International Journal of Research in Pharmacy and Pharmaceutical Sciences
ISSN: 2455-698X
Impact Factor: RJIF 5.22
www.pharmacyjournal.in
Volume 3; Issue 1; January 2018; Page No. 259-267

New spectrophotometric method for determination of Aripiprazole in pure form and pharmaceutical formulations using ceric (IV) ammonium Sulphate

Ragaa El Sheikh, * Ayman A Gouda, Lobna A Sadek
Chemistry Department, Faculty of Sciences, Zagazig University, Zagazig, Egypt

Abstract
Four simple, sensitive and accurate spectrophotometric methods have been developed for the determination of aripiprazole in pure form and pharmaceutical formulations. The methods are based on the oxidation of aripiprazole by a known excess of ceric(IV) ammonium sulphate (CAS) in acid medium followed by determination of unreacted CAS by adding a fixed amount of methylene blue (MB), amaranth (AM), indigo carmine (IC), and methyle orange (MO) dyes followed by measuring the absorbance at 664, 520, 610 and 510 nm, respectively. The experimental conditions affecting the reaction were studied and optimized. The beer's law was obeyed in the concentration ranges of 0.2-4.0, 0.5-6.0, 0.2-5.0 and 0.5-8.0 µg mL^{-1} using MB, AM, IC and MO methods, respectively with a correlation coefficient ≥ 0.9990. The calculated molar absorptivity values are 9.616×10^4, 3.377×10^4, 5.504×10^4 and 3.747×10^4 L mol^{-1} cm^{-1} using MB, AM, IC and MO methods, respectively. The limits of detection and quantification are also reported. Intra-day and inter-day precision and accuracy of the methods have been evaluated. The methods were successfully applied to the assay of aripiprazole in tablets and the results were statistically compared with those of the reference method by applying Student's *t*-test and *F*-test. No interference was observed from the common tablet excipients. The accuracy and reliability of the methods was further ascertained by performing recovery studies using standard-addition method.

Keywords: spectrophotometry; aripiprazole; ceric (IV) ammonium sulphate; dyes; pharmaceutical formulations

1. Introduction
Aripiprazole; 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxy] 3,4-dihydro-2 (1H)-quinolinone, (Figure 1) is a novel, atypical antipsychotic drug that is effective for the treatment of patients with schizophrenia or schizoaffective disorder. It has potent partial agonist activity at dopamine (D2) receptors, partial agonist activity at serotonin (5-HT1A) receptors, and antagonist activity at 5HT2A receptors. As a result, aripiprazole can improve both negative and positive symptoms of schizophrenia with lower propensity for extrapyramidal symptoms (EPS). Aripiprazole has moderate affinity for histamine and alpha-adrenergic receptors, and no appreciable affinity for cholinergic muscarinic receptors [1, 2].

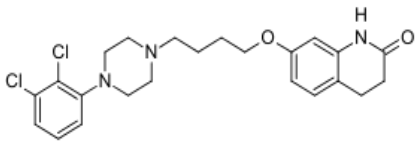

Fig 1: The chemical structure of aripiprazole

The literature survey has revealed some methods have been described for the analysis of aripiprazole including high performance liquid chromatography [3-9], gas-chromatography-mass spectrometry [10], Liquid chromatography-tandem mass spectrometry (LC-MS/MS) [11, 12] and capillary electrophoresis [13]. However, these methods are expensive, complex, time consuming and not available at most laboratories.
The spectrophotometric technique continues to be the most preferred method for the assay of different classes of drugs in pure and pharmaceutical formulations, due to its simplicity and reasonable sensitivity with significant economic advantages. There are several methods for the determination of aripiprazole using spectrophotometric technique in pharmaceutical dosage forms [14-29] (Table 1). These methods were associated with some major drawbacks such as decreased selectivity due to measurement in ultraviolet region, depending on critical experimental variables, few methods require a rigid pH control and tedious and time-consuming liquid–liquid extraction step and/or some other methods have a relatively narrow dynamic linear range, involve a heating step, and/or use of expensive reagent or large amounts of organic solvents. For these reasons, it was worthwhile to develop a new, simple, cost effective and selective spectrophotometric method for the determination of aripiprazole in pure form and pharmaceutical dosage forms.

Table 1: Comparison between the reported spectrophotometric methods for determination of aripiprazole.

Method	λ_{max} (nm)	Beer's law (μg mL^{-1})	LOD (μg mL^{-1})	Molar absorptivity (L mol^{-1} cm^{-1})	References
UV	218	2.5-20	0.01	2.2×10^5	[14]
UV	219	2- 10	-	5.2×10^5	[15]
UV	256	5. 30	-	7.4023×10^3	[16]
a- Sodium nitro prusside	430	2-10	-	1.83×10^4	[17]
b- cobalt thiocyanate	625	50-200	-	1.61×10^4	
Citric acid- acetic anhydride	590	2-12	0.37	3.374×10^4	[18]
a- 2,3-dichloro-5,6-dicyano-p-benzoquinone	457	10-120	2.44	2.87×10^3	[19]
b- Iodine	364	2-28	0.39	1.36×10^4	
c- Bromocresol green	413	2-24	0.50	1.70×10^4	
d- Bromocresol purple	400	2-20	0.30	2.20×10^4	
a- Fe (III)/ o-phenanthroline	508	0.5-7.0	0.098	8.88×10^4	[20]
b- Fe (III)/ bipyridyl	519	0.5-7.0	0.17	7.21×10^4	
c- Fe (III)/ ferricyanide	796	0.5-9.0	0.18	7.74×10^4	
Bromocresol green	414	10-60	-	6.5018×10^4	[21]
Fe (III)/ MBTH	490	2.0-12	0.5835	0.3419×10^5	[22]
a. Bromothymol blue	442	10-60	-	1.028×10^4	[23]
b. Metanil yellow	494	2.5-12.5	-	1.086×10^4	
c. Bromophenol blue	530	5-30	-	1.067×10^4	
N-bromosuccinimide/methylene blue	663	5.0-20	-	1.4906×10^4	[24]
Chloranilic acid	543	80-400	5.17	1.053×10^3	[25]
a. Bromophenol blue	408	2-20	0.2503	2.4×10^4	[26]
b. Bromothymol blue	406	1-14	0.1359	4.1×10^4	
Methyl orange	428	2-14	0.0716	10.3×10^4	[27]
Eriochrome black T	514	4-26	0.9523	2.2×10^4	[28]
N-bromosuccinimide / a. Methyl orange	522	0.2-3	0.061	5.1255×10^4	[29]
b. Amaranth	507	0.1-2.4	0.028	8.111×10^4	
c. Indigocarmine	610	0.2-3.8	0.056	6.9898×10^4	
Ce(IV) / a. MB	664	0.2-4.0	0.06	9.616×10^4	Present work
b. AM	520	0.5-6.0	0.14	3.377 10^4	
c. IC	610	0.2-5.0	0.05	5.504 10^4	
d. MO	510	0.5-8.0	0.15	3.747×10^4	

Cerium (IV) ammonium sulphate has been widely used as an effective analytical reagent in spectrophotometric methods for the determination of many pharmaceutical compounds [30-34]. CAS is a strong oxidant, and it has not been applied for the assay of aripiprazole in pure form and tablets.

This paper describes for the first time the application of acidic CAS to the spectrophotometric determination of aripiprazole using methylene blue (MB), amaranth (AM), indigo carmine (IC) and methyl orange (MO) as chromogenic agents. The proposed methods have the advantages of simplicity, sensitivity and rapidity besides being accurate precise and validated spectrophotometric method for the estimation of aripiprazole in pure and dosage forms and can be adopted by the pharmaceutical laboratories for industrial quality control.

2. Materials and Methods

2.1 Apparatus

Varian UV–Vis spectrophotometer (Cary 100 Conc., Australia) equipped with 10 mm quartz cell was used for absorbance measurements. It has a wavelength accuracy of ±0.2 nm with a scanning speed of 200 nm/min and a bandwidth of 2.0 nm in the wavelength range of 200–900 nm.

2.2 Materials and Reagents

All chemicals and reagents used were of analytical or pharmaceutical grade and all solutions were prepared fresh daily. Bidistilled water was used throughout the investigation.

2.2.1 Materials

Pharmaceutical grade aripiprazole was kindly supplied by Al-Andalus Medical Company, Cairo-Egypt. Aripiprazole tablets labeled to contain 15 mg aripiprazole per tablet (EL Obour Modern Pharmaceutical Industries, OPI Pharma, El Obour City, Egypt) and Aripiprex tablets, labeled to contain 10 mg aripiprazole per tablet (Al Andalous for Pharmaceutical Industries, Giza, Egypt) were purchased from local commercial markets.

2.2.2 Standard aripiprazole solution

A stock standard solution of aripiprazole (100 μg mL^{-1}) was prepared by dissolving an exact weight (10 mg) of pure aripiprazole in bidistilled water and diluted to 100 mL with bidistilled water in a 100 mL measuring flask. The working solution (20 μg mL^{-1}) of aripiprazole was obtained by dilution the stock solution 5.0-fold. The standard solution was found stable for at least one week without alteration when kept in an amber colored bottle and stored in a refrigerator when not in use.

2.2.3 Reagents

A stock solution of 5.0×10^{-3} mol L^{-1} CAS (E-Merk, Darmstadt, Germany) was freshly prepared by dissolving

316.2 mg CAS in the least amount of H_2SO_4 (2.0 mol L^{-1}) then completed to the mark in a 100 mL calibrated flask with the same acid and kept in a dark bottle and a refrigerator when not in use.

A stock solution of 2.0 mol L^{-1} H_2SO_4 was prepared by adding 10.8 mL of concentrated acid (Merck, Darmstadt, Germany, 98%, Sp. Gr. 1.84) to bidistilled water, cooled to room temperature, transfer to 100 mL with measuring flask, diluted to the mark and standardized as recorded [35].

A stock solution (1000 µg mL^{-1}) MB, AM, IC and MO dyes were first prepared by dissolving accurately weighed 112 mg of each dye (Sigma-aldrish, 90 % dye content) in bidistilled water and diluting to volume in a 100 mL calibrated flask. The solution was then diluted 10-fold to get the working concentration of 100 µg mL^{-1} for all dyes.

2.3 Recommended general procedures

Different aliquots (0.1-2.0 mL), (0.25-3.0 mL), (0.1-2.5 mL) and (0.25-4.0 mL) of a standard 20 µg mL^{-1} aripiprazole solution using MB, AM, IC and MO methods, respectively were transferred into a series of 10 mL calibrated flasks by means of a micro burette and the total volume was adjusted to 5.0 mL by adding adequate quantity of water. To each flask 1.0 mL of 2.0 mol L^{-1} H_2SO_4 and 1.0 mL of (5.0×10^{-3} mol L^{-1}) CAS solution were added, respectively. The flasks were stoppered, contents were mixed well, and the flasks were kept aside for 5.0 min with occasional shaking. Finally, 1.0 mL of (100 µg mL^{-1}) MB, AM, IC or MO dye solution was added to each flask and mixed well, and then the volume was diluted to the mark with bidistilled water. The color intensity of dyes was measured after 5.0 min against reagent blank solution treated similarly omitting the drug, at their corresponding λ_{max} 664, 520, 610 and 510 nm, respectively. The concentration of unknown was determined in each case from calibration graph or computed from the regression equation derived using Beer's law data.

2.4 Procedure for pharmaceutical formulations

The contents of twenty tablets of formulations were accurately weighed and ground into a fine powder. An accurate weight equivalent to 10 mg aripiprazole was dissolved in 20 mL of HCl (0.2 mol L^{-1}) with shaking for 5.0 min and filtered using a Whatman No. 42 filter paper. The filtrate was diluted to the mark with HCl (0.1 mol L^{-1}) in a 100 mL measuring flask to give and 100 µg mL^{-1} stock solution of aripiprazole for analysis by the proposed methods. Determine the nominal content of the tablets using the corresponding regression equation of the appropriate calibration graph.

3. Results and Discussion

3.1 Absorption spectra

The proposed spectrophotometric methods for the determination of aripiprazole involves two steps namely:

1. Oxidation of aripiprazole with a known excess of CAS in acidic medium at room temperature (25 ±2 °C).
2. Determination of the residual CAS by reacting it with a fixed amount of MB, AM, IC and MO dyes and measuring the increase in absorbance at λ_{max} 664, 520, 610 and 510 nm, respectively (figure 2).

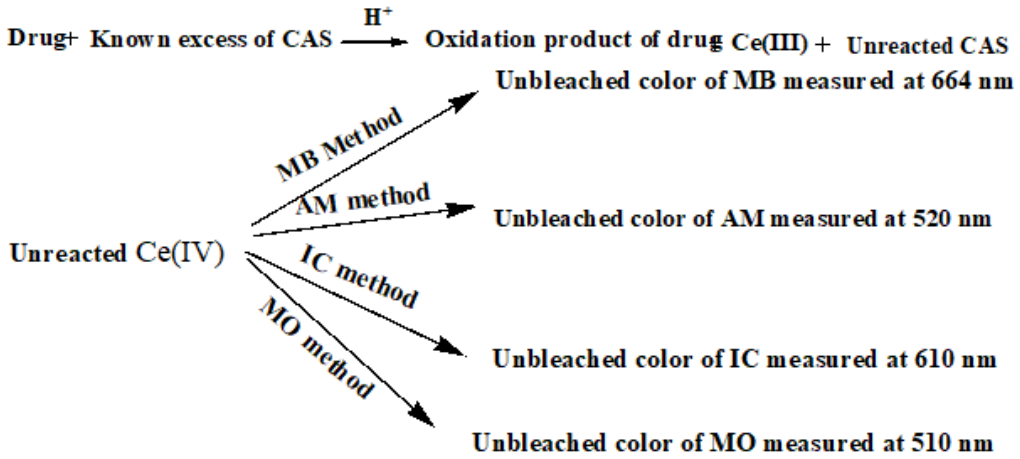

Fig 1: The suggested reaction pathway for the proposed spectrophotometric methods for determination of aripiprazole using CAS and dyes.

3.2 Optimization of the reaction conditions

The optimum conditions for the assay procedures and color development for each method have been established by varying the parameters one at a time, keeping the others fixed and observing the effect produced on the absorbance of the colored species.

3.2.1 Effect of acid type and concentration

To investigate the effect of acid concentration, different types of acids were examined (HCl, H_2SO_4, H_3PO_4, HNO_3 and CH_3COOH) to achieve maximum yield of redox reactions. The results indicated that the sulphuric acid (H_2SO_4) (2.0 mol L^{-1}) was the most suitable acid with CAS as oxidant. Moreover, different volumes (0.2–3.0 mL) of 2.0 mol L^{-1} H_2SO_4 were tested and found to be a constant absorbance was obtained with 0.5–1.5 mL of H_2SO_4 (2.0 mol L^{-1}), so 1.0 mL of H_2SO_4 (2.0 mol L^{-1}) was the optimum volume for subsequent studies (Figure 3).

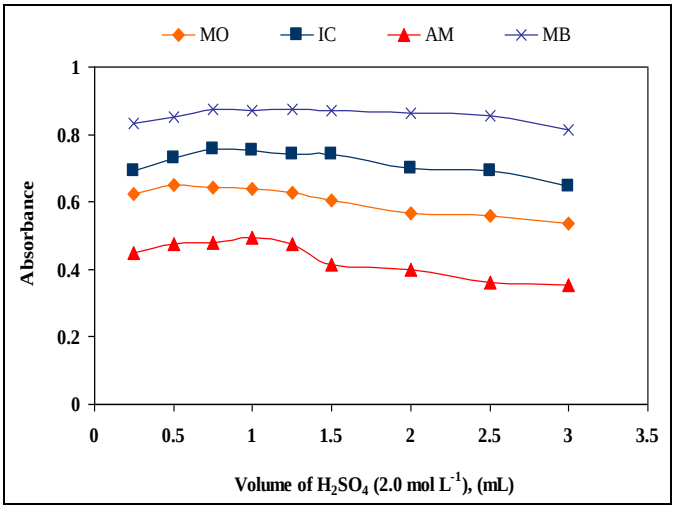

Fig 2: Effect of volume of H_2SO_4 (2.0 mol L^{-1}) on the absorbance of aripiprazole (10 µg mL^{-1}) with CAS (5.0 x 10^{-3} mol L^{-1}) and dyes.

3.2.2 Effect of CAS concentration

The influence of the concentration of CAS on the absorbance of the colored products was investigated using different volumes of 5.0 × 10^{-3} mol L^{-1} CAS solution from (0.25-3.0 mL). The results indicate that the maximum and constant absorbance was obtained using 1.0 mL of 5.0 × 10^{-3} mol L^{-1} CAS solution and the color intensity decreased above the upper limits. Therefore, 1.0 mL of 5.0 × 10^{-3} mol L^{-1} CAS was taken as the optimum concentration for all measurements (Figure 4).

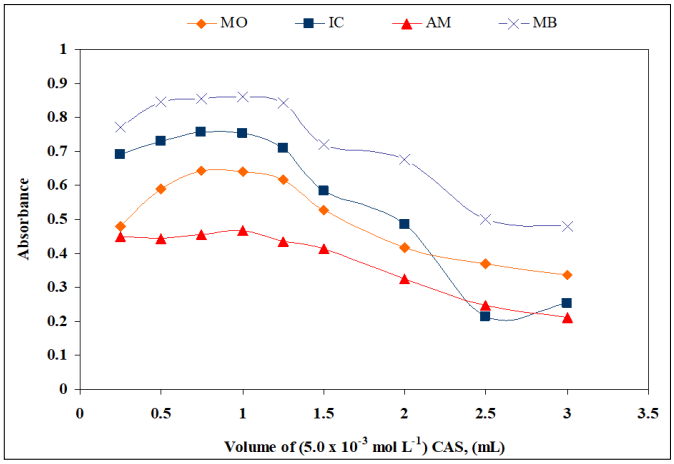

Fig. 3: Effect of volume of CAS (5.0 x 10^{-3} mol L^{-1}) on the reaction product of aripiprazole (10 µg mL^{-1}) with CAS and dyes in H_2SO_4 medium.

3.2.3 Effect of dye concentration

The effect of dye concentration on the intensity of the color developed was carried out to obtain the optimum concentration of dyes that produces the maximum and reproducible color intensity by reducing the residual of CAS. The effect dye concentration was studied using different volumes (0.25–3.0 mL) of the studied dyes (100 µg mL^{-1}). It was observed that maximum color intensity of the oxidation products was achieved with 1.0 mL of each dye solution. (Figure 5). The color was found to be stable up to 24 h.

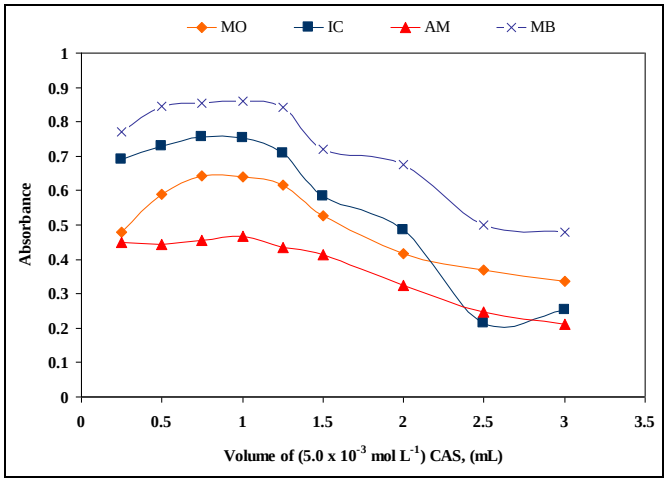

Fig 4: Effect of volume of dyes on the reaction product of aripiprazole (10 µg mL^{-1}) with CAS and dyes in H_2SO_4 medium.

3.2.4 Effect of temperature and mixing time

The effect of temperature was studied by heating a series of sample and blank solutions at different temperatures ranging from 20 to 60 °C in water bath. It was found that raising the temperature does not accelerate the oxidation process and does not give reproducible results, so maximum color intensity was obtained at room temperature (25±2 °C). The effect of mixing time required completing oxidation of aripiprazole and for reducing the excess oxidant was studied by measuring the absorbance of sample solution against blank solution prepared similarly at various time intervals 2.0–20 min. It was found that the contact times gave constant and reproducible absorbance values at 5.0 min. After oxidation process, 5.0 min standing time was found necessary for the complete bleaching of the dye color by the residual CAS and the absorbance of the unreacted dye was stable for at least 24 h, thereafter.

3.2.5 Effect of sequence of addition

After optimizing all other experimental variables, further experiments were performed to ascertain the influence of sequence of addition of reactants on the color development by measuring the absorbance. The optimum sequence of addition was aripiprazole–H_2SO_4–CAS–dye. Other sequences gave lower absorbance values under the same experimental conditions.

3.3 Method validation

The proposed methods have been validated for linearity, sensitivity, precision, accuracy, selectivity and recovery.

3.3.1. Linearity and sensitivity

Under the optimum conditions a linear correlation was found between absorbance at λ_{max} and the concentration of aripiprazole in the ranges of 0.2-4.0, 0.5-6.0, 0.2-4.8 and 0.5-8.0 µg mL^{-1} using MB, AM, IC and MO methods, respectively. The calibration graph is described by the equation:

$$A = a + b\,C \qquad (1)$$

Where A= absorbance, a= intercept, b= slope and C=

concentration in µg mL^{-1}, obtained by the method of least squares. Correlation coefficient, intercept and slope of the calibration data are summarized in Table 2. For accurate determination, Ringbom concentration range [36] was calculated by plotting log concentration of drug in µg mL^{-1} against transmittance % from which the linear portion of the curve gives an accurate range of microdetermination of aripiprazole and represented in Table 2. Sensitivity parameters such as apparent molar absorptivity and Sandell's sensitivity values, as well as the limits of detection and quantification, were calculated as per the current ICH guidelines [37] and illustrated in Table 2. The high molar absorptivity and lower Sandell's sensitivity values reflect the good and high sensitivity of the proposed methods. The validity of the proposed methods was evaluated by statistical analysis [38] between the results achieved from the proposed methods and that of the reported method [29]. Regarding the calculated Student's *t*-test and variance ratio *F*-test (Table 2), there is no significant difference between the proposed and reported methods regarding accuracy and precision.

The limits of detection (LOD) and quantification (LOQ) were calculated according to the same guidelines using the formulas [37, 38]:

$$LOD = 3.3\sigma/s \quad \text{and} \quad LOQ = 10\sigma/s \qquad (2)$$

Where σ is the standard deviation of five reagent blank determinations, and s is the slope of the calibration curve.

Table 2: Analytical parameters of the proposed methods for determination of Aripiprazole

Parameters	MB	AM	IC	MO
Wavelength, nm	664	520	610	510
Beer's law limits, µg mL^{-1}	0.2-4.0	0.5-6.0	0.2-5.0	0.5-8.0
Ringboom limits, µg mL^{-1}	0.5-3.5	1.0-5.0	0.5-4.0	1.0-7.0
Molar absorptivity, x 10^4 (L mol^{-1} cm^{-1})	9.616	3.377	5.504	3.747
Sandell sensitivity, ng cm^{-2}	4.66	13.28	8.15	11.97
Regression equation[a]				
Intercept (a)	0.0032	-0.0018	0.0033	-0.0003
SD of intercept (S_a)	0.025	0.015	0.029	0.024
Slope (b)	0.209	0.077	0.1138	0.0835
SD of slope (S_b)	0.036	0.011	0.031	0.017
Correlation coefficient, (r)	0.9996	0.9995	0.9994	0.9995
Mean ± SD	99.20±0.72	99.40±1.05	100.20±0.68	99.30±1.10
Relative standard deviation (RSD%)	0.73	1.06	0.68	1.10
Relative error (RE%)	0.76	1.11	0.71	1.16
Limit of detection (LOD), µg mL^{-1}	0.06	0.14	0.05	0.15
Limit of quantification (LOQ), µg mL^{-1}	0.20	0.47	0.17	0.50
Calculated *t*-value [b]	1.76	1.13	0.22	1.26
Calculated *F*-value [b]	1.46	1.45	1.64	1.60

[a] $A = a + bC$, where C is the concentration in µg mL^{-1}, A is the absorbance units, a is the intercept, b is the slope.

[b] The theoretical values of t and F are 2.57 and 5.05, respectively at confidence limit at 95% confidence level and five degrees of freedom (p= 0.05).

3.3.2 Accuracy and precision

To evaluate the precision of the proposed methods, solutions containing three different concentrations of aripiprazole were prepared and analyzed in six replicates. The analytical results obtained from this investigation are summarized in Table 3. Lower values of the relative standard deviation (RSD%) and percentage relative error (RE%) indicate the precision and accuracy of the proposed methods. The percentage relative error is calculated using the following equation:

$$\%\,R.E. = \left[\frac{found - taken}{taken} \right] \times 100 \qquad (3)$$

The assay procedure was repeated six times, and percentage relative standard deviation (RSD%) values were obtained within the same day to evaluate repeatability (intra-day precision) and over five different days to evaluate intermediate precision (inter-day precision).

For the same concentrations of drug inter- and intra-day accuracy of the proposed methods were also evaluated. The percentage recovery values with respect to found concentrations of each drug were evaluated to ascertain the accuracy of the methods. The recovery values close to 100% as compiled in Table 3 shows that the proposed methods are very accurate.

Table 3: Results of intra-day and inter-day accuracy and precision study for aripiprazole obtained by the proposed methods.

Method	Taken (µg mL^{-1})	Intra-day				Inter-day			
		Recovery %	Precision RSD % [a]	Accuracy RE %	Confidence Limit [b]	Recovery %	Precision RSD % [a]	Accuracy RE %	Confidence Limit [b]
MB	1.0	99.30	0.50	-0.70	0.993 ± 0.005	99.20	0.40	-0.80	0.992 ±n 0.004
	2.0	99.00	0.76	-1.0	1.98 ± 0.016	99.50	0.63	-0.50	1.99 ± 0.013
	3.0	99.60	0.92	-0.40	2.988 ± 0.029	99.30	1.10	-0.70	2.979 ± 0.034
AM	2.0	99.0	0.50	-1.0	1.98 ±0.01	99.10	0.60	-0.90	1.982 ± 0.012

	4.0	99.10	0.70	-0.90	3.964 ± 0.029	99.70	0.90	-0.30	3.988 ± 0.038
	6.0	99.40	1.20	-0.60	5.964 ± 0.075	100.30	1.10	0.30	6.018 ± 0.069
IC	1.0	99.60	0.45	-0.40	0.996 ± 0.005	99.70	0.38	-0.30	0.997 ± 0.004
	2.0	100.40	0.83	0.40	2.008 ± 0.017	100.20	0.56	0.20	2.004 ± 0.012
	3.0	99.40	1.40	-0.60	2.982 ± 0.044	100.10	0.86	0.10	3.003 ± 0.027
MO	2.0	99.80	0.37	-0.00	1.996 ± 0.008	99.10	0.50	-0.90	1.982 ± 0.01
	4.0	100.30	0.69	0.30	4.012± 0.029	99.30	0.82	-0.70	3.972 ± 0.034
	6.0	99.50	1.05	-0.50	5.97 ±0.066	100.60	1.20	0.60	6.036 ± 0.076

[a] RSD%, percentage relative standard deviation; RE%, percentage relative error.
[b] Mean ± standard error.

3.3.3 Robustness and ruggedness

Robustness was examined by evaluating the influence of small variation of method variables, including concentration of analytical reagent and reaction time on the performance of the proposed methods. In these experiments, one parameter was changed whereas the others were kept unchanged, and the recovery percentage was calculated each time. The analysis was performed with altered conditions by taking three different concentrations of aripiprazole and it was found that small variation of method variables did not significantly affect the procedures as shown by the RSD values in the ranges of 0.70-2.40%. This provided an indication for the reliability of the proposed methods during its routine application for the analysis of aripiprazole and so the proposed methods are considered robust. Ruggedness was expressed as the RSD and was also tested by applying the proposed methods to the assay of aripiprazole using the same operational conditions but using three different instruments as well as three different anaysts. The inter-analysts RSD were in the ranges 0.90-2.45%, whereas the inter-instruments RSD ranged from 0.70-2.20% suggesting that the developed methods were rugged. The results are shown in Table 4.

Table 4: Results of method robustness and ruggedness.

Methods	Nominal amount concentration (µg mL^{-1})	RSD%			
		Robustness		Ruggedness	
		Variable alerted [a]			
		Reagent volume (n=3)	Reaction time (n=3)	Different analysts (n=3)	Different instruments (n=3)
MB	1.0	1.20	0.80	1.10	0.90
	2.0	1.48	1.30	1.70	1.60
	4.0	1.70	2.0	2.40	2.20
AM	2.0	1.10	0.75	1.05	1.25
	4.0	1.50	1.20	1.40	1.80
	6.0	2.10	1.90	1.80	2.20
IC	1.0	0.70	1.10	0.90	1.20
	2.0	1.30	1.50	1.60	1.70
	4.0	2.20	2.20	2.30	2.20
MO	2.0	0.80	0.75	0.95	0.70
	4.0	1.60	1.50	1.50	1.20
	6.0	2.40	1.95	2.45	1.80

[a] Volume of (2.0 mol L^{-1}) H_2SO_4 is (1.0±0.2 mL) and reaction time is (5.0±2.0 min) after adding CAS were used.

3.4 Recovery studies

To ascertain the accuracy, reliability and validity of the proposed methods, recovery experiment was performed through standard addition technique. This study was performed by spiking three different levels of pure aripiprazole (50, 100 and 150% of the level present in the tablet) to a fixed amount of drug in tablet powder (pre-analysed) and the total concentration was found by the proposed methods. The determination with each level was repeated three times and the percent recovery of the added standard was calculated from:

$$\% \text{ Recovery} = \frac{[C_F - C_T]}{C_p} \times 100 \quad (4)$$

Where C_F is the total concentration of the analyte found, C_T is a concentration of the analyte present in the tablet preparation; C_P is a concentration of analyte (pure drug) added to tablets preparations. The results of this study presented in Table 5 revealed that the accuracy of the proposed methods was unaffected by the various excipients present in tablets which did not interfere in the assay.

Table 5: Results of recovery experiments by standard addition method for the determination of aripiprazole in tablets using the proposed methods.

Method	Taken drug (µg mL^{-1})	Pure drug Added (µg mL^{-1})	Aripiprazole tablets		Aripiprex tablets	
			Total found (µg mL^{-1})	Recovery [a] (%) ± SD	Total found (µg mL^{-1})	Recovery [a] (%) ± SD
MB	1.0	1.0	1.976	98.80±0.40	1.98	99.0±0.52
		2.0	2.982	99.40±0.76	2.994	99.80±0.85
		3.0	4.02	100.50±0.94	3.968	99.20±1.15
AM	1.0	1.0	2.004	100.20±0.38	1.988	99.40±0.44
		2.0	2.979	99.30±0.57	2.994	99.80±0.73
		4.0	4.955	99.10±1.10	4.985	99.70±1.30
IC	1.0	1.0	1.992	99.20±0.50	1.99	99.50±0.37
		2.0	2.988	99.60±0.80	3.009	100.30±0.68
		4.0	4.95	99.00±1.50	2.988	99.60±0.98
MO	1.0	2.0	2.982	99.40±0.40	2.973	99.10±0.52
		4.0	5.015	100.30±0.70	4.985	99.70±0.88
		6.0	7.05	100.70±1.20	6.951	99.30±1.10

[a] Average of six determinations.

3.5 Application of pharmaceutical formulations (tablets)

The proposed methods were applied to the determination of aripiprazole in tablets. The results in Table 6 showed that the methods are successful for the determination of aripiprazole and that the excipients in the dosage forms do not interfere. A statistical comparison of the results obtained from the assay of aripiprazole by the proposed methods and the reported method [29] by applying the Student's t-test for accuracy and F-test for precision, the calculated t-value and F-value at 95% confidence level did not exceed the tabulated values for five degrees of freedom [38] (Table 6). Hence, no significant difference between the proposed methods and the reported method at the 95 % confidence level with respect to accuracy and precision.

Table 6: Results of analysis of tablets by the proposed methods for the determination of aripiprazole and statistical comparison with the reported method.

Samples	Recovery [a] (%) ± SD				
	Proposed Methods				Reported method [29]
	MB	AM	IC	MO	
Aripiprazole tablets	99.70 ± 0.57	99.30 ± 0.85	100.10 ± 0.42	99.20 ± 0.74	99.63 ± 0.62
t-value [b]	0.19	0.70	1.40	1.0	
F-value [b]	1.18	1.88	2.18	1.42	
Aripiprex tablets	99.40 ± 0.84	99.80 ± 0.92	99.20 ± 0.39	99.80 ± 0.45	99.50 ± 0.69
t-value [b]	0.21	0.58	0.85	0.81	
F-value [b]	1.48	1.78	3.13	2.35	

[a] Average of six determinations.

[b] The theoretical values of *t* and *F* are 2.571 and 5.05, respectively at confidence limit at 95% confidence level and five degrees of freedom (p = 0.05).

4. Conclusions

A new, simple, rapid, useful and cost-effective spectrophotometric methods have been developed for determination of aripiprazole in pure form and tablets using CAS as oxidizing agent and validated as per the current ICH guidelines. The present spectrophotometric methods are characterized by simplicity of operation, high selectivity, comparable sensitivity, low-cost instrument, they do not involve any critical experimental variable and are free from tedious and time-consuming extraction steps and use of organic solvents unlike many of the previous methods reported for aripiprazole. The proposed methods have some additional advantages involve less stringent control of experimental parameters such as the stability of the colored system, accuracy, reproducibility, time of analysis, temperature independence and cheaper chemicals. These advantages encourage the application of the proposed methods in routine quality control analysis of aripiprazole in pure and dosage forms.

5. Conflict of Interests

The authors declare that they have no conflict of interests with the company name used in the paper.

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