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Green Chemistry and its Implementation in Pharmaceutical Analysis

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Green Chemistry and its Implementation in Pharmaceutical Analysis

Green Pharmaceutical Analysis

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Abstract: The expanding progression of industrial development was a pioneer for world economic growth. Green chemistry has been defined as 'the employment of techniques and methodologies that reduce or eliminate the use or production of feedstocks, products, by-products, solvents, and reagents that are harmful to human health or the environment'. The quality-by-design approach is well known in the pharmaceutical industry, and it has a great influence on analytical methods and procedures. In the green method of chemistry, the core consideration is directed towards the design of a material or the chemical procedure; four of twelve principles are associated with design, e.g., designing fewer hazardous chemical syntheses, designing harmless chemicals and products, designing for energy effectiveness, and designing for degradation. One of the most active fields of research and development in green chemistry is the establishment of analytical methodologies, leading to the beginning of so-called green analytical chemistry. The influences of green chemistry on pharmaceutical analysis, the environment, the population, the analyst, and companies are discussed in this review, and they are multidimensional. Every selection and analytical attitude have effects both in the end-product and everything that surrounds it.

Keywords: Green Chemistry, Green Analytical Procedure Index (GAPI), National Environmental Methods Index (NEMI) database, Pharmaceutical Analysis, LC-MS, HPLC.

1 Introduction

With the large and fast development in industry since 1940, environmental issues began to increase over the years; globalization and developments in the food industry have brought not only new products and ingredients but also risks and worries about consuming foods with unsafe contents [1]. Chemists and scientists work hard with the aim of reducing the undesirable side effects on human health like environmental contamination, consumption of harmful reagents and solvents, and waste generation. As a result of the improvement in analytical activities, new challenges that focused on the practical characteristics, such as methods, time of analysis, costs, safety considerations, and side effects of the environmental problems, have been well-studied, leading the laboratories to begin to evaluate the scale of their analysis by scaling down and minimizing the amount and volume of solvents, reagents, solutions, and chemicals to protect human health [1], as shown in Figure 1.

<Location of Figure 1>

'Green chemistry', 'clean chemistry', and 'benign chemistry' are all terms used to describe approaches that minimise the use of feedstocks and consumption of reagents and energy, as well as generation of wastes in the analytical and chemical industry, with the aim of protecting the environment and saving the materials [2-4]. Thus, there is a high awareness on greening the available analytical methods, by which several alternatives and schemes have been proposed [4]. This is based on reducing the amount of reagents, solvent depletion, waste minimisation and recycling, and passivation and degradation of toxic wastes. Another objective of such practices is the elimination of hazardous substances by replacing them with safer ones [5]. Twelve principles of green chemistry were introduced in 1990 by Anastas and Warner (**Table 1**) [6].

This review aims to illustrate the benefits of green chemistry, indicate ways of how to prepare green samples, and identify chromatographic methods and tools to assess the greenness of such methods.

2. The evolution of green chemistry

Many books dedicated to green analytical chemistry have been published, such as 'Green Analytical Chemistry' [2], 'Challenges in Green Analytical Chemistry' [2], and the 'Handbook of Green Analytical Chemistry' [4]. Special issues devoted to green analytical chemistry were also published in journals including Trends in Analytical Chemistry [7] and, more recently, Analytical and Bioanalytical Chemistry [8] and Bioanalysis [9–14]. Most of the twelve green chemistry principles apply to all areas of chemistry, while some of them apply precisely to analytical chemistry, e.g., the need for real-time monitoring for pollution prevention [15,16]; however, green analytical chemistry (GAC) is a branch of green chemistry concerned with different aspects of chemical analysis. It can be applied to sample preparation and the final determination step (**Figure 2**).

The presence or absence of the sample preparation step is a crucial aspect of analytical protocols and is often considered as the most polluting step in the entire chromatographic analysis, thus avoiding it is highly valuable [16]. Chromatography is a laboratory technique used for the separation of a mixture into its components, and it can be direct or indirect. Direct chromatographic methodologies meet the twelve principles of green chemistry by avoiding the consumption of organic solvents, sorbents, cartridges, fibres, etc., throughout sample preparation and by minimising the analysis time due to the absence of sample preparation procedures that permit further depletion of the analysis time [16]. The major disadvantage of direct chromatography is that it is only proper for samples with clean matrices [16] because the chromatographic columns might quickly degrade due to precipitation of sample components that do not elute from the column. Water, spirits, and petroleum fractions are examples of matrices that can usually be injected into chromatographic columns without sample pre-treatment; however, there are different ways of green sample preparations such as removing or minimizing the amount of solvents and reagents used in the analysis, miniaturisation of instruments and lowering the scale of analytical procedures, incorporating various operations and automation of sample preparation, sealing all vessels used throughout sample preparation, redemption and reusing the solvent, using green media such as ionic liquids, supercritical fluids, or superheated water, and implementing factors that magnify the efficacy of sample preparation, such as high temperature and/or pressure and microwave [16].

2.2 The impact of green chemistry on the environment and population

On behalf of the economic benefit, green chemistry accomplishes a great impact by reducing the quantity of materials needed to carry out analytical processes, such as solvents, solutions, water, and organic materials, and their storage [25]. In pharmaceutical analysis, the implementation of GAC allows substituting toxic chemicals with harmless and environmentally friendly alternatives, leading to move from waste to clean waste [16].

Due to the increase in the analytical activities nowadays, a great effect on environmental samples and the undesirable environmental constituents has been noticed. Recycling and pre-treatment of the residues generated by the pharmaceutical analysis become essential to return these residues to the environment with minimal harmful effects [17]; however, these processes are expensive, which leads to other economic issues that scientists should be aware of. Therefore, on-line and/ or off-line recycling with an additional benefit obtained by the recovery of costly and dangerous reagents. However, recycling should not sacrifice the accuracy and precision of the methodologies nor reduce the sampling throughput [17]. On the other hand, the population is impacted by pharmaceutical activities in different ways and on different fronts. A medication is made by different methods of analysis, reagents, solvents, operators, and techniques that influence the patient [17].

3. Chromatographic methods and their implementation in green chemistry

There are two main types of chromatography: gas chromatography (GC) and liquid chromatography (LC). Both types can be used for either preparative or analytical applications [18]. GC is a technique for the analysis of semi-volatile and volatile compounds. The application of the principles of green chemistry in GC can be implemented by removing or reducing the number of solvents used, avoiding the pre-treatment of the sample preparation step, and selecting the most environmentally safe carrier solvent, which is usually helium (He) due to its favourable chromatographic properties, such as high optimum linear velocity, non-toxic, non-flammable, inert, and safe to handle [18]. In LC, the separation occurs based on the interactions of the sample with the mobile and stationary phases (MP and SP, respectively). Thus, implementing green chemistry in GC is easier than in LC; however, there are a variety of methods for greening LC, such as the following:

3.1 Reducing the internal diameter of the column

The solvents used for separation could be minimised by reducing the MP flow rate, and this is possible when the internal diameter of the column is reduced. To obtain reasonable separations when the internal column diameter is reduced, the flow rate of the MP should be decreased by the square of the column diameter. As LC is often coupled with ultraviolet, fluorescence, and electrospray ionisation mass spectrometry as detectors, the reduction of the internal column diameter results in: improving the analytical sensitivity, due to the reduced dilution of the solutes in the MP and the presence of more concentrated bands at the detector and minimising the depletion of organic solvent and eventually the output of organic waste.

3.2 Reducing solvent consumption

Reduction of the solvent consumption can be performed by increasing the chromatographic productivity by reducing the particle size and shortening the column length [17]. Particle size reduction can be applied by using ultra-high-pressure LC, which leads to shortening of analysis time and depletion of column length and diameter, thus minimising the extra-column dispersion and enhancing MP delivery pressure [17].

3.3 Temperature optimisation

Temperature optimisation could affect the selectivity, efficiency, and detectability. It is considered easier than changing the MP or SP composition or buffering pH, but at the same time, elevated temperature has limitations, e.g., in case of using thermally unstable analytes or silica-based columns where the temperature should not exceed 60 °C [17]. When using this option in LC, there are some points that should be taken into consideration, e.g., the column should be provided with a thermostat and preheating of the MP must be attained before it enters the column and, with most detectors, cooled after it leaves the column. This assures that the signal of the detector will not be influenced by fluctuations in the eluent's temperature [17].

3.4 Using green components of the MP and SP

Mainly, in reverse phase liquid chromatography (RPLC), also known as hydrophobic chromatography, more than 90% of high-performance/pressure liquid chromatography (HPLC) are operated by RPLC [16]. In RPLC, the most used SP is octadecylsilyl silica (ODS, C18), in which chemically bonded to silica, thus it is less polar than the MP and analytes are eluted in order of decreasing polarity [19]. Mobile phases used in RPLC are acetonitrile/water and methanol/water mixtures, the earlier of which is more toxic; however, both acetonitrile and methanol are toxic, but menthol has lower disposal costs, therefore it is preferred. To follow the guide of 'greening the MP', water, acetone, methanol, and ethanol can be treated as environmentally friendly LC phases [16]; however, all of those solvents have advantages and disadvantages. For example, ethanol has the advantages of being less volatile and less dangerous with fewer dumping costs, but it is expensive. Acetone has the advantages of having reasonable solubility and forming a homogeneous mixture with other solvents such as water. On the other hand, it should be avoided as a MP, as it is a strong ultraviolet light absorber in the range up to 340 nm. Also, it is very volatile and difficult to be pumped in LC.

Another strategy that may benefit green LC is the use of monolithic SPs, a continuous unitary porous structure prepared by in situ polymerisation or consolidation inside the column tubing that may offer the use of high viscosity MPs such as an ethanol/water mixture [19]. They induce low-pressure drops by their macroporous structure, which allows the use of high MP flow rates that leads to shorter analysis time. This occurs by reducing the column diameter to save the solvent as well [16].

3.5 Using substances under supercritical conditions

Supercritical conditions include slight changes in the temperature, as well as the pressure, around or near the critical point of supercritical fluids (SFs). This results in changes to the physical properties like density, solubility, and volatility. Subsequently, carbon dioxide (CO_2) is an example of a supercritical fluid, which is considered an excellent choice for a green chromatographic MP due to its minor damaging environmental effects and cheap dumping costs, minimising the use of harmful solvents and additives and being safe in most cases [19]. The replacement of organic solvents with substances under supercritical conditions results in health, economic, and environmental benefits and huge improvements in the analytical field by making the experimental procedures much faster and cleaner. Additional advantages of supercritical fluids include good solubilising capacity, good mass transfer power, and reasonable selectivity, which allows us to explore more applications in separation techniques [19].

4. Tools of assessing the greenness of chromatographic methods

To evaluate the greenness of an analytical method, Galuzska et al. [19] developed a quantitative criterion named Eco-Scale, based on the approach proposed by Van Aken et al. [20]. This criterion is based on the application of penalty points, starting from the ideal 100-mark green analysis, amount of reagents used, hazards related to reagents and solvents, energy consumption, and wastes. Points for toxic reagents, waste generation, or high energetic demand are subtracted from the base 100 and based on the number of remaining points, the level of greenness of the analytical methods can be indicated. Therefore, the user can determine whether the procedure is ideally green, acceptable, or not. The Eco-Scale was modified to calculate the penalty points using mathematical equations, creating the green certificate (**Figure 2)**. Also, it classifies the methods using a colour code associated to a letter from A to G, with A being the greenest one [21]. Recently, another criterion was proposed, named the Green Analytical Procedure Index (GAPI), which is based on the National Environmental Methods Index (NEMI) database. NEMI was the first reported approach developed by United States' government agencies in collaboration with private companies to evaluate the persistent, bioaccumulative, and toxic (PBT) character of reagents and solvents, hazards, extreme pH conditions of the analysis (below 2 or above 12), and the amount of waste generated (more than 50 g) in a simple, visual circle diagram describing the four fields [21]. As shown in figure 2, NEMI is metric system based on a simple pictogram divided into four sections, each of them exhibiting various criterion (waste generation, reagents that are constant, toxic, whether reagents are hazardous, or the conditions are corrosive). These criteria are considered in a binary way: if a value of a criterion is achieved, the respective part of the pictogram is filled in with green colour; if not, it remains uncoloured [21]. To assess the green character of an analytical methodology, from sample selection to final determination, the GAPI is mainly used. GAPI was modified to include five different categories (health, environmental hazard, energy, waste, and safety hazard) and three levels of 'greenness' to calculate the environmental effect from each step of analytical methodologies (green, yellow, and red, representing low, medium,

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and high, respectively) [21]. If the sector of the diagram turns to green, then the method is green or environmentally friendly. Another NEMI modified pictogram with three levels of ‘greenness’ and four parts was proposed in 2011, including risks on operator, reagents consumption, consumption of energy, and number of wastes [21].

<Location of Figure 2>

4 Discussion

The emergence of the green chemistry concept in the United States can be attributed to a collaborative research effort involving interdisciplinary university teams, independent research groups, industry, scientific societies, and governmental agencies. Each of these entities has developed dedicated programs aimed at reducing pollution. The field of green chemistry encompasses a novel methodology for the production, manipulation, and utilization of chemical compounds with the explicit goal of mitigating risks to both human health and the natural environment. This novel methodology is alternatively referred to as environmentally benign chemistry, clean chemistry.

The concept of "benign-by-design chemistry" refers to the intentional design and development of chemical processes and products that prioritize safety, sustainability, and environmental friendliness.

The concept of green chemistry is sometimes delineated as a compilation of twelve principles that were initially articulated by Anastas and Warner, as shown in table 1 [1]. The principles encompass guidelines for professional chemists to effectively execute the development of novel chemical substances, syntheses, and technical processes. The initial principle elucidates the fundamental concept of green chemistry, which centres around safeguarding the environment against the detrimental effects of pollution. The remaining principles mostly address concerns related to atom economy, toxicity, energy use in solvents and other media, utilization of raw materials from renewable sources, and the breakdown of chemical products into environmentally benign chemicals.

This paper aims to discuss the 12 principles of green chemistry, which serve as a framework for designing chemical processes and products that are environmentally friendly and sustainable.

1. Prevention

The proactive prevention of trash is more advantageous than the reactive treatment or cleanup of waste subsequent to its generation [22-24].

2. The Concept of Atom Economy

Efforts should be made to optimize the integration of all materials employed in the synthetic process into the ultimate product [25,26].

3. Synthesis of Chemicals with Reduced Hazards

Whenever possible, it is advisable to develop synthetic procedures that employ and produce compounds with little or negligible toxicity to both human health and the environment [27].

4. The Development of Safer Chemicals: A Design Perspective

The design of chemical products should prioritize the achievement of their intended functionality while simultaneously minimizing their potential for toxicity [28].

5. Implementation of safer solvents and auxiliaries.

Efforts should be taken to minimize the reliance on auxiliary substances such as solvents and separation agents, aiming to render their use unnecessary whenever feasible and harmless when employed [28].

6. The concept of energy efficiency in design.

The environmental and economic implications of chemical processes necessitate the recognition and minimization of their energy consumption. Ideally, it is desirable to perform synthetic procedures under conditions of ambient temperature and pressure [29].

7. The utilization of renewable feedstocks

Whenever technically and economically feasible, it is preferable for a raw material or feedstock to be renewable rather than diminishing [29].

8. Decrease the utilization of derivatives.

It is advisable to reduce or prevent the utilization of unnecessary derivatization techniques, such as the employment of blocking groups, protection/deprotection, and temporary alteration of physical/chemical processes. This is due to the fact that these steps necessitate the use of extra reagents and have the potential to generate waste [30].

9. Catalysis

Catalysis is a chemical process that involves the acceleration of a reaction by a catalyst, which remains unchanged at the end of the catalytic reagents, which exhibit a high degree of selectivity, are considered to be more advantageous compared to stoichiometric reagents [30].

10. The concept of "Design for Degradation"

Refers to the intentional incorporation of degradation mechanisms into the design process of a product or system. This approach aims to enhance the sustainability and environmental performance of the product by it is imperative that chemical products are engineered in a manner that ensures their decomposition into harmless degradation products upon completion of their intended purpose, hence preventing their persistence in the environment [31].

11. The Application of Real-time Analysis in the Context of Pollution Prevention.

There is a need for further advancement in analytical approaches to enable real-time monitoring and control during the production process, in order to prevent the development of dangerous compounds [23].

12. The Implementation of Inherently Safer Chemistry as a Means of Preventing Accidents

The selection of substances and their respective forms in a chemical process should be conducted with the aim of minimizing the likelihood of chemical accidents, encompassing incidents such as releases, explosions, and fires.

<Location of Table 1>

4.1.The Effects of Green Chemistry

4.1.1. The analysis of pharmaceuticals

The chemical-pharmaceutical companies and laboratories are currently required to consider the principles of green chemistry in their analysis and beyond. The method selected, reagents utilized, accessories employed, personnel qualifications, and the time required for evaluating the quality of a product are all components of an environmentally conscious approach, as seen in Figure 3.

High performance liquid chromatography (HPLC) is widely regarded as the preferred approach for the analysis of active pharmaceutical components, as well as for the examination of contaminants and degradation products. Most of these procedures employ organic solvents, namely acetonitrile and/or methanol. Additionally, a significant number of individuals choose to utilize buffer solutions. This statement is irrefutable. However, many researchers have not made any efforts to explore alternative organic solvents in conjunction with the acetonitrile/methanol combination, nor have they incorporated buffer solutions into the mobile phase. What is the rationale behind this? The factors contributing to this issue include a deficiency in understanding, a disregard for the potential repercussions, and a preference for convenience and/or comfort [32-38].

<Location of Figure 3>

Buffer solutions, aside from necessitating a specific duration for their production, exhibit a limited period of stability, necessitating the need for fresh preparation and thereby leading to an extended dispensing duration. According to Kogawa and Salgado [39], the utilization of it necessitates a comprehensive cleansing procedure for both the column and the entire chromatographic system.

The presence of toxic organic solvents, such as acetonitrile and methanol, poses a significant risk to the health of individuals regularly exposed to these substances as shown in Figure 4. Furthermore, the appropriate management of waste is necessary to effectively dispose of these contaminants. The inclusion of this cost in the final product is a certainty, as stated by Pedroso et al. [34].

The accessories employed in the methodologies of analysis can also incorporate considerations of environmentally conscious practices. Chromatographic pre-columns are frequently deemed unnecessary; yet, they are employed due to the analyst's limited understanding, as they believe it to be an essential component. The analyst, due to a lack of expertise, performs unnecessary steps in the method to ensure that the result remains within the specified range, since they realize that omitting these steps will render the method erroneous and yield an out-of-specification outcome. There exists a category of devices that have the potential for reuse but are not being utilized in such a manner due to the company's practice of consistently purchasing new devices. This behaviour is driven by the convenience associated with discarding the old device and awaiting the arrival of a new one. This phenomenon has been discussed in the literature by [40-42].

Frequently, individuals possessing the necessary qualifications are tasked with the development of mundane assignments, which involve repetitive actions like to those performed by a robot. This approach tends to prioritize excessive processing of products and procedures, rather than fostering innovation, creation, and advancement within their respective domains of work. The current phenomenon under discussion can be categorized as a manifestation of intellectual inefficiency, which aligns with one of the eight recognized forms of waste in contemporary society. Kogawa et al. argue that the labour employed is highly skilled and experienced, although their performance in delivering services is subpar [37].
Is the duration of each step or analysis quantified? It is imperative. This phenomenon is an integral component in the field of green chemistry. The duration of an activity directly impacts the analyst's dependency on it, resulting in a reduced capacity to undertake further tasks. Consequently, this leads to decreased productivity and increased costs associated with the final product. The concept of time plays a crucial role in initiating and influencing the outcome of a process or service [43].

Hence, there is a present demand for more efficient and cost-effective methodologies, staffed by suitably experienced professionals, utilizing high-quality materials and accessories for analysis, and employing environmentally friendly reagents.

In the literature there are many physical-chemical and microbiological methods for the evaluation of drugs and pharmaceuticals which contemplate green analytical chemistry items such as HPLC methods using only ethanol and water in the mobile phase [40-44] spectrophotometry in the ultraviolet region (UV) using aqueous solution as diluent [45], spectrophotometry in the visible region (Vis) using aqueous solution as diluent [46], spectrophotometry in the infrared region (IR) using only potassium bromide as reagent [47], capillary electrophoresis (CE) with migration time less than 5 min and microbiological methods with results in 4 h [48].

<Location of Figure 4>

4.1.2. The global population.

The modern field of chemistry has diverse effects on several aspects of the population. The selection of analytical procedures and reagents employed by analysts or chemical-pharmaceutical operators has an impact on patients who regularly obtain their medication from pharmacies or health facilities. The utilization of a costly technique results in the production of a high-priced commodity inside the marketplace. The utilization of a costly technique, sometimes accompanied by optional accessories, results in the production of a higher-priced commodity within the market. According to Kogawa and Salgado [46], a costly technique involving supplementary components and many procedures, which may not always be obligatory, results in the production of a higher-priced commodity in the marketplace.

The utilization of a time-consuming methodology that yields results within a period of 24 hours or longer, such as the analysis of microbiological results for antibiotics, has the potential to increase the cost of products. Alternatively, if these results are not obtained prior to release, it may lead to inefficiencies that can contribute to the burden on the health system and the development of microbial resistance [49]. According to Taylor, the patient is unquestionably impacted by the analytical decision-making process in pharmaceutical analysis, the assessment of raw material quality, and the advancement of industrial or laboratory procedures [50]. The cost associated with each step of a process is transferred to the end product, which is subsequently borne by the patient. Furthermore, the impacts, whether positive or negative, also influence the cost of the final product.

4.1.3. The state of the planet.

The residues produced during chemical-pharmaceutical analyses necessitate pre-treatment prior to their release into the environment. Nevertheless, this procedure incurs a higher expense proportional to the toxicity and hazardous nature of the solvent.

One example of a compound that undergoes incineration is acetonitrile, which results in the generation of garbage that contributes to the phenomenon of acid rain. Despite employing a method to mitigate the harmful effects of the solvent, its usage still has adverse implications on human health [51]. Acid rain has been observed to cause detrimental effects on various aspects of the environment, including automobiles, structures, historical landmarks, plant life, bodies of water, and other related entities.

The vegetation has the potential to support agricultural plantations that provide sustenance for a significant number of individuals. The aquatic environment may experience alterations in pH levels, leading to modifications in the habitat that were previously conducive to the survival of specific creatures inhabiting the area. The isolation of such an effect is highly unlikely. Waste treatment is the process by which waste materials are managed, however, it is important to identify instances where trash is not subjected to treatment. The direct disposal of industrial waste into bodies of water might lead to the occurrence of ecological calamities. According to the World Health Organization [52], the presence of contaminants in water can lead to the mortality of fish and vegetation, resulting in a shift in the properties of the water and the occurrence of eutrophication.

4.1.4. Organization

Chemical-pharmaceutical companies are increasingly compelled to consider the principles of green chemistry and/or green analytical chemistry. This encompasses various aspects, ranging from the selection of reagents for pharmaceutical evaluation to interactions with collaborators and the provision of training for teams. The concept of green chemistry should be regarded as a sustainable notion, since it promotes the improvement of society, businesses, and interpersonal relationships towards a more environmentally friendly world. A corporation that prioritizes a contemporary and up-to-date approach is likely to achieve success. The organizational structure will consist exclusively of collaborators rather than employees. The structure will include of leaders rather than a single chief. The absence of vision is not limited to the final product, but extends across the entire chain, with the aim of achieving sustainability, environmental friendliness, and cleanliness [53]. Consequently, the organization experiences automatic growth. The company's aim is further enhanced as it serves as an exemplar and benchmark for ecological correctness, cleanliness, sustainability, and competitiveness within the market. The principle in question is exemplified by renowned companies such as Coca-Cola™, Google™, and Apple™ [54-56].

4.1.5. The operator (analyst)

The role of an analyst is a significant component in various industries and sectors. Analysts are responsible for conducting thorough research, gathering and the physical-chemical analyst maintains regular and frequent interaction with pharmaceutical analyses in their daily work. They are the primary individual impacted by the entirety of the analytic chain.

According to the World Health Organization, the human body rapidly absorbs toxic solvents like acetonitrile, which, upon metabolism, produces cyanide that hinders the process of respiration [49]. Another toxic solvent, which is likewise highly regarded in the field of pharmaceutical analysis, is methanol. The metabolites of this substance are excreted at a slower rate compared to ethanol. These metabolites, namely formaldehyde and mostly formic acid, are known to cause severe intoxication [57].

The analyst may encounter challenges related to the implementation of time-consuming and non-reproducible analytical techniques, which may necessitate the use of specialized equipment or involve multiple stages and reliance on other professionals. Furthermore, in addition to the potential exposure to toxic solvents and reagents, the analyst may also experience emotional strain [58].

The utilization of a time-consuming approach might lead to demotivation among analysts and result in the inefficient allocation of intellectual resources and effort. A precious resource is being allocated by a skilled individual who could perhaps engage in another endeavour. According to the findings of William Edwards Deming, one of the quality gurus, the utilization of ineffective methods can create a perception of professional inadequacy. It has been shown that in 85% of cases, the root cause of the problem lies not with the analyst, but rather with the method itself, indicating the need for improvement [59].

4.1.6. The future challenges

The strategy of addressing future challenges has been initiated by global leaders through various international conferences and agreements. These include the United Nations Conference on the Human Environment in Stockholm in 1972, Conference of Nairobi in 1982, United Nations Conference on Environment and Development in Rio de Janeiro in 1992, World Summit on Sustainable Development in Johannesburg in 2002, United Nations Conference on Sustainable Development in Rio de Janeiro in 2012, and the Paris Agreement in 2015 [28]. Within the realm of academia and professional settings, there exists a notable event known as the "Green & Sustainable Chemistry Conference." This conference serves as a platform for individuals from both academic and corporate backgrounds to showcase their research and engage in the sharing of ideas and knowledge [57]. These projects demonstrate the widespread support for green chemistry, which promotes sustainability, cleanliness, and ecological integrity. One potential approach to attaining an outcome that is perceived as unattainable is to devise strategies that focus on feasible objectives. It is imperative that we fulfil our respective responsibilities. When everyone contributes, regardless of the magnitude of their contribution, the collective assembly of these components yields a substantial outcome.

Ultimately, it is imperative to adopt optimistic viewpoints regarding the prospects of green chemistry, since it encapsulates the trajectory of our global landscape. The scope of green chemistry extends beyond the utilization of less harmful solvents in chemical analyses. This does not align with the principles and practices of green chemistry. Green chemistry encompasses a range of activities and attitudes, exhibiting a multifaceted nature [58]. The approach under consideration encompasses the entirety of the process while also aiming to reduce the usage of reagents, number of steps, overall expenses, and energy consumption. In the given context, it is imperative to consider the role of the protagonist. The well-being of collaborators, both in terms of their physical and mental health, serves as a distinguishing factor for firms. This is due to the recognition that an individual working in isolation can never possess the collective abilities and effectiveness of a cohesive team.

4.2. Exploring the Application of Eco-friendly Chemistry Principles in Pharmaceutical analysis

This review provided data that could be considered adequate to comment on the potential implications for green chemistry methods, particularly in the pharmaceutical field, where its implication is lacking; however, this review affirmed an implication for research to address the existing analytical problems and how to resolve them. Some of the examples of using green chemistry in pharmacy are:

4.2.1. Development of a model with multiple variables using desirability-based optimization for the assessment of antihypertensive combination by environmentally friendly HPLC technology with fluorescence detection.

An antihypertensive combination of atenolol, a ß1 selective adrenergic blocker, and hydrochlorothiazide, a thiazide diuretic, was analysed by a rapid and eco-friendly HPLC method combined with fluorescence detection [60]. To overcome all of the limitations of the reported methods in the literature, research was done to develop a new environmentally friendly, sensitive, and rapid reversed-phase high performance liquid chromatography with fluorescence detection (HPLC-FLD) method and complete separation of the two drugs in a shorter analysis time for the determination of this antihypertensive combination [60]. Atenolol and hydrochlorothiazide reference standards were kindly supplied by the National Organization for Drug Control and Research (NODCAR; Cairo, Egypt). The separation of the mixture was achieved using an Inertsil C18 analytical column (150 × 4.6 mm, 5miccro). The mobile phase used was ethanol:potassium dihydrogen phosphate at pH 3 (65:35 v/v), and the flow rate was 0.7 mL/min. The fluorescence detector operated at excitation and emission wavelengths of 230 and 310 nm (atenolol) and 270 and 375 nm (hydrochlorothiazide) [31], respectively. Moreover, ICH guidelines were followed for the validation of the developed method. The proposed method was found to be accurate and precise [60]. The linearity of the developed method covered a concentration of atenolol of 0.05–5 µg/mL and a concentration of hydrochlorothiazide of 0.02–1 µg/mL [60]. The greenness of the developed method was evaluated by the analytical Eco-Scale and the GAPI assessment tool and has proven to be an excellent eco-friendly alternative to the reported methods in the literature [60]. GAPI consists of five pentagrams, which represent the environmental impact of the method developed. It is coloured in three different colours: red, yellow, and green, corresponding to high, medium, and low impacts. When comparing the developed method with the reported chromatographic methods, it was found to be a successful eco-friendly alternative method [60].

4.2.2. Green separation of antihyperlipidemic combination using ultra-high performance liquid chromatography (UHPLC)

In Dr. Al-Tannak's laboratory, separation by ultra-high pressure liquid chromatography (UHPLC), a rapid chromatographic method with better resolution and economical use of MP compared to HPLC, and monolithic columns are considered effective separation methods with shorter analysis time without effecting the separation efficacy and resolution [61]. Scientists tried severely to decrease the particle size and the shape of the particles to separate them effectively, but this was accompanied by a dramatic increase in the backpressure. High backpressure is considered as one of the most important factors in chromatography's flow control, especially in UHPLC [61]. The separation of the antihyperlipidemic mixtures was carried out using two columns: silica-based particle packed column UHPLC and a monolithic column [61]. The key goal of this study was to fully separate an antihyperlipidemic combination using the two columns. The performance of both columns was compared. The resolution of the analytes on both columns was performed by applying GAC principles [61]. One of the principles of GAC is to shorten the time between the start of the analysis and obtaining a reliable analytical result, and this was achieved by using the adopted conditions, which allowed rapid separation of the analytes in a short time. Using substitute solvents that are non-toxic to the environment, shortening the analysis time, and obtaining accurate and precise analytical results are important characteristics of GAC principles. The systematic suitability of the two columns was compared for the separation of fenofibrate, its active metabolite (fenofibric acid), and pravastatin, using atorvastatin as an internal standard [61]. Separation on both columns was obtained using ethanol:potassium dihydrogen orthophosphate buffer pH = 3 (adjusted with orthophosphoric acid) (75:25 v/v) as the mobile phase and a flow rate of 0.8 mL/min. The analytes' peak detection was achieved using a photodiode array (PDA) detector at 287 nm, 214 nm, 236 nm, and 250 nm for fenofibrate, fenofibric acid, pravastatin, and atorvastatin, respectively. The reduction of backpressure was achieved with the monolithic column, where the analytes could be completely separated in less than 1.5 min at a flow rate of 5 mL/min. The principles of GAC were followed throughout the developed method using environmentally safe solvents [61].

4.2.3. Green Pharmaceutical Analysis of Rifaximin in dosage form by HPLC-MS and Microbiological Turbidimetry

Rifaximin (C43H51N3O11, 785 g mol−1) is an oral antimicrobial, derived from rifamycin, used for the treatment of hepatic encephalopathy, ulcerative colitis, irritable bowel syndrome, Clostridium difficile, travellers' diarrhoea, and acute diarrhoea [62]. It lacks analytical methods in official compendia for evaluation of the final product. An eco-friendly pharmaceutical analysis of rifaximin in tablets by liquid chromatography-mass spectrometry (LC–MS) and microbiological turbidimetry was done using HPLC analysis performed on an HPLC system

(Waters, Barueri, Brazil) equipped with a binary gradient chromatography pump (Model 1525 Waters; Waters, Barueri, Brazil), a manual injector (Model Breeze 7725i Rheodyne; Waters, Barueri, Brazil), a UV–vis detector (Model 2487 Waters; Waters, Barueri, Brazil), and an Eclipse Plus C18 5-μm column (150 mm × 4.6 mm, 5.0-μm particle size; Agilent, Santa Clara, CA) [62]. High-performance liquid chromatography coupled with mass spectrometry (HPLC-MS) analysis was performed on an HPLC system (Shimazdu, Kyoto, Japan) connected to an ion trap mass spectrometer (Bruker, Atibaia, Brazil) operating in positive ion electrospray ionization (ESI) mode [62]. The method was completely validated according to the International Conference on Harmonization guidelines and developed following the concept of quality-by-design. The separation was achieved using a C18 column, purified water + 0.1% glacial acetic acid and ethyl alcohol [52:48 (v/v)] as mobile phase, and a flow rate of 0.9 mL min^{-1} at 290 nm, and ambient room temperature [62]. Mass spectral analyses were performed using an ESI source and ion trap mass analyser [62]. The method can also be considered indicative of stability, as it is able to identify degradation products of rifaximin in tablets. Therefore, it can be used in routine analysis and stability studies by chemical-pharmaceuticals laboratories [62].

5 Conclusions

Green chemistry is a research field that has become a trend in analytical chemistry worldwide. Innovations toward more sustainable green analytical approaches to minimise toxicity without affecting analytical performance have been proposed. This could be evident at all steps of analysis by minimising operator risk and environmental contamination with lower consumption of chemicals and waste generation. As the interest in GAC enhances, different tools have been used for the evaluation of analytical methodologies, e.g., GREEnness. This freely downable software is a metric system for the assessment of greenness of the analytical procedures making the analysis quick and easy. The GAPI and Eco-Scale are other comprehensive tools that allow the greenness of the analytical procedures to be assessed. However, further developments are required as there are still analytical problems to be solved in a more environmentally friendly way, which demonstrates GAC as a fruitful research area.

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Author contribution

Obligatory (please include proper contribution categories for each author; applicable categories are listed on this website: https://casrai.org/credit/).

This section should be prepared according to the following scheme (an example):

Bashyer J. Al-Shatii: Writing – original draft, Writing – review & editing, Methodology, Formal Analysis; **Zahra Alsairafi :** participated in writing parts of the manuscript, final readings, and revisions; **Naser F. Al-Tannak:** originated the idea for this manuscript, participated in writing the manuscript and final revisions, Methodology, resources, Project administration.

Conflict of interest

Authors state no conflict of interest.

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Figure captions

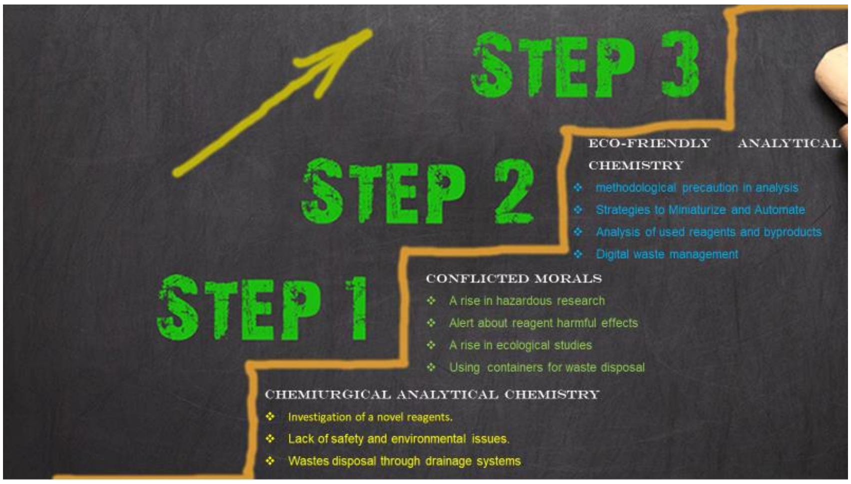
Figure 1: Analytical laboratories' developmental steps toward an ecological mindset.

Figure 2: Evolution of greenness indicators NEMI and GAPI through time.

Figure 3: The model of correct ecological thinking.

Figure 4: Solvent selection guide for green chemistry.

Figures



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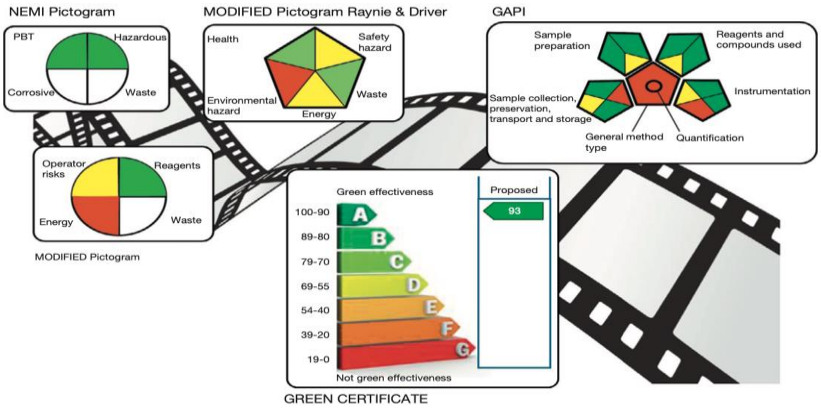

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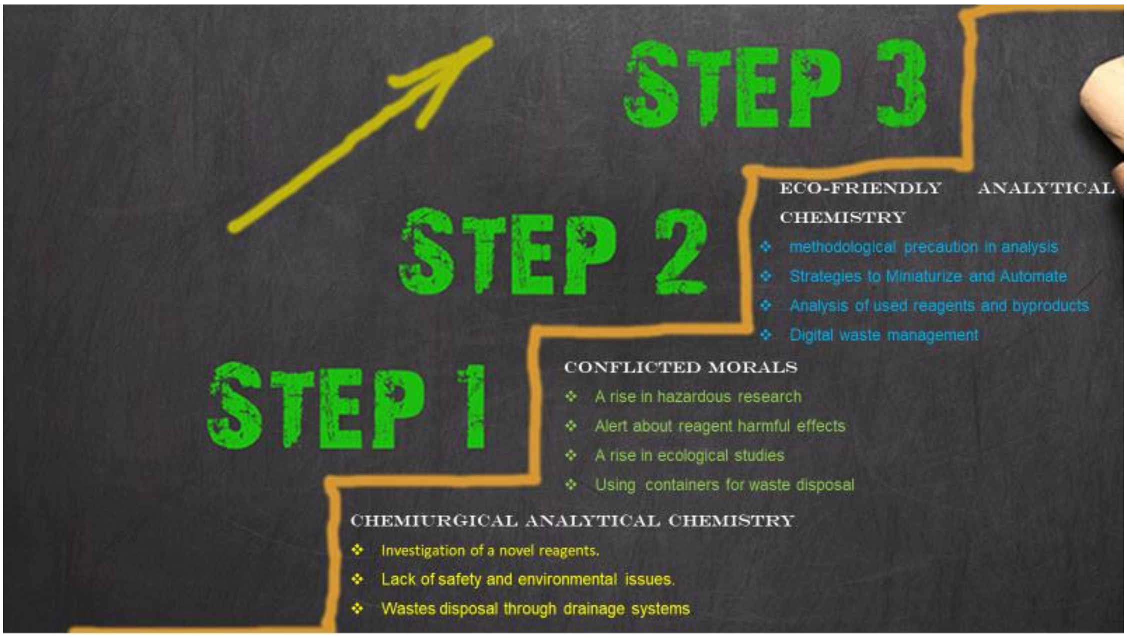
Tables and Table captions

Table 1. the 12 principles of green chemistry and their implementation in green analytical chemistry.

Principle	Explanation	Examples of implementation in green analytical chemistry
1. Prevention	Prevent waste to avoid the need of cleaning or decontamination procedures, it is better to prevent waste rather than treat or clean waste afterwards	Application of solventless extraction techniques, application of direct determination methodologies
2. Atom economy	Design synthetics methods to maximize the incorporation of all materials used in the process into the final products to reduce wastes and improve the synthesis yield.	-
3. less hazardous chemical synthesis	Design synthetics methods to use and generate substances that minimize toxicity to human health and the environment	On-line analytical waste detoxification
4. designing safer chemicals	Safer chemicals and products to accomplish their desired effect while minimizing their risks or toxic effects	-
5. safer solvents and auxiliaries	Safer solvents and reaction conditions to improve the use of water or eco-friendly solvents that do not contribute to smog formation or ozone layer depletion	Substitution of toxic solvents with less toxic ones; solventless extraction techniques: direct analysis
6. design for energy efficiency	Minimize the energy requirements of chemical processes and conduct synthetic methods at ambient temperature and pressure if possible	Application of microwave, ultrasound, or pressure-assisted extraction to minimize energy consumption (much shorter extraction time)
7. use of renewable feed stocks	Renewable raw materials or feedstock media fossil fuel whenever practicable	-
8. reduce derivatization	minimize or avoid unnecessary derivatization, if possible, as it requires additional reagents and generates waste	Derivatization should be avoided when possible
9. catalysis	Catalytic reagents are superior to stoichiometric	-
10. design for degradation	Design chemicals and products so they break down into innocuous products that do not persist in the environment	-
11. real-time analysis	real-time analysis for pollution prevention thus involving in-field analysis and real time monitoring prior to the formation of hazardous substances	Development of procedures that allow obtaining analytical results with short (preferably no) time delay

12. accident prevention	Minimize the potential for accidents like explosions, fires, and releases to the environment	Application of solventless techniques to prevents occupational exposure, real time monitoring, miniaturization

Figure 1



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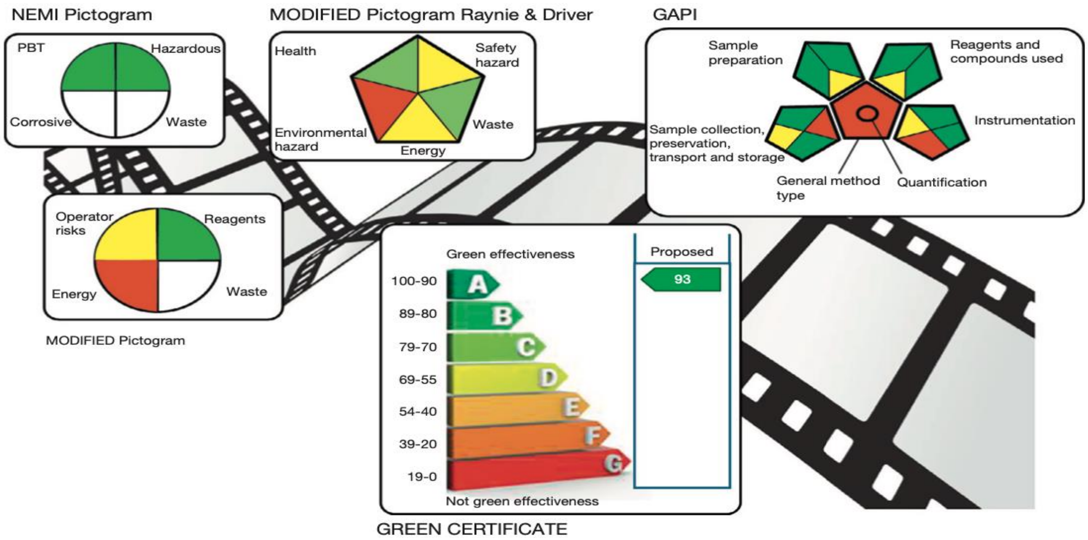

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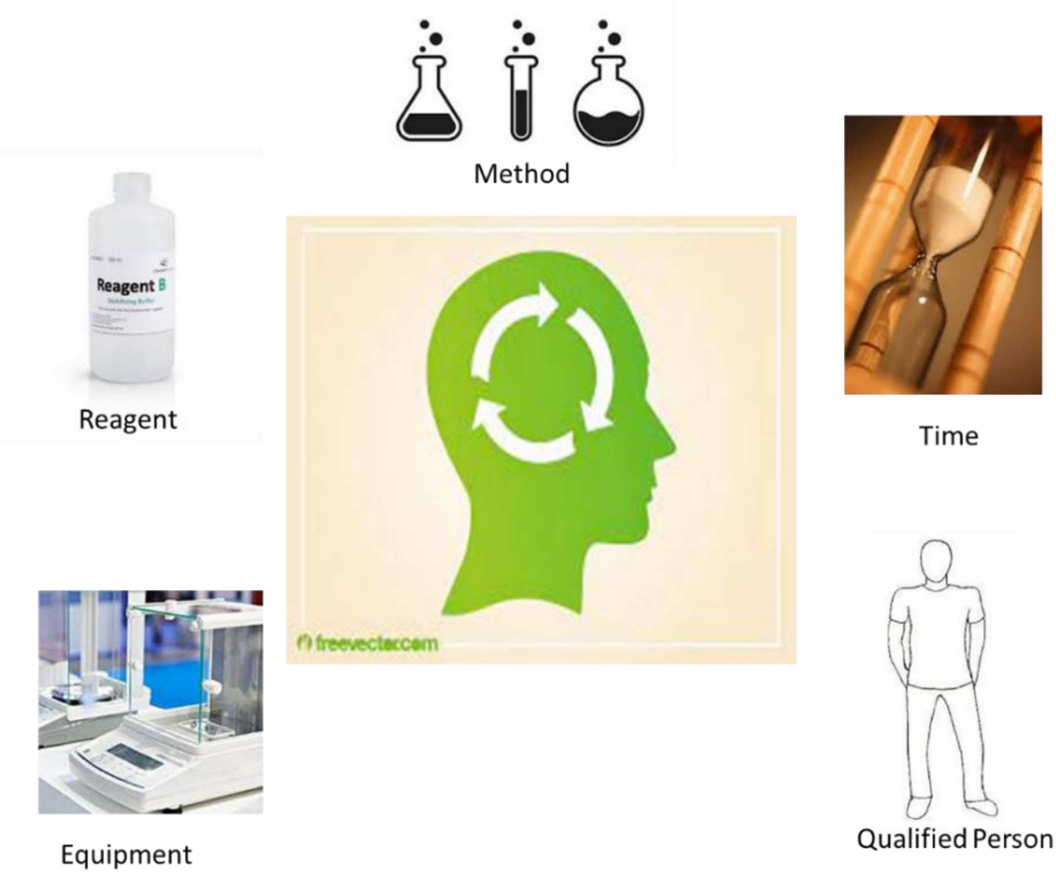
Figure 3



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