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GREEN ANALYTICAL CHEMISTRY IN PHARMACEUTICAL ANALYSIS: A SUSTAINABL APPROACH FOR QUALITY CONTROL (A REVIEW)'

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ABSTRACT

Green Analytical Chemistry (GAC) has emerged as a modern strategy to reduce the environmental footprint of pharmaceutical analytical procedures while maintaining analytical quality and regulatory compliance. Conventional pharmaceutical analysis relies heavily on toxic organic solvents, hazardous reagents, energy-intensive instrumentation, and generates considerable laboratory waste. Increasing awareness of sustainable development has encouraged the adoption of environmentally friendly analytical methodologies that minimize solvent consumption, reduce hazardous waste, improve analyst safety, and lower operational costs. Green Analytical Chemistry integrates the principles of green chemistry into analytical science through the use of safer solvents, miniaturized sample preparation techniques, energy-efficient instruments, and sustainable analytical practices. Recent advances in chromatographic techniques, including Ultra-High Performance Liquid Chromatography (UHPLC), High-Performance Thin Layer Chromatography (HPTLC), Capillary Electrophoresis (CE), and spectroscopic methods have significantly enhanced the sustainability of pharmaceutical quality control. Furthermore, several greenness assessment tools, including the National Environmental Methods Index (NEMI), Green Analytical Procedure Index (GAPI), Analytical Eco-Scale, Analytical GREEnness (AGREE), AGREEprep, Analytical Method Greenness Score (AMGS), and White Analytical Chemistry (WAC), have been developed to evaluate the environmental performance of analytical procedures systematically. This review discusses the fundamental concepts of Green Analytical Chemistry, the twelve principles governing sustainable analytical practices, green sample preparation methods, eco-friendly solvents, recent advances in analytical instrumentation, applications in pharmaceutical quality control, and current greenness assessment tools. The review also highlights regulatory perspectives, existing challenges, and future opportunities for implementing sustainable analytical methodologies in pharmaceutical industries. Adoption of Green Analytical Chemistry not only contributes to environmental protection but also improves laboratory safety, analytical efficiency, and economic sustainability.

KEYWORDS: Green Analytical Chemistry, Pharmaceutical Analysis, Sustainable Analytical Methods, UHPLC, Green Solvents, GAPI, AGREE, Eco-Scale, Pharmaceutical Quality Control.

INTRODUCTION[1,9]

Analytical chemistry plays a pivotal role throughout pharmaceutical research, development, manufacturing, quality assurance, stability testing, bioanalysis, and regulatory compliance. Reliable analytical techniques ensure the identity, purity, potency, and safety of pharmaceutical products before they reach patients. However, conventional analytical methodologies have traditionally relied on large volumes of toxic organic solvents such as acetonitrile, methanol, chloroform, tetrahydrofuran, and dichloromethane. These solvents contribute significantly to laboratory waste generation, occupational hazards, environmental contamination, and increased operational costs.

Over the past three decades, increasing environmental concerns and stricter sustainability goals have transformed the philosophy of analytical method development. Inspired by the principles of Green Chemistry introduced by Anastas and Warner in 1998, researchers recognized the necessity of extending environmental responsibility to analytical laboratories. This realization led to the development of Green Analytical Chemistry (GAC), which focuses on minimizing the ecological footprint of analytical procedures without compromising analytical quality.

Unlike traditional analytical optimization, which primarily emphasizes sensitivity, selectivity, precision, and accuracy, Green Analytical Chemistry introduces environmental sustainability as an additional performance criterion. Consequently, analytical methods are now evaluated not only for analytical excellence but also for solvent toxicity, waste generation, energy efficiency, operator safety, and overall sustainability.

The pharmaceutical industry has become one of the leading adopters of green analytical methodologies because analytical laboratories operate continuously and consume substantial quantities of chemicals each year. High-performance liquid chromatography (HPLC), one of the most widely employed pharmaceutical analytical techniques, typically consumes several liters of organic solvents per instrument each week. Replacing hazardous solvents with environmentally benign alternatives or reducing solvent consumption through ultra-high-performance liquid chromatography (UHPLC), micro-LC, or supercritical fluid chromatography (SFC) substantially decreases both environmental impact and operational expenses.

Green Analytical Chemistry extends beyond solvent replacement. It encompasses the entire analytical workflow, including sample collection, sample preparation, extraction, separation, detection, data processing, waste management, and instrument operation. Miniaturized sample preparation techniques such as solid-phase microextraction (SPME), dispersive liquid-liquid microextraction (DLLME), stir-bar sportive extraction (SBSE), and micro-solid phase extraction (µ-SPE) substantially reduce reagent consumption while improving extraction efficiency. Similarly, advances in portable analytical devices, microfluidics, and lab-on-a-chip systems enable rapid analysis using microliter-scale reagent volumes.

The concept of analytical sustainability has further evolved into White Analytical Chemistry (WAC), which integrates three complementary dimensions: analytical quality (red), environmental sustainability (green), and practical efficiency (blue). This holistic framework recognizes that environmentally friendly methods must also satisfy regulatory expectations and practical laboratory requirements.

Several assessment tools have been developed to quantify the greenness of analytical procedures objectively. The Analytical Eco-Scale evaluates analytical methods using penalty points assigned for hazardous reagents and waste generation. The Green Analytical Procedure Index (GAPI) provides a comprehensive pictographic representation of the environmental impact across the entire analytical workflow. More recently, the AGREE metric introduced a software-based scoring system based on the twelve principles of Green Analytical Chemistry, enabling standardized comparison between analytical methods. Newer tools such as

AGREEprep, ComplexGAPI, and RGB12 further extend sustainability assessment by incorporating sample preparation, analytical performance, and practical applicability.

Regulatory agencies have increasingly acknowledged the importance of environmentally sustainable analytical practices. Although current international guidelines, including ICH Q2(R2), USP <1225>, European Pharmacopoeia, and FDA analytical validation guidance, primarily emphasize analytical performance, there is growing interest in incorporating sustainability considerations into analytical method development through the Analytical Quality by Design (AQbD) framework. Green analytical methodologies not only support environmental stewardship but also improve laboratory efficiency, reduce operational costs, and facilitate compliance with corporate sustainability initiatives.

The rapid integration of artificial intelligence (AI), machine learning, chemometrics, digital laboratories, robotic automation, and predictive modelling is expected to further revolutionize Green Analytical Chemistry. AI-assisted optimization can identify environmentally preferable analytical conditions with minimal experimental trials, thereby reducing solvent consumption, energy usage, and method development time. These technologies are anticipated to play an increasingly important role in future pharmaceutical quality control laboratories.

Overall, Green Analytical Chemistry represents a paradigm shift in pharmaceutical analysis by integrating analytical excellence with environmental responsibility and sustainable laboratory practices. Continued technological innovation, regulatory support, and interdisciplinary collaboration will further strengthen the adoption of green analytical methodologies across pharmaceutical research and quality assurance.

2. Evolution of Green Analytical Chemistry[6,16]

2.1 Historical Development

The increasing awareness of environmental pollution and the need for sustainable industrial practices led to the emergence of Green Chemistry during the early 1990s. Before this period, analytical method development primarily focused on improving sensitivity, selectivity, precision, and accuracy, with limited consideration of environmental consequences. Analytical laboratories routinely consumed large volumes of hazardous organic solvents and generated significant quantities of chemical waste, resulting in increased disposal costs and environmental risks.

A major milestone occurred in 1998, when Paul T. Anastas and John C. Warner introduced the concept of Green Chemistry through their landmark publication Green Chemistry: Theory and Practice. Their work established the 12 Principles of Green Chemistry, which encouraged pollution prevention rather than waste treatment and promoted safer chemicals and sustainable industrial processes. Although these principles were originally intended for chemical synthesis, they soon inspired researchers to adapt similar concepts for analytical chemistry.

During the early 2000s, scientists recognized that analytical laboratories also contribute substantially to chemical waste generation and occupational exposure to hazardous reagents. This realization led to the development of Green Analytical Chemistry (GAC), which extends the philosophy of Green Chemistry to analytical science by minimizing the environmental impact of analytical procedures while maintaining analytical reliability and regulatory compliance.

The field experienced rapid growth with advances in miniaturized analytical techniques, solvent-free extraction methods, capillary electrophoresis, supercritical fluid chromatography, and portable analytical devices. Researchers increasingly focused on reducing solvent consumption, decreasing sample size, improving energy efficiency, and replacing toxic reagents with environmentally benign alternatives.

The concept of sustainability continued to evolve beyond environmental protection. Researchers recognized that analytical methods should simultaneously satisfy three essential criteria.

- Excellent analytical performance
- Environmental sustainability
- Practical applicability

This holistic approach resulted in the development of *White Analytical Chemistry (WAC)*, which integrates analytical quality, ecological responsibility, and operational efficiency into a unified framework. Today, GAC is considered an essential component of modern pharmaceutical quality control, analytical method development, and regulatory science.

Table 1: Historical Evolution of Green Analytical Chemistry.

Sr. No.	Year	Milestone	Significance
1.	1991	Green Chemistry concept introduced	Foundation of sustainable
2.	1998	Anastas and Warner proposed 12 Principles of Green Chemistry	Basis for sustainable analytical methods
3.	Early 2000s	Green Analytical Chemistry introduced	Environmental focus in analytical science
4.	2010	Analytical Eco-Scale widely adopted	First quantitative greenness metric
5.	2011	GAPI introduced	Whole analytical process assessment
6.	2020	AGREE metric developed	Standardized greenness scoring
7.	2022	AGREEprep introduced	Sample preparation evaluation
8.	2023–2025	AI-assisted green analytical optimization	Future direction of sustainable laboratories

2.2 Background

The pharmaceutical industry depends heavily on analytical chemistry to ensure the identity, purity, potency, safety, and quality of drug substances and finished pharmaceutical products. Throughout drug discovery, formulation development, manufacturing, stability testing, and post-marketing surveillance, analytical methods play a central role in maintaining compliance with regulatory requirements and protecting public health.

Conventional analytical techniques such as High-Performance Liquid Chromatography (HPLC), Gas Chromatography (GC), and other chromatographic methods are widely accepted because of their accuracy and reliability. However, these methods frequently require large volumes of organic solvents such as acetonitrile, methanol, tetrahydrofuran, and chloroform. These solvents are often toxic, flammable, expensive to dispose of, and contribute significantly to laboratory waste and environmental pollution.

Growing awareness of environmental sustainability has encouraged researchers to redesign analytical methods that maintain analytical performance while reducing their ecological footprint. This need has led to the development of *Green Analytical Chemistry (GAC)*, an emerging discipline that applies the concepts of green chemistry to analytical science. The goal of GAC is to reduce hazardous chemicals, minimize waste generation, improve energy efficiency, and enhance laboratory safety without compromising analytical quality. The increasing adoption of GAC aligns with global sustainability initiatives and supports environmentally responsible pharmaceutical manufacturing.

2.3 Evolution of Green Analytical Chemistry

Green chemistry was formally introduced in the early 1990s by Paul Anastas and John Warner, who proposed the Twelve Principles of Green Chemistry. These principles emphasize pollution prevention, safer chemical synthesis, waste reduction, energy conservation, and the use of renewable resources. Analytical scientists subsequently adapted these principles to analytical laboratories, giving rise to Green Analytical Chemistry.

Initially, green analytical practices focused primarily on reducing solvent consumption. Over time, advances in analytical instrumentation, miniaturized separation techniques, automation, and environmentally benign solvents expanded the scope of GAC. Modern green analytical methods now integrate sustainable sample preparation, solvent replacement, energy-efficient instrumentation, and quantitative greenness assessment tools to evaluate environmental performance.

Today, Green Analytical Chemistry has become an important component of sustainable pharmaceutical quality control, aligning scientific innovation with environmental responsibility.

2.4 Need for Green Analytical Chemistry in Pharmaceutical Analysis

Traditional analytical laboratories consume considerable amounts of hazardous solvents and generate substantial quantities of chemical waste. Disposal of this waste requires specialized treatment, increasing operational costs and environmental risks.

Implementation of Green Analytical Chemistry provides several important advantages

- Reduction in hazardous solvent consumption.
- Lower chemical waste generation.
- Improved occupational health and laboratory safety.
- Reduced analytical costs.
- Improved energy efficiency.
- Compliance with environmental sustainability initiatives.
- Support for sustainable pharmaceutical manufacturing.
- Enhanced public and environmental health protection.

As pharmaceutical industries move toward environmentally responsible production, green analytical methodologies have become increasingly important for routine quality control and research laboratories.

2.5 Objectives of Green Analytical Chemistry

The primary objective of Green Analytical Chemistry is to design analytical procedures that provide reliable analytical results while minimizing adverse environmental impacts.

Specific objectives include

- Minimize consumption of hazardous chemicals.
- Replace toxic solvents with environmentally benign alternatives.
- Reduce sample size and reagent consumption.
- Develop rapid analytical methods with shorter run times.
- Improve energy efficiency.
- Reduce laboratory waste generation.
- Promote safe working environments.
- Maintain analytical accuracy, precision, sensitivity, and robustness.
- Support sustainable pharmaceutical development.
- Green Analytical Chemistry for Pharmaceutical Analysis: Recent Advances, Regulatory Perspectives, and Future Directions

2.6 Principles of Green Analytical Chemistry

Green Analytical Chemistry is based on 12 principles, which adapt the concepts of Green Chemistry specifically for analytical applications. These principles encourage scientists to reduce environmental impact throughout every stage of the analytical process.

Principle 1: Direct Analytical Techniques

Whenever possible, analytical measurements should be performed directly without extensive sample preparation. Direct analysis minimizes reagent consumption, reduces waste generation, and shortens analysis time.

Principle 2: Minimal Sample Size

Using the smallest possible sample quantity reduces solvent requirements, decreases waste production, and preserves valuable biological or pharmaceutical samples.

Principle 3: In Situ Analysis

Whenever feasible, analyses should be conducted directly at the sampling site using portable or field-deployable instruments. This approach minimizes sample transportation, storage requirements, and potential contamination.

Principle 4: Integration of Analytical Processes

Combining sampling, extraction, separation, and detection into integrated analytical systems improves efficiency while reducing chemical consumption.

Principle 5: Automation and Miniaturization

Miniaturized analytical systems such as microfluidics, lab-on-a-chip devices, and microextraction techniques significantly reduce solvent consumption, analysis time, and laboratory waste.

Principle 6: Reduced Derivatization

Chemical derivatization should be avoided unless absolutely necessary because additional reagents increase waste generation and environmental burden.

Principle 7: Waste Minimization

Analytical procedures should generate the smallest possible amount of chemical waste while maintaining analytical performance.

Principle 8: Safer Solvents

Highly toxic solvents should be replaced with environmentally friendly alternatives such as ethanol, water, ethyl lactate, or supercritical carbon dioxide.

Principle 9: Energy Efficiency

Analytical instruments should consume minimal energy through efficient operation, shorter run times, and optimized instrument design.

Principle 10: Renewable Reagents

Renewable and biodegradable chemicals should be preferred whenever possible to reduce dependence on petroleum-derived materials.

Principle 11: Operator Safety

Analytical procedures should minimize operator exposure to hazardous chemicals through safer reagents, automation, and enclosed analytical systems.

Principle 12: Life-Cycle Thinking

The environmental impact of analytical methods should be evaluated throughout the entire analytical lifecycle, including reagent production, instrument operation, waste disposal, and recycling.

Table 2: Twelve Principles of Green Analytical Chemistry.

Sr. No.	Principle	Main Objective
	Direct analysis	Reduce sample preparation
	Minimal sample size	Lower reagent consumption
	In situ analysis	Reduce transportation
	Integration	Simplify workflow
	Miniaturization	Reduce solvent use
	Avoid derivatization	Lower chemical waste
	Waste minimization	Environmental protection
	Safer solvents	Reduce toxicity
	Energy efficiency	Lower power consumption
	Renewable materials	Sustainability
	Operator safety	Occupational health
	Life-cycle assessment	Overall environmental evaluation

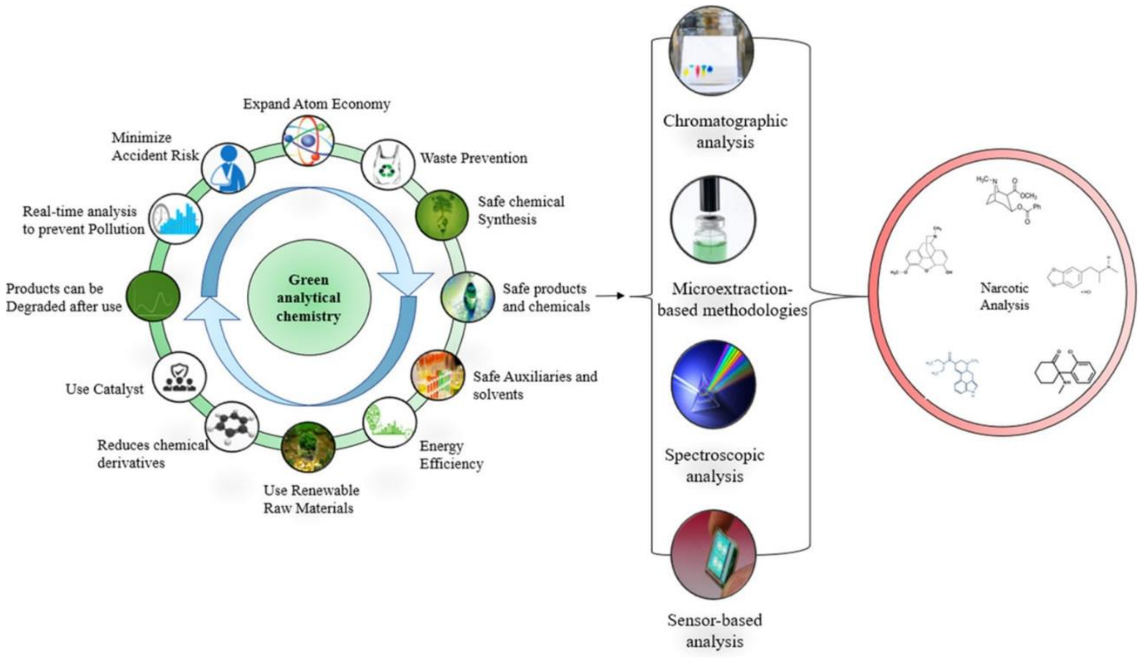

Fig. No. 1: Principles of Green Analytical Chemistry.

These principles help reduce environmental impact while maintaining analytical performance.

A. Green Analytical Technique

Several analytical techniques have been modified according to green chemistry principles.

1. Green HPLC/UHPLC

- Reduced solvent consumption
- Short analytical run time
- Water–ethanol mobile phases
- Higher efficiency with lower waste generation

2. HPTLC

- Low solvent requirement
- Simultaneous analysis of multiple samples
- Cost-effective and environmentally friendly

3. Capillary Electrophoresis

- Minimal solvent usage
- High separation efficiency
- Rapid analysis

4. Spectroscopic Methods

1. UV–Visible spectroscopy
2. FTIR spectroscopy
3. Raman spectroscopy
4. Near-Infrared (NIR) spectroscopy

These techniques often require little or no hazardous solvent, making them inherently greener.

B. Green Sample Preparation

Sample preparation contributes significantly to solvent consumption. Green alternatives include

1. Solid Phase Extraction (SPE)
2. Solid Phase Microextraction (SPME)
3. Microextraction techniques

4. QuEChERS
5. Ultrasound-assisted extraction
6. Microwave-assisted extraction
7. Solvent-free extraction

These methods reduce solvent use, shorten extraction time, and improve analytical efficiency.

C. Green Solvents

Traditional organic solvents are gradually being replaced by environmentally benign alternatives.

Common green solvents include.

- Water
- Ethanol
- Ethyl lactate
- Supercritical carbon dioxide (CO_2)
- Deep eutectic solvents
- Ionic liquids

These solvents exhibit lower toxicity, improved biodegradability, and reduced environmental impact.

Fig. No. 1.2: Procedure of Greeness Assessment.

D. Greenness Assessment Tools

Several tools evaluate the environmental friendliness of analytical methods.

- NEMI: Simple pictogram indicating hazardous chemicals and waste.
- GAPI: Comprehensive evaluation covering the complete analytical workflow.
- Analytical Eco-Scale: Assigns penalty points based on chemicals, energy, and waste.

- AGREE: Software-based tool evaluating all twelve principles of Green Analytical Chemistry.
- AMGS: Quantitative scoring system for comparing analytical methods.
- White Analytical Chemistry (WAC): Integrates analytical performance, environmental sustainability, and practical applicability.

  These tools enable objective comparison of different analytical procedures.

E. Applications in Pharmaceutical Quality Control

Green analytical methods are widely applied in

- Raw material analysis
- Assay of pharmaceutical dosage forms
- Stability-indicating studies
- Dissolution testing
- Cleaning validation
- Bioanalytical studies
- Impurity profiling
- Forced degradation studies
- Analytical method validation

Their adoption improves sustainability while ensuring compliance with pharmaceutical quality standards.

F. Challenges

Despite significant progress, several challenges remain

- Limited availability of green solvent alternatives
- High initial cost of advanced instrumentation
- Lack of universal greenness assessment standards
- Complexity of validating green analytical methods
- Limited regulatory guidance
- Need for trained personnel

G. Future Perspectives

- Future developments in Green Analytical Chemistry are expected to include:
- Artificial intelligence-assisted analytical method development
- Automated green laboratories

- Miniaturized analytical devices
- Digital quality control systems
- Sustainable pharmaceutical manufacturing
- Broader adoption of green metrics in regulatory submissions
- These advancements will further improve environmental sustainability and analytical efficiency.

2.7 Transition from Green to White Analytical Chemistry

Although Green Analytical Chemistry successfully addresses environmental concerns, researchers recognized that environmental sustainability alone does not guarantee a practical analytical method. A method must also provide excellent analytical performance while remaining economically feasible and operationally efficient.

This realization led to the development of White Analytical Chemistry (WAC), a comprehensive analytical philosophy integrating three complementary dimensions

- Red dimension: Analytical quality (accuracy, precision, sensitivity, robustness)
- Green dimension: Environmental sustainability
- Blue dimension: Practical and economic efficiency (cost, time, instrument availability, automation)

Unlike conventional greenness assessment, White Analytical Chemistry evaluates the overall balance among analytical excellence, environmental responsibility, and laboratory productivity. This approach aligns well with the pharmaceutical industry's increasing emphasis on sustainable quality management and regulatory compliance.

The RGB12 assessment tool was subsequently developed to quantify these three dimensions, providing a comprehensive evaluation of analytical methods suitable for pharmaceutical laboratories.

3. Green Assessment Metrics for Pharmaceutical Analytical Methods[17,19]

The development of environmentally sustainable analytical methods requires objective tools to evaluate the "greenness" of an analytical procedure. Green assessment metrics provide systematic approaches for comparing analytical methods based on factors such as solvent consumption, reagent toxicity, energy usage, waste generation, occupational safety, and sample preparation requirements. These metrics help researchers design, optimize, and select analytical procedures that balance analytical performance with environmental sustainability.

Several assessment tools have been proposed over the past decade, each differing in scope, methodology, and evaluation criteria. The most widely used metrics in pharmaceutical analysis include the National Environmental Methods Index (NEMI), Analytical Eco-Scale, Green Analytical Procedure Index (GAPI), Analytical GREEnness Metric (AGREE), AGREEprep, ComplexGAPI, and RGB12. Together, these tools support sustainable method development and facilitate transparent reporting in scientific publications.

3.1 National Environmental Methods Index (NEMI)

The National Environmental Methods Index (NEMI) was the first graphical tool developed to evaluate the environmental friendliness of analytical methods. It presents results in a simple circular pictogram divided into four quadrants, each representing one environmental criterion.

- Persistent, Bioaccumulative, and Toxic (PBT) chemicals
- Hazardous reagents
- Corrosive chemicals
- Waste generation

Each quadrant is colored *green* if the method satisfies the criterion or remains blank if it does not. Although NEMI is easy to understand and quick to apply, it provides only qualitative information and cannot distinguish between methods with similar environmental characteristics.

Advantages

- Simple and rapid evaluation
- Easy visual interpretation
- Suitable for preliminary comparisons

Limitations

- Limited evaluation criteria
- No numerical score
- Insufficient discrimination between analytical methods

3.2 Analytical Eco-Scale

The Analytical Eco-Scale is a semi-quantitative assessment tool based on a penalty point system. Every analytical method begins with an ideal score of *100*, and penalty points are deducted for factors that negatively affect environmental sustainability, including

- Hazardous chemicals
- Large solvent volumes
- High energy consumption
- Waste generation
- Occupational hazards

The final Eco-Scale score is interpreted as follows.

Eco-Scale Score	Interpretation
>75	Excellent green method
50–75	Excellent green method
<50	Inadequate green method

The Eco-Scale is widely used because it provides a numerical measure of greenness while remaining relatively simple to calculate.

Advantages

- Quantitative scoring system
- Easy comparison between methods
- Widely accepted in pharmaceutical research

Limitations

- Subjective assignment of penalty points
- Limited evaluation of sample preparation
- Does not fully assess the entire analytical workflow

3.3 Green Analytical Procedure Index (GAPI)

The Green Analytical Procedure Index (GAPI) was introduced to provide a comprehensive evaluation of the entire analytical process. Unlike previous metrics, GAPI assesses every stage of the analytical workflow, including

- Sample collection
- Sample transportation
- Sample preparation

- Reagent consumption
- Instrumentation
- Energy requirements
- Waste generation
- Final determination

The results are displayed as a multi-section pentagonal pictogram using three colors

- Green – low environmental impact
- Yellow– moderate environmental impact
- Red – high environmental impact

This visual representation allows rapid identification of environmentally unfavorable stages of an analytical procedure.

Advantages

- Whole analytical workflow assessment
- Excellent visual presentation
- Identifies stages requiring improvement

Limitations

- No overall numerical score
- Interpretation may vary among researchers
- Less suitable for statistical comparison

3.4 AGREE (Analytical GREEnness Metric)

AGREE is one of the most advanced and widely accepted green assessment tools. It evaluates analytical methods according to the 12 Principles of Green Analytical Chemistry and provides

- A circular pictogram
- Individual scores for each principle
- An overall greenness score ranging from *0 to 1*

Interpretation

- 0.80–1.00: Excellent green analytical method
- 0.50–0.79: Moderate greenness

- <0.50: Poor environmental performance

Because AGREE incorporates all twelve principles into a standardized software-based evaluation, it has become the preferred metric for recent pharmaceutical analytical publications.

Advantages

- Comprehensive evaluation
- Numerical scoring
- Software-assisted assessment
- High reproducibility
- International acceptance

Limitations

- Requires specialized software
- Some weighting factors remain subjective
- Limited assessment of sample preparation details

3.5 AGREEprep

AGREEprep extends the AGREE concept specifically to sample preparation, often the most environmentally impactful stage of pharmaceutical analysis. It evaluates factors such as:

- Sample amount
- Solvent type
- Solvent volume
- Extraction technique
- Energy consumption
- Waste production
- Operator safety
- Automation

Because sample preparation contributes significantly to laboratory waste, AGREEprep enables researchers to optimize extraction procedures independently from instrumental analysis.

Advantages

- Detailed sample preparation evaluation
- Complements AGREE
- Useful for pharmaceutical extraction methods

Limitations

- Limited to sample preparation
- Requires additional assessment tools for complete analysis

3.6 ComplexGAPI

ComplexGAPI combines the strengths of GAPI with a more detailed evaluation of sample preparation. It provides improved visualization of environmental impacts across multiple analytical stages while maintaining the intuitive color-coded approach.

This metric is particularly useful for complex pharmaceutical analyses involving multistep extraction, purification, and chromatographic separation.

ADVANTAGES

- Comprehensive workflow assessment
- Improved visualization
- Better discrimination of complex methods

Limitations

- More complex interpretation
- Limited software availability

3.7 RGB12 (White Analytical Chemistry Metric)

The RGB12 metric was developed as part of the White Analytical Chemistry concept. Unlike previous metrics that focus primarily on environmental sustainability, RGB12 evaluates analytical methods across three dimensions

- Red: Analytical performance (accuracy, precision, sensitivity)
- Green: Environmental sustainability
- Blue: Practical efficiency (cost, time, automation, accessibility)

RGB12 provides a balanced evaluation of analytical methods by integrating quality, sustainability, and practicality, making it particularly suitable for pharmaceutical quality control laboratories.

ADVANTAGES

- Holistic assessment
- Incorporates analytical performance
- Supports method selection for routine use

Limitations

- More complex evaluation
- Limited adoption compared with AGREE

Table 3: Comparison of Green Assessment Metrics.

Sr. No.	Metric	Type	Numerical Score	Visual Output	Sample Preparation	Whole Workflow	Major Strength
1.	NEMI	Qualitative	No	Yes	Limited	No	Simple screening
2.	Eco-Scale	Semi-quantitative	Yes	Yes	Limited	Partial	Numerical comparison
3.	GAPI	Qualitative	Yes	Yes	Yes	Yes	Comprehensive workflow
4.	AGREE	Quantitative	Yes	Yes	Partial	Yes	Based on 12 GAC principles
5.	AGREE prep	Quantitative	Yes	Yes	Excellent	No	Based on 12 GAC principles
6.	Complex GAPI	Qualitative	No	Yes	Excellent	Yes	Sample preparation focus
7.	RGB12	Quantitative	Yes	Yes	Yes	Yes	Integrates quality and sustainability

Table 4: Recommended Applications of Green Metrics.

Sr. No.	Analytical Situation	Recommended Metric
1.	Preliminary greenness evaluation	NEMI
2.	Routine pharmaceutical analysis	Eco-Scale
3.	Complete analytical workflow	GAPI
4.	Journal publication	AGREE
5.	Sample preparation optimization	AGREEprep
6.	Complex extraction procedures	ComplexGAPI
7.	Overall sustainability assessment	RGB12

CONCLUSION[4,20]

Green assessment metrics have become indispensable tools in modern pharmaceutical analytical chemistry. While NEMI and Eco-Scale remain useful for rapid evaluations, GAPI and AGREE provide more comprehensive assessments of analytical sustainability. AGREEprep addresses the environmental impact of sample preparation, ComplexGAPI enhances workflow visualization, and RGB12 integrates analytical quality, environmental responsibility, and practical efficiency within the framework of White Analytical Chemistry. The combined use of these metrics enables researchers to develop analytical methods that are scientifically robust, environmentally sustainable, and suitable for routine pharmaceutical applications.

This section is suitable for inclusion in a review article and provides a comprehensive overview of the major green analytical assessment metrics used in pharmaceutical analysis.

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