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Green Analytical Chemistry in Pharmaceutical Analysis integrating Sustainability with innovation

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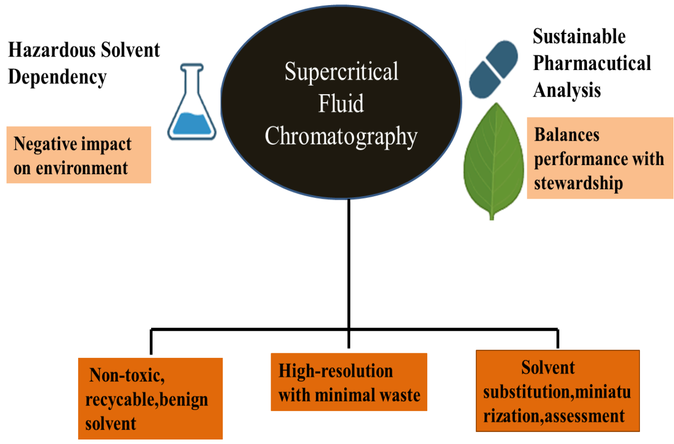
Abstract

The goal of green analytical chemistry (GAC) is to reduce the negative effects of chemical analysis on the environment and human health by incorporating green chemistry principles into contemporary analytical procedures. Supercritical Fluid Chromatography (SFC) is a crucial green analytical method in pharmaceutical analysis, and this review emphasises its efficiency, sustainability, and decreased dependency on hazardous organic solvents. SFC uses supercritical CO_2, a non-toxic, recyclable, and environmentally benign mobile phase, in contrast to traditional chromatographic techniques that use dangerous solvents like acetonitrile and methanol. This allows for quick, high-resolution separations with little waste production. The article covers the basic ideas, separation mechanisms, equipment, and various uses of SFC, especially in drug analysis, impurity profiling, and chiral separations. Innovations in green chemistry, including solvent substitution, miniaturised techniques, and sustainability assessment tools, further support eco-friendly pharmaceutical analysis. All things considered, SFC is a strong, sustainable substitute that balances analytical performance with environmental stewardship and legal compliance.



1. Introduction

1.1 Green Chemistry

The growing area of "green analytical chemistry" (GAC) aims to reduce the harmful effects of chemical analysis on the environment and people's health by using green chemistry ideas in testing methods. The fast growth of cities and the increase in people have made it harder for humans and nature to work together, quickly using up natural resources. We really need to find ways to use natural resources in a balanced way and protect the environment. The concept of "Green Chemistry" came about because of these problems, with the aim of reducing environmental pollution and developing sustainable alternatives to traditional industrial chemicals [2,3]. GAC tries to align analytical methods with the broader goals of sustainability by using fewer harmful chemicals, reducing energy consumption, and avoiding the creation of dangerous waste. The 12 principles of green chemistry form a detailed guide for creating and using environmentally friendly analytical methods, and they serve as the foundation of GAC [4].

1.2 Principles of green chemistry

The pharmaceutical industry faces big challenges when it comes to cost and how well it works, especially in countries that are still developing. Green chemistry aims to develop chemical methods and products that reduce or eliminate the creation and use of harmful substances. Because of this, the pharmaceutical industry is really worried about using green chemistry ideas to fix both money and environmental problems [5]. By promoting the use and making of safer and more eco-friendly chemicals, the idea of reducing harmful chemicals aims to develop new industrial methods [6]. The reason for using renewable materials in chemical processes is to make things more sustainable and reduce harm to the environment. Cellulose, lignin, and other materials from wood, as well as lactic acid and chitin, are all examples of renewable materials, as shown in Figure 1[7].

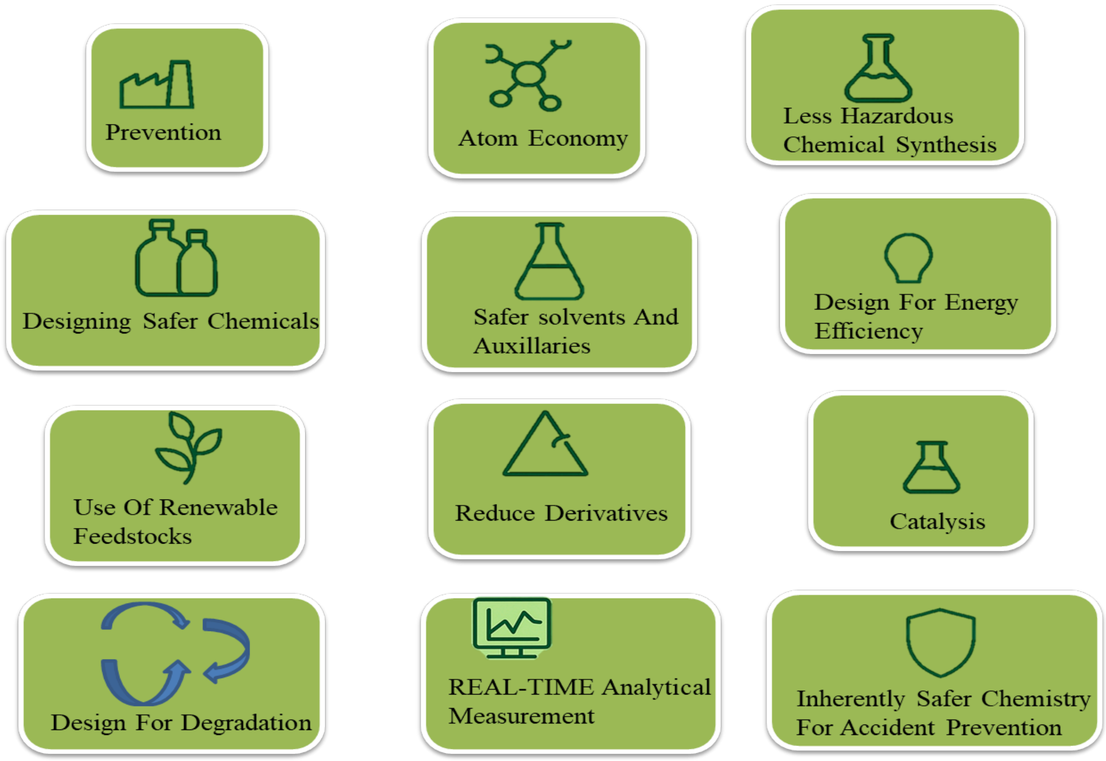


Figure 1: Principles of Green Chemistry

2. Supercritical Fluid Chromatography

Green Analytical Chemistry aims to develop testing methods that keep the same level of accuracy and effectiveness but have less harm on the environment, by using less dangerous chemicals and making the process more eco-friendly. Traditional liquid chromatography methods, such as HPLC, often use organic solvents like acetonitrile, methanol, and tetrahydrofuran, which can be harmful and create dangerous waste [8]. In contrast, Supercritical Fluid Chromatography (SFC) is a more environmentally friendly approach because it uses supercritical CO_2 as the mobile phase. This substance is not toxic, is widely available, cost-effective, and can be reused, making SFC a better choice for green analytical techniques. SFC allows for fast and efficient separations with minimal harm to the environment by combining the dissolving ability of liquid chromatography (LC) with the high speed and low resistance of gas chromatography (GC) [9]. Over the last ten years, SFC has been widely used in quality control, separating chiral compounds, pharmaceutical research and development, identifying impurities, and analysing natural products.

This review highlights key aspects of SFC, with a focus on innovation, how it works sustainably, and its use in pharmaceutical sciences [10].

2.1 PRINCIPLES OF SUPERCRITICAL FLUID CHROMATOGRAPHY

A supercritical fluid is a substance that is heated and pressurised beyond its critical point, so it has characteristics of both gases and liquids. Right now, the fluid has a density like a liquid, which helps it dissolve substances well, but its viscosity is more like a gas, making it easier for materials to spread out and move around quickly. These features make SCFs perfect for chromatography, where moving substances through the system and separating them effectively is very important [11]. Carbon dioxide is the most commonly used supercritical fluid in supercritical fluid chromatography. This is because it has a relatively low critical temperature of 31.1°C and a critical pressure of 73.8 bar. CO2 is a good alternative to organic solvents because it is easy to get, not harmful, and won't catch fire. To change the direction of the mobile phase and make it easier for polar substances to dissolve, people often add co- solvents such as methanol, ethanol, or acetonitrile [12].

2.3 Mechanisms of Separation in SFC

In supercritical fluid chromatography, factors like how well substances dissolve, how they move through the system, and how they interact with the moving liquid, the fixed material, and the compounds being analysed all play a role in how the separation happens. SFC separations are mainly caused by these mechanisms.

2.4 Solubility-Based Separation

Changes in temperature and pressure can affect how soluble different substances are, which in turn changes how long they take to separate, because supercritical fluids have adjustable solvating power [13].

2.5 Partitioning Mechanism

SFC works by separating substances between the supercritical mobile phase and the stationary phase, similar to how reversed-phase chromatography operates. Keeping nonpolar compounds is mostly because of hydrophobic interactions [14].

2.6 Adsorption Mechanism

In normal-phase SFC, the substances interact with polar stationary phases, and they form dipole interactions, hydrogen bonds, and van der Waals forces [15].

2.7 Chiral Recognition

To achieve chiral SFC separations, enantiomers must interact with chiral selectors present in the stationary phase. These interactions might include things like steric effects, π-π interactions, and hydrogen bonding [16].

3. Application of Green Solvents

A key step in making methods more eco-friendly and sustainable is the use of water, ionic liquids (ILs), supercritical carbon dioxide (SC-CO2), and biobased solvents in analytical processes [17,18]. This replaces traditional water-based mobile phases or buffer solutions with green and eco-friendly solvents—for organic solvents [19]. Ethanol is considered the most environmentally friendly option compared to potentially harmful solvents like methanol and acetonitrile [20]. These solvents are designed to reduce their negative impact on the environment, lower their toxicity, and enhance sustainability. Besides that, supercritical carbon dioxide ($scCO_2$) used in supercritical fluid chromatography (SFC) and ionic liquids, which are non-volatile and can be reused, are good alternatives to traditional organic solvents [21].

4. Green sample preparation technique

4.1 Solid Phase Microextraction (SPME)

SPME shortens the time needed to prepare samples and does away with the need for solvents. For volatile and semi-volatile substances, it works well [22].

4.2 Microwave-Assisted Extraction (MAE)

MAE uses microwave energy to speed up extraction, cutting down on solvent volume and extraction time [23].

4.3 Ultrasound-Assisted Extraction (UAE)

UAE uses sound waves to release analytes efficiently and with little solvent [24].

4.4 Miniaturised Techniques

Sustainability is supported by methods like microfluidics and lab-on-a-chip systems, which reduce reagent consumption and energy input [25].

5. Instrument

Supercritical CO2 is the main substance used to move compounds through the system in Supercritical Fluid Chromatography equipment, which is part of green analytical chemistry. This method uses much less harmful organic solvents and helps reduce harm to the environment. The system includes a modifier pump that puts in small amounts of polar co- solvents, such as ethanol or methanol, to help dissolve things better, and a high-pressure CO2 pump, along with a cooling part to keep the CO2 in a liquid state before it is pressurised. A column oven manages the temperature, which is between 35 and 70 degrees Celsius, and this temperature influences the density of CO2 and how well the separation works. At the same time, an autosampler delivers the samples with controlled pressure. Different types of stationary phases, like silica, diol, C18, amino, and chiral columns, enable effective compound separation. To maintain CO2 in its supercritical state, a back-pressure regulator keeps the pressure consistent. UV/Vis, flame ionisation, and mass spectrometry are typical ways to detect substances; mass spectrometry is very sensitive and has very little background interference. This equipment enables quick, energy-saving, and eco-friendly analysis that follows green chemistry principles [26-29].

6. Applications of SFC

There are applications for food, environmental, and pharmaceutical products. Other examples of materials that can be used are pesticides, herbicides, polymers, explosives, and fossil fuels. This method can help study different groups of medicines, like antibiotics, prostaglandins, barbiturates, steroids, Taxol, vitamins, non-steroidal anti-inflammatory drugs, and other similar substances. For some pharmaceutical mixtures, separating the chiral components should be possible. Because carbon dioxide, which is the most commonly known supercritical fluid, isn't good at dissolving polar substances, supercritical fluid chromatography is mainly used for non-polar mixtures. Requests to analyse fragrant materials or other types of hydrocarbons can lead to the use of supercritical fluid chromatography in the petroleum industry [30,31,32].

7. Innovation in green chemistry

Modern green techniques such as supercritical fluid extraction, ultrasound-assisted extraction, and biocatalytic conversions help make analytical processes more friendly to the environment. Using green solvents, automating workflows, and working with smaller sample sizes help reduce risks and make processes run more smoothly [33]. Tools such as the Analytical Greenness metric (AGREE), the Green Analytical Procedure Index (GAPI), and Sample Preparation Sustainability metrics offer clear ways to measure how eco-friendly a method really is. Thanks to these developments, green analytical chemistry is now at the intersection of environmental responsibility and high-quality analytical practices [34]. By implementing solvent-free synthesis methods, using biocatalysts for sustainable and selective chemical reactions, and applying real-time process analytical technology (PAT) to minimise waste, innovations in green chemistry are transforming the pharmaceutical manufacturing sector [35]. Through advanced synthetic approaches, leading companies such as Boehringer Ingelheim and GSK have seen significant improvements in energy efficiency, reductions in greenhouse gas emissions, and lower consumption of solvents. Also, continuous-flow synthesis and the ideas behind the circular economy help us use fewer resources and make products last longer in a sustainable way. At the same time, artificial intelligence helps green chemistry by making better sustainable methods and improving how chemical reactions work [36].

8. Application in Pharmaceutical Analysis

Green chemistry is used in pharmaceutical analysis in many different ways, and it aims to create methods that help protect the environment without affecting how well the analysis works. Techniques like Green Liquid Chromatography (GLC) and Supercritical Fluid Chromatography (SFC) help reduce or avoid the use of harmful organic solvents, which lowers the amount of chemical waste [37]. Spectroscopic methods such as Near-Infrared (NIR) and Raman allow for quick, non-destructive, and real-time testing of medicines, making it easier to check quality without needing a lot of sample preparation. Capillary electrophoresis and microextraction methods also help in using less solvent and improving detection sensitivity. These methods follow green chemistry standards and help meet the rules for safety and sustainability in pharmaceutical quality control and research [38].

9. Challenges and Future Perspectives

Challenges and future directions in using green chemistry for making drugs involve things like technical difficulties, expensive setup costs, and the need to train workers and get the whole industry on board with these changes. Regulatory challenges and the difficulty of adding new green technologies to current production processes are big problems, as shown in Figure 2 [39].

Conclusion

This review demonstrates that Green Analytical Chemistry (GAC) is an essential tactic for minimising pharmaceutical analysis's environmental impact while preserving analytical precision and dependability. Because Supercritical Fluid Chromatography (SFC) uses supercritical CO2 as a non-toxic, recyclable, and environmentally benign mobile phase, it is a highly effective green alternative to traditional chromatographic techniques. SFC closely adheres to the 12 principles of green chemistry by reducing waste production and the use of hazardous organic solvents. Its capacity to provide quick, high-resolution is especially useful for chiral separations, impurity profiling, and drug analysis. Its eco-friendly profile is further strengthened by the use of sustainability assessment tools, automation, miniaturised systems, and green solvents. It is anticipated that ongoing developments and greater industry awareness will improve its wider implementation despite obstacles like high operating costs, technical complexity, and regulatory barriers. All things considered, incorporating SFC into GAC offers a solid route toward environmentally conscious, effective, and sustainable pharmaceutical analysis.

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