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# Stability Indicating Method Development and Validation for the Determination of Armodafinil in Pharmaceutical Tablet Dosage Form by RP-HPLC

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**Research Article**

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**Keywords:** RP-HPLC, Armodafinil, Forced degradation.

## ABSTRACT

Therapeutic drug monitoring in terms of quality is very much important in pharmaceutical industries. Some of the barriers are like finding out the purity and maintaining uniformity content in pharmaceutical dosage form. To overcome such problems, the present research deals with the development of a stability indicating reverse phase HPLC with PDA detector method for the determination of Armodafinil Agilent XDB-C18, 150 × 4.6 mm, 5 µm or Equivalent column. The flow rate was kept at 1.0 ml/min and the injection volume 10 mL and the run time is 8 min and drug Rt is 3.354. The separation was performed at 30°C. Eluents were monitored by PDA detector set at 223 nm. The developed method was statistically validated and results for the linearity is 0.999 and for System suitability, theoretical plates are 2500 and its tailing factor is 1.64, Precision is 0.1, LOQ is 1.00 µg/ml, LOD is 0.33 µg/ml, accuracy is 100.19, Robustness (flow rate, mobile phase) is complied.

## INTRODUCTION

Armodafinil [1-3] is the Enantiomer pure compound of the euro-genic modafinil (Provigil). It consists of only the (R) (−) enantiomer of the racemic modafinil. Armodafinil is currently FDA-approved to treat excessive daytime sleepiness associated with obstructive sleep apnea, narcolepsy and shift work disorder. It is commonly used off-label to treat attention deficit hyperactivity disorder, chronic fatigue syndrome and major depressive disorder. It has been shown to improve vigilance in air traffic controllers. Literature review [4-7] reveals very less works done, it became very interesting to pursue the work and to implement the therapeutic drug monitoring in terms of stability.

## EXPERIMENTAL PROCEDURE

### Drug Profile

| | | |
|---|---|---|
| IUPAC name | : | (−)-2-[(R)-(diphenylmethyl)sulfinyl]acetamide |
| Molecular formula | : | $C_{15}H_{15}NO_2S$ |
| Molecular weight | : | 273.35 |
| PKa value | : | 8.839 |
| Melting Point | : | 156-158°C |

### HPLC Instrumentation and Conditions

Instrumentation and analytical conditions: The analysis of the drug was carried out on a HPLC system equipped with a reverse phase HPLC with PDA detector method for the determination of Armodafinil Agilent XDB-C18, 50 × 4.6 mm, 5 µm or Equivalent column. A mobile phase consisting of Phosphate Buffer: Acetonitrile (65:35 v/v) was employed in this study. The flow rate was kept at 1.0 ml/min and the injection volume 10 mL and the run time is 8 min. The separation was performed at 30°C. Eluents were monitored by PDA detector detector (Waters 2695 Separation Module Equipped with 2996 PDA) set at 223nm.

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### Chemicals and Reagents

All the chemicals used were of analytical grade and procured from Qualigens India Ltd., Rankem Chemicals Ltd. The chemicals used for the study were, Potassium di-hydrogen phosphate purchased from Merck, Methanol purchased from Rankem, Water and Acetonitrile from Rankem and other chemicals are Ortho Phosphoric acid, Hydrochloric Acid, Sodium Hydrogen Peroxide and Sodium Hydroxide.

### Preparation of phosphate buffer

Accurately weighed 2.72 gm of potassium dihydrogen phosphate in 1000 ml of Volumetric flask add about 900 ml of milli-Q water and sonicate and make up to the final volume with milli-Q water, add 1 ml of Triethylamine and then PH 5.6 is adjusted with dilute orthophosphoric acid solution.

### Preparation of mobile phase

Mix 600 ml of phosphate buffer pH 5.6 and 400 ml of Acetonitrile (HPLC grade) in a ratio of (65:35% v/v) degassed in ultra-sonic water bath for 5 minutes. Filtered through 0.45 µ filter under vacuum filtration

### Diluent

Prepare filter and degass the mixture of HPLC grade water & methanol in a Ratio of (20:80% v/v).

### Preparation of standard solution of Armodafinil

Accurately Weighed and transferred 10 mg of Armadofinil working Standards into a 10 ml clean dry volumetric flask, add 7 ml of methanol, sonicated for 5 minutes and make up to the final volume with methanol (standard stock 1000 µg/ml). From the filtered solution 0.5 ml was pipette out into a 10 ml volumetric flask made up with diluents.

### Assay of Armodafinil 1 N Armod 20 Tablets

### Preparation of sample solution of Armodafinil

Twenty tablets were weighed and crushed into powder, in order to calculate the average weight of each tablet. From that powder weight equivalent to 50 mg of Armodafinil was transferred into a 100 ml volumetric flask, 70 ml of diluent added and sonicated for 25 min, further the volume made up with diluent and filtered. From the filtered solution 0.2 ml was pipetted out into a 10 ml volumetric flask and made up to 10 ml with diluent. The peak areas were measured at 223 nm and concentrations in the samples were determined by interpolation from calibration plot previously obtained.

### Estimation of Armodafinil in tablet dosage form

Assay was performed by using the regression equation (y = 100769x + 27300, R2=0.9991) obtained from the standard curve of Temozolomide API.

### Forced Degradation Studies

The drug was subjected to stress conditions in various ways to observe the rate and extent of degradation that is likely to occur in the course of storage and/or after administration to body. The various degradation pathways studied are Acid degradation, alkaline degradation, Oxidative degradation, Thermal degradation, Photo degradation.

## METHOD VALIDATION

### Linearity and Calibration Curve

The linearity of an analytical method is its ability to elicit test results that are directly proportional to the concentration of analytes in samples within a given range or proportional by means of well-defined mathematical transformations. Linearity may be demonstrated directly on the test substance (by dilution of a standard stock solution) and/or by using separate weight of synthetic mixtures of the test product components, using the proposed procedure [8-11].

### Accuracy

Accuracy was best determined by the standard addition method. Previously analyzed samples of Armodafinil API were added with standard drug solutions and are analyzed by the proposed method. Recovery (%) and RSD (%) were calculated for each concentration.

### Precision

Precision was determined as both repeatability and intermediate precision, in accordance with ICH guidelines. Repeatability of sample injection was determined as intra-variation and intermediate variation was determined by measurement of inter day variation. For these determinations, three concentrations of the solutions of Armodafinil API were used.

### Robustness

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The concept of robustness of an analytical procedure has been defined by the ICH as "a measure of its capacity to remain unaffected by small but deliberate variations in method parameters". The robustness of a method is the ability to remain unaffected by small changes in parameters such as pH of the mobile phase, temperature, % organic solvent strength and buffer concentration etc. To determine the robustness of the method experimental conditions are purposely altered and chromatographic characters are evaluated. Influence of small changes in chromatographic conditions such as change in flow rate ( ± 0.1 ml/min), temperature ( ± 2°C), wavelength of detection ( ± 2 nm) and water content in mobile phase ( ± 2%) were studied to determine the robustness of the method.

**Limit of Detection (LOD)**

The limit of detection (LOD) of an analytical method may be defined as the concentration, which gives rise to an instrument signal that is significantly different from the blank. For spectroscopic techniques or other methods that rely upon a calibration curve for quantitative measurements, the IUPAC approach employs the standard deviation of the intercept (Sa), which may be related to LOD and the slope of the calibration curve, b, by

**Limit of Quantitation (LOQ)**

The LOQ is the concentration that can be quantitated reliably with a specified level of accuracy and precision. The LOQ represent the concentration of analyte that would yield a signal-to-noise ratio of 10.

LOQ = 10 Sa/b

Where, Sa is the standard deviation of the peak area ratio of analyte to IS (5 injections) of the drugs and b is slope of the corresponding calibration curve.

**Specificity**

The specificity of the method was determined by exposing the drug sample to acidic (0.1 N HCl), basic (0.1N NaOH) and oxidizing (3% $H_2O_2$) stress conditions. The resulting solutions were then analyzed and the analyte peak was evaluated both for peak purity and for resolution from the nearest eluting peak.

**Stability**

Stability of pharmaceutical product may be defined as, the capacity of a particular formulation in a specific container or closure system, to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications.

Stability of Armodafinil API was determined after storage of the drug solution for 24 hours at room temperature (25 ± 2°C).

## RESULTS AND DISCUSSION

**Optimization of Chromatographic Conditions**

The chromatographic conditions were optimized by different means i.e. using different column, different mobile phase, different flow rate, different detection wavelength and different diluents for sample preparation etc. and finally the prescribed method is accepted. Chromatographic conditions were listed in **Tables 1 and 2** and **Figures 1-3**.

**Accuracy - Recover Study**

The recovery of the method, determined by adding a previously analyzed test solution with additional drug standard solution, was 100.19%. The values of recovery (%) and RSD (%) listed in **Tables 4 and 5** indicate the method is accurate-chromatogram was shown in **Figures 4 and 5**.

**Table 1.** Analytical method development trials.

| Trial | Column | Flow rate (ml/min) | Temp | Mobile phase | Wave length | Observation | Remarks |
|---|---|---|---|---|---|---|---|
| 1 | Agilent XDB, $C_{18}$, 50×4.6 mm, 5 µm or Equivalent | 1.0 ml/min | 30°C | Phosphate Buffer: Methanol (70:30) | 223 nm | Broad peak was observed. | Method rejected |
| 2 | Agilent XDB, $C_{18}$, 150×4.6 mm, 5 µm or Equivalent | 1.0 ml/min | 30°C | Phosphate Buffer: Acetonitrile (90:10) | 223 nm | No peak was observed | Method rejected |
| 3 | Agilent XDB, 150×4.6 mm, 5 µm or Equivalent | 1.0 ml/min | 30°C | Phosphate Buffer: Acetonitrile (80:20) | 223 nm | No peak was observed | Method rejected |
| 4 | Agilent XDB, $C_{18}$, 150×4.6 mm, 5 µm or Equivalent | 1.0 ml/min | 30°C | Phosphate Buffer: Acetonitrile (75:25) | 223 nm | Poor plate count | Method rejected |
| 5 | Agilent XDB, $C_{18}$, 250×4.6 mm, 5 µm or Equivalent | 1.0 ml/min | 30°C | Phosphate Buffer: Acetonitrile (70:30) | 223 nm | Peak with more tailing is observed. | Method rejected |
| 6 | Agilent XDB, $C_{18}$, 150×4.6 mm, 5 µm or Equivalent | 1.0 ml/min | 30°C | Phosphate Buffer: Acetonitrile (65:35) | 223 nm | A sharp peak with good plate count is observed. | Method accepted |

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**Table 2.** Optimized chromatographic conditions.

| Column | Agilent XDB C18, 150 × 4.6 mm, 5 µ |
|---|---|
| Detector wavelength | 223 nm |
| Column temperature | 30°C |
| Injection volume | 10 µL |
| Run time | 8 min |
| Diluent | Water: Methanol (20:80) |
| Mobile phase | Buffer: Acetonitrile (65:35) |
| Drug RT | 3.354 |
| Elution technique | Isocratic |

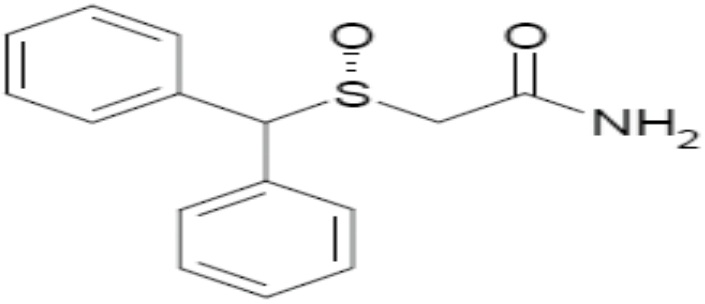


**Figure 1.** Chemical structure of Armodafinil.

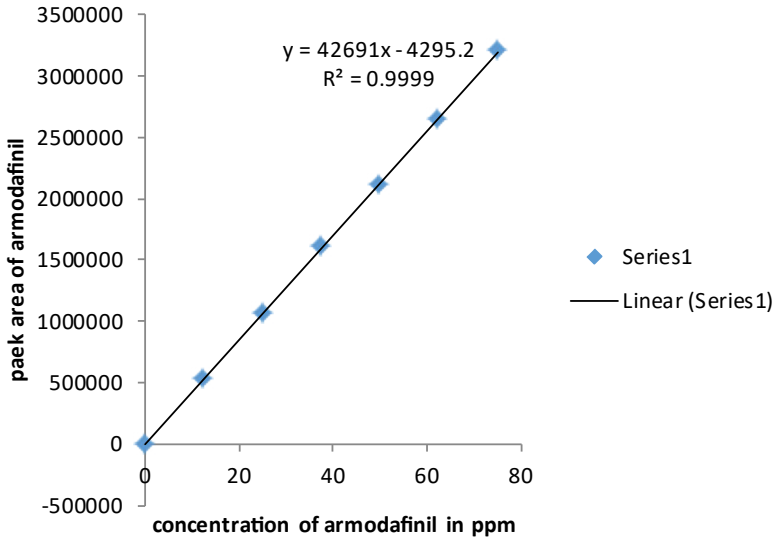


**Figure 2.** Calibration curve of Armodafinil API.

**Precision: System Precision and Method Precision**

This method was carried out and the high values of mean assay and low values of standard deviation and % RSD (RSD NMT 2.0%) within a day and day to day variations for armodafinil revealed that the proposed method is precise and the final result obtained % RSD is 0.1. Results obtained are shown in **Figures 6 and 7** and **Tables 6 and 7**.

**Robustness**

Influence of small changes in chromatographic conditions such as change in flow rate ( ± 0.1 ml/min), Temperature ( ± 2°C), Wavelength of detection ( ± 2 nm) & buffer in mobile phase ( ± 2%) studied to determine the robustness of the method are also in favor of (**Table 4**, % RSD < 2%) the developed RP-HPLC method for the analysis of Armodafinil API. Results obtained are shown in **Figure 10** and **Table 8.**

**Linearity**

In the linearity, correlation coefficient obtained is 0.999. Chromatograph of calibration curve is shown in **Figure 2** and observe **Table 4**.

**LOD & LOQ**

The Minimum concentration level at which the analyte can be reliable detected (LOD) & quantified (LOQ) were found to be

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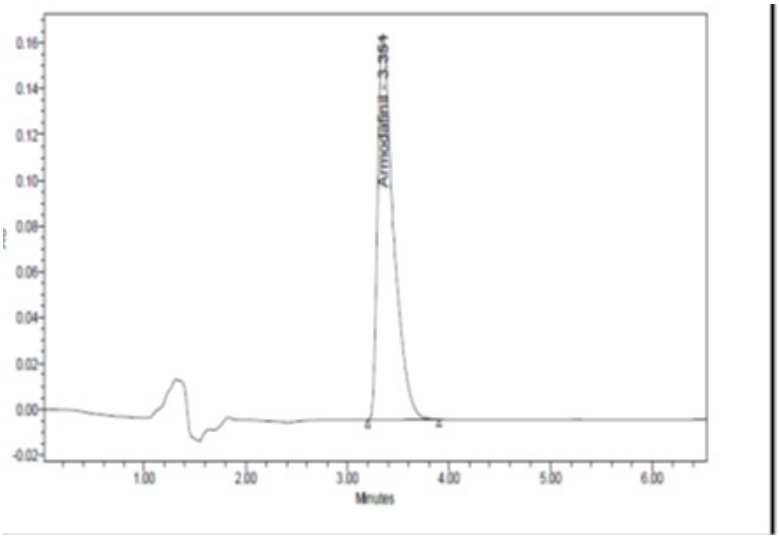


**Figure 3.** Chromatograph of optimized trial.

**Table 4.** Calibration of the HPLC method for armodafinil.

| Linearity Level (%) | Concentration (ppm) | Area |
|---|---|---|
| 20 | 12.5 | 524067 |
| 50 | 25 | 1056889 |
| 70 | 37.5 | 1616960 |
| 100 | 50 | 2120262 |
| 120 | 62.5 | 2647995 |
| 150 | 75 | 3210254 |
| -- | Linearity concentration | 12.5-75PPM |
| -- | Slope | 42691 |
| -- | Intercept | 4295 |
| -- | Correlation coefficient | 0.999 |

**Table 5.** Results of accuracy.

| Accuracy | Area | % Recovery | Mean Recovery |
|---|---|---|---|
| S1: 50% | 919713 | 101.11 | Mean=100.72% |
| S2: 50% | 913107 | 100.38 | S.D. = 0.365 |
| S3: 50% | 915759 | 100.67 | % RSD = 0.36 |
| S4: 100% | 1810501 | 99.52 | Mean = 99.88% |
| S5: 100% | 1824997 | 100.31 | S.D. = 0.404 |
| S6: 100% | 1815611 | 99.80 | % RSD = 0.40 |
| S7: 150% | 2725468 | 99.87 | Mean =99.98% |
| S8: 150% | 2735077 | 100.23 | S.D. = 0.2119 |
| S9: 150% | 2734699 | 99.84 | % RSD = 0.21 |

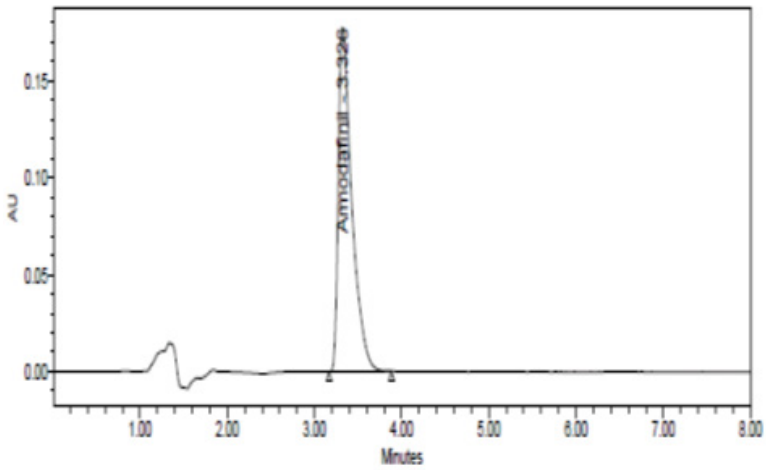


**Figure 4.** Chromatogram of System suitability standard.

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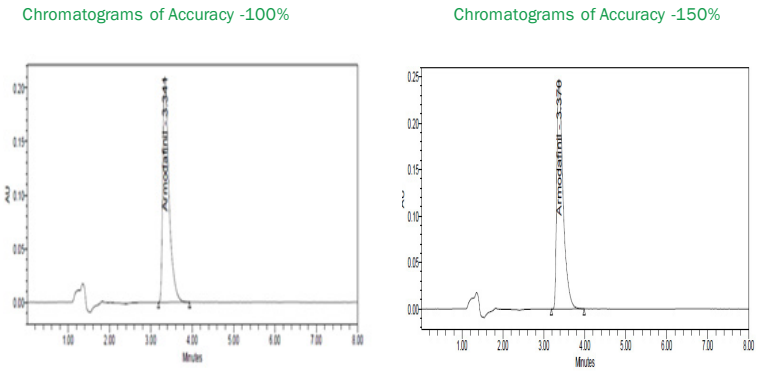


**Figure 5.** Chromatogram of accuracy.

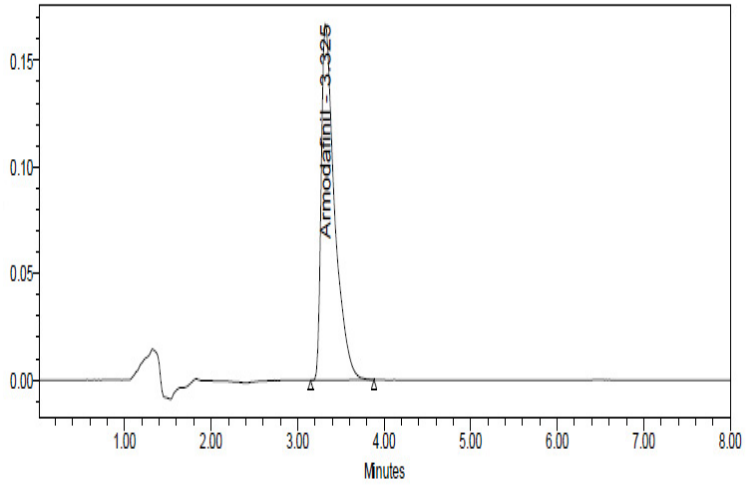


**Figure 6.** Chromatogram of System precision.

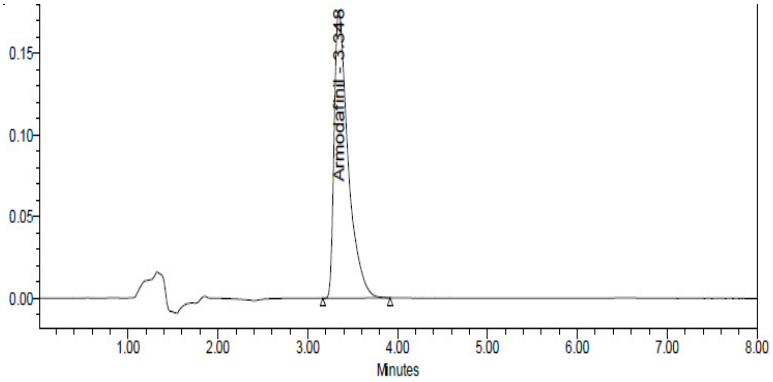


**Figure 7.** Chromatogram of Method precision.

**Table 6.** Results of system precision.

| System Suitability | Areas |
|---|---|
| 1 | 1822152 |
| 2 | 1825225 |
| 3 | 1810134 |
| 4 | 1810210 |
| 5 | 1810976 |
| 6 | 1815203 |
| AVG | 1815650 |
| SD | 6573.01 |
| % RSD | 0.36 |

0.33 µg/ml and 1.006 µg/ml respectively. Chromatograms obtained are shown in **Figure 8**.

**Specificity:** No peak was found at the retention time of armodafinil peak. Observe the peaks in **Figure 9.0, 9.1, 9.2.**

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**Table 7.** Results of method precision.

| Sample No | Sample Areas | %Assay |
|---|---|---|
| 1. | 1815404 | 99.79 |
| 2. | 1811942 | 99.60 |
| 3 | 1819899 | 100.03 |
| 4 | 1816055 | 99.82 |
| 5 | 1815040 | 99.77 |
| 6 | 1816870 | 99.87 |
| AVG | 1815868 | 99.81 |
| Standard Deviation | 2592.30 | 0.1425 |
| Relation standard Deviation (% RSD) | 0.10 | -- |

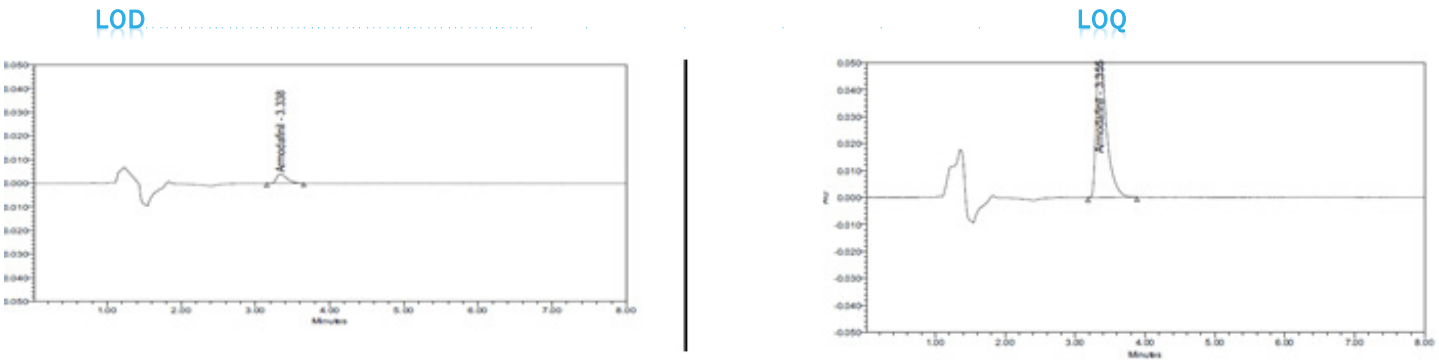


**Figure 8.** Chromatogram of LOD and LOQ.precision.

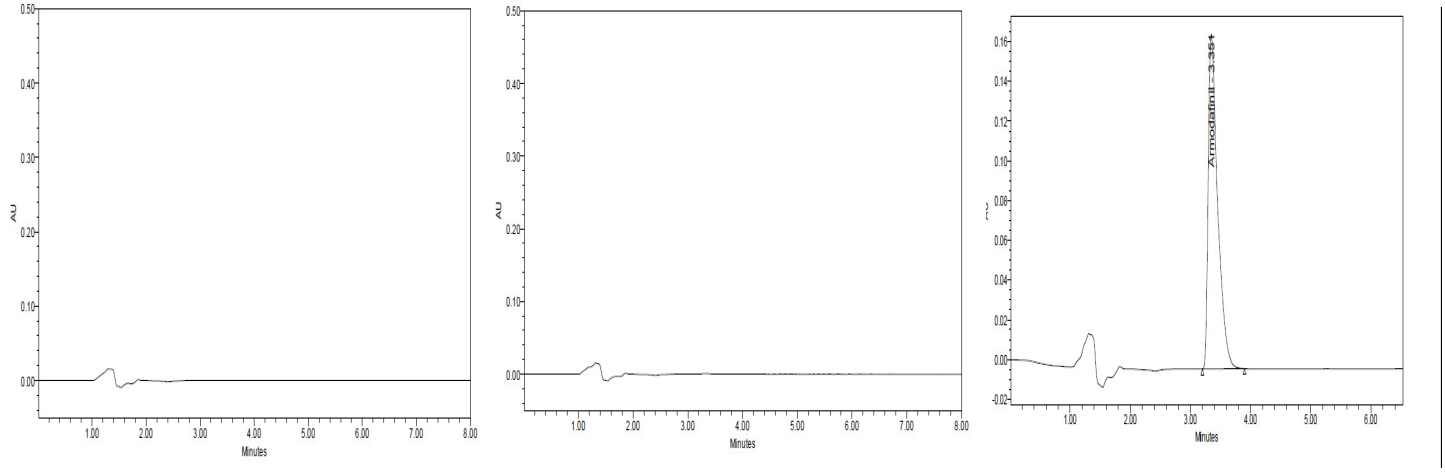


**Figure 9.0.** Chromatography of Mobile phase **Figure 9.1.** Chromatography of placebo **Figure 9.2.** Chromatographyof drug peak

**System Suitability:** Theoretical plates are about 2500 and tailing factor obtained was 1.64. Observe the **Table 3** and chromatograms obtained are shown in **Figure 4.**

**Summary:** Method validation parameters are shown in **Table 9**.

### Stability in Analytical Solution

It is important to mention here that the armodafinil API was stable in solution form up to 72 hours at 25°C.

### Forced Degradation Studies

Forced degradation studies based on peak purity results, obtained from the analysis of force degradation samples using described method, it can be concluded that the absence of co-eluting peak along with the main peak of armodafinil indicated that the developed method is specific for the estimation of armodafinil in presence of degradation products. The results of the forced degradation studies were given in **Table 10** and **Figures 11-15.**

### Estimation of Armodafinil in Tablet Dosage Form

Assay was performed by using the regression equation (y = 100769x + 27300, R2=0.9991) obtained from the standard curve of temozolomide API. Results obtained are given in **Table 5**. The assay of containing armodafinil was found to be 99.8% as per the method.

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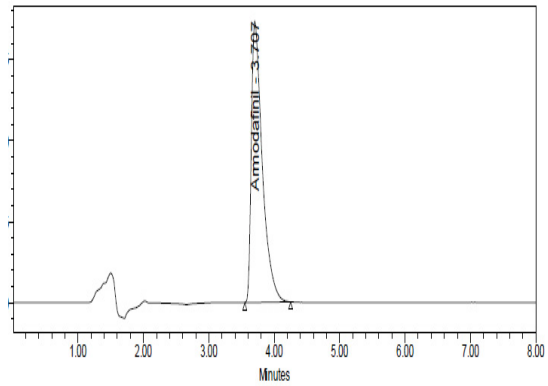
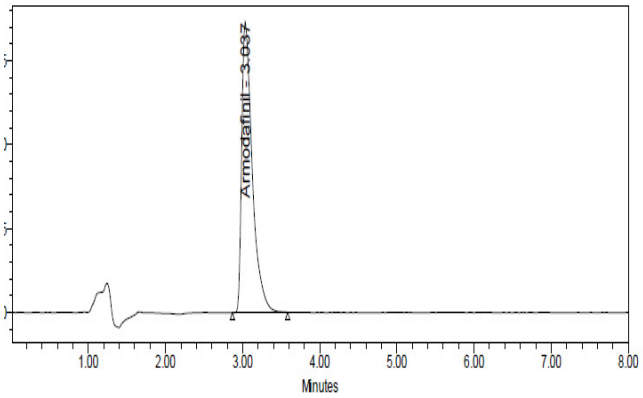
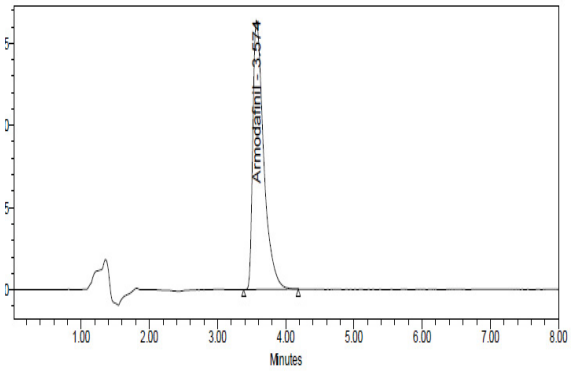
Flow minus Chromatograms



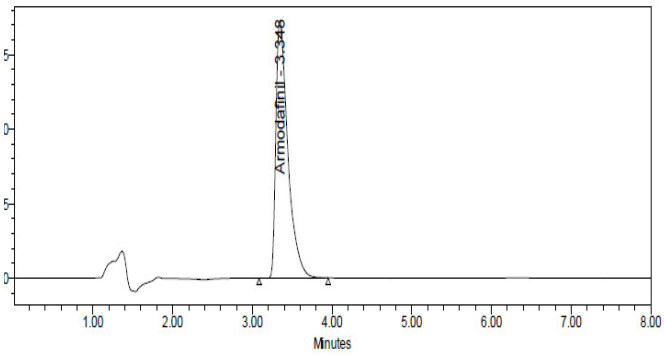

Flow plus Chromatograms (1.0 ml/min)



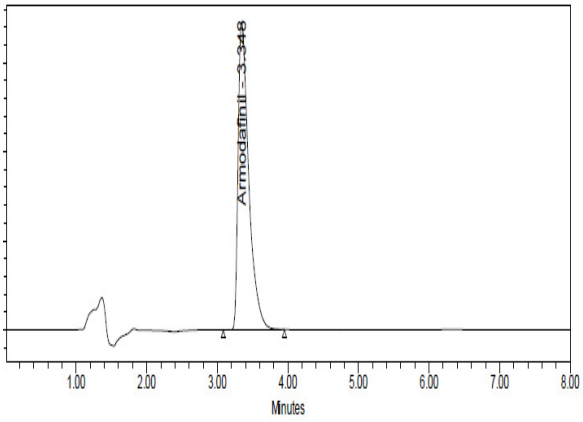

Mobile phase changes Chromatograms (70:30)




Mobile phase changes Chromatograms (60:40)




Temperature changes chromatograms (25ºC)




Temperature changes chromatograms (35ºC)

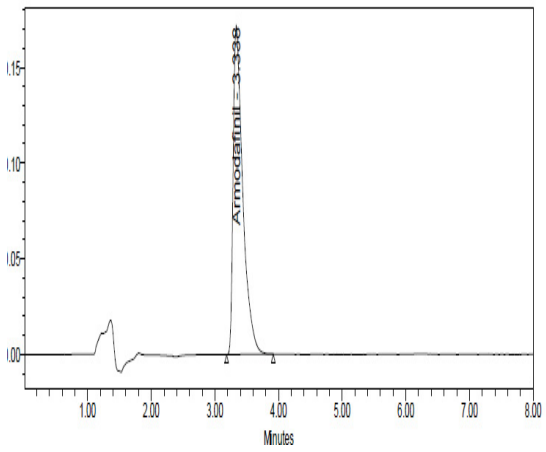



**Figure 10.** Chromatograms of robustness.

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**Table 8.** Results of robustness.

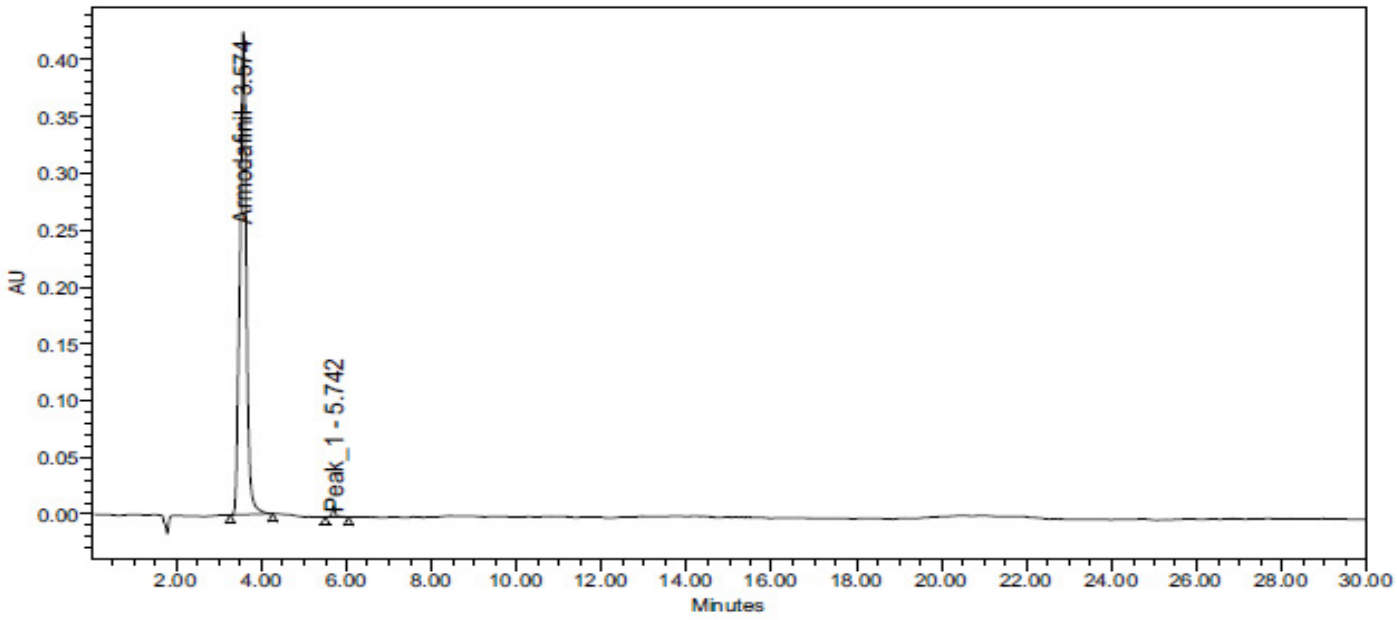
| Inj. Sample | Change parameter | modification | Peak area 1 | Peak area 2 | mean | % RSD |
|---|---|---|---|---|---|---|
| Armodafinil | Flow rate | 0.8 ml/min | 2018950 | 2008764 | 2008857 | 0.1 |
| | | 1 .1 ml/min | 1620562 | 1615142 | 1617852 | 0.23 |
| | Mobile phase | 60:40 | 1805335 | 1811345 | 1808340 | 0.23 |
| | | 70:30 | 1816046 | 1815471 | 1816258 | 0.1 |
| | temperature | 25°C | 1803514 | 1807444 | 1805479 | 0.2 |
| | | 35°C | 1799955 | 1798639 | 1799297 | 0.1 |

**Table 9.** Summary of method validation parameters.

| S. No | Parameters | Limit | Observation |
|---|---|---|---|
| 1 | System suitability | Theoretical plates should not less than 2000<br>Tailing factor should not more than 2.0 | Theoretical plates<br>2500<br>Tailing factor 1.64 |
| 2 | Precision | RSD NMT 2.0% | 0.1 |
| 3 | Linearity | Correlation coefficient<br>NLT0.99 | 0.999 |
| 4 | Accuracy | %Recovery range 98-102 | 100.19 |
| 5 | Robustness (flow, mobile phase) | System suitability parameters should comply | Complies |

**Table 10.** Summary of forced degradation studies.

| Mode of degradation | Conditions | Armodafinil | | |
|---|---|---|---|---|
| | | % Degradation w.r.t. control | Purity angle | Purity Threshold |
| Control | No treatment | - | - | - |
| Acid degradation 1N HCl | 60°C/30 min | 4.04 | 0.350 | 0.495 |
| Alkali degradation 0.1N NaOH | 60°C/30 min | 7.97 | 0.12 | 0.30 |
| Peroxide degradation 10% W/V $H_2O_2$ | 60°C/30 min | 10.02 | 0.131 | 0.353 |
| Thermal degradation | 105°C/6 hrs | 7.4 | 0.271 | 0.456 |
| Photolytic | UV/7 days | 6.4 | 0.252 | 0.492 |




| | Peak Name | RT | Area | % Area | USP Plate Count | USP Tailing | Purity1 Angle | Purity1 Threshold |
|---|---|---|---|---|---|---|---|---|
| 1 | Armodafinil | 3.574 | 1749932 | 98.59 | 2644 | 1.02 | 0.350 | 0.495 |
| 2 | Peak _1 | 5.742 | 14054 | 1.41 | 4000 | 1.12 | 0.140 | 0.210 |

**Figure 11.** Chromatogram of Acid Degradation (1N HCL).

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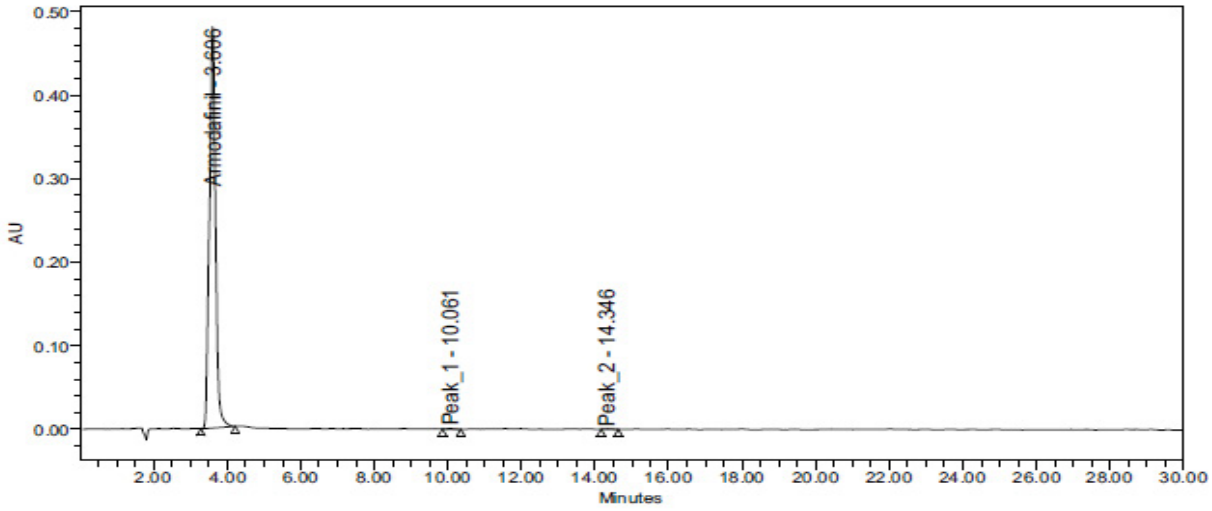
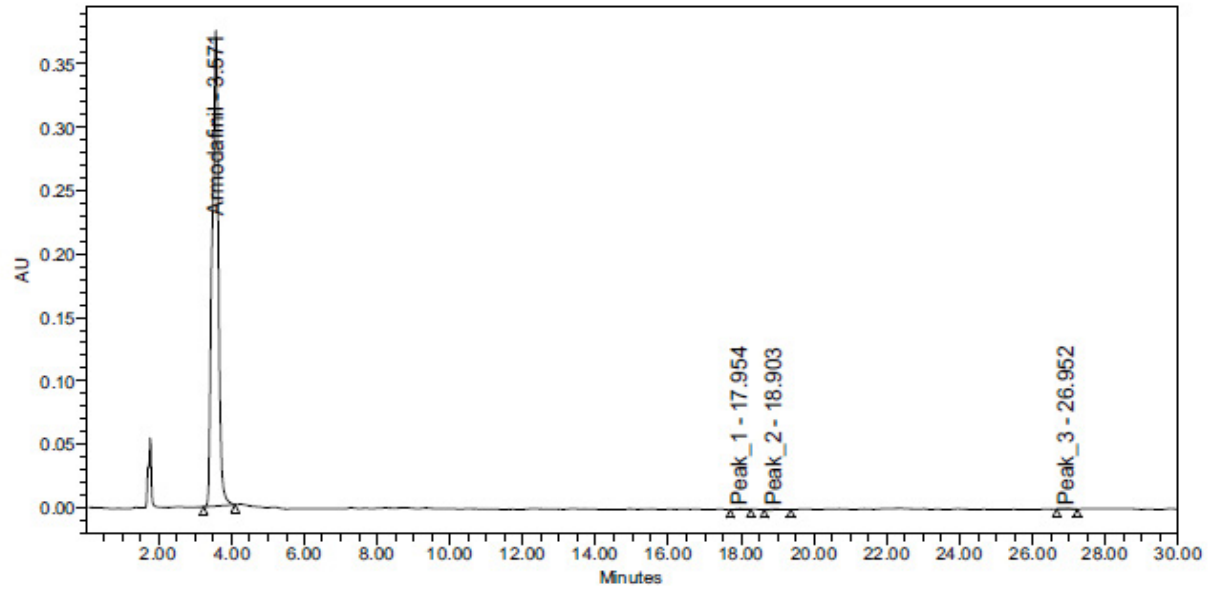



| | Peak Name | RT | Area | % Area | USP Plate Count | USP Tailing | Purity1 Angle | Purity1 Threshold |
|---|---|---|---|---|---|---|---|---|
| 1 | Armodafinil | 3.606 | 1678315 | 98.18 | 1875 | 1.03 | 0.121 | 0.304 |
| 2 | Peak_1 | 10.061 | 10804 | 0.92 | 6766 | 1.16 | 0.008 | 0.183 |
| 3 | Peak_2 | 14.346 | 10000 | 0.88 | 19669 | 1.29 | 0.062 | 0.161 |

**Figure 12.** Chromatogram of base degradation (0.1 N NaOH).




| | Peak Name | RT | Area | % Area | USP Plate Count | USP Tailing | Purity1 Angle | Purity1 Threshold |
|---|---|---|---|---|---|---|---|---|
| 1 | Armodafinil | 3.571 | 1637637 | 97.21 | 1039 | 0.97 | 0.131 | 0.353 |
| 2 | Peak_1 | 17.954 | 10188 | 0.64 | 44121 | 1.13 | 0.120 | 0.202 |
| 3 | Peak_2 | 18.903 | 12466 | 1.08 | 19775 | 1.41 | 0.124 | 0.407 |
| 4 | Peak_3 | 26.952 | 12054 | 1.07 | 36571 | 0.96 | 0.010 | 0.212 |

**Figure 13.** Chromatogram of oxidation degradation (10% $H_2O_2$).

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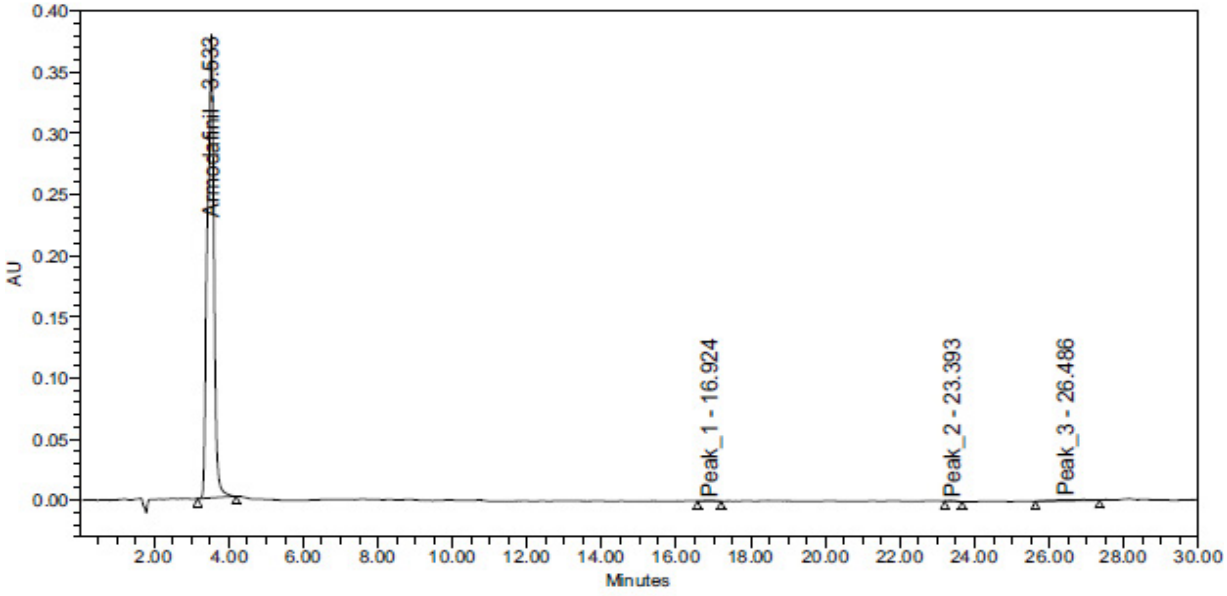
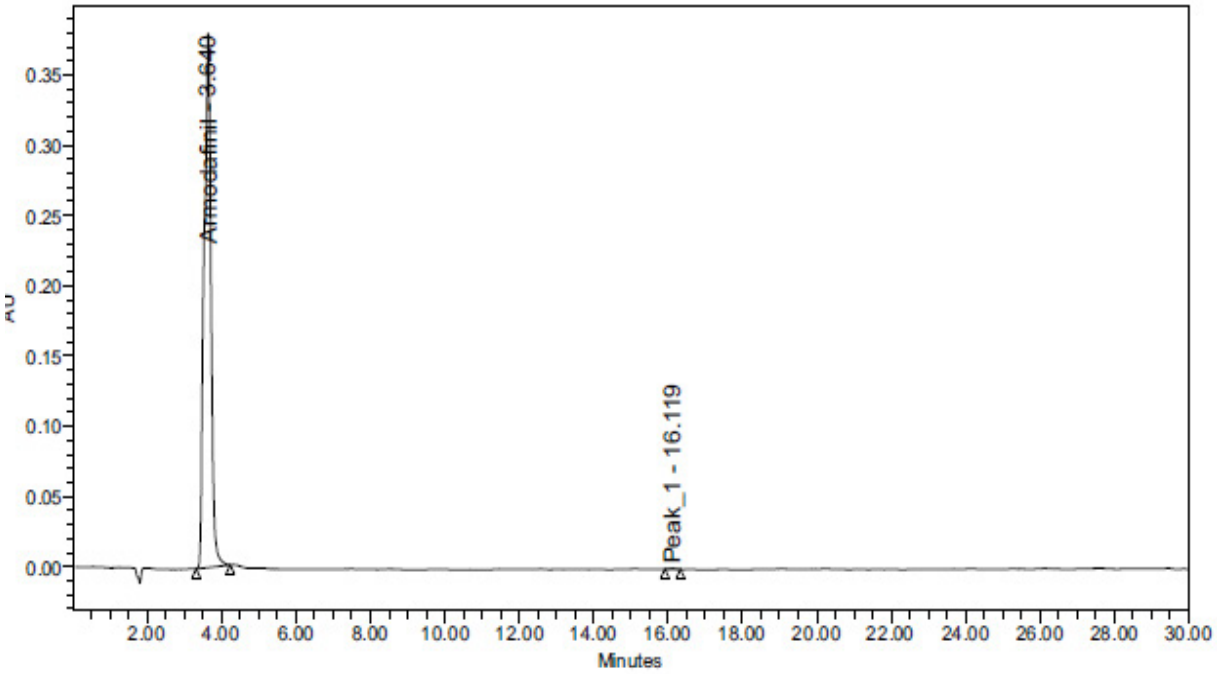



| | Peak Name | RT | Area | % Area | USP Plate Count | USP Tailing | Purity1 Angle | Purity1 Threshold |
|---|---|---|---|---|---|---|---|---|
| 1 | Armodafinil | 3.533 | 1689303 | 98.38 | 2896 | 0.95 | 0.271 | 0.456 |
| 2 | Peak_1 | 16.924 | 4674 | 0.84 | 14141 | 0.91 | 0.220 | 0.449 |
| 3 | Peak_2 | 23.393 | 4071 | 0.72 | 34674 | 1.18 | 0.228 | 0.642 |
| 4 | Peak_3 | 26.486 | 4816 | 2.95 | 7337 | 1.02 | 0.200 | 0.303 |

**Figure 14.** Chromatogram of thermal degradation.




| | Peak Name | RT | Area | % Area | USP Plate Count | USP Tailing | Purity1 Angle | Purity1 Threshold |
|---|---|---|---|---|---|---|---|---|
| 1 | Armodafinil | 3.640 | 1706934 | 98.91 | 1005 | 0.96 | 0.252 | 0.492 |
| 2 | Peak_1 | 16.119 | 7870 | 1.09 | 30593 | 0.98 | 0.052 | 0.133 |

**Figure 15.** Chromatogram of photolytic degradation.

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## CONCLUSION

From the above results furnished, the proposed RP-HPLC method was found to be simple, precise, accurate and sensitive for the determination of armodafinil in pharmaceutical dosage form. These are within short analysis time and the low value of RSD in comparison to the previous papers published; indicate that the proposed method is highly precise and accurate. High percentage of recoveries suggests that the proposed method is accurate. Forced degradation studies based on peak purity results, obtained from the analysis of force degradation samples using described method. It can be concluded that the absence of co-eluting peak along with the main peak of armodafinil indicated that the developed method is specific for the estimation of armodafinil in the presence of degradation products.

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