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An Overview of Recent Advances in Green Chemistry Strategies for Pharmaceutical Synthesis

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ABSTRACT

Green Chemistry (GC) is an emerging and dynamic field that is gaining considerable attention in both academic and industrial settings. A core strategy in GC involves replacing hazardous solvents with safer, more environmentally benign alternatives that can be seamlessly integrated into chemical processes. One of the most prominent branches of GC is Green Analytical Chemistry (GAC), which emphasizes the reduction or elimination of toxic, harmful, and environmentally persistent chemicals through the innovative design of products and processes. This approach represents a modern and science-driven method for environmental protection, playing a significant role in addressing issues such as global warming, acid rain, and climate change. At its foundation, green chemistry promotes higher efficiency, improved selectivity, and reduced waste generation making it a vital tool in combating environmental pollution. In the chemical industry, the primary objective is to reduce negative impacts on both human health and the environment. Achieving this requires researchers to focus on extending the life cycle of chemicals through strategies that involve risk minimization and the evaluation of potential hazards in a sustainable manner. With the global population expected to reach 9 billion by 2055, it becomes increasingly important to preserve critical resources like food, energy, fibers, and animal feed. The future depends on sustainable, renewable innovations that can help meet these growing demands. Green chemistry also faces interdisciplinary challenges. To fully understand and apply GC principles, collaboration across diverse scientific and engineering disciplines is necessary. Even emerging fields such as biochemistry and nano-chemistry hold significant potential to contribute meaningfully to advancements in green chemistry research.

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1. INTRODUCTION

Green Chemistry is an innovative approach to designing chemical processes and products that aims to minimize or eliminate the use and generation of substances that are harmful, toxic, or bio-accumulative to humans and the environment. It emphasizes the development of environmentally benign raw materials and production methods that support both ecological health and human well-being. This discipline encourages scientists and researchers to create systems that align with natural bio-geochemical cycles, fostering a more sustainable and balanced way of living. Unlike environmental chemistry which primarily focuses on identifying pollution sources, understanding environmental processes, and measuring contamination green chemistry is proactive. It seeks to address environmental challenges by creating safer alternatives and cleaner technologies that prevent pollution at its source, thereby contributing to a healthier planet and sustainable development.

2. Definition

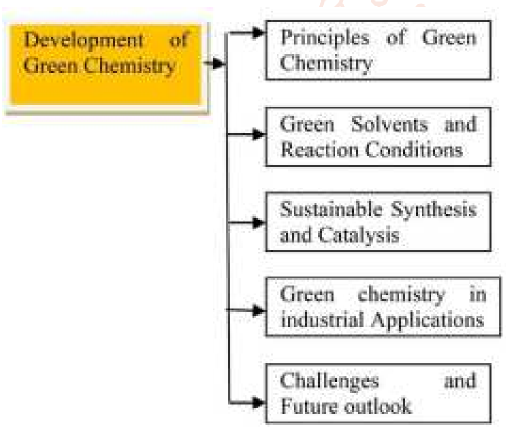
Green chemistry, also known as sustainable chemistry, is a branch of chemistry and chemical engineering that focuses on designing chemical products and processes in ways that significantly reduce or completely eliminate the use and production of hazardous substances. Its goal is to promote safety, efficiency, and environmental responsibility throughout the chemical lifecycle.

3. History

The term green chemistry was coined in 1991 by Paul T. Anastas as part of a U.S. Environmental Protection Agency (EPA) initiative aimed at promoting sustainable practices in chemical research and industry. This program encouraged collaboration between industry, academia, and government to foster environmentally responsible technological innovation. In 1995, the U.S. launched the Presidential Green Chemistry Challenge, a national effort to recognize and support outstanding contributions in sustainable chemistry. The following year, in 1996, the International Union of Pure and Applied Chemistry (IUPAC) established the Working Party on Green Chemistry to promote global cooperation in the field. Notably, in 1990, the Royal Society of Chemistry (RSC) took a pioneering step by publishing the first book and two dedicated journals on green chemistry, laying a foundation for research and awareness. Green chemistry represents a modern approach to the synthesis, application, and management of chemicals, aiming to reduce risks to human health and the environment. This movement includes principles such as clean chemistry, atom economy, and the development of safer alternatives.

Atom economy

Environmentally benign chemistry



4. Principles of Green Chemistry

1. Prevention of Waste

It is more effective to prevent the formation of hazardous substances than to treat or manage waste after it has been produced. This principle emphasizes designing chemical processes that inherently avoid the generation of toxic, explosive, or environmentally harmful by-products.

Examples:

- Discouraging the production of nuclear, non-nuclear weapons, explosives, and hazardous biochemical agents in both industrialized and developing nations, as these contribute significantly to environmental pollution.
- Limiting the excessive use of natural resources like coal and petroleum, whose combustion emits harmful gases, leading to environmental problems such as acid rain and global warming.

2. Atom Economy

Chemical reactions should be designed to maximize the incorporation of all starting materials into the final product. This approach minimizes waste and ensures that raw materials are used efficiently.

Example:

In a reaction where one mole of benzene reacts with 4.5 moles of oxygen to form one mole of maleic anhydride, two moles of carbon dioxide, and two moles of water:

Atom Economy = (Mass of desired product Total mass of reactants) × 100 = (98222) × 100≈44.1%\text {Atom Economy} = \left (\frac {\text {Mass of desired product}} {\text {Total mass of reactants}} \right) \times 100 = \left (\frac{98}{222} \right) \times 100 \approx 44.1\% Atom Economy = (Total mass of reactants Mass of desired product) × 100= (22298) ×100≈44.1%

This indicates that only 44.1% of the reactant mass is retained in the desired product, suggesting room for improved efficiency.

3. Designing Safer Chemical Syntheses

Chemical processes should be designed to use and generate substances that are non-toxic and environmentally benign. The goal is to minimize health and ecological hazards associated with chemical manufacturing and use.

Example:

The synthesis of a chemical product should avoid intermediates or reagents that could harm human health or damage ecosystems, favoring alternative methods and materials with a lower environmental impact.

4. Avoiding Hazardous Chemical Syntheses

Chemical reactions should be designed to prevent the use or production of highly toxic, hazardous, or environmentally damaging substances.

Examples:

- Avoid the synthesis of organ mercury compounds, which were responsible for the **Minamata disaster**.
- Prevent the production of methyl isocyanate (MIC), the compound that caused the **Bhopal gas tragedy**.

5. Designing Safer Chemicals

Chemicals should be designed to perform their intended function while minimizing toxicity, bioaccumulation, and harmful environmental transformation.

Example:

- **2,4-Dichlorophenoxyacetic acid (2,4-D)** is a selective herbicide that targets only broadleaf weeds, reducing harm to other plant species and the environment.

6. Use of Safer Solvents and Auxiliaries

Auxiliary substances such as solvents, separation agents, or additives should be as non-toxic and environmentally benign as possible.

Example:

- **Supercritical carbon dioxide** is considered a green solvent because it is non-toxic, non-flammable, and does not contribute to pollution or mutations.

7. Energy Efficiency

Chemical processes should be optimized to reduce energy consumption. Reactions that proceed at ambient temperature and pressure are preferred, especially with the help of effective catalysts.

Example:

- The **Haber process** for ammonia synthesis: N2+3H2→2NH3N_2 + 3H_2 \rightarrow 2NH_3 N2+3H2→2NH3 is conducted at 673–723 K and 200 atm using an iron catalyst to improve energy efficiency.

8. Use of Renewable Feedstocks

Whenever possible, raw materials should come from renewable sources rather than finite ones like petroleum or nuclear fuel. Renewable feedstocks are replenished through natural or biochemical cycles.

Example:

- **Furfural** can be obtained from agricultural waste such as **bagasse**, and residues from wheat and rice crops.

9. Reducing Derivatization

Unnecessary derivatization steps such as using protective groups or blocking agents should be avoided, as they increase waste and require additional reagents and steps.

Example:

- In the industrial synthesis of **semi-synthetic antibiotics** like **ampicillin** and **amoxicillin**, enzymatic methods are used to avoid protecting groups and reduce chemical waste.

10. Designing for Degradation

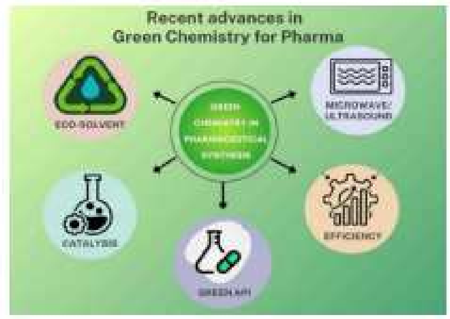
Chemical products should be designed to degrade safely and completely into harmless substances after use, avoiding environmental persistence and biomagnifications.

Example:

- **Polylactic acid (PLA)** is biodegradable, bioactive thermoplastic polyester that breaks down into non-toxic components via biological and physical processes.

11. Real-Time Monitoring for Pollution Prevention

It is critical to monitor chemical processes in real time tracking parameters such as temperature, pressure, and product formation to prevent the formation of hazardous by-products and ensure process control.



Sustainable Solvent Selection in Pharmaceutical Synthesis

Within the scope of green chemistry, minimizing the use of solvents has become a significant concern in industrial organic synthesis due to their environmental and health hazards. In the pharmaceutical sector, solvents contribute to over 60% of the total materials processed or discarded as waste. Therefore, selecting appropriate and environmentally friendly solvents is a key consideration when developing sustainable synthetic processes, particularly in drug manufacturing.

Catalysis and Green Chemistry in Pharmaceutical Synthesis

Catalysis plays a pivotal role in enabling green chemistry practices. It involves using substances known as catalysts to accelerate chemical reactions without being consumed in the process. Catalysts enhance reaction efficiency, reduce energy requirements, and minimize waste. They are generally categorized as either heterogeneous catalysts (in a different phase from the reactants) or homogeneous catalysts (in the same phase), and both types are integral to advancing sustainability in chemical synthesis

Green Synthesis of Active Pharmaceutical Ingredients (APIs)

There are currently over 900 small-molecule drugs (with molecular weights under 500 Da) approved for prescription or commercial use. These compounds vary in structure and synthesis complexity, yet many share a common feature: they are nitrogen-containing heterocycles, often composed of monocyclic or polycyclic structures with nitrogen and oxygen atoms. Despite this, the majority of these APIs are still manufactured using conventional, non-green synthetic routes.

Green Techniques for Reaction Optimization

Optimizing reaction conditions to improve yields and selectivity, while simultaneously reducing resource consumption and by-product formation, remains a central objective in organic synthesis. Green chemistry encourages refining reaction parameters to enhance efficiency, enabling higher yields and fewer environmental burdens.

Microwave and Ultrasound-Assisted Green Synthesis

Microwave-assisted synthesis offers a rapid, energy-efficient, and reproducible alternative to traditional methods, making it highly suitable for green pharmaceutical chemistry. These techniques have emerged as cost-effective and environmentally friendly tools for synthesizing pharmaceutical compounds and dosage forms. Microwave irradiation reduces reaction times and energy use, aligning well with green chemistry goals.

Flow Chemistry in Pharmaceutical Synthesis

Flow chemistry, also known as continuous flow synthesis, involves conducting reactions in a continuous stream rather than in discrete batches. This technique provides precise control over reaction parameters such as temperature, pressure, and reaction time, enhancing safety and scalability. It supports efficient heat and mass transfer, reduces energy usage, and minimizes waste features that strongly align with the core principles of green chemistry.

Green Extraction Methods for Natural Products

Green extraction techniques aim to reduce or eliminate the use of harmful solvents, lower energy consumption, and minimize waste generation. Common green extraction methods include supercritical fluid extraction (using safer solvents like CO_2 or ethanol), ultrasound-assisted extraction, and microwave-assisted extraction. These sustainable approaches are widely used for isolating bioactive compounds from natural sources, with reduced environmental impact.

Biocatalysis and Enzymatic Synthesis in Green Chemistry

Biocatalysis involves using natural biological catalysts primarily enzymes to perform chemical transformations. Enzymes are highly specific, biodegradable proteins that offer environmentally friendly alternatives to traditional chemical reagents. Although enzymatic processes can be costly, they are increasingly adopted in green chemistry due to their low toxicity, mild reaction conditions, and sustainable nature.

Chemoenzymatic Synthesis in the Pharmaceutical Industry

Chemoenzymatic synthesis represents a modern and versatile strategy that combines the strengths of both chemical and enzymatic pathways. By integrating these two approaches, this method enables more environmentally sustainable routes for the synthesis of active pharmaceutical ingredients (APIs). Particularly when aligned with green chemistry principles, chemoenzymatic methods can significantly reduce environmental impact. However, to ensure true sustainability, the entire synthetic process not just the choice of chemicals must be critically evaluated, including energy use, waste generation, and reaction conditions.

Green Analytical Techniques for Monitoring Pharmaceutical Synthesis

In recent years, there has been growing interest in applying green analytical methods within pharmaceutical manufacturing. These methods are design

Table 1: Categories of sustainable chemistry and description

S. No.	Categories of sustainable chemistry	Description
1.	Organic synthesis	Green principles are used for organic synthesis
2.	catalyst development	Development of environmental friendly catalyst is concentrated which is safety
3.	Analysis process	GAC process are used here
4.	Extraction process	Harmless extraction process are conducted
5.	Sample preparation process	Types are sample collection, conditioning and storing
6.	Renewable products	Material properties are chosen according to sustainability
7.	Sustainable development	Proposal are created for educational purpose
8.	Material and inorganic substances	Greener routes of synthesis

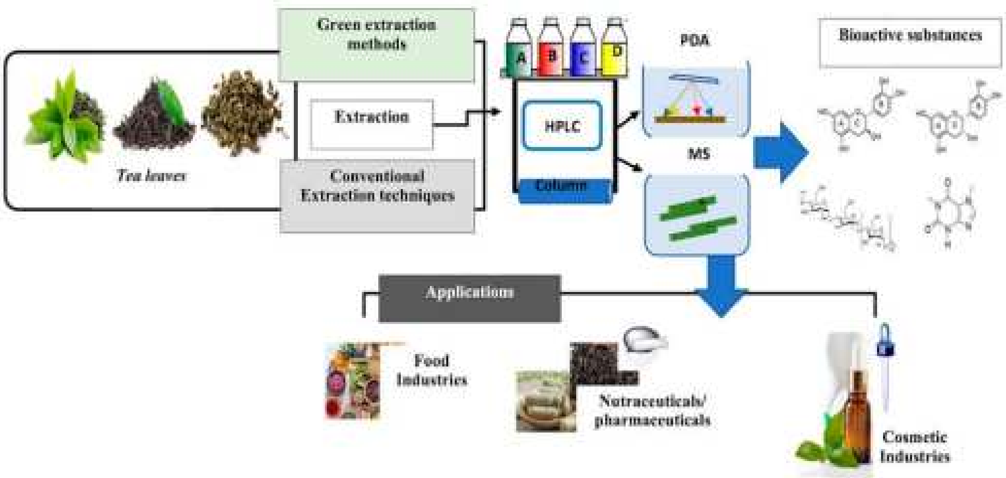


Figure 1: Green solvent extraction technique

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