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New Spectrophotometric Methods For The Determination Of Aripiprazole In Pure Form And In Pharmaceutical Formulations

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ABSTRACT

Three simple spectrophotometric methods (A, B and C) are described for the determination of aripiprazole (APZ) in pure form and in pharmaceutical formulations. Method A is based on the oxidative coupling reaction between APZ with 2, 6- dichloroquinone-4-chlorimide (DCQC) and the color developed was measured at 620 nm. Method B is based on the replacement of sulfonate group of 1, 2 - napthoquinone- 4- sulphonic acid (NQS) by an imino group of APZ producing a colored product which absorbs maximally at 485 nm. Method C is based on the formation of a colored complex between APZ and sodium nitroprusside (SNP) in presence of hydroxyl amine and alkali, which exhibits maximum absorption at 515 nm. The optimum experimental parameters for the color production are selected. Beer's law is valid with in a concentration range of 2.5 - 12.5 μg/ml for methods A, B and 5-40 μg/ml for method C. The results obtained are reproducible and are statistically validated and found to be suitable for the assay of APZ in pharmaceutical formulations.

KEYWORDS

Aripiprazole;
Spectrophotometry;
DCQC;
NQS;
SNP.

INTRODUCTION

Aripiprazole[1-4] (APZ) is a third generation atypical antipsychotic drug and is chemically known as 7-[4-[4- (2, 3-dichlorophenyl) piperazin-1-yl] butoxy]-3, 4-dihydro-1H-quinolin-2-one. Aripiprazole has a mechanism of action that differs from all currently available typical and atypical antipsychotic agents. Aripiprazole is a high-affinity, partial agonist of the dopamine D_2 receptor. As a partial agonist,

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aripiprazole functions as a dopamine system stabilizer, reducing dopaminergic neurotransmission when such activity is excessive and enhancing it when such activity is deficient. This restores dopamine neurotransmission to the normal range. As a partial agonist of the 5-HT_{1A} receptor and an antagonist of the 5-HT_{2A} receptor, aripiprazole could be considered a serotonin system stabilizer as well. The favorable therapeutic and side effect profile of aripiprazole (e.g., efficacy for both the positive and negative signs and symptoms of schizophrenia and lower incidence of EPS, prolactin elevation, and weight gain) is likely mediated by its partial agonist activity at D_2 and 5-HT_{1A} receptors and its antagonist activity at 5-HT_2 receptors.

Aripiprazole also binds with high affinity to dopamine D_3 receptors. It binds with moderate affinity to dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha$_1$-adrenergic, and histamine H_1 receptors, and the serotonin reuptake site. It has no appreciable affinity for cholinergic muscarinic receptors.

Literature survey reveals that, two chromatographic methods[5, 6] have been reported for the estimation of APZ in human and rat plasma. To the best of our knowledge, there is no work in the literature reported about the visible spectrophotometric methods for the analysis of APZ in either biological fluids or pharmaceutical formulations. Hence the author has made an attempt to develop simple and sensitive spectrophotometric methods for the estimation of APZ in pure drug and in pharmaceutical formulations. Method A is based on the oxidative coupling reaction between APZ with 2, 6- dichloroquinone-4-chlorimide (DCQC) and the color developed was measured at 620 nm. Method B is based on the replacement of sulfonate group of 1, 2 - napthoquinone-4-sulphonic acid (NQS) by an imino group of APZ producing a colored product which absorbs maximally at 485 nm. Method C is based on the formation of a colored complex between APZ and sodium nitroprusside (SNP) in presence of hydroxyl amine (HA) and alkali, which exhibits maximum absorption at 515 nm.

EXPERIMENTAL

Apparatus

All spectral and absorbance measurements were made on a systronic model 106 digital spectrophotometer with 10mm matched quartz cells.

Reagents and standards

All chemicals used were of analytical reagent grade. Double distilled water was used throughout. APZ was obtained from Dr.Reddy's Labs Hyderabad. Arzu and Arip MT are the commercial tablet formulations labeled to contain 10 and 15mg of APZ per tablet respectively.

DCQC (0.04%) solution was prepared by dissolving 40 mg of DCQC in 100 ml of isopropanol. pH 9.4 buffer solution was prepared by mixing 250 ml of 0.2 M boric acid with 160 ml 0f 0.2 N NaOH solution and diluted to 1000 ml with distilled water and pH was adjusted to 9.4. NQS (0.5%) solution was prepared by dissolving 500 mg of NQS in 100 ml of distilled water. pH 8.0 buffer solution was prepared by mixing 30 ml of potassium hydrogen phosphate (0.067 M) and 770 ml of disodium hydrogen phosphate (0.067 M) and the pH of the solution was adjusted to 8.0. SNP (2%) solution was prepared by dissolving 2g of SNP in 100 ml of distilled water. HA (5%) solution was prepared by dissolving 5g of hydroxyl amine hydrochloride in 100 ml of distilled water. Na_2CO_3 (10%) solution was prepared by dissolving 10 g of sodium carbonate in 100 ml of distilled water.

Stock standard solution (1000μg/ml) was freshly prepared by dissolving 100mg of APZ in 100ml of methanol and then this solution was further diluted with methanol so as to obtain a working standard solution of 50 μg/ml for method A,B and 100 μg/ml for method.

General procedure and calibration

Method A (Using DCQC)

In to 10 ml measuring flasks, different aliquots of working standard solution (0.5- 2.5 ml) were transferred to provide final concentration range 2.5 - 12.5 μg/ml. To each flask, 5 ml of buffer solution (pH 9.4) and 1.5 ml of DCQC were successively added

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and kept a side for 15 min. The solutions were made up to volume with isopropanol. The absorbance of each solution was measured at 610 nm against the reagent blank. The calibration graph was then prepared by plotting the absorbance versus concentration of the drug. The concentration of the unknown was read from the calibration graph or computed from the regression equation.

Method B (Using NQS)

In to 10 ml measuring flasks, different aliquots of working standard solution (0.5- 2.5 ml) were transferred to provide final concentration range 2.5- 12.5 μg/ml. To each flask, 1.5ml of NQS and 5 ml of buffer solution (pH 8.0) were successively added and kept a side for 30 min. The solutions were made up to volume with methanol. The absorbance of each solution was measured at 485 nm against the reagent blank. The calibration graph was then prepared by plotting the absorbance versus concentration of the drug. The concentration of the unknown was read from the calibration graph or computed from the regression equation.

Method C (Using SNP)

In to 10 ml measuring flasks, different aliquots of working standard solution (0.5-4.0 ml) were transferred to provide final concentration range 5.0 - 40.0 μg,/ml. To each flask, 1 ml of SNP and 1 ml of HA were added and shaken for 2 min. then 2 ml of Na_2CO_3 was added and shaken for 25 min and made up to volume with distilled water. The absorbance of each solution was measured at 515 nm against the reagent blank. The calibration graph was then prepared by plotting the absorbance versus concentration of the drug. The concentration of the unknown was read from the calibration graph or computed from the regression equation.

Determination procedure for APZ in pharmaceutical formulations

Twenty tablets were weighed accurately and ground in to a fine powder. An amount of powder equivalent to 100 mg of APZ was weighed into a 100ml volumetric flask, 50 ml of the methanol was added and shaken thoroughly for about 10 min, then the volume was made up to the mark with the methanol , mixed well and filtered using a quantitative filter paper. The assay of the tablets was completed according to the general procedures.

RESULTS AND DISCUSSION

The optical characteristics such as Beer's law limits, Sandell's sensitivity, molar absorptivity, percent relative standard deviation (calculated from eight replicate samples containing 3/4th of the amount of the upper beer's law limits) were calculated for all the

TABLE 1: Optical and regression characteristics, precision and accuracy of the proposed methods for APZ

Parameter	Method A	Method B	Method C
λ_{max} (nm)	620	485	515
Beer's law limits (μg ml^{-1})	2.5-12.5	2.5-12.5	5.0-40.0
Detection limits (μg ml^{-1})	0.049	0.056	0.183
Molar absorptivity (L mole^{-1} cm^{-1})	2.96 x 10^4	3.25 x 10^4	9.0 x 10^3
Sandell's sensitivity (μg cm^{-2} / 0.001 absorbance unit)	0.015	0.013	0.049
Optimum photometric range(μg ml^{-1})	3.5-10.5	3.5-10.5	6.0-38.0
Regression equation (Y = a + bC)			
Slope (b)	6.6 x 10^{-2}	7.2 x 10^{-2}	2.0 x 10^{-2}
Standard deviation of slope (S_b)	0.13 x 10^{-3}	0.16 x 10^{-3}	0.05 x 10^{-3}
Intercept (a)	1.0 x 10^{-3}	-1.70 x 10^{-3}	0.41x 10^{-3}
Standard deviation of intercept (S_a)	1.08 x 10^{-3}	1.37 x 10^{-3}	1.25 x 10^{-3}
Standard error of estimation (S_e)	1.03 x 10^{-3}	1.30 x 10^{-3}	1.45 x 10^{-3}
Correlation coefficient (r)	0.9999	0.9999	0.9999
Relative standard deviation (%) [a]	0.112	0.097	0.105
% Range of error (Confidence limits)[a]			
0.05 level	0.094	0.082	0.088
0.01 level	0.139	0.121	0.130
% Error in bulk samples[b]	-0.094	0.241	-0.350

[a] Average of eight determinations
[b] Average of three determinations
In Y =a + bC, Y is absorbance and C is concentration

TABLE 2: Results of analysis of tablet formulations containing APZ

Formulation	Labeled amount (mg)	Method A			Method B			Method C			Recovery [a] (%) of reference method[d]
		Recovery[a] (%)	t [b]	F [c]	Recovery[a] (%)	t [b]	F [c]	Recovery[a] (%)	t [b]	F [c]	
Arzu (Lupin)	10	100.07	2.23	2.54	100.04	1.39	1.28	100.01	0.94	1.88	100.11
Arip MT (Torrent)	15	100.03	1.65	2.18	100.02	1.96	1.89	100.03	1.69	1.38	100.01

methods and the results are summarized in TABLE 1. Regression characteristics like standard deviation of slope (S_b), standard deviation of intercept (S_a), standard error of estimation (S_e), % range of error (0.05 and 0.01 confidence limits) and detection limit were calculated for all the methods and are shown in TABLE 1.

Application in pharmaceutical analysis and a statistical comparative study

The proposed methods (A, B and C) were applied to the spectrophotometric determination of APZ in commercial pharmaceutical formulations. The results obtained were compared statistically by the student's t-test and the variance ratio F-test with those obtained by applying the UV spectrophotometric method for APZ developed in our laboratory on samples of the same batch and given in TABLE 2.

The student's t-test values obtained at the 95% confidence level and five degrees of freedom did not exceed the theoretical tabulated value of t = 2.57, indicating no significant difference between the methods compared. The F-value (5.05) also showed that, there is no significant difference between the precision of the proposed methods and the reference method. The proposed methods can be used for routine quality control and analysis of the APZ in bulk as well as in their dosage forms.

CONCLUSION

The proposed methods are simple, accurate and offer advantages of reagent availability and stability, less time consumption and high sensitivity. Hence these methods can be useful for routine quality control analysis of APZ in pure as well as in pharmaceutical formulations.

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