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A Comprehensive Review on The Aspect of Green Analytical Chemistry in Pharmaceutical Analysis

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ABSTRACT:

The aim of this review is to elaborate the concept of Green Analytical Chemistry and explore its utility in pharmaceutical analysis sector. Several article and literature reviews were studied to understand the concept of Green Analytical Chemistry and the impact it has in safeguarding the environment and ensuring sustainability of resources. The 12 principles of Green Analytical Chemistry have contributed significantly in implementing Green Analytical Chemistry in the agricultural, industrial as well as petrochemical sector. Metrices like Analytical Eco-Scale, Analytical Greenness, Atomic Efficiency Score and Green Analytical Procedure Index have proved to be a significant contributor in analysing the greenness of the analytical procedures and techniques. It is essential to understand the strategies that are required for implementing Green Analytical Chemistry in pharmaceutical analysis like miniaturization, green solvent usage, energy efficient technologies, automation & online analysis. The challenges & limitations of Green Analytical Chemistry like economic and logistical barriers to adopting green methods, balancing green practices with regulatory requirements and analytical performance, etc need to be overcome efficiently in order to ensure their optimum application and implementation in the coming future. The future perspectives of Green Analytical Chemistry including role of artificial intelligence and machine learning in optimizing green methods & potential for integrating Green Analytical Chemistry with other sustainable practices in the pharmaceutical industry need to be given special emphasis to maximise the benefits of Green Analytical Chemistry in the coming future.

Keywords: Green Analytical Chemistry, green solvents, green analytical chemistry metrices, Supercritical fluid chromatography, Solid phase microextraction.

INTRODUCTION

Prior to the 1990s, the environmental impact of chemical procedures was frequently ignored. Back then, the primary concern was predominantly on constructing particularly sensitive and reliable analytical techniques. In the 1990s and early 2000s, environmental concerns, such as the negative effects of toxic chemicals alongside the necessity of sustainable practices, gained attention. Consequently, the notion of green chemistry gained prominence and started to influence several subdivisions of chemistry, including analytical chemistry[1]. Green chemistry (GC), a field introduced by Paul Anastas and John Warner in 1998, is an important scientific aspect that focusses on the design, manufacture, use and ultimate disposal of chemical products and processes. It focusses on the reduction & elimination of hazardous substances, aiming for sustainable and environmentally friendly practices[2]. The goal of GAC is to provide safer, more effective methods for drug detection and quantification that don't negatively impact the environment or public health[3]. For the sake of environmental accountability, safety, financial efficiency, regulatory conformity, resource efficiency, sustainability, safety and creative thinking, GC must be incorporated into analytical chemistry curriculum. Since environmental regulations are getting more stringent, understanding GAC guarantees that future chemical scientists can create techniques that satisfy environmental guidelines[4].

In a period when environmental responsibility and sustainability are vital, analytical chemists' familiarity of GAC principles is becoming more and more significant. 12 sustainability-focused principles serve as foundation for GAC for creating efficient and sustainable processes[5]. These guidelines encompass numerous areas of concern, including energy efficiency, waste reduction, and the use of safer materials. As market trends progressively prefer green solutions, chemists may gain a competitive edge and contribute to environmental conservation by embracing GAC principles[6]. The adoption of these principles can have a significant positive impact on various sectors, ranging from research and industry to environmental and public health[7]. In addition to lessening the negative effects of chemical analyses on the environment, the concepts of GAC are essential for boosting sustainable practices, increasing resource efficiency, and improving human safety. By embracing these ideas, analytical chemistry may develop into a more responsible discipline that is in line with the demands of a sustainable future, which will be advantageous to industry, society, and the environment[8].

The 12 principles are given below.

Prevention**:** Preventing waste is preferable to treating or cleaning it up once it is produced. This idea focuses on creating chemical processes that produce as little waste as possible, which lessens the need for expensive and resource-intensive waste management.

Atom Economy*:* Synthetic techniques have to be developed to optimize the integration of all process elements into the finished output. The goal of atom economics is to minimize the production of byproducts while optimizing the integration of raw materials into the final product.

Less Hazardous Chemical Syntheses: Synthetic processes should, if possible, be developed to employ and produce materials with little or no toxicity to the environment and human health. By choosing synthetic methods that use fewer harmful compounds, this concept lowers hazards to the environment and human health.

Designing Safer Chemicals: Chemicals could be manufactured to serve their intended purpose with the least amount of toxicity possible. When designing safer chemicals, one must take into account the possible hazards of chemical products in order to produce molecules that are both intrinsically safer and yet effective.

Safer Solvents and Auxiliaries: Because solvents have an impact on the environmental impact of chemical processes, it is important to minimize the use of auxiliary substances and, when necessary, choose safer alternatives. Examples of these include solvents and separation agents.

Design for Energy Efficiency: Chemical processes' energy needs should be reduced in order to reduce their negative effects on the environment and the economy. Synthetic procedures should ideally be carried out at room temperature and pressure. Economic and environmental costs are decreased when energy consumption is decreased through effective process design.

Use of Renewable Feedstocks: Wherever it is technically and financially possible, a feedstock or raw material should be regenerative rather than depleting. By using renewable feedstocks, environmental effects are reduced and reliance on scarce resources is lessened.

Reduce Derivatives: Because unnecessary derivatization (blocking group usage, protection/deprotection, and temporary physical/chemical process change) might result in waste and the need for additional reagents, it should be reduced or avoided. Reagent consumption and waste production are decreased by minimizing derivatization.

Catalysis: Compared to stoichiometric reagents, catalytic reagents (as selective as feasible) are preferable. By facilitating more efficient reactions, catalysis reduces waste and energy consumption.

Design for Degradation: Chemical items should be manufactured to decompose into harmless degradation products at the end of their useful lives and not linger in the environment. By ensuring that chemical products decompose into innocuous compounds, degradation-designing helps to avoid long-term environmental damage.

Real-time analysis for pollution prevention: To enable real-time, in-process monitoring and management before hazardous compounds arise, analytical procedures must be improved. By enabling monitoring and regulation of chemical processes, real-time analysis helps to avoid the production of dangerous chemicals.

Inherently Safer Chemistry for Accident Prevention: The choice of substances and their forms in a chemical process should reduce the risk of chemical accidents, such as leaks, explosions, and fires. This idea focuses on choosing materials and circumstances that reduce the possibility of chemical mishaps, improving process reliability[9-11].

Importance of GAC in reducing environmental impact and promoting sustainability

Eliminating harmful pollution: Toxic and hazardous materials that pose major risks to both human health and the environment are commonly used in conventional analytical procedures. By prioritising safer, less toxic chemicals, solvents, and reagents, GAC reduces the likelihood that dangerous compounds may find their way into the environment. For instance, ecologically friendly alternatives like biodegradable reagents or aqueous-based solvents can be used in place of hazardous organic solvents that commonly affect water sources. Many conventional methods result in byproducts that are hard to decompose and can persist in the environment for a long time. Through the production of innocuous and biodegradable byproducts, GAC encourages behaviours that lessen long-term environmental contamination. Additionally, real-time analysis makes it possible to monitor and manage environmental pollution at its source, assisting in the reduction of pollutants before they become hazardous[12].

Minimizing chemical waste: Traditional analytical procedures can generate large amounts of chemical waste, especially hazardous solvents and reagents. GAC reduces waste and the requirement for intricate waste disposal procedures by using fewer chemicals in analysis. Solvent consumption is significantly decreased using techniques such as supercritical fluid chromatography (SFC), microwave-assisted extraction (MAE), and solid-phase microextraction (SPME). Green analytical techniques sometimes call for lower sample sizes, which means that less reagents and solvents are needed. As a result, less waste is produced and the environmental impact of disposing of chemicals is reduced. Large volumes of samples for analysis or thorough sample preparation are frequently needed for traditional analytical procedures, which results in substantial waste. GAC places a strong emphasis on the advancement of in-situ and real-time analytical methods that can examine samples while they are being received. This method minimizes waste production by reducing the need for extra sample handling, processing, and transportation[13].

Reducing energy requirements: A lot of conventional analytical methods, such distillation or some types of chromatography, need high pressures or temperatures, which uses a lot of energy. Energy-efficient techniques that may be carried out at room temperature or using less power are encouraged by GAC. For instance, compared to traditional processes, microwave-assisted treatments are more energy-efficient, lowering total energy use. GAC uses more compact, effective instruments. Lab-on-a-chip technologies and other analytical devices that are smaller in size need less energy and resources to function. These little devices frequently produce accurate, timely results with little waste[14].

Use of renewable materials and reagents: In order to lessen dependency on non-renewable resources, GAC encourages the use of sustainable and biodegradable products. with example, substituting bio-based solvents with petroleum-based ones. In order to minimize total resource consumption, GAC promotes the use of materials that are readily recyclable or reusable after use. GAC can lessen its reliance on chemicals or metals that might not be readily available. Reusing or recycling the materials, solvents, or reagents used in the analysis is a key component of many green analytical techniques. For instance, recycling solvents or reusing solid-phase extraction materials makes the operation more sustainable by lowering the demand for new raw materials and disposing of used materials less frequently. GAC encourages labs to employ closed-loop systems, which reduce waste and ecological impact by continually recycling and reusing reagents and chemicals[15].

Emphasis on green solvents & solvent-free techniques: Green solvents, which are harmless, biodegradable, and have no effect on the environment, are promoted by GAC. For instance, more hazardous and volatile solvents like hexane or chloroform are frequently substituted with water, ionic liquids, deep eutectic solvents, hydrotropes or supercritical carbon dioxide. The development of solvent-free analytical methods, including solid-phase microextraction (SPME) or dry analytical methods, is one of the most notable trends in GAC. These techniques greatly reduce waste and the usage of hazardous materials by extracting or analyzing chemicals without requiring additional chemical solvents[16].

Regulatory Compliance: Firms that use green analytical techniques have a greater capacity to abide by increasingly stringent environmental requirements. In accordance with international environmental regulations, this entails minimizing the creation of hazardous waste, cutting emissions, and making sure that safe disposal procedures are followed. The idea of GAC may be used in a variety of fields, such as forensics, environmental monitoring, food safety, and medicines. Reducing chemical analysis's environmental effect is essential in these industries to satisfy legal requirements and business sustainability objectives. These sectors may reduce their overall environmental impact and help create a more environmentally friendly future by implementing GAC principles[17].

GAC metrices utilizes in pharmaceutical analysis

Several metrics have been developed to evaluate how environmentally friendly analytical procedures are the Analytical Eco-Scale, Green Analytical Procedure Index (GAPI), National Environmental Methods Index (NEMI), Analytical GREEnness (AGREE) and RGB additive colour model are some important parameters for assessing how analytical processes affect the environment. By taking into consideration several facets of the analytical process, these indications collectively provide the procedure's green index[18].

Analytical eco-scale

Environmentally friendly techniques are greatly aided by Green Analytical Chemistry (GAC). GAC measures are widely used to assess the environmental impact of analytical techniques in addition to their recovery, reproducibility, and sensitivity[19]. The greatest tool for determining the procedure's "greenness" is this one. One example of a semi-quantitative tool is the base score of 100. Based on risks toxic agents, energy use, and trash output, penalty points are deducted. A final score of greater than 75 indicates an exceptional and top-notch green analytical approach. The specific analytical procedure will have a burden or harsh environmental impact if the score is less than 50[20].

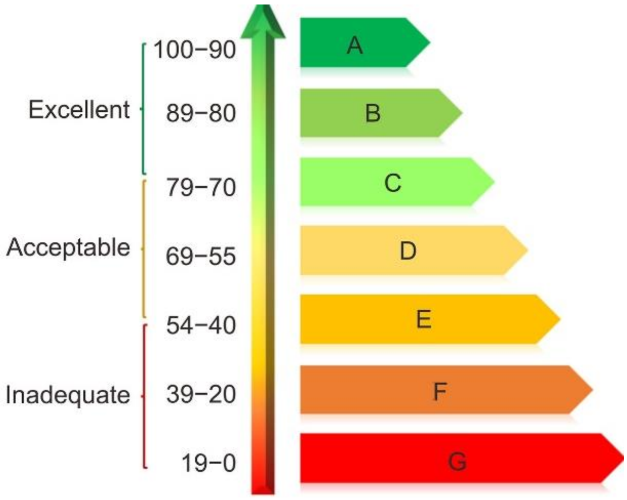

Figure 1: Analytical eco-scale for assessing greenness of analytical procedure[21]

Green Analytical Procedure Index (GAPI)

One technique that is mostly used to assess how environmentally friendly analytical methods are is the Green Analytical Procedure Index (GAPI). It makes use of a pentagonal pictogram that is color-coded and separated into sections of 5. Additionally, it assesses the entire process, including sample collection, preparation, analysis, and waste disposal. Comparing and identifying ways that require more greenness is made much easier by this representation. GAPI serves as an appropriate reference for environmentally friendly analytical techniques in both the academic and industrial domains[21].

Table 1: Different colour representing impact in environment[22]

Colour	Impact on environment
Green	Low impact
Yellow	Moderate impact
Red	**High impact**

Figure 2: Colour depicting the intensity of the impact in environment[21]

National Environmental Methods Index (NEMI)

The U.S. Geological Survey (USGS) created the National Environmental methodologies Index (NEMI) to assist agencies and analysts in identifying and comparing methodologies. Water, soil, and other environmental samples are also checked and monitored with it. NEMI is specifically utilized in the context of Green Analytical Chemistry (GAC) to determine the environmental impact of analytical procedures. It supports analytical techniques that use fewer chemicals, are less toxic, and produce less waste[23].

To illustrate the greenness and environmental friendliness of the analytical processes, NEMI use a four-quadrant pictogram. The use of hazardous substances is represented by each of the four quadrants.

Table 2: Quadrant representing the Greenness[24]

Quadrant	Green Criteria
Green-filled quadrant	Met green criteria
Empty quadrant	Does not meet green criteria

Table 3: Description Criteria of different Quadrants[21]

Quadrant	Description of Criteria
Persistent, Bio-accumulative and Toxic (PBT) Chemicals	Checks if the reagents are PBT substances
Hazardous waste	Check the amount and type
Corrosivity	Check pH of reagents
Hazardous solvents	Check the solvent

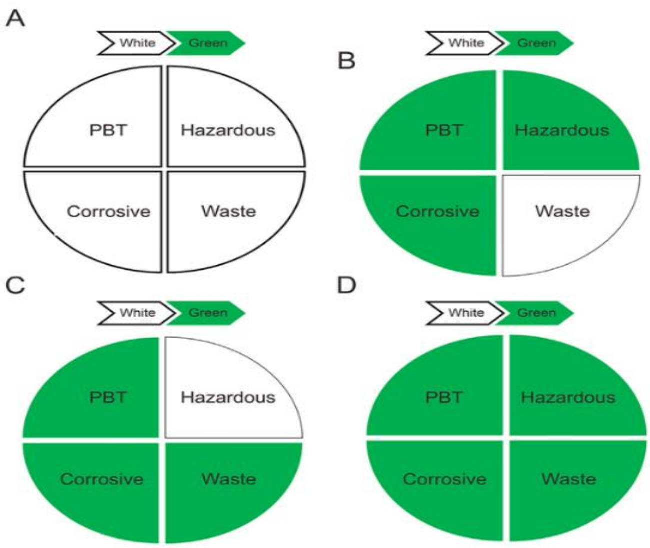

Figure 3: A: Does not meet any green criteria B: Only waste criteria does not meet C: Hazardous solvents used D: Methods met all criteria of Green Chemistry[21]

Analytical GREEnness (AGREE)

AGREE is a contemporary instrument that evaluates the environmental friendliness of analytical techniques based on the 12 Green Analytical Chemistry principles. A circular visual diagram is provided by AGREE. It will be split up into twelve parts. Green will indicate adherence to green criteria, and red will indicate non-compliance. This makes it easy to quickly and clearly determine which analytical techniques are environmentally friendly and which require improvement[25].

AGREE's primary benefit is its intuitive design. It does take into account every element, including sample size, waste production, and solvent toxicity. Additionally, AGREE is publicly available as software that enables the automatic calculation of scores, hence optimizing the sustainability of the approach. Because of its excellent recovery and visual clarity, it is frequently utilized in academic and research settings to provide environmentally friendly analytical methods[26].

Table 4: 0 & 1 depicting compliance with Greenness[27]

Score	Meaning
0	Less or no compliance with GAC Principle
1	More Environment friendly, full compliance

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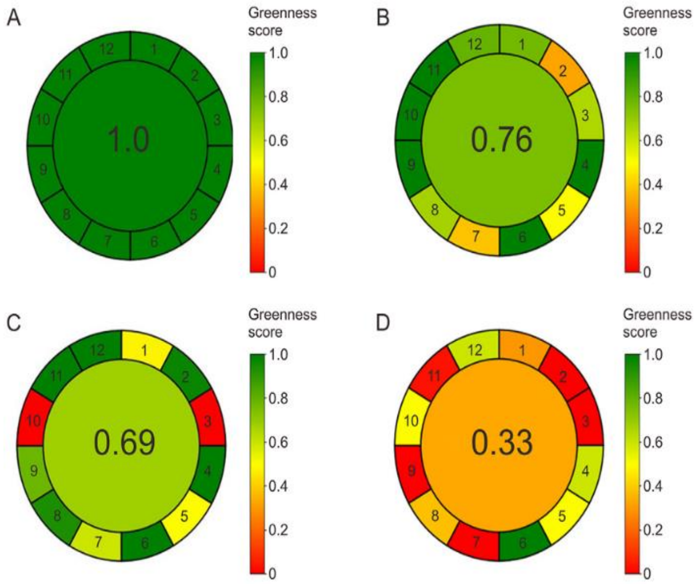

Figure 4: Depicting Greenness of analytical methods, A: Shows is in full compliance with GAC Principle B: Compliance with GAC C: Less Compliance with GAC D: No compliance with GAC[21]

RGB additive colour model

One of the Green Analytical Chemistry matrices utilized for environmental sustainability is the RGB additive colour model. It is founded on the idea that a broad variety of colours may be created by combining three hues—red, green, and blue light in varying intensities[28].

Determining the strength of the green colour in relation to other red and blue components is how greenness is determined. The colour that appears last will be green if the green component has a high value and the red and blue components have low values in comparison to green. The outcome will appear white if the values of the three components green, red, and blue are high, equal, and the same. Three will not seem completely white if their values are equal but mild. The green component should be higher than the others in order to manage greenness in GAC[29].

Table 5: Meaning of Different colours in RGB additive colour model[30]

Colour	Relation
Green	Safety and eco-friendliness
Red	Analytical Performance
Blue	Productivity/Practical effectiveness

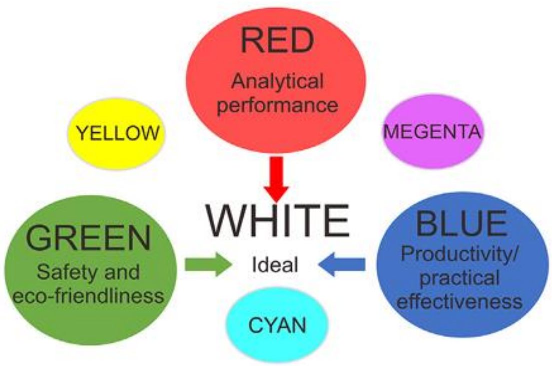

Figure 5: The Pictogram of RGB additive colour model[21]

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Table 6: Comparative table of different types GAC metrices[20,21,23,25,28]

Tool	Output type	Perception	Quantitative score	Advantages	Disadvantages
Analytical Eco-Scale	Score in number	Text based score	✓	Simple and easy	No visualization
GAPI	Pictogram	Pentagram	✕	Visual	No output in numbers
NEMI	4 Quadrants	Circle (Quadrant)	✕	Very simple	Lack of information
AGREE	Colour graded pictogram (0-1)	Score	✓	Uses 12 Principles	Software is needed
RGB Model	RGB colour (0-1)	Blended colour	✓	Use multiple tools	Complex

Green analytical techniques employed in pharmaceutical analysis

Green Chromatographic Techniques: One popular method of separating and distinguishing chemicals in pharmaceutical analysis is chromatography. Large volumes of hazardous solvents are frequently needed for traditional chromatographic techniques, which result in significant waste. Green chromatography seeks to increase sustainability and reduce solvent usage[31]. Supercritical Fluid Chromatography (SFC) is considered a green technology since it uses nontoxic carbon dioxide and uses less solvent and trash, which lessens its negative effects on the environment. The CO_2 utilized in SFC is recovered from the environment and recycled for use in preparatory procedures. It offers the financial advantages of using fewer solvents and disposing of trash, as well as the comparatively cheap cost of CO_2. To reduce the energy required for CO_2 production, recycling, and cooling, enhance sample transfer without high make-up flow rates, creative solutions are needed. Moreover, in order to enable multi-detection of samples examined in parallel, and guarantee high mass spectrometric sensitivity without the need for extra liquids, modern advancements are needed. Thus, SFC has the potential to be a very environmentally friendly separation and purification technique[32]. Another green chromatography is Reversed-Phase Chromatography (RPC) using green solvents. Although RPC is a frequently employed analytical technique in pharmaceutical drug research and production, there is growing interest in greening these procedures. It will help to lessen their negative effects on the environment and enhance the safety of analysts' health. One important tactic is to swap out dangerous solvents like methanol and acetonitrile for more environmentally friendly ones[33]. Utilizing green solvents improves lab safety, lowers waste disposal expenses, and lessens the adverse environmental effects of chemical analysis. An environmentally friendly alternative to hazardous solvents is the use of green solvents such as ethanol, isopropanol, n-propanol, acetone, ethyl acetate, ethyl lactate, propylene carbonate, and water[34]. In order to increase environmental and health friendliness without sacrificing technique performance, RPC was developed to decrease or remove harmful compounds from analytical procedures[35]. Miniaturized Chromatography offers several ecological benefits like reduced solvent and sample volume, less time, effort, expense, and waste, as well as lower energy usage compared to standard mass spectrometry techniques. Along with major improvements in environmental effect and analyst health (toxicological), miniaturization offers analytical and methodological benefits[36]. Traditional LC's drawbacks can be solved by miniature LC. More effective tandem mass spectrometry is made possible by decreasing the inner diameter of the column, which also boosts ion sensitivity and decreases chromatographic dilution. For instance, over 90% less solvent is used when a 25 cm × 4.6 mm column is replaced with a 10 cm x 2.1 mm column[37].

Microwave-Assisted Extraction (MAE): When compared to conventional extraction techniques, MAE has advantages including quicker extraction periods and lower solvent costs. Unlike traditional extraction methods, MAE generates heat through molecular interactions and distributes microwave energy directly to the materials. Because MAE uses less energy than conventional extraction techniques, it is a more affordable option. By using less solvent, it lowers solvent consumption and has a lesser environmental effect. The procedure can even use no solvent at all, which minimizes waste and lessens the environmental effect of disposing of solvents. For example, essential oils may be extracted from plant material using dry MAE, which does not require solvents[38].

Solid-Phase Microextraction (SPME): SPME is as an environmentally benign sample preparation technique that lessens dependency on hazardous solvents. It is acknowledged for supporting environmental sustainability and green chemistry concepts.

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The extraction phase volume is extremely tiny when using the SPME microextraction technology. The method generates very little laboratory waste, is fast, needs little to no sample preparation, and utilizes little to no solvent. Due to its microextraction nature, SPME greatly lowers laboratory waste. It also provides special chances for in vivo sampling, which eliminates the need for labour-intensive techniques. Because SPME is readily automated, manual handling is reduced and efficiency is increased. This method is simple to use and physically sound for direct environmental water or air monitoring. It is a useful technique for on-site sample processing in chemical analysis since it is field-compatible[39].

Green Spectroscopic Techniques: One of such techniques is Near-Infrared (NIR) Spectroscopy. Reliance on hazardous chemicals and solvents is decreased using NIR spectroscopy. By using less solvent, it is an inherently green analytical method that supports the ideas of green chemistry. Without preparing a sample, solvent purity may be swiftly and securely checked with NIR spectroscopy[40]. Moreover, solvents or possibly hazardous chemicals are not needed for NIR spectroscopy. It is a quick substitute for laborious, solvent-intensive wet-chemistry techniques. By improving sorting accuracy, which lessens dependency on new materials and the environmental effect of recycling, NIR spectroscopy helps to promote more environmentally friendly recycling procedures. NIR spectroscopy may be used to lower material prices or solvent disposal expenses through solvent recycling[41]. Raman spectroscopy is another green spectroscopy method whose primary goal is to streamline analysis and shorten sample research times. It helps with plant stress diagnosis, crop monitoring, and sustainability advancement. By offering quick assessments of solvent concentrations, Raman spectroscopy facilitates solvent reduction in chemical reactions by enabling comprehension of the solvent exchange or distillation process. During solvent exchange and distillation processes, this method enables real-time solvent content monitoring, enabling prompt optimization and corrections. Raman spectroscopy eliminates the need to wait for offline analysis, which saves reactor time and improves process comprehension. Additionally, it might be used for recycling waste plastic when precise, large-scale sorting procedures are needed[42].

Voltametric and Electrochemical Methods: Because of its ease of use, small size, minimal time consumption, affordability, mobility, and high sensitivity, voltammetry is highly regarded. Because voltametric sensors may be used with portable, easily navigable, and field-deployable electrochemical apparatus for on-site and simple analyte analysis, their application has grown. A promising technology for creating next-generation voltametric sensors is screen printing. This makes it possible to produce disposable, single-use sensors in large quantities at a fair price with excellent repeatability[43]. Disposable screen-printed electrodes (SPEs) offer greater versatility with a wide variety of electro-magnetic topologies, reduce the quantity of sample required, and do away with pretreatment steps. Moreover, sustainable electrochemical methods contribute to pollution reduction by replacing conventional chemical processes that often employ hazardous reagents with more benign alternatives. Because they enable processes that might change energy systems toward more environmentally friendly approaches, electrochemical reactions play a critical role in advancing sustainable energy practices. These reactions provide effective channels for energy conversion and storage by using electric current and potential difference to propel chemical changes[44]. The development of renewable energy systems, such as fuel cells and batteries, is a notable field where electrochemical processes show promise. Fuel cells, for example, may efficiently transform chemical energy into electrical energy, enabling the creation of greener energy with fewer pollutants. Similar to this, batteries' electrochemical processes provide improvements in energy storage, which are crucial for sporadic renewable energy sources like solar and wind. By using these strategies, the energy footprint associated with conventional synthesis processes may be greatly reduced and goods can be produced under gentler circumstances, thus supporting the concept of GAC[45].

High-Throughput Screening (HTS) with green chemistry principles: HTS is being adapted to incorporate green chemistry principles including reducing plastic waste, minimizing reagent and energy consumption, and implementing innovative technologies. The integration of automation and miniaturization also contributes to more sustainable practices in drug discovery. Reducing waste is one of the main tactics for making HTS greener. Miniaturizing assays contributes to a decrease in the use of costly reagents. Automated methods for precise dispensing guarantee that only the necessary amounts are used, reducing the wastage of priceless samples and reagents. Non-contact dispensers, for instance, may handle a variety of liquid classes and dispense precise, small amounts, reducing handling mistakes and reagent costs[46]. Another crucial component of greening HTS is the use of eco-friendly reagents. In a drug development setting, HTS finds more environmentally friendly options. Technologies that use less energy are essential to sustainable HTS. By enabling the quick and precise distribution of intricate procedures, automation lowers energy usage. Miniaturizing HTS techniques and implementing cutting-edge technology also help to lower energy usage, which makes the drug development process more sustainable[47].

Hyphenated techniques: Combining two or more analytical techniques to increase the sensitivity, selectivity, and efficiency of analysis is known as hyphenated techniques in analytical chemistry. These approaches provide strong analytical tools for complicated materials by frequently combining detection techniques (like spectroscopy or mass spectrometry) with separation techniques (like chromatography). Hyphenated methods can be used or changed in GAC in ways that enhance efficiency, lessen their impact on the environment, and adhere to sustainability principles[48]. Combining Gas Chromatography with Mass Spectrometry (GC-MS) enables more effective analysis with less sample preparation and frequently uses less solvents. It enables quicker analysis and extremely sensitive detection with small sample quantities, which lowers the total amount of energy and reagent used[49].

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Compared to ordinary liquid chromatography combined with less sensitive detectors, Liquid Chromatography combined with Mass Spectrometry (LC-MS) usually employs fewer amounts of solvents. Sample quantities and solvent usage are further decreased by recent advancements in micro- and nano-LC technology. Greener solvents like aqueous or bio-based solvents can help LC-MS by lowering its dependency on dangerous organic solvents including methanol and acetonitrile[50]. Certain substances can occasionally be directly analyzed using ionization methods such as electrospray ionization (ESI) in LC-MS without the need for significant solvent or sample preparation. Additionally, this approach reduces requirement for wasteful & unnecessary reagents by enabling sensitive detection with little sample preparation[51]. Combination of HPLC with UV detection (HPLC-UV) enables effective analysis with reduced solvent quantities. Micro-HPLC and other innovations in tiny HPLC systems use less energy and solvent[52]. Compared to other detection techniques like fluorescence or electrochemical detection, UV detectors are more ecologically friendly since they don't require extra reagents or solvents[53]. Additionally, the environmental effect is lessened when eco-friendly solvents, such as water-based combinations, are used in HPLC[54]. Gas Chromatography-Flame Ionization Detection (GC-FID) reduces waste output when it is used with green solvents such as CO_2 or water as the carrier gas. Very little sample is needed for analysis thanks to the technique's excellent sample volume efficiency. Because the FID detector is non-destructive, waste production is decreased because no dangerous chemicals are needed for detection. GC-FID eliminates the need for unnecessary reagents or solvents and enables the analysis of complicated combinations with little sample preparation[55]. Since capillary electrophoresis is a low-solvent method by nature, it improves sensitivity while using less solvent in analysis when combined with mass spectrometry (CE-MS). Compared to other methods like HPLC, CE employs low electric fields for separation, which requires less energy. The MS detector reduces waste by enabling very sensitive detection without the need for extra reagents and by analyzing tiny sample amounts[56]. With less sample preparation and reagent consumption, trace elements in complicated matrices may be analyzed thanks to the Inductively Coupled Plasma - Mass Spectrometry (ICP-MS) coupling. With low sample quantities and little waste, ICP-MS's very sensitive detection makes it possible to analyze trace metals in environmental and pharmaceutical samples. ICP-MS advancements like laser ablation ICP-MS enable direct solid sampling with less sample preparation and chemical usage[57]. An environmentally friendly substitute for conventional solvent extraction techniques is UAE (Ultrasound Assisted Extraction). It cuts down on processing time and solvent usage when used in conjunction with chromatography, such as HPLC or GC. By accelerating the extraction process and lowering the time and effort needed for sample preparation, the application of ultrasonic waves increases overall efficiency[58]. Another green hyphenation technique is Fourier Transform Infrared Spectroscopy (FTIR) – Hyphenated with Chromatography or Mass Spectrometry. For detecting functional groups in pharmaceutical substances, FTIR is a non-destructive method that may be used with mass spectrometry or chromatography to minimize sample preparation and solvent usage. Additionally, the environmental effect is reduced because FTIR analyses both liquid and solid samples without the need for chemical reagents. Moreover, FTIR frequently works straight upon sample materials with no the need of solvents, and when combined with chromatography, it enables efficient separation with less chemical usage[59].

Challenges and limitations

Notwithstanding its many benefits, the pharmaceutical industry encounters some challenges and limitations when putting Green Analytical Chemistry (GAC) into practice. These difficulties could be caused by the technological and operational characteristics of the sector, as well as financial and regulatory constraints. Understanding these challenges is essential to successfully integrating green practices across pharmaceutical operations. The initial cost barrier may discourage industries from implementing green practices, especially if the financial return is uncertain or delayed[60]. Making the switch to more environmentally friendly analytical technologies usually require a large upfront investment in new equipment, green chemicals, and solvents, which might be more expensive than traditional ones. Furthermore, implementing inventive, environmentally friendly methods may require lengthy regulatory approval and validation processes to ensure that they meet pharmaceutical product safety requirements. Regulatory agencies such as the FDA or EMA may have strict guidelines regarding traditional testing techniques, even though GAC principles foster sustainable activities. Furthermore, changing to greener analytical techniques (e.g., SFC instead of HPLC) needs capital expenditure that may be unfeasible for smaller pharmaceutical firms. Absence of regulatory approval can be a barrier to wider adoption, which can delay or interfere with the shift to the greener practices and approaches[61].

Several traditional analytical techniques, such spectroscopy and chromatography, do not yet have fully environmentally friendly alternatives. They cannot simultaneously ensure greenness and achieve the sensitivity, accuracy & robustness required for high-quality pharmaceutical analysis . For instance, it could be difficult to replace techniques like gas chromatography (GC) or high-performance liquid chromatography (HPLC), which rely on traditional solvents, in some areas of drug quality control and stability testing. The lack of environmentally friendly alternatives to several techniques hinders the widespread application of GAC principles in pharmaceutical testing[62]. Less environmentally harmful green chemicals, reagents, and solvents may be more expensive and harder to get than their conventional counterparts. In some places or markets, green alternatives could be difficult to locate or unavailable. Due to the lack of environmentally friendly products in some countries, multinational pharmaceutical companies may face challenges. Additionally, because green products are more expensive, smaller enterprises can be deterred from making the switch. A major concern in the pharmaceutical sector is the potential for greener methods to fall short of traditional ones in terms of sensitivity, selectivity, and accuracy[63].

The trade-off amongst performance and sustainability is a major problem in pharmaceutical analysis, where precision is essential (for example, in quality control, stability testing, and drug discovery). Pharmaceutical companies may be hesitant to use greener methods if they are concerned that they won't meet the exacting standards of specificity and precision required for quality control and drug development[64]. For GAC to be widely used, a skilled workforce that can understand and apply sustainable ideas in analytical techniques is required. However, there aren't many educational and training programs that are specifically focused on GAC at the moment, particularly in the area of pharmacological analysis. Due to a lack of specialised training, staff members may not be equipped to use GAC principles appropriately, which could lead to improper or inefficient application of green approaches[65]. Green metrics like GAPI, AGREE, AES, and Analytical Eco-Scale are designed to measure the environmental impact of analytical processes, however they can be challenging to use and comprehend. Pharmaceutical companies may not have the means or expertise to routinely use these metrics. It induces challenges in evaluating the environmental impact of their operations, especially when numerous variables are involved (e.g., solvent selection, waste management, power use). Because assessing the long-term viability of specific systems is subjective and complex, there may be confusion or inappropriate usage of these markers. Businesses may find it difficult to apply these KPIs across their entire process portfolio[66].

Future perspectives

As green chemistry principles expand, green metrics will also become more sophisticated. New metrics may emerge to assess not only the greenness of analytical methods but also their sustainability throughout the entire drug development lifecycle. In the years ahead, green analytical tools will be incorporated more and more into standard pharmaceutical procedures[67]. Greener alternatives to conventional techniques, such as MAE, SFC, and green solvents, will be used more frequently for pharmaceutical discovery, quality assurance, and stability testing. As a result, more regulatory agencies will adopt these indicators, which will help to standardise the definition of greener medications and ensure their uniform industry-wide application[68]. By enhancing the effectiveness, affordability, and environmental sustainability of analytical processes, GAC has the potential to completely transform the pharmaceutical industry. Reduced waste, reduced solvent consumption, energy savings, and enhanced safety are just a few benefits of using GAC in pharmaceutical analysis, all of which significantly contribute to the industry's sustainability goals. It also aligns with global trends towards greener and more sustainable practices across a range of businesses[69].

Advances in analytical instruments will have a big impact on GAC's future in the pharmaceutical industry. Newer technologies that consume less energy, generate less trash, and employ cleaner chemicals will soon be available. Miniaturising instruments and developing portable analytical devices will not only increase analytical efficiency but also contribute to a reduction in the environmental impact[70,71]. Going ahead, GAC in the pharmaceutical sector will include more collaboration among academic institutions, pharmaceutical companies, regulatory agencies, and green chemistry organisations. By sharing best practices and knowledge, the pharmaceutical industry may cooperate to overcome challenges related to GAC implementation and accelerate the transition to more ecologically friendly operations. As government and regulatory agencies realise the importance of sustainability, more supportive legislation will likely be developed to encourage the adoption of green analytical techniques. Regulatory bodies such as the FDA and EMA may revise their guidelines to explicitly include green chemistry principles, opening up more transparent channels for the endorsement of eco-friendly procedures[72,73].

Conclusion

There are several implications of GAC in pharmaceutical industry. By diminishing the utilize of hazardous solvents, reducing waste, conserving energy, and encouraging the adoption of eco-friendly materials and cutting-edge technologies, GAC is a revolutionary development in the pharmaceutical industry that provides a sustainable, effective, and morally sound method of chemical analysis. Environmentally friendly techniques are made possible by their integration at every stage of the drug development lifecycle, from early discovery to manufacturing and quality control, without sacrificing analytical performance or regulatory compliance. GAC lowers operating costs by using fewer reagents and energy, improves workplace safety by limiting analyst exposure to hazardous chemicals, and enables quick, high-throughput analysis using contemporary green technologies like solvent-free extraction, miniaturized instrumentation, and real-time process analytical tools[60,62].

There are implications of GAC in terms of regulatory alignments as well. Since the concepts of GAC complement the changing regulatory landscape that places an increasing emphasis on sustainability, risk-based approaches, and lifecycle management of analytical techniques, GAC has significant implications for regulatory alignment. Adoption of adaptable, science-driven frameworks like Quality by Design (QbD) and Analytical QbD (AQbD) is encouraged by regulatory agencies like the FDA, EMA, and ICH (through guidelines like ICH Q8–Q14). These frameworks naturally integrate GAC by encouraging effective, reliable, and ecologically conscious analytical practices. GAC supports important regulatory goals including method robustness, process comprehension, and continuous improvement, all of which promote inspection preparedness and regulatory compliance, even if it is not yet a recognized regulatory requirement [64,66].

Despite the clear advantages, there are several barriers to the widespread application of GAC in the pharmaceutical sector, such as high upfront costs, regulatory limitations, and technological limitations[74]. However, these challenges are not unsolvable. The increasing need for more ecologically friendly pharmaceutical manufacturing including analytical procedures can be mitigated by technological advancements, more accessible green materials, and regulatory support[75,76]. Future corporate and academic levels will place greater emphasis on GC education and training. The demand for environmentally friendly products in the pharmaceutical business is expected to increase as people's awareness of sustainability grows. This covers not just APIs but also goods that have been approved because to their positive environmental effects, eco-friendly packaging, and eco-friendly production processes[77]. Ultimately, GAC has a promising future in the pharmaceutical industry as the industry becomes more aware of the need for greener and more ecologically friendly practices. With continued research and collaboration between academic institutions, industry, and regulatory bodies, the pharmaceutical industry can reduce its environmental effect while maintaining the stringent quality control and safety standards that are essential for public health[78,79].

Conflict of interest

The authors declare no conflicts of interest.

Author(s) contribution

Bibhas Pandit conceptualized the article's original idea. Projesh Saha performed the literature review. Manuscript preparation was done by Upasna Rai. Sujan Banerjee prepared the conclusion section. The abstract and references section was prepared by Arnab Rakshit and Manisha Dahal respectively.

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