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# SIMULTANEOUS RP-HPLC DETERMINATION OF ARMODAFINIL, CLONIDINE, AND VILOXAZINE HYDROCHLORIDE: ICH VALIDATION AND COMPUTATIONAL GREEN, BLUE, AND WHITE METRIC PROFILING

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**ABSTRACT**
Attention-deficit/hyperactivity disorder (ADHD) is a widespread neurological condition commonly managed with a combination of armodafinil, clonidine, and viloxazine hydrochloride. Despite their concurrent clinical use, no validated simultaneous analytical method exists for their quantification, representing a critical gap in pharmaceutical quality control. This study presents the development and ICH Q2(R1) validation of an environmentally sustainable reverse-phase high-performance liquid chromatography (RP-HPLC) method. A sustainable RP-HPLC method was developed for the simultaneous determination of three drugs in a single analytical run. Chromatographic separation was performed on a Sunfire C18 column using a Waters 2695D system with UV detection at 230 nm. Separation was conducted at a flow rate of 1.0 mL/min with an injection volume of 10 µL. The 14-minute run yielded well-resolved peaks with excellent linearity ($R^2 > 0.99$). Intraday and interday RSDs remained below 2%, confirming high precision and accuracy, while low LOD and LOQ values demonstrated adequate sensitivity, and robustness and solution stability studies further validated its reliability for routine use. Comprehensive sustainability evaluation using AGREE prep, AGREE, GAPI, GWAPE, WAC, and BAGI tools revealed superior greenness, blueness, and whiteness scores compared to previously reported individual methods, demonstrating reduced solvent hazards, minimised waste generation, and enhanced analytical efficiency. The proposed method provides a scientifically valid, economical and eco-compatible solution to the simultaneous pharmaceutical quality check analysis, with direct applicability to regulatory submissions and industrial laboratory workflows. Its green analytical profile further positions it as a model for sustainable method development in multi-drug formulation analysis.
**Keywords:** Armodafinil, Clonidine, Viloxazine Hydrochloride, Computational Evaluation, Greenness, Validation, AGREE, GAPI

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## INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder typically emerging in childhood and persisting into adulthood. A meta-analysis of 53 studies reported ADHD prevalence of 7.6% among 96,907 children aged 3–12 years (95% CI: 6.1–9.4%) and 5.6% among adolescents aged 12–18 years (95% CI: 4.8–7%.[1,2] Armodafinil, Clonidine, and Viloxazine are among the key medications used in the treatment of ADHD, and their chemical structures are illustrated in Fig.-1. Armodafinil is a psychostimulant that promotes wakefulness and has been shown to improve attention, memory, and fatigue in both healthy adults and individuals with neurodevelopmental disorders that share symptoms with ADHD. It is generally well tolerated, with most reported adverse events being mild and non-serious. Clonidine, both in its immediate release and extended-release formulations, is both safe and effective for the treatment of ADHD in kids and teenagers. Similarly, Viloxazine extended-release has shown significant improvement in functional impairments in children and adolescents with ADHD across four Phase 3 placebo-controlled clinical trials.

Chemically, Armodafinil is known as 2-[(R)-(diphenyl methyl) sulfinyl] acetamide ($C_{15}H_{15}NO_2S$). Several techniques for analysis have been reported for its quantification, such as UV–Visspectroscopy [3], HPLC [4], LC MS/MS[5], and capillary electrophoresis.[6] Modafinil, a closely related compound, has also


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been analysed using HPLC with UV detection,[7] LC–MS[8], GC–MS.[9] Clonidine, chemically described as 2-(2,6-dichlorophenyl) imidazoline, is an imidazoline derivative that selectively targets central α2-adrenergic receptors. A range of analytical techniques has been established for the quantification of clonidine hydrochloride, including spectrophotometric methods[10], HPLC[11], LC–MS[12], colourimetric assays[13], and capillary electrophoresis.[14] Viloxazine, chemically known as (±)-2-[(2-ethoxyphenoxy)methyl]morpholine ($C_{13}H_{19}NO_3$; MW: 237.3 g/mol), was approved by the U.S. FDA in April 2021 for the management of ADHD. Pharmacologically, Viloxazine primarily acts as a selective norepinephrine reuptake inhibitor (NRI), and additionally, it acts as a partial agonist at the serotonin 5-$HT_2$ C receptor and an antagonist at the 5-$HT_2$B receptor. Several analytical methods, including high-performance liquid chromatography (HPLC), have been reported for its quantification[15] and spectroscopic techniques.[16] Despite many techniques having been proposed for the analysis of these medications, there has not been enough investigation of a technique that can simultaneously analyse the ADHD medicines with sustainability and environmental consciousness. In addition, most of the proposed techniques have mainly focused on the analytical efficiency of the technique without taking into account other parameters such as the sustainability of the method, applicability, safety of solvents used, simplicity of the technique, and the analytical efficiency of the process. In recent years, the concept of sustainable analytical chemistry has expanded to involve the incorporation of environmental aspects, analytical aspects, and applicability at once in method development. White Analytical Chemistry (WAC), an advancement of Green Analytical Chemistry (GAC), integrates green, analytical, and practical considerations to develop comprehensively sustainable methods. The latest investigations have found that traditional assessment parameters for greenness, like Analytical Eco-Scale, GAPI, and AGREE, are based solely on environmental aspects, while modern assessment strategies like BAGI and WAC have incorporated analytical, functional, economic, and practical aspects along with environmental concerns.[17-18] This current study is focused on the creation and verification of an eco-friendly method for identifying ADHD treatment medications, including a thorough examination of the environmental and practical performance of the methodology through modern tools for assessing greenness. This research has helped contribute towards achieving one of the Sustainable Development Goals of the United Nations, SDG3: Good Health & Well-Being, and SDG 12: Responsible Consumption and Production through environmentally responsible analytical practices through the development of an efficient and sustainable pharmaceutical analytical approach. To summarise the main features of these evaluation systems, Table-1provides a comparison of greenness, blueness, and whiteness assessment tools used for analytical method evaluation.

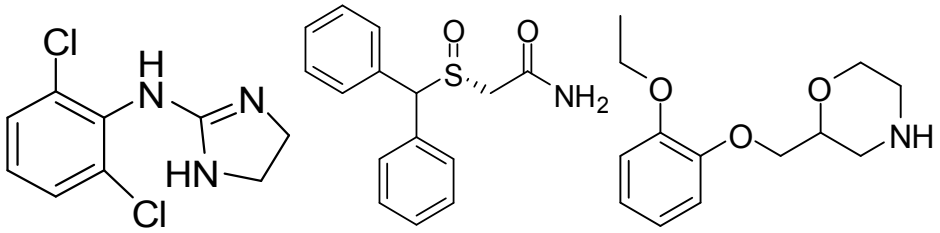



Fig.-1: Structure of Clonidine, Armodafinil, and Viloxazine

Table-1: Comparison of Greenness, Blueness, and Whiteness Evaluation Tools for Analytical Methods

| S. No. | Tool | Scope / Focus | Evaluation Criteria | Output Format | Strengths |
|---|---|---|---|---|---|
| 1 | AGREEprep[19] | Sample preparation technique | Solvent/reagent use, waste, energy, sample size, material selection | Numerical score (0–1) | Specifically designed for sample preparation, quantitative assessment |
| 2 | AGREE[20] | The entire analytical method | 12 principles of Green Analytical Chemistry (GAC) | Circular diagram + score (0–1) | Holistic greenness evaluation: quick comparison |
| 3 | GAPI[21] | Entire analytical workflow (sample to | Sample collection, preparation, reagents, instrumentation, | Pictogram (green/yellow/red) | Qualitative and semi-quantitative; highlights critical stages |

| | | | | | |
|---|---|---|---|---|---|
| | | reporting) | waste | | |
| 4 | GWAPE[22] | Sustainability of method and logistics | Reagents, instruments, transport, storage, hazards, waste, throughput, calibration | Component scores + total score | Broad sustainability assessment, including safety and logistics |
| 5 | BAGI[23] | Feasibility & practicality (Blue Analytical Chemistry) | 10 criteria: analysis type, number of analytes, throughput, reagents, instrumentation, preconcentration, automation, sample prep, sample amount | Composite score | Complements green metrics with emphasis on practicality |
| 6 | WAC[24] | Overall method performance | Integration of 12 principles combining green, red, and blue aspects | Composite 'whiteness' score | Balanced evaluation of sustainability, practicality, and efficiency |

A review of the available literature indicates that green analysis for simultaneous analysis has not been reported yet. of Armodafinil, Clonidine, and Viloxazine Hydrochloride. This gap highlights the need for an environmentally sustainable approach that can ensure that the study aimed to develop a green and sustainable RP-HPLC method for the simultaneous quantification of these compounds in a single run, validated in accordance with ICH Q2(R1) guidelines to confirm its accuracy, precision, robustness, and overall reliability.

## EXPERIMENITAL

### Solutions Preparation

Stock solutions of armodafinil, clonidine, and viloxazine (5 mg each) were prepared in 50 mL volumetric flasks using Milli-Q water and sonicated briefly to ensure complete dissolution. A 5-ppm working solution was obtained by transferring 2.5 mL of the stock solution into a 50 mL volumetric flask and diluting to volume with Milli-Q water, followed by sonication at 30 °C for 5 minutes to ensure uniformity.

### Method Optimization

Separation of armodafinil, clonidine, and viloxazine was optimised by evaluating various mobile phase compositions, solvent systems, and flow rates. Chromatographic parameters, including retention factor, peak symmetry, and theoretical plate number, were assessed under different experimental conditions, as presentedin Table-2.

Table-2: Chromatographic Performance under Various Mobile Phase Conditions

| Mobile Phase Composition and Ratio | Flow rate (mL/Min.) | λ (nm) | Results | Symmetry | Theoretical Plates |
|---|---|---|---|---|---|
| Water: MeOH (70: 30) | 1 | 230 | Clonidine and Viloxazine eluted at 10.1 min and 25.0 min, respectively; Armodafinil did not elute under these conditions. | 1.67,2.27 | 2849 and 3143 |
| Water: MeOH (50: 50) | 1 | 230 | Clonidine, Viloxazine, and Armodafinil eluted at 7.0 min, 16.3 min, and 28.0 min, respectively. | 1.62, 2.11, and 2.3 | 2896, 3180 and 2973 |

| | | | | | |
|---|---|---|---|---|---|
| Water: MeOH (20: 80) | 1 | 230 | Clonidine, Viloxazine, and Armodafinil co-eluted, resulting in merged peaks. | - | - |
| Water:MeOH (20: 80) | 0.7 | 230 | No significant improvement was observed; Clonidine and Viloxazine peaks remained merged | - | - |
| Water: MeOH: IPA (20: 75: 5) | 1 | 230 | Peak tailing and Broad Peak observed | 1.75, 2.19, and 2.47 | 2745, 3439, 2841 |
| Water: ACN (75: 25) | 1 | 230 | Clonidine was well separated, whereas Viloxazine and Armodafinil co-eluted | - | - |

These findings indicate the need for additional optimisation, such as the implementation of gradient elution with refined solvent ratios, to achieve optimal resolution of all analytes.

**Instrumentation and Analytical Conditions of HPLC**

Method development and validation were performed using a Waters 2695 Separation Module equipped with a Waters 2996 photodiode array detector at a detection wavelength of 230 nm. Chromatographic separation of viloxazine, armodafinil, and clonidine was achieved on a Sunfire C18 column (4.6 mm × 150 mm, 3.5 µm particle size). Gradient elution was employed using methanol and water as the mobile phase, with the initial composition being was 30:70 (methanol: water). This was then changed to 75:25 (methanol: water) after 7 minutes. Afterwards, the change from 75:25 (methanol: water) was increased to 97:3 (methanol: water) after 2 minutes.

**System Suitability**

System suitability was evaluated by analysing solutions at 100 µg/mL, with parameters including retention time, peak tailing, theoretical plates, and %RSD assessed to confirm chromatographic system performance.

**Specificity**

Specificity, defined as the method's ability to differentiate analytes from excipient interference, was evaluated by analysing five solutions of identical concentration, with %RSD values of peak areas calculated to confirm method specificity.

**Linearity**

Seven calibration standards of concentrations 40, 60, 80, 100, 120, 140, and 160 % were prepared in duplicate. The peak area of each solution was measured, and a standard calibration curve was plotted. Linearity was evaluated by linear regression analysis of peak area versus concentration.

**Limit of Detection (LoD) and Limit of Quantitation (LoQ)**

LOD and LOQ were found using ICH guidelines based on the linear relationship, with LOD taken as a signal-to-noise ratio of 3:1 and LOQ as a signal-to-noise ratio of 10:1.

$$LoD = 3.3\sigma/S$$

$$LoQ = 10\sigma/S$$

Where σ = the standard deviation of the response, S = the slope of the calibration curve

**Accuracy**

Accuracy was established by calculating the per cent recovery at 50%, 100%, and 150% of the required concentration through the preparation of samples at 50 µg/mL, 100 µg/mL, and 150 µg/mL concentrations.

**Precision**

Precision was tested by making six sets of three replicate solutions at 100 µg/mL, with %RSD and % recovery calculated for each set. Repeatability (intra-day precision) was assessed through sample analysis

within a single day, and intermediate precision (inter-day) was measured by repeating the assay on several days under identical analytical conditions.

**Robustness**

Robustness was evaluated using 100 µg/mL solutions, subjecting the method to deliberate variations such as column oven temperature changes of ±2 °C. The % recovery was calculated to assess the method's resilience to such variations.

**Solution Stability**

The solution stability study provides data on the stability of the drug test solution under room temperature conditions. The % recovery was calculated for the test solution.

## RESULTS AND DISCUSSION

**System Suitability & Specificity**

System suitability was evaluated using 100 µg/mL solutions. The per cent RSD of peak areas was less than 2%, the resolution between neighbouring peaks exceeded 2, and the tailing factor stayed less than 1.5. Theoretical plates exceeded 5000, indicating sufficient chromatographic system suitability, as illustrated below in Fig.-2 and Table-3. No interference from excipient peaks was detected at the respective retention times to viloxazine, armodafinil, and clonidine in the prepared samples. Furthermore, the analytes showed no interference from excipients, with %RSD values within the acceptance limit of less than 2.0%, demonstrating the method's specificity.

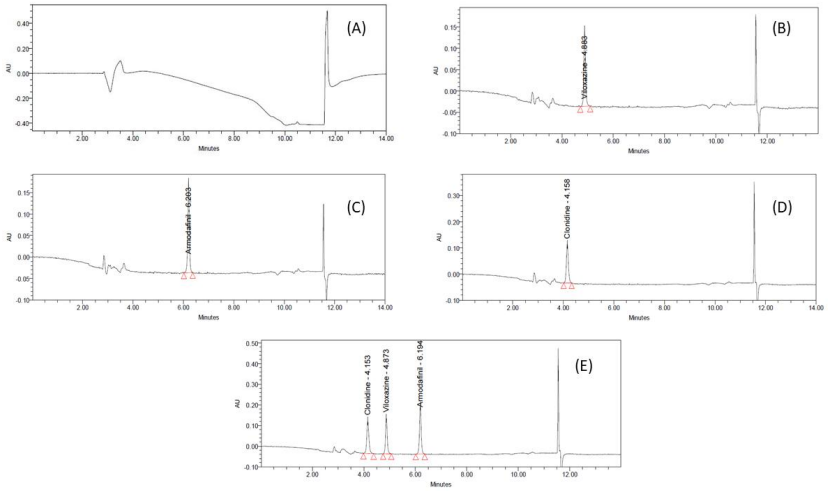



Fig.-2: HPLC Chromatogram of (A)Blank, (B) Viloxazine, (C) Armodafinil, (D) Clonidine, (E) Mixture of Clonidine, Viloxazine, and Armodafinil

Table-3: System Suitability Parameters

| Name | RT (Min.) | Mean Area | RSD(%) | Asymmetry 10% | Plates PM USP | Tailing |
|---|---|---|---|---|---|---|
| A | 6.18 | 1105771 | 1.32 | 0.96 | 6566 | 0.99 |
| C | 4.15 | 942710 | 1.99 | 0.95 | 6896 | 0.98 |
| V | 4.86 | 838252 | 1.64 | 0.94 | 7456 | 0.97 |

**Linearity**

A, C, and V with 40, 60, 80, 100, 120, 140, and 160 % show linearity equations of y = 11776x - 1818.5, y = 9905.1x – 47691, and y = 8995.7x – 15357. The $R^2$ was 0.9963, 0.9957, and 0.9948 simultaneously (Table-4) (Fig.-3).

Table-4: Linearity Study of Armodafinil, Clonidine, and Viloxazine

| Concentration | Set | Area | | | Mean | | |
|---|---|---|---|---|---|---|---|
| (%) | | Armodafinil | Clonidine | Viloxazine | Armodafinil | Clonidine | Viloxazine |
| 40 | 1 | 456117 | 337998 | 342110 | 467812 | 341412 | 330541 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2 | 484185 | 332877 | 327236 | | | |
| | 3 | 463134 | 353361 | 322278 | | | |
| 60 | 1 | 690867 | 546432 | 537042 | 697845 | 527954 | 550812 |
| | 2 | 680399 | 522674 | 570090 | | | |
| | 3 | 722270 | 514755 | 545304 | | | |
| 80 | 1 | 939620 | 718470 | 684172 | 907845 | 736892 | 691082 |
| | 2 | 898767 | 762683 | 673805 | | | |
| | 3 | 885149 | 729523 | 715270 | | | |
| 100 | 1 | 1169810 | 957366 | 932900 | 1199805 | 967036 | 901353 |
| | 2 | 1241798 | 942860 | 892339 | | | |
| | 3 | 1187807 | 1000882 | 878819 | | | |
| 120 | 1 | 1453163 | 1232109 | 996083 | 1467841 | 1190443 | 1021624 |
| | 2 | 1431145 | 1178539 | 1057380 | | | |
| | 3 | 1519215 | 1160682 | 1011407 | | | |
| 140 | 1 | 1692007 | 1301181 | 1269075 | 1634789 | 1334545 | 1281894 |
| | 2 | 1618441 | 1381254 | 1249847 | | | |
| | 3 | 1593919 | 1321200 | 1326760 | | | |
| 160 | 1 | 1808397 | 1486438 | 1461591 | 1854766 | 1501453 | 1412165 |
| | 2 | 1919683 | 1463917 | 1398043 | | | |
| | 3 | 1836218 | 1554004 | 1376861 | | | |

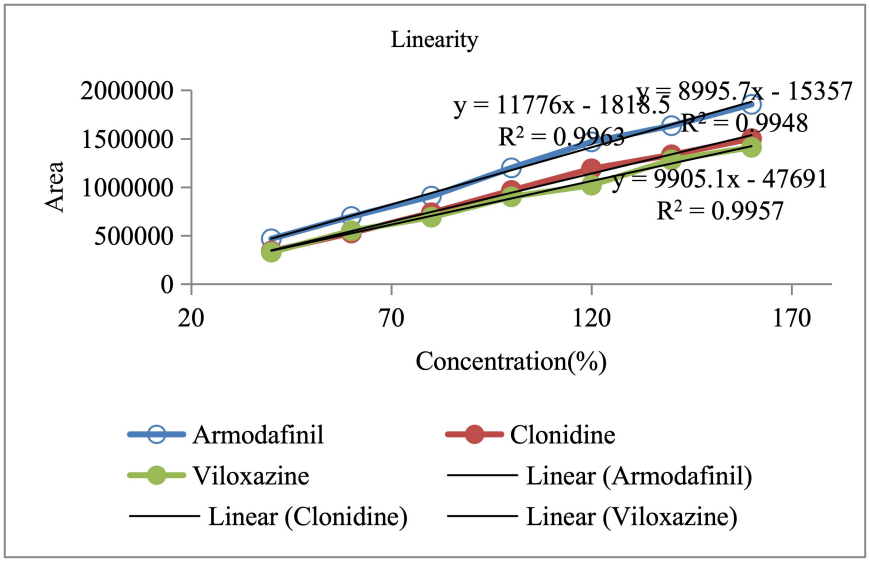



Fig.-3: Linearity Curve of Armodafinil, Clonidine, and Viloxazine

The X-axis represents concentration (%) and the Y-axis represents peak area (absorbance units), where $R^2$ denotes the correlation coefficient and Y = mX + C represents the linear regression equation.

**Accuracy**

The % recovery for Clonidine, Viloxazine, and Armodafinil was used to check the accuracy of the proposed method. 50, 100, and 150 give % recovery between 98 to 100. Values were suitable according to the ICH Q2(R1) guideline (Table-5).

Table-5: Accuracy Study- Sample Preparation and Recovery Assessment Data

| API | Level | Mean Area | RSD | (%) Recovery | % Mean recovery |
|---|---|---|---|---|---|
| A | 50% | 593294 | 1.88 | 98.12 | 99.17 |
| C | | 491192 | 1.45 | 99.29 | |
| V | | 468176 | 1.87 | 100.12 | |
| A | 100% | 120260 | 0.82 | 99.45 | 98.57 |
| C | | 970227 | 0.13 | 98.06 | |
| V | | 918492 | 1.83 | 98.21 | |

| | | | | | |
|---|---|---|---|---|---|
| A | 150% | 1784531 | 1.07 | 98.38 | 98.81 |
| C | | 1478523 | 0.4 | 99.62 | |
| V | | 1381093 | 0.01 | 98.45 | |

**LoD and LoQ**

The LOD values for A, C, and V were 0.0890, 0.043, and 0.063 µg/mL, respectively, while the corresponding LOQ values were 0.276, 0.129, and 0.190 µg/mL. These were determined using the standard deviation of the response and the slope of the calibration curve, in accordance with ICH Q2(R1) guidelines, with S/N ratios below 3.3 for LOD and below 10 for LOQ. All obtained values met the acceptable criteria, confirming method compliance, as presented below in Table-6.

Table-6: LoD and LoQ Data for Armodafinil, Clonidine, and Viloxazine

| LoD | | |
|---|---|---|
| Armodafinil (µg/mL) | Clonidine (µg/mL) | Viloxazine (µg/mL) |
| 0.089 | 0.04 | 0.06 |
| LoQ | | |
| Armodafinil (µg/mL) | Clonidine (µg/mL) | Viloxazine (µg/mL) |
| 0.27 | 0.12 | 0.19 |

**Precision**

Precision was assessed by injecting six replicates of the same concentration solution and calculating the mean and percentage RSD for each substance. Both intraday (repeatability) and interday (intermediate precision) studies demonstrated %RSD values below 2%, indicating acceptable precision of the method according to ICH Q2(R1) guidelines (Table-7).

Table-7: Precession Study Data of Armodafinil, Clonidine, and Viloxazine

| | Intraday Precision | | | Interday Precision | | |
|---|---|---|---|---|---|---|
| Name | A | C | V | A | C | V |
| Average | 1095464 | 910192.2 | 847014 | 1089987 | 909693 | 842779 |
| % RSD | 0.81 | 0.96 | 0.89 | 0.88 | 0.99 | 0.95 |

**Robustness**

The method did not exhibit significant variation upon repeated analysis. The working standard solution was injected five times consecutively, and the %RSD was calculated across all injections to confirm method precision. The acceptance criteria were set as %RSD ≤ 2 and resolution between two adjacent peaks ≥ 2, both of which were satisfactorily met, confirming the system's suitability (Table-8).

Table-8: Robustness Study Evaluation Data

| API | 28◦ C | | 32◦ C | |
|---|---|---|---|---|
| | Area Mean | RSD (%) | Area Mean | RSD (%) |
| Armodafinil | 1209282 | 1.32 | 1356322 | 1.44 |
| Clonidine | 989418 | 1.99 | 100418 | 1.96 |
| Viloxazine | 932514 | 1.64 | 932514 | 1.82 |

**Solution Stability**

The stability of the solution was assessed every 12 hours, with the findings compared to those from freshly prepared samples. The percentage recovery was determined in comparison to the standard. At 12 hours, Armodafinil (A) showed a recovery of 95.16%, Clonidine (C) 95.66%, and Viloxazine (V) 98.33%. This point was considered the onset of degradation, indicating reduced solution stability. Beyond 12 hours (i.e., at 24, 36, and 48 hours), all three drugs exhibited progressively lower percentage recovery, confirming decreased stability over time (Table-9).

Table-9: Solution Stability Study

| Time | A | C | V |
|---|---|---|---|
| 12 Hours | | | |
| Mean | 95.16 | 95.66 | 98.33 |
| % Recovery | 95.16 | 95.66 | 98.33 |

| | | | |
|---|---|---|---|
| 24 Hours | | | |
| Mean | 92.16 | 92 | 94.66 |
| % Recovery | 92.16 | 92 | 94.66 |
| 36 Hours | | | |
| Mean | 88.5 | 88.33 | 91.16 |
| % Recovery | 88.5 | 88.33 | 91.16 |
| 48 Hours | | | |
| Mean | 85.16 | 85 | 87.83 |
| % Recovery | 85.16 | 85 | 87.83 |

**Greenness of the Method**

**AGREEprep**

An important parameter in method development is sample preparation. The AGREEprep evaluation provides a score that considers sample preparation, energy consumption, and waste management. In this study, the score decreased primarily due to the relatively high solvent consumption during standard solution preparation, while all other criteria achieved values close to 1. The overall AGREEprep score obtained was 0.66 out of 1, highlighting its eco-friendly analytical characteristics (Fig.-4A).

**AGREE**

The relatively high solvent consumption during sample preparation contributed to a decrease in the AGREEprep score. In contrast, no excessive solvent use was observed during sample analysis or waste management, which resulted in higher scores for these parameters. Moreover, the use of methanol and water, both considered green solvents, further supports the method's sustainability. The simultaneous quantification of multiple analytes also contributed positively to the method's greenness. Consequently, the overall AGREEprep score was 0.67, which is considered satisfactory (Fig.-4B).

**GAPI**

The GAPI tool assesses the analytical approach using a colour-coded system to reflect environmental effect: red for high risk, yellow for moderate effect, and green for eco-friendly methods. According to the GAPI pictogram, the developed method showed a predominance of green zones, confirming its eco-friendly nature and overall greenness towards the environment (Fig.-4C).

**GWAPE**

The GWAPE tool employs a scoring scale from 1 to 5, where higher scores indicate greater greenness of the method. The proposed 15-minute method, utilising methanol and water as solvents and allowing simultaneous quantification of multiple analytes, achieved a score of 3.7. This value reflects satisfactory compliance with green analytical chemistry principles and demonstrates the eco-friendly nature of the method (Fig.-4D).

**WAC**

The White Analytical Chemistry (WAC) evaluation considers three main aspects: analytical performance, green chemistry, and practical applicability.

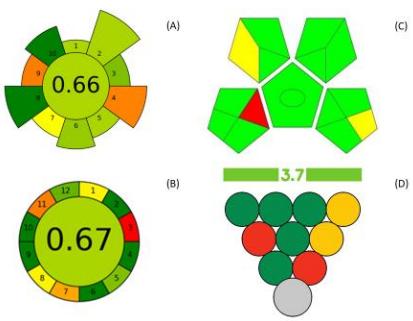



Fig.-4: Score of AGREEprep, AGREE, GAPI, and GWAPE

For the proposed method, the analytical performance score was 93.8, the green chemistry score was 97.5, and the practical applicability score was 97.5. Combining these values, the overall whiteness index was 96.3, highlighting the excellent balance of performance, sustainability, and practicality achieved by the method (Fig.-5).

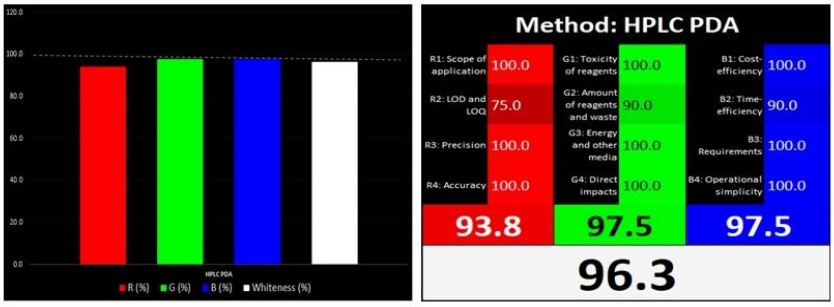



Fig.-5: Score of WAC

**BAGI**

BAGI assesses the applicability of the method using tested assays, assigning a score, a colour, and a picture. This metric's score range runs from 25 to 100. The calculated score for the proposed method from BAGI is 82.5, indicating good practicality of the proposed method (Fig.-6).


Fig.-6: Score of BAGI

**Comparison of the Proposed Method with Existing Reported Analytical Methods**

A comparative evaluation of previously reported analytical methods for armodafinil, clonidine, and viloxazine indicated that their chromatographic performance was largely shaped by choices such as buffer use, solvent strength, and pH adjustments, which supported adequate separation but led to high reagent consumption and increased non-green waste. Green assessment tools, including AGREEprep, AGREE, GAPI, GWAPE, WAC, and BAGI, consistently reflected low sustainability due to buffer-heavy mobile phases and extensive use of organic solvents. In the present work, the chromatographic approach was redesigned with environmental performance as a key factor, eliminating additives and buffers to lower chemical load while maintaining essential parameters such as resolution, peak shape, and analysis time. Re-evaluation using the same green tools showed notable improvements across all indices, demonstrating that optimising solvent composition and simplifying chromatographic conditions can enhance both analytical effectiveness and environmental compatibility, resulting in a greener and more efficient multi-analyte method.

**Armodafinil**[25]

The comparative evaluation shows that the proposed RP-HPLC method provides clear advantages over the armodafinil method in terms of greenness, robustness, and overall analytical performance. Its higher eco-scale, blueness, and whiteness scores indicate lower environmental impact, greater methodological simplicity, and improved balance between accuracy and precision. In contrast, the armodafinil method exhibits more red and yellow indicators, reflecting higher reagent toxicity, greater waste generation, and reduced operational efficiency. The GAPI profile further supports the results, highlighting the superior sustainability of the proposed method and establishing it as a more reliable approach and eco-friendly choice for routine pharmaceutical analysis (Fig.-7).

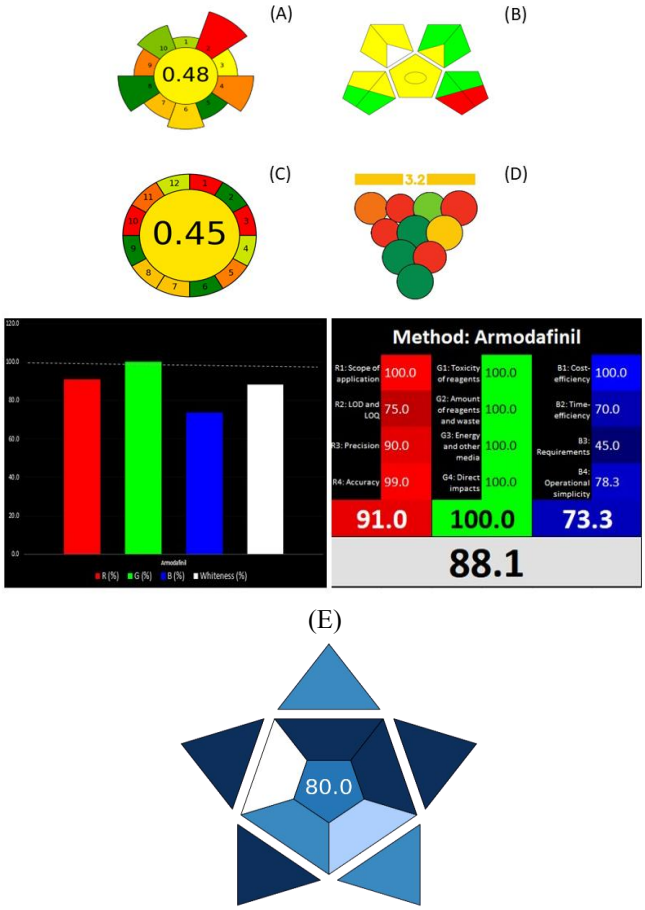



Fig.-7: Greenness and Sustainability Scores of the Armodafinil Method Evaluated using AGREEprep, AGREE, GAPI, GWAPE, WAC, and BAGI Tools

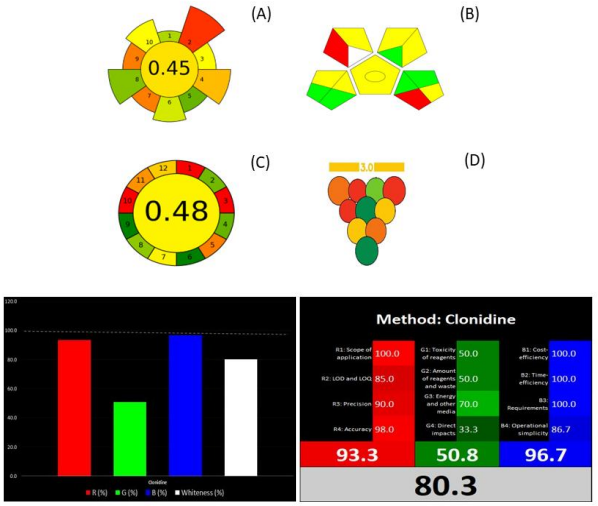
**Clonidine**[26]

A comparison of the suggested method and existing clonidine approaches revealed that the recommended methodology has several advantages, which are outlined below. provides a substantially greener analytical profile while maintaining consistent performance. Its greenness indicators show lower reagent toxicity and less waste generation, and fewer red-zone components, reflecting better alignment with sustainable analytical practices. In terms of operational efficiency, the Clonidine method performs exceptionally well, especially in cost-efficiency and time-efficiency. However, the proposed method remains operationally simple and provides a balanced overall performance, as supported by its comparable blueness and whiteness scores. When these factors are considered together, the proposed method emerges as a more environmentally responsible alternative that still meets analytical and practical expectations. This combination of reduced environmental impact and strong analytical capability makes the proposed method a suitable and eco-friendly solution for routine laboratory applications(Fig.-8).

**Viloxazine**[27]

The comparison indicates that the Proposed Method demonstrates a more balanced and sustainable analytical profile than the Viloxazine method. While the Viloxazine procedure performs well in accuracy and scope, its greenness score is significantly reduced due to high reagent toxicity, greater solvent use, and higher energy demands.

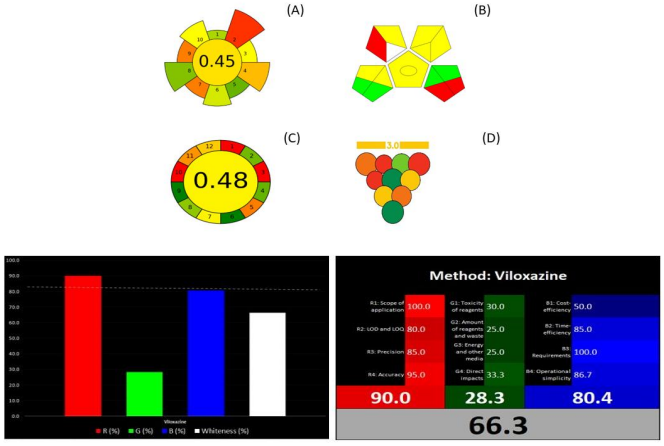
The Proposed Method, by contrast, minimises these environmental burdens and achieves stronger greenness and whiteness values. Its improved operational efficiency further strengthens its overall performance. Thus, the Proposed Method offers a more environmentally responsible yet analytically reliable alternative (Fig.-9).



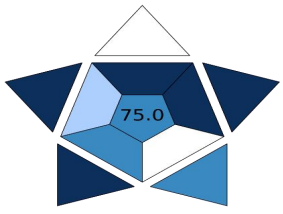

(E)


(F)

Fig.-8: Greenness and Sustainability Scores of the Clonidine Method Evaluated using AGREEprep, AGREE, GAPI, GWAPE, WAC, and BAGI Tools




(E)




(F)

Fig.-9: Greenness and Sustainability Scores of the Viloxazine Method Evaluated using AGREEprep, AGREE, GAPI, GWAPE, WAC, and BAGI Tools

## CONCLUSION

A novel, eco-friendly RP-HPLC method was successfully developed and validated for the combined analysis of armodafinil, clonidine, and viloxazine in a single chromatographic run. The method showed good separation, strong analytical performance, and met ICH Q2(R1) validation requirements. These requirements included specificity, accuracy, precision, linearity, robustness, sensitivity, and solution stability. A thorough sustainability assessment using AGREEprep, AGREE, GAPI, GWAPE, WAC, and BAGI confirmed reduced solvent use, less waste generation, simpler analytical processes, and better overall sustainability. Traditional greenness evaluation methods, such as the Analytical Eco-Scale, GAPI, and AGREE, generally focus on environmental concerns; WAC and BAGI allowed for a wider evaluation of analytical practicality and functionality. A comparative analysis with methods reported earlier confirmed the analytical and environmental advantages of the new method. Thus, the proposed RP-HPLC method provides a simple, sensitive, reproducible, and sustainable option for routine pharmaceutical quality control. Additionally, this study supports SDG-3: Good Health and Well-Being by encouraging reliable and safer pharmaceutical analysis practices and SDG-12: Responsible Consumption and Production through reduced solvent use, less chemical waste, and environmentally friendly analytical methods. Future studies could broaden the method's use to biological samples, stability studies, and industrial pharmaceutical analysis.

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## CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

The present work is related to *SDG-12: Responsible Consumption and Production.* All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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