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Review Article

A Concise Review- An Analytical Method Development and Validation of Armodafinil

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Abstract

The HPLC method for Armodafinil both bulk & in combination are given in Table 1 which includes parameters like matrix, stationary phase, mobile phase composition, detection wavelength RF value, retention time etc. HPTLC method reported in Table 2 includes parameter like matrix, stationary phase, mobile phase, RF, DL etc. The table 3 includes the GC-MS method for Armodafinil which involve the parameters like Matrix, stationary phase, mobile phase composition, Carrier gas, Retention time, flow rate etc. The table 4 includes the Capillary Electrophoresis method for Armodafinil which involve the parameters like Matrix, Capillaries wavelength, Separation Voltage, Temperature and pressure etc. Spectrometric methods for Armodafinil include UV-Visible Spectroscopy.

Keywords: RP-HPLC; armodafinil; method development and validation

Introduction

Armodafinil is the R-enantiomer of modafinil, a wake-promoting drug that predominantly affects brain areas involved in wakefulness control [1]. The US Food and Medicine Administration has licensed the drug for the treatment of individuals with excessive drowsiness caused by obstructive sleep apnea, narcolepsy, or shift work disorder [2]. The working mechanism is still a mystery. The dopamine transporter in the striatum and the norepinephrine transporter in the thalamus are both sensitive to modafinil [3]. Hypocretin, histamine, -adrenergic, -aminobutyric acid and/or glutamate receptors are all affected by modafinil [4]. 2-[(R)-(diphenylmethyl) sulfinyl] acetamide and 2-(R-benzhydrylsulfinyl) acetamide are the chemical names for armodafinil [5].

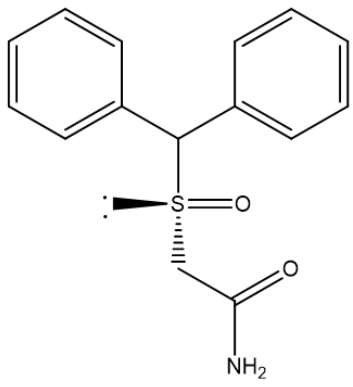

Figure 1: Armodafinil Structure.

Armodafinil Pharmacodynamics:

Modafinil and its R-enantiomer, armodafinil, have uncertain therapeutic mechanisms in vivo [6]. Armodafinil inhibits dopamine re-uptake via binding to the dopamine transporter. It is not, however, a dopamine receptor

agonist that acts directly or indirectly. In some animal brain regions, these binding inhibitory effects have been linked to higher extracellular dopamine levels [5]. Modafinil has complicated pharmacodynamic features since it interacts with a number of central pathways, including the catecholaminergic system. Both the R- and S-enantiomers bind to DAT35 and raise DA levels in many brain locations, including the prefrontal cortex (PCF), enhancing executive functions such as attention, impulse control, and memory [7].

Amodafinil pharmacokinetics:

Absorption: After numerous or a single oral administration, modafinil is absorbed at least 40 to 65 percent (oral bioavailability) and reaches maximum plasma concentrations (Cmax) 2–4 hours later. Because of its limited water solubility, it is not suitable for intravenous delivery in humans [7]. Oral administration of armodafinil causes rapid absorption, with peak plasma concentrations appearing in about 2 hours in the fasting condition. Food has no effect on armodafinil's overall bioavailability; however, the time to peak concentration can be delayed by 2–4 hours [5].

Distribution: Modafinil has a plasma protein binding of around60%, primarily to albumin, and an apparent volume of distribution of 0.8 L/kg following single or several oral doses, indicating that it can easily permeate tissues [7]. About 60% of modafinil is linked to plasma proteins, primarily albumin [8].

Metabolism: Modafinil is extensively degraded in the liver, largely via amide hydrolysis to form an acid metabolite, into inactive metabolites; ((±)2-[(diphenylmethyl) sulfinyl] acetic acid; modafinic acid) catalyzed by an esterase and/or amidase; ii) by S-oxidation via cytochrome CYP3A4 or CYP3A5 to produce a sulfone (2- [(diphenylmethyl) sulfanilyl] acetamide); iii) by aromatic ring hydroxylation; and iv) by glucuronide conjugation [7]. The principal metabolic process is amide hydrolysis, which does not require cytochrome P450 (CYP) activity. Cytochrome CYP3A4/5 plays a role in sulfone production [8].

Excretion: The elimination half-life is roughly 12–15 hours, owing to the kinetics of the R-enantiomer, as the S-enantiomer has a half-life of 4–5 hours [9]. Individuals with cirrhosis had a 60% reduction in modafinil clearance, while patients with chronic hepatic insufficiency have a doubled Cmax [10]. The main urinary metabolite, modafinil acid, accounts for 35 percent to 60 percent of the dosage [11].

Analytical accounts on Armodafinil:

The widespread literature survey exposed multiple analytical techniques like UV spectrophotometry method, HPLC, HPTLC, LC-MS/MS, for the determination of Armodafinil in bulk and pharmaceutical formulation. These reported methods describe the evaluation of armodafinil in various dosage forms like tablets and matrix like human plasma.

Chromatographic overview:

HPLC Method

P. Vivek Sagar et. al. outlined a stability showing RP HPLC method for the estimation of armodafinil in tablet dosage form. Chromatography was carried out using isocratic elution on a 4.6 x 250 mm stainless steel Hibar C18 column filled with octadecylsilane bound to porous silica (C18) with a particle size of 5 micron. The mobile phase is made up of 50:50 v/v acetonitrile and water. The effluent is measured at 220 nm and the flow rate is 1.0 ml/min. The retention time for armodafinil was 3.8 minutes [12].

Kambham Venkateswarlu et. al. given a validated stability indicating RP-HPLC method for estimation of Armodafinil in pharmaceutical dosage forms; also presented characterization of its base hydrolytic product. The separation was carried out on a C18 column with a 45:55 percent v/v combination of water and methanol as the mobile phase. At 1ml/min, eluents were identified at 220nm. Milder stress conditions were used first, followed by greater circumstances. For Armodafinil, the linearity of the suggested approach was tested in the range of 20-120g/ml. It was discovered that the retention time was 8.1 minutes [13].

Devi Ramesh et. al. performed an analytical approach for development and validation of new LC-MS/MS method for the determination of armodafinil in human plasma. Using 0.2 percent formic acid: methanol (15:85 v/v) as mobile phase on a hypurity advance C-18 column (5; 100 4.6 mm) at a flow rate of 1.0 ml/min, chromatographic separation was obtained in 3.0 minutes. The linearity of the drug concentration range of 50-10000 ng/mL was demonstrated (r2 = 0.9989) [14].

Ramisetti Nageswara Rao et. al. given an enantioselective HPLC resolution of synthetic intermediates of armodafinil and related substances; where armodafinil was studied on polysaccharide-based stationary phases, viz. cellulose tris-(3,5-dimethylphenylcarbamate) (Chiralcel OD-H) and amylose tris-(3,5-dimethylphenylcarbamate) (Chiralpak AD-H) by HPLC. When comparing the cellulose-based Chiralcel OD-H column to the amylose-based Chiralpak AD-H column, a satisfactory separation was achieved. A mobile phase containing n-hexane–ethanol–TFA (75:25:0.15 v/v/v) was used to achieve baseline separation with Rs A1.38. At 225 nm, a photodiode array detector was used to detect the enantiomers, while a polarimetric detector was used to identify the enantiomers [15].

CN Prathyusha Naik et. al. performed stability indicating assay method of armodafinil. The C8 (250 x 4.6 mm, 5m) column was used to separate the mobile phase of water and methanol (10 percent v/v OPA) 55:45 percent v/v. At 1ml/min, eluents were identified at 225 nm. Stress tests were carried out utilising acid, base, oxidizing agents, light, and heat to achieve a 10-20% deterioration rate. Between 10 and 150 mcg/ml, linearity was discovered. The LOD and LOQ were determined to be 0.78 and 2.37 g/ml, respectively [16].

Deepti Jain et. al. outlined intrinsic stability study of armodafinil hydrochloride by forced degradation and impurity profiling. Armodafinil and its degradation products were satisfactorily separated on a Zorbax Eclipse Plus C18 column (250 4.6 mm, 5 m) in 20 minutes using a gradient of 0.1 percent formic acid and acetonitrile at 1 ml/min flow rate with a photodiode-array detector set to 252 nm. In alkaline settings, the drug was significantly damaged, followed by acidic and neutral conditions, with no degradation found in thermal, oxidative, or ultra-violet degradation conditions [17].

Krishna veni Nagappan et. al. performed development and validation of stability indicating RP HPLC method for the estimation of armodafinil and characterization of its base degradation product by LC-MS/MS. The separation was performed on a Hibar Purospher C18 (250 mm 4.6 mm; 5) column with 0.01 M ammonium formate (pH 4.5, adjusted with acetic acid) as the mobile phase and 45:55 percent v/v methanol as the stationary phase. The eluents were measured at 220 nm and the flow rate was kept constant at 1 mL/min. To obtain sufficient degradation, stress experiments were conducted with 1 mg/mL of the drug solution, starting with mild circumstances and progressing to severe conditions [18].

Sr. No.	Drug	Matrix/ Dosage form	Stationary Phase	Mobile Phase	Detection (nm)	Flow Rate (ml/min)	Ret. Time (min.)	Detector	Ref. No.
1.	Armodafinil	Tablet	Stainless steel Hibar C18 column (4.6 x 250 mm; 5µm)	Acetonitrile and water (50:50 v/v)	220 nm	1.0 ml/ min	3.8 min.	UV detector	12
2.	Armodafinil	-	C18 column (250 × 4.6mm; 5µm)	water: methanol (45:55% v/v)	220 nm	1.0 ml/min	8.1 min.	UV-PDA detector	13
3.	Armodafinil	Human Plasma	Hy purity advance C-18 column (100 × 4.6 mm; 5µm)	0.2% formic acid: methanol (15:85% v/v)	-	1.0 ml/min	3.0 min.	-	14
4.	Armodafinil	Its related substances	Chiral Pak AD-H column (25064.6 mm id; 5 lm)	n-hexane: ethanol: TFA (75:25:0.15 v/v/v)	225 nm	0.8 mL/min	-	SPDM10AVP PDA detector	15
5.	Armodafinil	-	C8 (250 × 4.6mm, 5µm)	water: methanol (10% OPA) (55:45 v/v)	225nm	1.0 ml/min	8.2 min.	PDA detector	16
6.	Armodafinil	Degradation product	Zorbax Eclipse Plus C18 column (250 × 4.6 mm, 5 µm)	0.1% formic acid and acetonitrile (in gradient mode)	252 nm	1.0 ml/min	4.82 min.	Photodiode-array detector	17
7.	Armodafinil	-	Hibar Purospher C18 column (250 mm × 4.6 mm; 5µ)	0.01 M ammonium formate (pH 4.5, Adjusted with acetic acid): methanol (45:55 % v/v)	220 nm	1.0 ml/min	6.42 min.	SPD-M20A PDA detector	18
8.	Armodafinil	Tablets	Delvosil ODS – UG-5 C18 column (250×4.6 mm, 5µ)	acetonitrile and pH 2.5 phosphate buffer, adjusted to pH 2.5 with the help of dilute orthophosphoric acid (60:40, v/v).	220 nm	1.2 ml/min	4.45 min.	Waters 2489 U.V-Visible detector/2695 Separation Module	19
9.	Armodafinil	Human Plasma	Waters symmetry, C18 column (4.6 × 150 mm, 5 µm)	Mobile phase A: mixture of water with 0.1% formic acid.	-	0.7 ml/min	1.63 min.	PDA detector	20

				Mobile phase B: mixture of acetonitrile: water with 0.1% formic acid (95:5% v/v). The isocratic elution was carried out at a 90:10% v/v					
10.	Armodafinil	Tablets	Hypersil ODS C-18 column (150 x 4.6 mm, 5µ)	methanol: phosphate buffer 3.0 (60:40 %v/v)	225 nm	1.0 ml/min	4.2 min.	-	21
11.	Armodafinil	Tablets	Chirobiotic T column (250 x 4.6 mm, 5 µm)	Methanol: triethylamine (100/0.05, v/v)	225 nm	1.0 ml/min	6.0 min.	UV/VI'S detector	22
12.	Armodafinil	-	Kromasil C18 (Hichrome) column (25 cm × 4.6 mm i.d.; particle size 5 m)4	acetonitrile: 0.02 M ammonium acetate as a mobile phase in gradient elution mode	225 nm	1.0 ml/min	1.30 min.	SPD-M20A diode array detector	23

Table 1: HPLC method for analysis of Amphetamine.

HPTLC Method

Dr. Hitendra S. Joshi et. al. reported stability indicating HPTLC method for estimation of modafinil in the bulk and tablet formulation; where the stationary phase was aluminium foil TLC plates precoated with silica gel 60F 254, while the mobile phase was ethyl acetate, acetone, and methanol in the volume ratio of (7:2:1 v/v). For modafinil, a compact band (Rf 0.420.02) was obtained. A solid linear connection (r 2=0.9995) was found between peak area and concentration in the range of 80-320 ng/spot using linear regression analysis [24].

Sr. No.	Drug	Matrix/ Dosage Form	Stationary Phase	Mobile Phase	Detection	Rf	Linearity Range	Ref. No.
1.	ARM	Tablets	Merck TLC plates pre-coated with silica gel 60 F254 (10 cm ×10 cm with 250 µm layer thicknesses)	ethyl acetate: acetone: methanol (7:2:1 v/v/v)	232 nm	0.42	80-320 ng /spot	24

Table 2: HPTLC method for analysis of Armodafinil.

Gas Chromatography/Mass Spectrometry:

Manabolu Surya Surendra Babu et. al. reported a direct standard headspace method for the determination of chloroacetic acid and dichloroacetic acid in armodafinil drug substance by GC-MS. Cl-AcOH and DCl-AcOH were separated by helium carrier gas on a DB-624 column (30 m x 0.32 mm, 1.8 m), which contains 6 percent cyanopropyl phenyl and 94 percent dimethylpolysiloxane stationary phase. For Cl-AcOH, the limits of detection (LOD) and limits of quantification (LOQ) were 0.00003 g mL1 and 0.00009 g mL1, respectively, while for DCl-AcOH analyte, they were 0.00003 g mL1 and 0.00009 g mL1, respectively [25].

Sr. No.	Drug	Matrix/ Dosage Form	Stationary Phase	Carrier Gas	Retention time (min.)	Flow Rate	Ref. No.
1.	ARM	-	DB-624 column (30 m x 0.32 mm, 1.8 µm), containing 6% cyanopropyl phenyl and 94% dimethylpolysiloxane	Helium	-	-	25

Table 3: Gas Chromatography/Mass Spectrometry method for analysis of Armodafinil.

capillary electrophoresis:

Wei Wang et. al. outlined enantiomeric separation and determination of the enantiomeric impurity of armodafinil by capillary electrophoresis with sulfobutyl ether-β-cyclodextrin as chiral selector method where the following conditions were used: 20 mmol/L phosphate buffer, pH 7.5, 20 mmol/L sulfobutyl ether—cyclodextrin, and 20% methanol, at 25 °C. The ideal settings resulted in a good resolution of 3.3 for the two enantiomers of modafinil. (S)-modafinil had a limit of detection (LOD) of 1.25 g/mL and a limit of quantification (LOQ) of 2.50 g/mL, respectively [26].

Khaldun M. AL Azzam et. al. reported enantioselective determination of modafinil in pharmaceutical formulations by capillary electrophoresis, and computational calculation of their inclusion complexes. Using a bare fused-silica capillary with a background electrolyte (BGE) of 25 mM H3PO41 M tris solution; pH 8.0; containing 30 mg mL1 of ulphated-cyclodextrin (S-CD), good chiral separation of the racemic mixture was accomplished in less than 5 minutes with a resolution factor of Rs=2.51. The separation was done in normal polarity mode at 25 degrees Celsius, 18 kV, and with hydrostatic injection [27].

Khaldun M. Al Azzam et. al. outlined the determination of the binding constants of modafinil enantiomers with ulphated b-cyclodextrin chiral selector by capillary electrophoresis using three different linear plotting methods. With S-b-CD, a CE approach for separating the enantiomers of modafinil was described. The electrophoretic settings were based on our prior work [15], with the standard being injected hydrodynamically (50 mbar) for 5 seconds under the following conditions: The BGE was 25 mM H3PO4 – 1 M tris solution, pH 8.0; S-b-CD, 30 mg/mL; voltage, 18 kV; capillary temperature, 251C; detector wavelength, 225 nm; and the BGE was 25 mM H3PO4 – 1 M tris solution, pH 8.0; (12.19 mM) [28].

Sr. No.	Drug	Matrix/ Dosage Form	Detection	Capillaries (Fused Silica Capillary)	Separation Voltage	Temp./ Pressure	Ref. No.
1.	ARM	-	225 nm	untreated 50 µm I.D. fused-silica capillary with a total length of 50 cm and an effective length of 41.5 cm	20 kV	50 mbar	26
2.	ARM	Tablet	225 nm	50 µm i. d×56 cm, (detection length, 8.5 cm from the outlet end of the capillary	18 kV	50 mbar	27
3.	ARM	-	225 nm	Uncoated bare fused-silica capillary 50 mm id 56 cm, (detection length, 8.5 cm from the outlet end of the capillary) from Agilent Technologies	18 kV	50 mbar	28

Table 4: Capillary Electrophoresis method for analysis of Armodafinil.

Spectrophotometric overview:

UV-Visible Spectroscopy Method:

Tejaswi Jonnalagadda et. al. reported a simple visible spectrophotometric method for the determination of armodafinil in bulk and pharmaceutical dosage form. In the range of 10- 50 g/ml, the drug follows Beer Lambert law, with a correlation coefficient of 0.999. Armodafinil's percentage recovery in pharmaceutical dosage form is between 96 and 106 percent. The oxidative coupling reaction of 3-methyl-2-benzathiazoline hydrazone (MBTH) in the presence of ferric chloride is the basis for this approach (Fecl3). With the solvent system methanol: water, an absorption-maxima were discovered at 596nm [29].

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