracy of the methods was ascertained by comparing the results by proposed and reference methods (UV) statistically by t- and F-tests (Table-2). The comparison shows that there is no significant difference between the results of studied methods and those of reference ones. The similarity of the results is obvious evidence that during the application of these methods, the excipients that are usually present in pharmaceutical formulations do not interfere in the assay of

TABLE 2
DETERMINATION OF ARIPIPRAZOLE IN PHARMACEUTICAL FORMULATIONS

Sample[?] (Tablets)	Labeled method (mg)	UV* Method	Amount obtained (mg)					
			Proposed method			Recovery (%)		
			A	B	C	A	B	C
T_1	2	1.99 ± 0.007	1.99 ± 0.011 F=2.01 t=0.53	1.99 ± 0.013 F=3.04 t=0.55	1.99±0.009 F=1.41 t=0.87	99.72±0.55	99.99 ± 0.68	99.96±0.46
T_2	5	4.98±0.022	4.99±0.027 F=1.54 t=0.46	5.01±0.020 F=1.36 t=0.78	4.99±0.024 F=1.25 t=1.08	99.88±0.54	100.10±0.37	99.97±0.49
T_3	10	9.99±0.067	9.97±0.044 F=2.28 t=0.33	10.00±0.038 F=3.10 t=0.27	9.97±0.040 F=2.81 t=0.27	99.92±0.44	100.00±0.38	99.77±0.40
T_4	20	19.81±0.065	19.89±0.08 F=1.36 T=1.94	19.82±0.11 F=3.07 T=0.19	19.86±0.13 F=0.85 T=2.07	99.4±0.38	99.13±0.56	99.34±0.65

[?]Four different batches of tablets from a pharmaceutical company.

proposed methods. As an additional check of accuracy of the proposed methods recovery experiments were carried out. The recoveries of the added amounts of standard drug were studied at 3 different levels. Each level was repeated for 6 times. From the amount of drug found, the % recovery was calculated in the usual way.

The higher λ_{max} values of all the proposed methods have a decessive advantage since the interference from the associated ingredients should be generally less at higher wavelengths than at lower wavelengths. Thus the proposed visible spectrophotometric methods are simple and sensitive with reasonable precision, accuracy and constitute better alternatives to the existing ones to the routine determination of aripiprazole in bulk forms and pharmaceutical formulations.

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