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GREEN CHEMISTRY APPROACHES IN PHARMACEUTICAL SYNTHESIS: A COMPREHENSIVE REVIEW

Md Saif, Md Aman Iqbal, Mohammad Alamgir, Nakul Gupta, Preet Sagar*

IIMT College of Pharmacy, knowledge park III, Greater Noida, Uttar Pradesh, India, 201310.

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***Corresponding Author: Preet Sagar**
IIMT College of Pharmacy, knowledge park III, Greater Noida, Uttar Pradesh, India, 201310.

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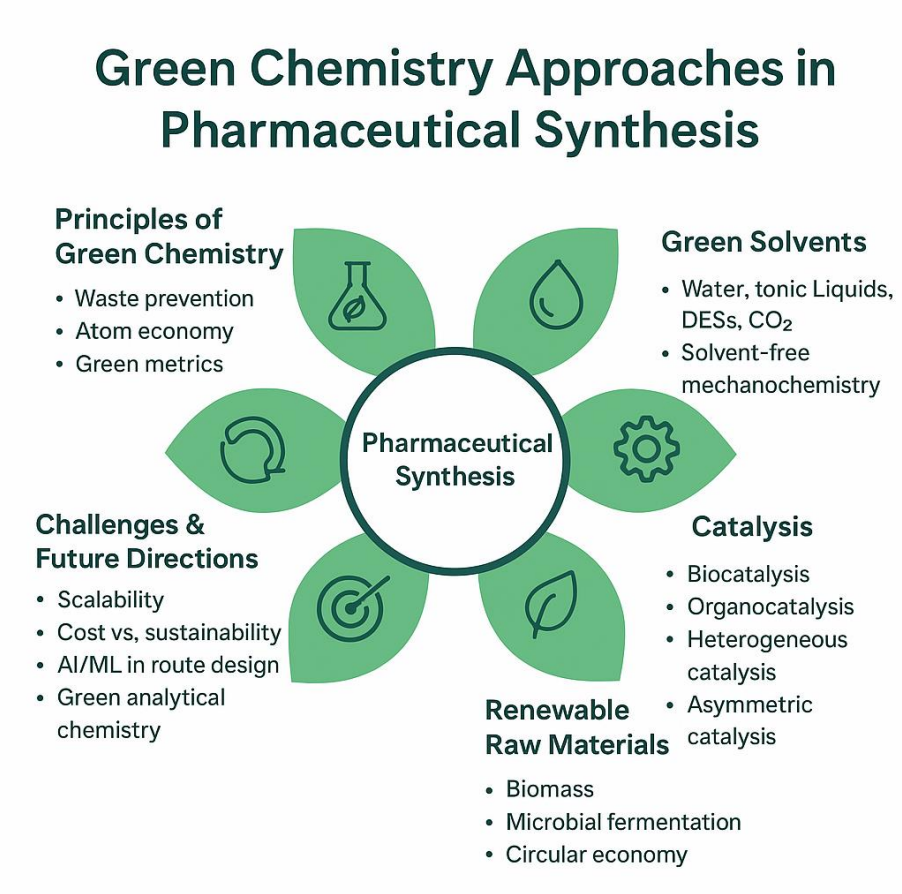
ABSTRACT

The pharmaceutical industry has transformed global healthcare, yet the way drugs are traditionally synthesized often comes at a high environmental cost. Conventional methods rely on toxic solvents, hazardous reagents, and energy-intensive processes, producing large amounts of waste. Green chemistry offers a way forward by encouraging safer, cleaner, and more efficient approaches to drug development. This review highlights recent progress in applying green chemistry to pharmaceutical synthesis, including the use of sustainable solvents such as water, ionic liquids, and deep eutectic solvents, as well as advances in catalysis through biocatalysts, organocatalysts, and photocatalytic systems. Energy-efficient tools like microwave, ultrasound, and continuous-flow chemistry are also reshaping manufacturing practices. In addition, the integration of renewable raw materials and circular economy strategies is helping to reduce reliance on fossil resources. While challenges such as scalability, costs, and regulatory hurdles remain, future opportunities lie in digital tools, automation, and green analytical techniques. Together, these developments show that green chemistry is not just an environmental ideal but a practical necessity for a more sustainable and responsible pharmaceutical industry.

KEYWORDS: Green chemistry, Pharmaceutical synthesis, Sustainable solvents, Biocatalysis, Continuous flow chemistry, Renewable feedstocks, Circular economy

Graphical abstract



1. INTRODUCTION

The pharmaceutical industry has transformed modern healthcare by providing life-saving medicines, vaccines, and diagnostics. However, the conventional routes used to synthesize these drugs often place a heavy burden on the environment. They typically rely on hazardous solvents, toxic reagents, and energy-intensive operations, leading to the generation of significant amounts of waste [1–3]. To illustrate, bulk chemical manufacturing usually has an **E-factor** (waste-to-product ratio) in the range of 1–5, whereas pharmaceutical processes often exceed 25–100 [4]. This wide gap makes it clear that traditional drug synthesis practices are environmentally unsustainable.

In response to these concerns, Anastas and Warner put forward the concept of **green chemistry** in 1998, defining twelve principles aimed at reducing the ecological footprint of chemical processes [5]. These principles emphasize atom economy, waste prevention, safer solvents, renewable feedstocks, and the use of catalysis. While initially seen as aspirational, over the past two decades they have been increasingly integrated into pharmaceutical research and manufacturing.

This transition has been further reinforced by regulatory guidance. For example, the **International Council for Harmonisation (ICH) Q11** highlights process design and lifecycle management in line with green chemistry principles [6]. Likewise, agencies such as the **U.S. Food and Drug Administration (FDA)** and the **European Medicines Agency (EMA)** actively encourage the implementation of sustainable practices [7]. Taken together, these developments position green chemistry not only as a scientific necessity but also as a regulatory and ethical imperative for the pharmaceutical sector.

2. PRINCIPLES OF GREEN CHEMISTRY IN PHARMACEUTICALS

The **twelve principles of green chemistry** provide clear, actionable strategies to minimize environmental impact while improving process efficiency. For the pharmaceutical industry, principles such as **atom economy, catalysis, waste prevention, and the use of safer solvents** are especially important [5].

A practical example of these principles can be seen in the synthesis of the **antimalarial drug tafenoquine**. Researchers developed a solvent-free, one-pot process that reduced waste by nearly threefold compared to conventional methods [8]. This improvement not only lowered the **E-factor** but also enhanced overall process efficiency.

Green chemistry also benefits **public health** by reducing dependence on toxic reagents and solvents, which in turn minimizes risks for both workers and the environment [9]. Industry case studies further highlight the value of green metrics such as **Process Mass Intensity (PMI)** and the **E-factor**, which enable companies to systematically evaluate and redesign processes for improved sustainability [10].

Catalysis represents another cornerstone of green chemistry, allowing stoichiometric reagents to be replaced with catalytic systems that use fewer materials and less energy. Recent advances in **biocatalysis** and **machine learning–assisted catalyst design** are making these approaches increasingly feasible at the industrial scale [11,12].

Despite these advances, the pharmaceutical industry still faces barriers to widespread adoption of green chemistry. Issues such as **cost, the inertia of established processes, and scalability challenges** continue to slow progress [13]. Nevertheless, ongoing research, combined with regulatory encouragement, is steadily driving the industry toward more sustainable practices.

Table 1: principles of Green Chemistry in Pharmaceuticals.

Case Study / Concept	Green Chemistry Principle Applied	Key Outcomes	Reference Year
Tafenoquine synthesis	Waste prevention, solvent-free one-pot synthesis	3× reduction in waste, improved E-factor	2023
Public health impact	Safer solvents, reduced toxic reagents	Reduced occupational risk and pollution	2024
Metrics in pharma	Atom economy, PMI, E-factor	Improved sustainability evaluation	2023
Catalysis & innovation	Catalysis under mild conditions	Higher efficiency, scalable processes	2024–25

3. GREEN SOLVENT SYSTEMS

Solvents represent the single largest source of waste in pharmaceutical manufacturing, often contributing more than **80% of the total process mass** [14]. As a result, replacing hazardous solvents with greener alternatives has become one of the top priorities in sustainable drug development.

3.1 Deep Eutectic Solvents (DESs)

Deep eutectic solvents (DESs) are formed by mixing a hydrogen bond donor with an acceptor, such as choline chloride and urea. These solvents are non-volatile, biodegradable, inexpensive, and highly tunable. Beyond their use in synthesis, DESs have shown promise in **drug formulation and delivery**. For example, a recent study reported that DESs improved the solubility and permeability of **dapsone**, a poorly soluble class IV drug [15]. This demonstrates their dual role in both pharmaceutical chemistry and drug delivery applications.

3.2 Solvent-Free Approaches

The idea of a **"solvent-free revolution"** has gained momentum in recent years. Mechanochemistry, in which reactions are initiated through grinding or milling, eliminates the need for solvents altogether. This strategy has been successfully applied in the synthesis of **active pharmaceutical ingredients (APIs)** and intermediates, offering significant reductions in waste and minimizing solvent-handling risks [16]. Thermal solvent-free reactions provide another avenue, lowering both solvent use and energy demand while maintaining efficiency.

3.3 Ionic Liquids

Ionic liquids (ILs), composed entirely of ions, are highly versatile solvents with customizable polarity and solvation properties. Their negligible vapor pressure makes them attractive replacements for conventional solvents such as **DMF**. A notable example is the use of ionic liquids in the synthesis of **quinolones**, where they not only improved reaction efficiency but also enabled recyclability of the solvent system [17].

3.4 Water as a Green Solvent

Long regarded as the "universal solvent," **water** has recently been revisited as a medium for organic synthesis under green chemistry frameworks. For instance, researchers reported the water-mediated synthesis of **oxindole-fused spirotetrahydrofurans** using a simple, metal-free protocol [18]. The method delivered excellent yields, reaffirming water's role as an environmentally friendly solvent for pharmaceutical transformations.

3.5 Green Solvents in Extraction

The application of green solvents extends beyond synthesis into **extraction processes**, particularly for natural products. A 2025 review highlighted the use of DESs and other sustainable solvents, in combination with enabling technologies such as **microwave-assisted** and **enzymatic extraction**, to isolate compounds like carotenoids, anthocyanins, and betalains [19]. These approaches not only increased extraction yields but also reduced energy consumption and preserved product quality, showcasing the versatility of green solvents in pharmaceutical research and development.

Table 2: Summary of Green Solvent Applications in Pharmaceuticals.

Solvent System	***Application in Pharma***	***Advantages***	***Example/Outcome***
Deep eutectic solvents (DESs)	*Drug solubility & delivery*	*Biocompatible, enhanced permeability*	*Dapsone formulation*
Ionic liquids	*API synthesis (quinolones)*	*Non-volatile, recyclable*	*Reduced toxicity vs. DMF*
Water	*Heterocyclic synthesis*	*Safe, metal-free, eco-friendly*	*Oxindole derivatives*
Solvent-free mechanochemistry	*General synthesis*	*Minimal waste, safer for workers*	*Quinolone synthesis*
Green solvents in extraction	*Pigment recovery (carotenoids, anthocyanins)*	*Effective with microwave/enzymes*	*Improved yields*

4. CATALYSIS IN GREEN CHEMISTRY

Catalysis plays a **central role in green pharmaceutical synthesis**, enabling chemical transformations under mild conditions with high selectivity. By improving **atom economy** and minimizing by-products, catalytic methods significantly reduce waste compared to traditional stoichiometric approaches.

4.1 Biocatalysis

Enzymes and engineered microorganisms are increasingly being used to drive sustainable drug synthesis. For example, a 2022 study demonstrated the application of **amine dehydrogenases** for the efficient production of **chiral amines**, which serve as key intermediates in antidepressants and antiviral agents [20]. By using computational tools to screen billions of enzyme sequences, researchers identified new biocatalysts with strong industrial potential, showcasing the synergy between biotechnology and computational chemistry.

4.2 Organocatalysis

Organocatalysis offers a metal-free, environmentally friendly alternative to conventional catalysis. Reactions such as **asymmetric aldol** and **Michael additions**, promoted by small organic molecules, deliver high enantioselectivity without the need for toxic metals [21]. These methods are particularly attractive in pharmaceutical manufacturing, where even trace levels of metal contamination can pose regulatory challenges.

4.3 Heterogeneous Catalysis

Heterogeneous catalysts, including **metal–organic frameworks (MOFs)** and supported nanoparticles, combine recyclability with tunable catalytic properties. Recent advances highlight their use in pharmaceutical transformations where they improve reaction efficiency, extend catalyst lifetimes, and minimize metal leaching [22]. Their recoverability also supports large-scale continuous processes, aligning well with industrial sustainability goals.

4.4 Asymmetric Catalysis

Given that more than **half of marketed drugs are chiral**, **asymmetric catalysis** remains a cornerstone of pharmaceutical synthesis. It provides direct access to **enantiomerically pure APIs** without relying on energy- and resource-intensive resolution techniques [23]. Advances

in ligand design and transition-metal catalysis continue to expand its scope, making asymmetric synthesis one of the most sustainable routes to complex drug molecules.

4.5 Flow and Photocatalysis

Catalysis also extends into modern **process intensification strategies**. **Flow catalytic processes** enable scalable, continuous production of APIs while improving safety, reproducibility, and overall efficiency [24]. Meanwhile, **photocatalysis** has emerged as a versatile tool—not only for constructing complex molecules under mild conditions but also for **environmental remediation**, such as degrading pharmaceutical residues in wastewater streams [25]. This dual role positions photocatalysis as an important technology bridging green synthesis and environmental protection.

Table 3: Catalytic Strategies and Applications.

Catalytic Strategy	Role in Pharma	Advantages	Example
Biocatalysis	Chiral amine production	High selectivity, mild conditions	Amine dehydrogenases
Organocatalysis	API synthesis	Metal-free, eco-friendly	Aldol & Michael reactions
Heterogeneous catalysis	Recyclable systems	Reduced contamination	MOFs in drug synthesis
Asymmetric catalysis	Enantioselective synthesis	Fewer steps, mild conditions	Chiral APIs
Photocatalysis	Wastewater treatment, drug synthesis	Eliminates toxic by-products	Degradation of pollutants

5. ENERGY-EFFICIENT SYNTHETIC TECHNOLOGIES

Energy use is one of the most important contributors to the environmental impact of pharmaceutical manufacturing. Traditional heating methods often require long reaction times, high temperatures, and significant energy input, which in turn increases the carbon footprint of drug production. To address this challenge, several **energy-efficient technologies** have emerged, offering faster, cleaner, and more sustainable alternatives to conventional approaches [26].

5.1 Microwave-Assisted Organic Synthesis (MAOS)

Microwave irradiation provides rapid and uniform energy transfer to reactants, drastically shortening reaction times while improving yields. MAOS has been shown to deliver **solvent-free, high-yielding transformations** of APIs [27]. For example, numerous heterocycles and drug intermediates that typically require several hours under conventional heating have been

synthesized within minutes using microwave conditions. Beyond efficiency, microwave reactors also reduce solvent consumption and improve reproducibility, making them a valuable tool for green pharmaceutical synthesis.

5.2 Ultrasound-Assisted Synthesis

Ultrasound-assisted methods rely on acoustic cavitation, where microscopic bubbles form and collapse to create localized "hot spots" with high pressure and temperature. These microenvironments promote enhanced mass transfer and reduced activation barriers [28]. Ultrasound has been applied to the synthesis of **heteroaryl compounds** and other drug intermediates under mild conditions, offering shorter reaction times and lower solvent usage. Its simplicity and compatibility with existing setups make it an attractive technique for greener manufacturing.

5.3 Photoredox Catalysis

Photoredox catalysis harnesses visible light, a renewable energy source, to drive chemical transformations. This technique enables **novel bond-forming reactions** with excellent selectivity in API synthesis [29]. Importantly, photocatalysis has also proven effective for **late-stage functionalization**, allowing greener and more efficient modification of complex molecules. In addition, its role in environmental applications—such as the degradation of pharmaceutical pollutants—further strengthens its relevance to sustainable chemistry.

5.4 Continuous Flow Chemistry

Continuous flow chemistry is increasingly recognized as a transformative technology in the pharmaceutical industry. Unlike traditional batch processes, flow reactors offer precise control over reaction parameters such as temperature, pressure, and residence time. This leads to improved **reproducibility, safety, and scalability** [30]. Recent reviews highlight the successful application of flow chemistry in **large-scale API synthesis**, where it reduces solvent requirements, shortens reaction times, and improves energy efficiency [31]. Its modular design also makes it highly adaptable to process intensification strategies.

5.5 Integration of Automation

The integration of **automation and biocatalysis** within continuous-flow setups is pushing efficiency even further. Automated systems ensure consistency, reduce human error, and allow for **high-throughput production** of APIs [32]. This approach fits within the

framework of **Industry 4.0**, where digitalization, artificial intelligence, and smart technologies are reshaping pharmaceutical process development. The synergy between automation and green chemistry promises not only sustainability but also higher productivity and quality assurance.

Table 4: Comparison of Energy-Efficient Synthetic Technologies.

Technology	Mechanism	Application in Pharma	Benefit
Microwave-assisted synthesis	Direct dielectric heating	API synthesis (solvent-free)	Faster kinetics, higher yield
Ultrasound-assisted synthesis	Cavitation-driven reactions	Organic transformations	Lower energy input
Photoredox catalysis	Visible light activation	Complex transformations	Reduced harsh conditions
Continuous flow chemistry	Continuous reactors	API manufacturing	Safer, scalable, less waste
Automation & biocatalysis	Integrated systems	High-throughput API synthesis	Consistency, low energy

6. RENEWABLE AND BIO-BASED RAW MATERIALS

Another major pillar of green chemistry is the shift from fossil-based reagents to renewable raw materials[33]. This approach not only reduces carbon footprints but also improves resource security.

6.1 Biomass-Derived Intermediates

Agricultural and forestry residues serve as feedstocks in **biorefinery models**, producing platform chemicals like levulinic acid and succinic acid. These compounds are essential intermediates for APIs and excipients[34]. Such approaches also reduce waste by integrating multiple value chains.

6.2 Microbial Fermentation

Microbial fermentation has revolutionized access to pharmaceutical precursors. For example, the microbial production of **shikimic acid**, a key precursor of the antiviral **Tamiflu**, eliminates reliance on star anise, which is subject to seasonal and geopolitical limitations[35]. Similarly, engineered microorganisms have been used to produce succinic acid and amino acid-based intermediates[36].

6.3 Circular Economy in Pharma

Circular economy models are being explored in pharmaceutical manufacturing. Waste products, such as glycerol from biodiesel production, can be converted into valuable intermediates[37]. This approach closes the loop by recycling waste streams into productive inputs.

6.4 Bio-Based Materials in Packaging

Green chemistry also extends to packaging. Renewable fibers and biodegradable polymers are being developed for eco-friendly **pharmaceutical packaging**[38]. This reduces the reliance on petroleum-based plastics and mitigates post-consumer waste problems.

Table 5: Renewable Raw Materials and Applications.

Renewable Feedstock	Application	Advantage	Example
Biomass (agri waste, forestry)	API precursors	Cost-effective, renewable	Biorefinery models
Microbial fermentation	Shikimic acid, succinic acid	Avoids seasonal/geopolitical supply issues	Tamiflu precursor
Amino acids/terpenes	Synthetic intermediates	Low toxicity	Chiral building blocks
Circular economy	Waste-to-product models	Closed-loop sustainability	Bio-based electrodes

7. CHALLENGES AND FUTURE DIRECTIONS

Despite significant progress, the widespread adoption of green chemistry in the pharmaceutical sector faces multiple barriers.

Economic challenges remain a major concern. Green solvents and catalysts, while more sustainable, often come with higher upfront costs[39]. Pharmaceutical companies, already constrained by strict timelines and regulatory frameworks, may hesitate to invest in newer, less established technologies unless long-term savings are guaranteed.

Scalability issues further complicate adoption. Many green methods, such as biotransformations, work well at laboratory scale but face difficulties during industrial scale-up[40]. Enzyme instability, long reaction times, and challenges in product isolation often limit their broader application.

Technical barriers are also evident. For instance, some ionic liquids and DESs, despite their promise, have not been fully optimized for large-scale pharmaceutical synthesis[41].

Similarly, the design of recyclable heterogeneous catalysts that retain activity across multiple cycles remains an ongoing challenge[42].

Regulatory hurdles add another layer of complexity. The pharmaceutical industry is one of the most heavily regulated sectors. Any change in synthetic methodology must undergo rigorous validation, which can slow the adoption of new, greener technologies[43].

Looking forward, several trends hold promise:

- **AI and Machine Learning**: Computational approaches are being applied to retrosynthetic planning, solvent selection, and catalyst design, offering predictive power for greener processes[44].
- **Green Analytical Chemistry**: Analytical methods themselves must be optimized for sustainability. Miniaturized techniques and solvent-free methods are emerging as promising solutions[45].
- **Circular Economy Models**: Integration of renewable feedstocks and recycling of pharmaceutical waste into valuable inputs are key to long-term decarbonization[46].
- **Policy Incentives**: Stronger collaboration between governments, academia, and industry, supported by regulatory flexibility and incentives, will accelerate green adoption[47].

Table 6: Challenges and Solutions.

Challenge	Barrier	Possible Solution
Cost of green solvents/catalysts	Industrial reluctance	Policy incentives, process optimization
Scalability	Limited large-scale adoption	Continuous flow, bioreactors
Dependence on rare metals	Limited supply, high cost	Organocatalysis, enzyme engineering
Green analytical chemistry	Hazardous reagents in analysis	Miniaturization, solvent-free methods
Integration of AI/ML	Lack of adoption in pharma	Computational retrosynthesis tools

8. CONCLUSION

Green chemistry is no longer a theoretical framework but a **practical necessity** for the pharmaceutical industry. The principles of atom economy, catalysis, renewable feedstocks, and waste prevention have moved from academic discussions into industrial application[48]. Examples such as solvent-free **tafenoquine synthesis**, microbial production of **shikimic acid**,

and the increasing adoption of **continuous flow chemistry** show that sustainability can be aligned with efficiency and profitability[8,35,31].

Future success will depend on overcoming economic and scalability barriers while integrating modern tools such as **machine learning**, **automation**, and **digital process development**[44,32]. Moreover, the adoption of **circular economy principles** and **green analytical chemistry** will expand sustainability beyond synthesis to the entire drug development pipeline[45,46].

Ultimately, embracing green chemistry is not only about environmental stewardship—it is about ensuring that pharmaceutical innovation remains socially responsible, economically viable, and scientifically advanced in the decades to come.

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