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A Compact Analytical Profile of Aripiprazole: Analytical Methodologies

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Authors' contributions

This work was carried out in collaboration among all authors. Author SK designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors KAB and OVA managed the analyses of the study. Authors MR, KP and Indukala managed the literature searches. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Aripiprazole (APZ) is an antipsychotic drug that belongs to benzisoxazole derivatives and is used to treat schizophrenia as well as acute manic or mixed effects in patients with bipolar 1 disorder. APZ is used to treat certain mental, mood disorders such as bipolar disorder, Schizophrenia, Tourette's syndrome, and irritability associated with autistic disorder. It may also be used in combination with other medication to treat depression. The present review article would be useful for prospective studies for researchers interested in APZ formulation production and quality management. Using a thorough computer assisted literature survey; this review touches upon the various reported analytical methods for the quantification of APZ both in API (Active Pharmaceutical Ingredient) and pharmaceutical dosage forms. The present write-up also encompasses the various published research articles like Spectroscopy techniques, X- Ray Diffraction (XRD), Electro Chemical Technique, Differential Scanning Calorimeter (DSC) and Capillary Electrophoresis. This is the first review article in this series with focus on the analytical profile of APZ. Although, several methods were reported in the literature, HPLC stands out first for the quantification of APZ.

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Keywords: Active pharmaceutical Ingredient; anti-psychotic drug; analytical profile; aripiprazole; DSC; quantification.

1. INTRODUCTION

The variety of clinical symptoms that occur during the course of illness, treating Bipolar Affective Disorder (BAD) remains a challenge for psychiatrists. Many antipsychotic medications are used to treat this complex condition, either alone or in combination. Non compliance of pharmacotherapy is also a major issue with the care of bipolar disorder patients, and it has a number of negative effects, including an elevated risk of suicide. As a result, after doing rigorous research and consulting with psychologists, APZ has been recommended to be used to treat bipolar disorder [1]. APZ is a new second-generation antipsychotic drug that is used to treat schizophrenia as well as acute manic or combined symptoms in people with bipolar 1 disorder [2]. It is also used in the treatment of Tourette's syndrome in children (16-18 years old) at a dosage of 5-20 mg/day in patients weighing less than 50 kg [3]. It is used orally once a day as a tablet or solution. APZ is an atypical antipsychotic that acts as a partial dopamine D2 receptor agonist, partial serotonin1A (5-HT1A) receptor agonist, and 5-HT2A receptor agonist. Since its pharmacological mechanism is different from other second-generation anti-psychotic, APZ is considered as third-generation antipsychotic and a dopamine–serotonin reuptake inhibitor [4]. APZ (Fig. 1) is designated as derivative of quinolone, which is colorless or flake crystalline in nature [5]. APZ is 7-[4-[4-(2, 3-dichlorophenyl)-1-piperazinyl] butoxy]-3, 4-dihydrocarbostyril having $C_{23}H_{27}Cl_2N_3O_2$ as empirical formula, and its molecular weight is 448.38 g/mol. APZ has a role as a H1 receptor antagonist, a seratonergic agonist, a second generation antipsychotic and a drug metabolite. This drug stabilizes dopamine and serotonin activity in the limbic and cortical system. The various physiochemical properties of APZ is depicted in Table 1.

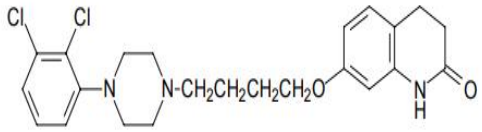

Fig. 1. Structure of Aripiprazole

2. PROPERTIES OF APZ

In Biopharmaceutical classification system (BCS), APZ had low solubility and low permeability [7]. APZ is soluble in organic solvents such as ethanol, DMSO (Dimethyl Sulphoxide), and Dimethyl Formamide (DMF) which should be purged with an inert gas. APZ is soluble in these solvents at around 1, 25, and 30 mg/ml, respectively. APZ practically insoluble in water and solubility in water is increased with lowering of pH with in physiological range. Since APZ is only slightly soluble in aqueous buffers, it should first be dissolved in DMF and then diluted with the appropriate aqueous buffer [8,9]

3. PHARMACOLOGY

3.1 Mechanism of action

APZ is a partial agonist and antagonist at dopamine D2, D3, and serotonin 5-HT_{1A} receptors and is an antagonist at 5-HT_{2A} receptors (Fig. 2). In a hyper dopaminergic condition, it binds to the d2 receptor with high affinity and functions as a functional antagonist. In a hypo dopaminergic condition, it also acts as a functional agonist. This distinct profile can confer the benefit of reduced susceptibility to EPS (Electrophysiology studies) and hyper prolactinemia. Because of the sophistication of the mechanism of action, this agent's classification has changed from partial agonist to functional selectivity [10].

Table 1. Physiochemical properties of APZ

Chemical and Physical Name	Observation	Reference
Molecular weight	448.4 g/mol	[5]
Molecular Formula	$C_{23}H_{27}Cl_2N_3O_2$	[5]
pKa	7.6	[5]
Boiling Point	139.0-139.5 °C	[5]
Melting point	137-140°C	[5]
Solubility	0.00001%	[5]
Refractivity	124.34 $m^3 \cdot mol^{-1}$	[6]
log p	4.9	[5]

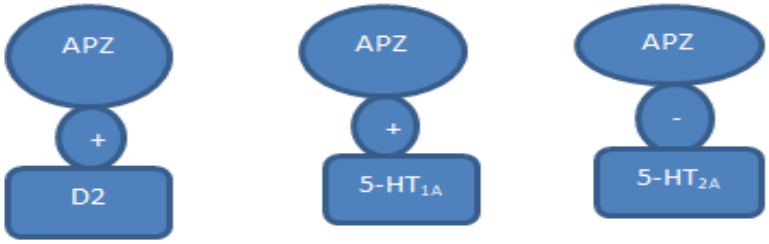

Fig. 2. Pictorial representation of mechanism of action of APZ

Table 2. Pharmacokinetic parameters of APZ

Parameter	Observation	Reference
Peak plasma concentration (c_{max})	3-5 h	[10,11,12]
Mean elimination half-life	75-146 h	[10,11,12]
Human plasma protein binding	≥ 99%	[10,11,12]
Metabolism	majorly CYP2D6 and CYP3A4	[10,11,12]
Elimination	25% in urine and 55% in feces	[10,11,12]

3.2 Pharmacodynamics and Pharmacokinetics

APZ has a high affinity for dopamine D2 and D3, as well as serotonin 5-HT1A and 5-HT2A receptors (Ki values of 0.34, 0.8, 1.7, and 3.4 nm, respectively), a mild affinity for dopamine D4, serotonin 5-HT2C and 5-HT7, alpha1-adrenergic, and histamine H1 receptors (Ki values of 44, 15, 39, 57, and61 nm respectively) and moderate affinity for the serotonin reuptake site (k_1=98 nm) [10]. The data of pharmacokinetic parameters is disclosed in Table 2.

3.3 Safety and Adverse Reaction

According to FDA, APZ is laid into pregnancy category C; since it is unclear if APZ can cause fetal damage or impair reproductive potential when given to a pregnant woman. This medication should be used only when specifically required during breastfeeding. Babies born to mothers who used this drug in the final three months of their pregnancy may develop muscle weakness or shakiness, drowsiness, and feeding difficulties [13]. The most common side effects are Neuroleptic Malignant Syndrome (NMS), high blood sugar, weight gain, and Tardive dyskinesia (TD).

4. ANALYTICAL STATUS OF APZ

The primary goal of this study is to classify, outline, and analyze the various reported analytical methods for determining APZ alone and in mixtures, as well as in formulations. The determinations are classified into seven main categories: (1) spectrophotometric methods; (2) chromatographic methods; (3) hyphenated techniques; (4) capillary electrophoretic methods; (5) electrochemical techniques; (6) XRD; (7) DSC.

APZ have been analyzed by various methods which have been described in different literatures. Among the reported analytical methods, HPLC was found to be the most developed and validated method for the estimation of APZ, followed by other methods (Fig. 3). This review has become needful in view of the rapid progress in APZ research and development, its assay in both bulk and pharmaceutical dosage forms as well as their determination in biological fluids.

4.1 Spectroscopy Technique Available on APZ

First and foremost important group of methods which find an important place in pharmacopoeias are spectrophotometric methods based on natural UV absorption and chemical reactions. Spectrophotometry is the quantitative measurement of the reflection or transmission properties of a material as a function of wavelength. The advantages of these methods are low time and labor consumption. The precision of these methods is also excellent. Spectrometric methods are one of the most

versatile instrumental techniques for qualitative and quantitative analysis of drug candidates, because of the simplicity, economy and dependability. Samiran Dey et al. [14] have published a UV-sensitive approach for determining APZ in bulk and pharmaceutical dosage form. The absorption maximum was found to be 256 nm. The linearity was observed in the range of 5- 30µg/ml, with a correlation co-efficient of 0.9995. J.Nagamalika et al. [15] reported APZ determination by UV spectroscopy in tablet dosage form. The absorbance of APZ was estimated at 218 nm in the 200-400 nm wavelength range. It was discovered that the linear calibration scale was 2.5 to 20 µg/ml. Sandeep Kandikonda [16] et al. have reported spectrophotometric quantification of APZ in pharmaceutical formulations using a multivariate technique. This approach is based on the application of a linear regression equation to the relationship between concentration and absorbance at five different wavelengths. The absorption maxima at 255 nm followed Beer's law in the range of 5-30 µg/ml. UV derivative spectroscopy of APZ in bulk drug formulation has been documented by sarmasherya balaram et al. [17] and the absorption peak was found to be at 217 nm. The process was linear and obeyed Beers' law in the range of 1.0-6.0 µg/ml. Visible spectroscopy of APZ in bulk drug formulation was recorded by Dhanu Radha et al. [18] and the maximum absorption was found to be 520 nm. The linearity concentration range was observed from 0.2-0.8 µg/ml. This process is based on the use of double distilled water to create a charge transfer colored complex of APZ with N-bromosuccinimide and complex with chloramines. T.R Jain et al. [19] have reported visible spectrophotometric method for APZ in tablet dosage form. In this study, an acidic solution of APZ formed colored ion- association complex with bromo cresol green and the formed yellowish orange chromogen showed absorption maxima at 414 nm and obeyed beers law in the concentration range of 10- 60µg/ml (Table 3).

4.1.1 Raman spectroscopy

Thermal stability of APZ monohydrate investigated by Raman spectroscopy has been reported by Alejandro Pedro Ayala et al. In this work the dehydration process of the APZ was investigated using Raman scattering, hot stage microscopy and DSC. The temperature evolution of the Raman spectra was analyzed through the multivariate statistical method of principal component analysis [20].

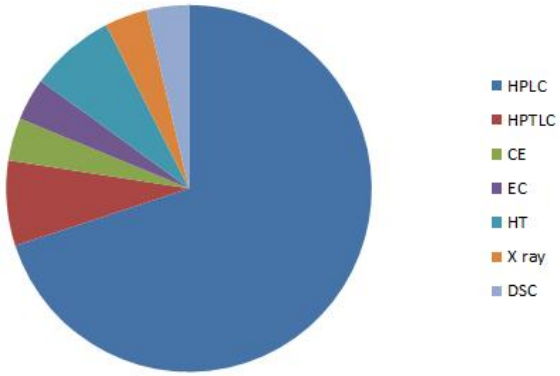

Fig. 3. Distribution of analytical method described in the literature for the determination of APZ

Table 3. Summary of linearity curve data (spectroscopic method)

Method	Solvent used	Strength of stock solution (µg/ml.)	Wavelength (nm)	Linearity (µg/ml)	Reference
UV	Ethyl alcohol	1000	256	5-30	[14]
UV	Phosphoric acid and acetonitrile	2.5 -20	218	2.5 -20	[15]
UV	Ethanol	100	255	5-30	[16]
UV	Acetonitrile	100	217	1-6	[17]
Visible	Ethanol	100	520	0.2-0.8	[18]
Visible	Sulphuric acid	100	414	10-60	[19]

4.2 Chromatographic Techniques for the Determination of APZ

4.2.1 HPLC

HPLC is one of the most widely used instrumental analytical techniques in academia and industry for solving pharmaceutical research problems. Among the various analytical techniques, HPLC constitutes the most popular chromatographic method for separating mixture of drugs. In addition, LC generally offers reliable methods characterized by sensitivity, ruggedness and accuracy. Reversed phase high-pressure liquid chromatography is based on the use of solid particulate or monolithic support as the stationary phase. Mixtures of organic solvents with buffers containing acidic or basic additives employed as mobile phases have been widely applied to separate moderately hydrophilic and hydrophobic compounds. The sensitive and reproducible ion pair RPLC method was developed and validated by N. Nikolic K et al. [2] for determination of APZ and its nine impurities. Separation of APZ was carried out using Phenomenex Luna® C18 column (250 mm × 4.6 mm, 5.0 µm) consisted of a gradient mobile phase A- phosphate buffer pH 3.0 and mobile phase B- acetonitrile at the working temperature of 25°C. The flow rate used was 1.0 ml/min. The detection was carried out at 215 nm using a diode array detector. Naved Ahmed et al. [3] reported the quantitative detection of APZ in bulk and pharmaceutical formulation. The separation and quantification were accomplished on a waters spherisorb 5 (ODS 250 mm x 4.6 mm, 5.0 µm) C18 column with an acetonitrile: methanol: buffer (20:40:40 v/v/v) pH 3.5 as mobile phase and the flow rate was set at 1.0 ml/min with a detection wavelength of 254 nm. The retention time of the drug was found to be 7.7±0.1 minutes and the system exhibits strong linearity between the 5-25 µg/ml. For the analysis of APZ in tablet dosage form, a rapid, clear, and validated reversed-phase high-performance liquid chromatographic method has been developed by R. Kalachelvi et al. [4]. In this study APZ was separated on an ODS analytical column at a flow rate of 1.5 ml/min using (40:60 v/v) mixture of acetonitrile and tri ethanolamine buffer as mobile phase. The effluent was monitored by UV detection at 254 nm. Calibration plots were linear in the range of 20 to 60 µg ml^{-1} and the LOD and LOQ were found out to be 0.411 and 1.248 µg ml^{-1}, respectively. A rapid and accurate stability indicating HPLC method with an isocratic mode of analysis was developed by Mallikarjuna rao et al. [21] for the estimation of APZ in bulk and its formulation. The separation was performed using C18 Column (250 mm x 4.6 mm, 5 µm) with the mobile phase comprised of acetonitrile and methanol in the ratio of (35:65 v/v). The flow rate was set to 1ml min^{-1}, and the effluent was monitored at 254 nm. APZ elution time was found out to be at 4.58±0.40 min and linear regression analysis data for the calibration plot showed the good linearity response in the concentration range of 10 - 100 µg/ml. Vijaya gouri korlakunta et al. [22] reported a simple, sensitive and validated RP-HPLC method for the quantification of potential genotoxic impurities of APZ drug substance. The separation of the drug and its potential impurities were successfully analyzed byalliance-Waters 2695 separations module® C18 column, (150 mm x 4.6 mm, 5µm) using mobile phase prepared by combining (60:40 v/v) of acetonitrile and dil. ortho phosphoric acid buffer(3ml in 1000ml). Flow rate was set at 1.0 ml min^{-1} and injection volume used was 20µL. Sonali N. kawade et al [23] developed a sensitive HPLC method using C18 phenomenex (250 mm X 4.6mm, 5 µm) column using mobile phase of phosphate buffer pH 4.2 and methanol(70: 30 v/v). The detection wavelength was carried out 255 nm. The linearity was achieved in the concentration range of 10 to 60 µg/ml and the method was completely validated as per ICH guidelines. Nandini R. Pai [24] reported the stability indicating HPLC method for the quantitative determination of APZ and its impurities. Successful separation of the drug from the synthetic impurities and degradation products were achieved on Zorbax C18 column (150 x 4.6x 5 µm) using a gradient elution of 0.2% trifluoroacetic acid in water and 0.2% trifluoroacetic acid in methanol. Yumiko Akamine et al. [25] reported the column-switching HPLC-UV method for the simultaneous determination of APZ, and its active metabolite, dehydro aripiprazole in human plasma. 1 mL of plasma was collected using a mixture of chloroform/n-heptane (3:7, v/v) and the extract was injected into a column I (TSK BSA-ODS/S precolumn, 5 µm) for cleanup and a column II (C18 STR ODSII analytical column, 5 µm) for separation. Peaks were observed using a UV detector calibrated to a wavelength of 254 nm. Narayana M B et al. [26] have documented a validated specific stability indicating reversed-phase liquid chromatographic method for the quantitative determination of APZ and its related substances. YMC PACK C18 was used as column and the mobile phase consisted of a mixture of sodium dihydrogen orthophosphate

dehydrate with 1-Hexane sulfonic acid sodium and the pH was adjusted to 3.0 with ortho-phosphoric acid in water and acetonitrile using a simple linear gradient. The detection was carried out at 215 nm. The estimation of APZ in pharmaceutical formulations was developed by B.S. sastry et al. [27]. The RP-HPLC analysis was performed isocratically on a phenomenex Luna C18 column (250 mm x 4.6 mm, 5 µm particle size) using acetonitrile and sodium acetonitrile (55:45 v/v) as the mobile phase at a flow rate of 1.0 ml/min. A UV detector was set to 254 nm to monitor the analyte. Yoshihiko shimokawa et al. [28] has reported HPLC method for the determination of APZ in rat plasma and brain. Separation was done by Nova-Pak phenyl column at the flow rate of 1.0 ml/min. The mobile phase used was acetonitrile: methanol: 20 mM sodium sulfate: acetic acid (27:25:48:1, v/v/v/v) using detection wavelength at 254 nm. Fred´erique Lancelin et al. [29] have documented a high-performance liquid chromatography method with diode array detection (HPLC-DAD) for quantification of APZ and dehydro-aripiprazole, in human plasma. The separation was carried out on a C18 reversed-phase column, using an ammonium buffer–acetonitrile mobile phase (40:60, v/v). The total run time was achieved at 7 min and the flow-rate used was 1.0 ml/min. N. Srinivasa rao et al. [30] developed a stability indicating liquid chromatographic assay procedure for the quantitative estimation of APZ in tablets using a Zorbax (150 mm x4.6 mm, C_{18} column with 5 µm particles) . A mobile phase consisting of ammonium acetate buffer, acetonitrile and methanol was used at the flow rate of 1.5 ml/min. The identification was controlled at a wavelength of 254 nm while the column temperature was held at 25°C. Prasenjit Mondal et al. [31] published a simple and sensitive LC method using Purospher star C18 column (250× 4.6 mm, 5 µm) using (90:10 v/v) of methanol: water as mobile phase at a flow rate of 1mlmin^{-1}. The detection was carried out using UV detector at 256 nm. Santosh Ashok Kumbh et al. [32] published a specific and sensitive RP-HPLC method for APZ determination used in nano emulsion pre-formulation screening. The separation technique was accomplished by delivering mobile phases of methanol-acetonitrile, (80:20 v/v) at 1.0 ml.min^{-1} flow rate by HIQ SIL C_{18} (250 mm x4.6 mm 5 µm) column and detection wavelength at 218 nm. The method generated linear calibration plots with a correlation coefficient (r^2) of 0.9991 using the least square regression method in the 5 to 50 µg.ml^{-1} range. G Raveendra babu et al. [33] developed an isocratic reversed phase LC method using a phenomenex Luna C18 (150 x 4.6 mm, 5 µm) column and the mobile phase consisting of acetonitrile and phosphate buffer 0.05M (40:60 v/v) were used. The detector was set at 227 nm and the flow rate was set at 1.0 ml min^{-1} to monitor the elution of the drug. The method obeyed beers law in the concentration range of 25µg ml^{-1} to 200 µg ml^{-1}. A simple, precise, and accurate isocratic reversed-phase (RP) stability-indicating HPLC assay method was developed and validated by R. S. Thakkar et al., [34] for determination of APZ in bulk and solid pharmaceutical dosage form. The method used isocratic elution mode using C8 (250×4.0 mm, 5 µm particle size) column for HPLC and a C8 (50×2.1mm, 1.7 µm particle size) column for UPLC. The mobile phase composed of acetonitrile: 20 mM ammonium acetate (90:10, v/v), the flow rate was set at 1.0 ml/min and 0.250 ml/min for HPLC and UPLC, respectively, and detection was performed at 240 nm for both methods. D.V.SubbaRao et al. [35] published HPLC method for the quantitative determination of APZ in both bulk drug and pharmaceutical dosage form using Kromasil C_8 (150 mm x 4.6 mm, 5 µm) column with a simple mobile phase combination delivered in an isocratic mode, and quantification by ultraviolet detection at 215 nm and a flow rate at 1.0 ml min^{-1}. The mobile phase composed of 65:35 (v/v) mixtures of sodium dihydrogen phosphate buffer and acetonitrile. Simultaneous determination of APZ and five of its chemical related impurities in tablet dosage forms were reported by soponar et al. [36] using a Zorbax SB-C18 column (150 mm x 4.6 µm) and the detection using UV detector at 254 nm. The brief HPLC methodologies reported in the literature for the estimation of APZ are discussed in Table 4.

4.2.2 HPTLC

A simple validated high-performance thin-layer chromatography method has been proposed by Hemant tawale et al. [37] for the determination of APZ in a tablet dosage form. This method was validated for linearity, accuracy, range, precision and robustness according to ICH Q2 (R1) guidelines. Another study of HPTLC was also prepared by M D Faizandde shmukh et al. [38]. The details are enclosed in Table 5.

Table 4. Summary of HPLC methodologies

Column	Mobile phase	Detector	Wavelength (nm)	Linearity (µg/ml)	Reference
Phenomenex Luna® C18 column(250 mm × 4.6 mm, 5 µm)	Phosphate buffer: acetonitrile (Gradient mode)	PDA	215	0.05-2.5	[2]
Waters spherisorb C18 (250 mm x 24.6 mm, 5 µm)	Acetonitrile: MeoH buffer pH 3.5 (20:40:40 v/v/v)	UV	254	5-25	[3]
C18 column ODS Analytical Column (250mm × 4.6 mm, 5 µm)	Acetonitile: TEA buffer pH 3.5 (40:60 v/v)	UV	254	20-60	[4]
Symmetry C18 column (250 mm× 4.6 mm,5 µm)	Acetonitrile: MeOH (35:65 v/v)	UV	254	10-100	[21]
Alliance-Waters 2695 C18 column x 4.6mm,5µm)	Acetonitrile: OPAbuffer (3 in 1000 ml) (150mm (60:40v/v)	UV	215	0.016-0.323	[22]
Phenomenex C18column (250mm x 4.6mm, 5 µm)	Phosphate buffer pH 4.2: MeOH (70:30)	UV	255	10-60	[23]
Zorbax C18 [24] column (150 mm x 4.6 Mm, 5 µm)	0.2% TFA in water: 0.2% TFA in MeOH (Gradient mode)	UV	254	0.20-2.0	[24]
ColumnI(TSK BSA-ODS/S precolumn,5 µm) and a column II (C18 STR ODSII analytical column, 5 µm)	Phosphate buffer: Acetonitrile: perchloric acid (82.25:17.5:0.25 v/v/v)	UV	254	1-500 (ng/ml)	[25]
YMC PACK C18 (150 mm x 4.6 mm, 5 µm)	Sodium dihydrogen orthophosphate dehydrate with 1 hexanesulfoni acid sodium orthophosphoric acid in water (Gradient mode)	PDA	215	150-450	[26]

Column	Mobile phase	Detector	Wavelength (nm)	Linearity (µg/ml)	Reference
Phenomenex Luna C18 column (250 mm x4.6 mm, 5 µm)	Acetonitrile: sodium acetate buffer pH 4.5 (55:45v/v)	UV	254	2-12	[27]
Nova-pak phenyl column(150 mm ×3.9mm.,4 µm)	Acetonitrile: MeOH-20mM sodium sulphate-acetic acid (27:25:48:1 v/v/v/v)	UV	254	10-2000 ng/ml (plasma) 30-6000 ng/g (Rat brain)	[28]
C18RP column, (100 mm× 4.6 mm, 3.5 µm)	Ammonium buffer: acetonitrile (40:60v/v)	UV	217	2-2000 ng/ml	[29]
Zorbax C18 Column (150 mm x 4.6 mm, 5 µm)	Ammonium acetate buffer:acetonitrile: MeOH (50:40:10 v/v/v)	UV	254	100-800	[30]
Purospher star C18column (250× 4.6 mm,)	MeOH:water (90:10v/v)	UV	256	5-25	[31]
HIQ SIL C18 (250 mm x4.6 mm, 5 µm)	MeOH: Acetonitrile (80:20v/v)	UV	218	5-50	[32]
Phenomenex Luna C18(150x4.6mm, 5 µm) column.	Acetonitrile : Phosphate buffer0.05M (40:60 v/v)	UV	227	25-200	[33]
C8 (250 x4.0 mm,5 µm) column for HPLC and a C8 (50 x 2.1mm, 1.7 µm)	Acetonitrile: 20mM ammonium acetate (90:10v/v)	UV	240	40-160	[34]
Kromasil C8, (150mm×4.6mm, 5µm) column	Mixture of buffer: sod.dihydrogen phosphate pH 2.5 :Acetonitrile (65:35 v/v)	UV	215	0.5	[35]
Zorbax SB-C18 column (150 mm x 4.6 m 5µm)	MeOH: water: orthophosphoric acid (55:45:0.4 v/v/v)	UV	254	50-150	[36]

4.2.3 Hyphenated technique

The hyphenated technique is a sophisticated, repeatable and flexible method for estimating analytes in a variety of biological and pharmaceutical samples. M. V. V. N. Murali Krishna et al [39] investigated degradation impurities in APZ oral solution using LC-MS method. Hui-Ching Huang et al. [40] developed and validated a new method for detecting APZ and its main metabolite, dehydro aripiprazole, in plasma using gas chromatography–mass spectrometry (GC–MS). The studies are shown in Table 6.

4.2.4 Capillary electrophoretic method

Alessandro Musenga et al. [41] published capillary electrophoresis method in plasma of schizophrenic patients for therapeutic drug monitoring purposes. Good analytical performances were obtained with the CE method, using uncoated fused silica capillaries and a background electrolyte composed of 50mM phosphate buffer at pH 2.5. With 20 kV voltages, aripiprazole was detectable at 214 nm and loxapine was used as the internal standard. After validation, the developed method was successfully applied to human plasma samples drawn from schizophrenic patients undergoing therapy with abilify 10mg tablets (active ingredient- aripiprazole). Accuracy was satisfactory, with recovery value higher than 91.0%.

4.2.5 Electro chemical technique available for APZ

Derya Asangil et al. [42] created voltammetric methods for measuring APZ in medicinal dosage forms and biological samples. Anodic behavior of aripiprazole (ARP) was studied using electrochemical methods. Charge transfer, diffusion and surface coverage co effificients of adsorbed molecules and the number of electrons transferred in electrode mechanisms were calculated. For quasi-reversible and adsorption-controlled electrochemical oxidation of APZ at 1.15V versus Ag/AgCl at pH 4.0 in Britton–Robinson buffer (BR) on glassy carbon electrode, electrons transferred in electrode mechanisms is measured. In the absence of stripping mode, linearity varies from 11.4M (5.11mg/L) to 157M (70.41mg/L), and in the presence of stripping mode, linearity ranges from 0.221M (0.10mg/L) to 13.6M (6.10mg/L). The limit of detection (LOD) in stripping voltammetry was estimated to be 0.11M (0.05mg/L).

4.2.6 X- ray diffraction

APZ was also studied using X-ray powder diffraction. The diffraction pattern was captured with a Rigaku DMAX Rapid diffractometer (Rigaku/MSC, Woodlands, TX) and an attached capillary goniometer using Cu K radiation at 46 kV/40mA. Crystal diffraction patterns were reported in one of the experiments using a Bruker D8 SMART 1000 or APEX II CCD fine focus sealed tube diffractometer with graphite monochromated CuK (1.54178) radiation title [43]. Qi Zhou et al. [44] reported improving the solubility of APZ by multi component crystallization. The crystal structures were calculated at 296K using a Bruker APEX-II CCD diffractometer and graphite monochromatic Mo-K alpharadiation (λ=0.71073Å). Powder X-ray diffraction (PXRD) patterns were captured using a Bruker D8 dvance X-ray powder diffractometer with Cu-Kα radiation at 40 KV and 40 Ma.

Table 5. HPTLC methods for the determination of APZ

Mobile phase	Stationary phase	Wavelength	Rf value	Linearity	Reference
Toluene: methanol (8.5:1.5 v/v)	Silicagel60 F 254 Coated aluminum sheet	254 nm	0.48 ± 0.02	100-500 ng/spot	[37]
Carbon tetrachloride: MeOH: triethylamine (2.5:2.4:0.1 *v/v/v*).	Thin layered aluminum plates coated with 200 µm layer of silica gel 60 F_{254} (10 cm × 10 cm)	255nm	0.58 ± 0.02.	300-1800 ng/spot	[38]

Table 6. Hyphenated technique for the determination of APZ

Method	Mobile phase	Statioary column	Evaluation	Reference
LC-MS	0.1% v/v Trifluoro acetic acid in water and acetonitrile	ACE C18 (4.6 mm x 250 mm, 5 µm)	This approach detected degradation impurities that were produced during the stress analysis	[39]
GC-MS	Elution was carried Out with 1.5 ml (x2) of a freshly prepared mixture of ethyl acetate: 28-30 ammonium - hydroxide (98:2)	BPX5 5% phenyl Polysilphenylen –siloxane capillary column (25 m × i.d. 0.22 mm; Film thickness 0.25m)	Applied to a pharmacokinetic study of aripiprazole in blood samples of psychiatric patients	[40]

4.2.7 Analysis of APZ with differential scanning calorimetry

DSC measurements were performed using a Mettler Toledo DSC1 instrument (Mettler, Zurich, Switzerland). 3-5 mg samples were placed in aluminum pans with pinhole lids and heated at a steady heating rate of 10 C/min under a nitrogen flux of 50 cm3/min in the 30~300˚C temperature range [44]. In this work, a new APZ salt with adipic acid (ADI) and its acetone hemisolvate were obtained successfully, along with a known APZ salt with salicylic acid (SAL). Their comprehensive characterizations were conducted using X-ray diffraction and differential scanning calorimetry. The crystal structures of the APZ-ADI salt acetone hemisolvate and APZ SAL salt were elucidated by single-crystal X-ray diffraction for the first time, demonstrating the proton transfer from a carboxyl group of acid to ARI piperazine. Theoretical calculations were also performed on weak interactions. Moreover, comparative studies on pharmaceutical properties, including powder hygroscopicity, stability, solubility, and the intrinsic dissolution rate, were carried out. The results indicated that the solubility and intrinsic dissolution rate of the APZ-ADI salt and its acetone hemisolvate significantly improved, clearly outperforming that of the APZ-SAL salt and the untreated APZ. The study presented one potential alternative salt of aripiprazole and provided a potential strategy to increase the solubility of poorly water-soluble drugs.

5. CONCLUSION

The detailed comprehensive analysis summarizes the present state of the analytical methodologies for quantifying APZ in API and other pharmaceutical formulations. This review is also targeted at outlining the various reported analytical methods and other related aspects of APZ. Although several methods were reported in the literature for the estimation of APZ, HPLC was found to be the most developed and validated method, followed by spectro photometric and other analytical methods. The analytical methods available in the scientific literature for identification and quantification of APZ cover different techniques. Nevertheless, HPLC-based methods represent the principal analytical technique for determination of APZ in both pharmaceutical and biological matrices. The advantages of performing analytical studies through HPLC-based methods are related to the high specificity, speed of analysis, accuracy, and sensitivity. Despite the fact that HPLC was the most preferred method, it uses toxic solvents, buffer solutions, long columns, which provide long runs and retention times, as well as large amount of waste. Therefore, the priority to develop ecologically correct, conscious and sustainable methods is very important and necessary for the quality control of APZ, optimizing the productivity without harming the environment and health of the operators. Given the increased awareness of the need to implement green procedures, new approaches

for reducing the usage of these consumables and waste generation for pharmaceuticals are need to be developed in future. It is important to note, however, that as technology advances, more analytical methods are being created, which may demand a future review.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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