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VALIDATED HPLC METHOD FOR DETERMINATION OF ARIPRAZOLE IN PHARMACEUTICALS

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ABSTRACT

The development of analytical methods for drug identification, purity evaluation, and quantification has received a lot of attention in the field of pharmaceutical analysis in recent years. This review provides a general overview of HPLC method development and validation. A general and very simple approach to developing HPLC methods for compound separation was discussed. Before developing an HPLC method, it is critical to understand the physicochemical properties of the primary compound. The composition of the buffer and mobile phase (organic and pH) has a significant impact on separation selectivity. Finally, the gradient slope, temperature, and flow rate, as well as the type and concentration of mobilephase modifiers, can be optimized. The optimized method is validated using various parameters (e.g., specificity, precision, accuracy, detection limit, linearity, and so on) following ICH guidelines Our method was found to be simple and high throughput analysis than the other analytical methods for Aripiprazole available in the literature.

Keywords: HPLC, Development, Aripiprazole.

1. INTRODUCTION

Aripiprazole is an antipsychotic medicine that is used for the treatment of schizophrenia in both adults and children who are at least 13 years old. Aripiprazole (brand name Abilify) is furthermore utilized for the treatment of Tourette's disorder or manifestations of autistic disorder (irritability, aggression, mood fluctuations, temper outbursts, and self-harm) in children aged 6 years or older; bipolar I disorder (manic depression) in individuals aged 10 years or older, either in conjunction with a mood stabilizer or as mono therapy; major depressive disorder in adults in conjunction with an antidepressant.

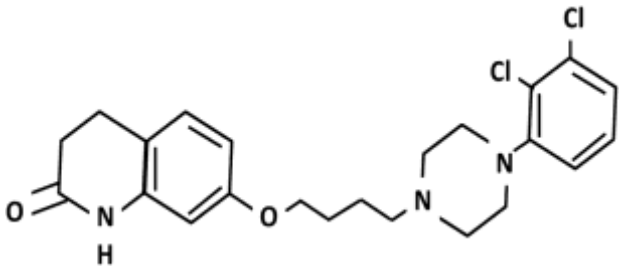

Fig 1: Aripiprazole Structure

Aripiprazole, sold under the brand names Abilify and Aristada, among others, is an atypical antipsychotic primarily used in the treatment of schizophrenia, bipolar disorder, and irritability associated with autism spectrum disorder; other uses include as an add-on treatment for major depressive disorder and tic disorders. Aripiprazole is taken by mouth or via injection into a muscle. A Cochrane review found low-quality evidence of effectiveness in treating schizophrenia.

Physicochemical properties of Aripiprazole

Chemical Name	7-{4-[4-(2,3-dichlorophenyl)-piperazin-1-yl]butoxy}-3,4-dihydroquinolin-2(1H)-one
Molecular Formula	C23H27Cl2N3O2
Molecular Weight	448.39 g/mol
Absorption	Well absorbed orally, peak plasma concentration in 3-5 hours
Metabolism	Primarily metabolized in the liver via CYP3A4 and CYP2D6
Half-life	Approximately 75 hours
Bioavailability	87%

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Protein binding	>99%
Metabolism	Liver (mostly via CYP3A4 and 2D6
Elimination half-life	75 hours (active metabolite is 94 hours)
Excretion	Kidney (27%; <1% unchanged) faeces (60%; 18% unchanged)

2. MATERIALS AND METHODS

Materials and Methods:

Instrumentation: The study will utilize a high-performance liquid chromatography (HPLC) system equipped with:

- A binary solvent delivery system.
- UV-Vis or PDA detector.
- C18 reverse-phase column with specific dimensions for optimal resolution.
- Chromatographic data acquisition software.

3. RESULTS AND DISCUSSION

Method development and optimization

Column chemistry, solvent selectivity (solvent type), solvent strength (volume fraction of organic solvent(s) in the mobile phase), additive strength, detection wavelength and flow rate were varied to determine the chromatographic conditions giving the best separation. The mobile phase conditions were optimized, so there was no interference with the aripiprazole peak from solvent or excipient peaks. Other criteria, for example the time required for analysis, assay sensitivity, solvent noise and use of the same solvent system for extraction of the drug from formulation matrices during drug analysis, were also considered. After each change of mobile phase the column was equilibrated by passage of at least twenty column volumes of the new mobile phase. To investigate the appropriate wavelength for determination of aripiprazole, UV–visible spectra in the range 200–400 nm were acquired from a solution of the drug in the mobile phase (Elico, India; model SL-164 spectrophotometer). From the UV spectra obtained the wavelength selected for monitoring the drug was 254 nm. Solutions of the drug in the mobile phase were injected directly for HPLC analysis and the responses (peak area) were recorded at 254 nm. It was observed there was no interference from the mobile phase or baseline disturbance at 254 nm. Therefore, it was, concluded that 254 nm was the most appropriate wavelength for analysis of the substance with suitable sensitivity.

Chromatography

Symmetrical peaks were obtained for aripiprazole. Typical chromatograms obtained from a blank and from a solution of the drug are illustrated in Figure 2 (a&b). The retention time of aripiprazole was 3.8 min and the overall chromatographic run time was 8.0 min

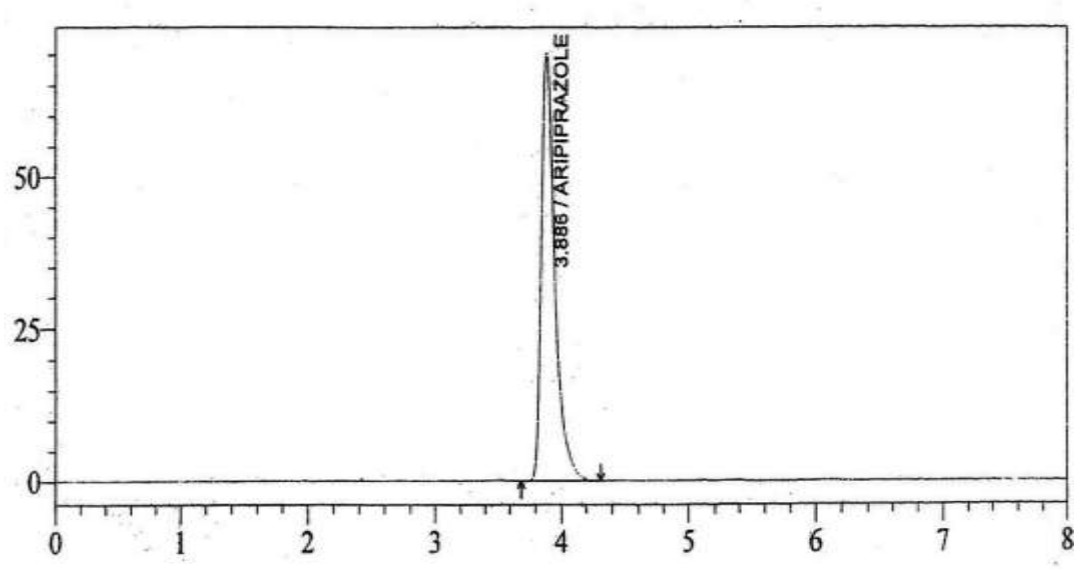

Fig 2: Typical chromatograms obtained from blank and (b) aripiprazole solution

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Linear regression data for detection of aripiprazole

Sr. No.	Spiked Concentration ($\mu g.mL^{-1}$)	Measured Concentration ($\mu g.mL^{-1}$)
01	5.00	5.01 ± 0.06
02	10.00	9.62 ± 0.09
03	20.00	20.09 ± 0.07
04	30	30.44 ± 0.09
05	40	40.69 ± 0.12
06	50	50.66 ± 0.70
07	Equation	y=15310x+12472
08	r^2	0.9991

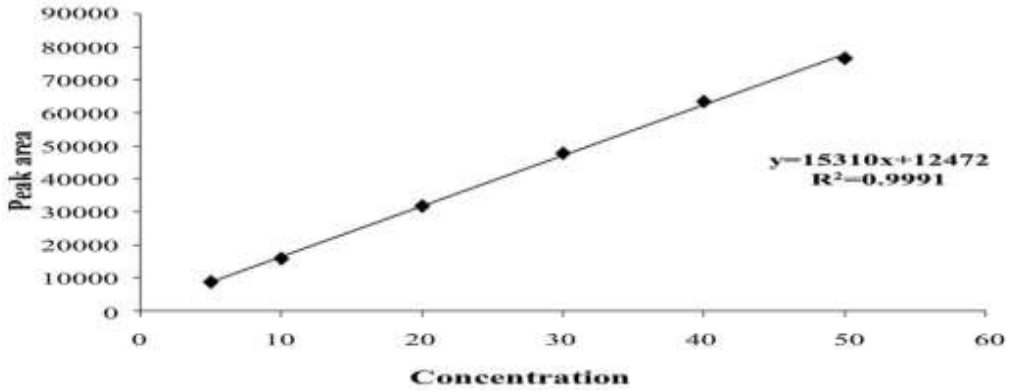

Fig 3: Representative calibration curve of aripiprazole

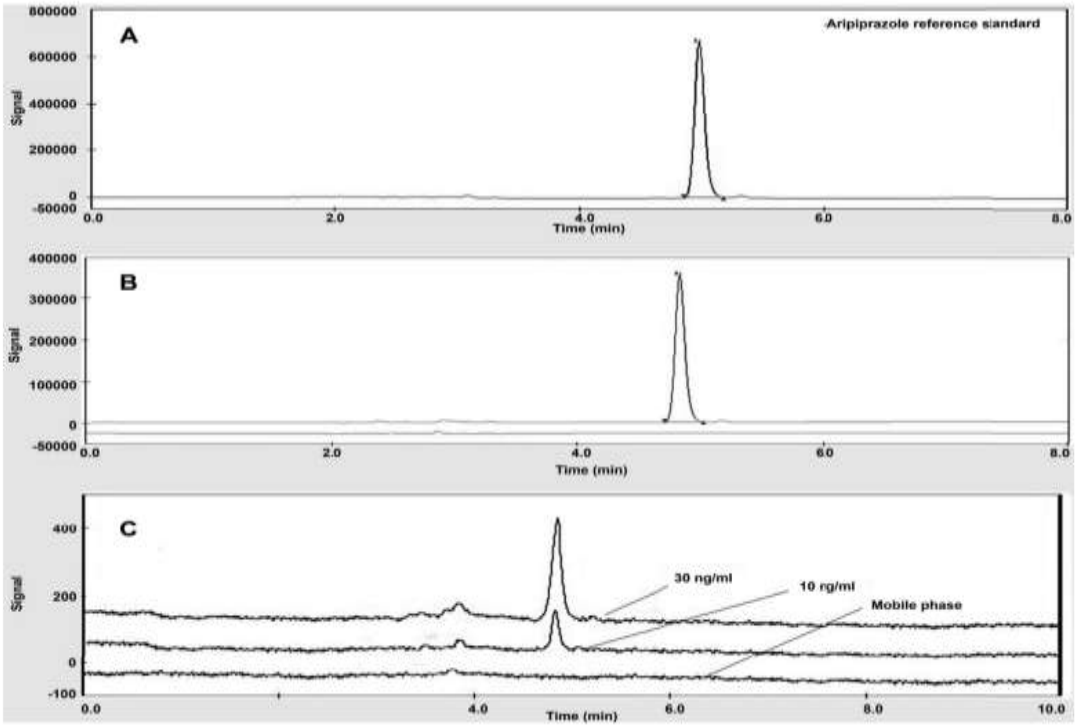

Fig 4: Representative chromatograms of, A. standard aripiprazole; B. overlay chromatograms of blank and loaded formulation; C. LOD and LOQ

System Suitability

To ensure system reproducibility, sensitivity, and specificity, various system suitability checks were performed. For the current analysis, the theoretical plate for the system suitability sample of aripiprazole (Fig. 1A) was found to be

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9665±500 and symmetry factor was 1.134±0.12. Simultaneously, CV% for the retention time and the peak area for five system suitability injections of aripiprazole were below 5% and 2%, respectively. No interference had been observed from the reference standard injection of aripiprazole on the following blank mobile phase injection. Thus, it can be said that there was no carryover of the analyte from the previous injection to analyte with high concentration Fig.

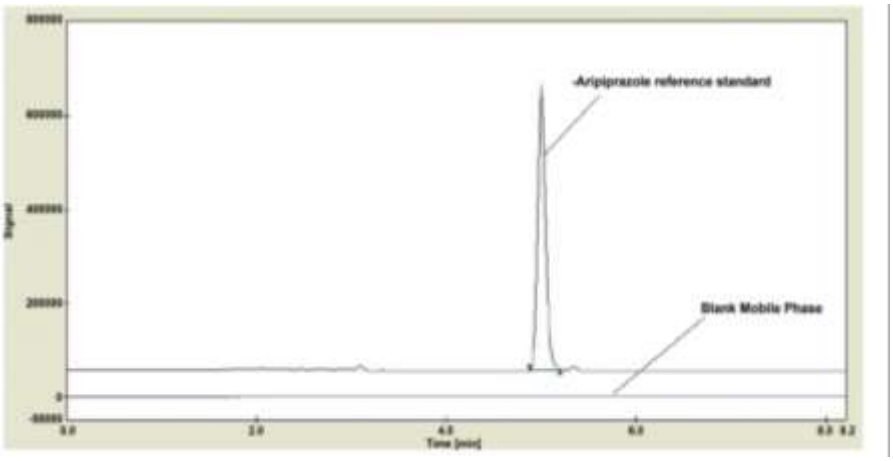

Fig 5: Representative chromatogram of aripiprazole reference standard and subsequent blank mobile phase

Method Validation

Linearity

The linearity of the method was tested using the calibration solutions described above. Plot of concentrations against responses were linear in the range of 20-60 µg mL^{-1} (Figure 3).The mean regression equation was $Y = 1.2958 \times 10^4$ x + 1422.2. The correlation coefficient was 0.9999.

Specificity and Selectivity

The chromatograms showed in Fig. (1B) expressed that various excipients or matrices in formulation were not influencing the analysis of aripiprazole in nanoemulsion. Fig. (1B) showed the overlay of chromatograms of blank nanoemulsion (nanoemulsion vehicle) and nanoemulsion containing aripiprazole extracted with the mobile phase. All results showed that the developed method is specific and selective for the detection of aripiprazole in formulation.

Limits of detection and quantification

The limit of detection (LOD) isdefined as the lowest concentrationof an analyte that can be readily detected but not necessarily quantified. It is usually regarded as the amount for which the signal-to-noise ratio (SNR) is 3:1. The limit of quantitation (LOQ) is defined as the lowest concentration of ananalyte that can be quantified with acceptable precision and accuracy. It is usually regarded as the amount for which the SNR is 10:1.Two types of solution, blank solution andsolutionscontainingknown,progressivelydecreasingconcentrationsoftheanalyte,were prepared and analyzed. LOD and LOQ were0.411 and 1.248µgmL^{-1}, respectively.

LOD and LOQ Detection

The developed method showed that signal to noise ratio was more than 10:1 at concentration of 10.0 ng.mL-1 and can be considered as LOD, whereas, the signal to noise ratio was more than 10:1 at 30.0 ng.mL-1 concentration (Fig. 1C) and therefore, 30.0 ng.mL-1 was considered as LOQ for aripiprazole analysis for the developed method.

Accuracy

Recoverystudies were performed in triplicate after spiking raw material in volumetric flasks with amounts of aripiprazole equivalent to 80, 100 and 120% of the standard concentration of aripiprazole (40 µg mL^{-1}) as in the analytical method. The results obtained (Table 1) indicate that recovery were excellent, notless than99% and that relative standard deviations also less than 2%.

Table 1. Accuracy of the method.

Drug	Spike level, %	Concentration added, µg mL^{-1}	Mean amount recovered, µg mL^{-1}, n=3	Recovery, %, $n = 3$	RSD, %, $n = 3$
Aripiprazole tablets	80	32	32.24	100.75	0.86
	100	40	39.93	99.82	0.95
	120	48	48.02	100.04	0.97

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Precision

Intra-day precision was calculated from results obtained from five-fold replicate analysis of sample sat three different concentrations on the same day. Inter-day precision was calculated from results from the same samples analyzed on five consecutive days. The results obtained are listed in Table.

Table 2. Intra-day and inter-day precision of the method.

Concentration Added, µg mL^{-1}	Intra-day precision		Inter-day precision	
	Mean amount found, µg mL^{-1}, n = 5	RSD, %, n = 5	Mean amount Found, µg mL^{-1}, n = 5	RSD, %, n = 5
32	32.04	0.98	32.61	0.99
40	40.12	0.95	39.99	1.07
48	47.98	1.01	48.12	0.96

Evaluation of the accuracy and precision of the HPLC analysis of aripiprazole.

Spiked Concentration (µg.mL^{-1})	Measured Concentration (µg.mL^{-1})					
	Intra-day (n=3)			Inter-day (n=9)		
	Mean ± SD	Accuracy (%)	CV (%)	Mean ± SD	Accuracy (%)	CV (%)
15	14.83 ± 0.13	98.24–99.91	0.89	14.74± 0.16	97.03–99.92	1.06
25	25.05 ± 0.14	99.74 – 100.88	0.59	24.82± 0.27	98.05–100.88	1.11
40	39.89 ± 0.15	99.32 - 100.06	0.37	39.70± 0.25	98.38–100.07	0.63

Specificity

The specificity of the method was tested by chromatographing a mixture of commonly used tablet excipients, for example starch, lactose and magnesium stearate (blank placebo) and comparing the chromatogram with that obtained from a mixture of drug and the same additives (placebo). The chromatograms obtained (Figures 4 & 5) showed separation of the analyte from the excipients was complete, i.e. there was no interference from the excipients under the chromatographic conditions used for the analysis.

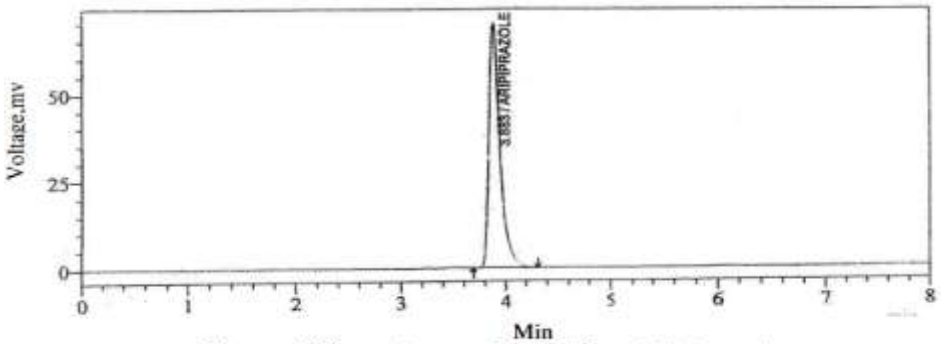

Figure 4. Chromatogram obtained from tablet sample.

Fig 6:

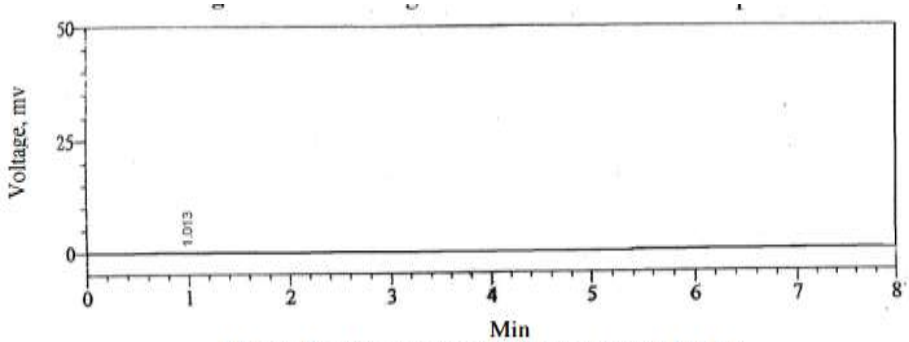

Figure 5. Chromatogram obtained from placebo.

Fig 7:

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Stability

The stability of aripiprazole in solution was checked by determining the percentage deviation of the amounts present in solution after 72 h at room temperature in comparison with the amount at zero time. The results obtained after 72 h showed no significant variation; the percentage deviation was less than 2% of the initial amount. This is indicative of good stability of each component in the mixture over a period of 72 h.

Application of the method to tablets

The method was used for determination of aripiprazole in a tablet formulation. The results obtained Table showed the amount found was that expected and RSD (%) values were low, which confirms the method is suitable for routine analysis of the compound in pharmaceutical preparations. A typical chromatogram obtained from analysis of a tablet formulation is shown in Figure.

Table 3. Results from analysis of aripiprazole in tablets.

Label claim. mg per tablet	30
Amount found, mg per tablet	29.98
Amount found, %, n = 6	99.93
RSD, %, n = 6	0.021

4. CONCLUSION

This RP-HPLC method for analysis of aripiprazole in formulations is very simple, sensitive, and accurate. The run time is 8 min only; so many samples can also be processed and analyzed in a short period of time. The procedure described is suitable for the routine estimation of aripiprazole in pharmaceutical formulations.

The development of analytical methods for drug identification, purity evaluation, and quantification has received a lot of attention in the field of pharmaceutical analysis in recent years. This review provides a general overview of HPLC method development and validation. A general and very simple approach to developing HPLC methods for compound separation was discussed. Before developing an HPLC method, it is critical to understand the physicochemical properties of the primary compound. The composition of the buffer and mobile phase (organic and pH) has a significant impact on separation selectivity. Finally, the gradient slope, temperature, and flow rate, as well as the type and concentration of mobile phase modifiers, can be optimized. The optimized method is validated using various parameters (e.g., specificity, precision, accuracy, detection limit, linearity, and so on) following ICH guidelines

Our method was found to be simple and high throughput analysis than the other analytical methods for aripiprazole available in the literature.

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