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Review Article

Green Chemistry in Pharmaceuticals: Emerging Strategies for Sustainable Drug Discovery, Manufacturing, Analysis, Packaging, and Waste Management

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ABSTRACT

The pharmaceutical industry is vital to public health, but it also has a big influence on the environment because of things like waste production, hazardous reagents, and solvent-intensive synthesis. The goal of green pharmaceutical development is to apply green chemistry concepts at every stage of a product's life cycle, from molecular design to end-of-life care. Waste prevention, atom economy, safer chemistry, energy-efficient synthesis, and green analytical chemistry are among the modern green strategies included in this review. In addition to sustainable formulation techniques and cutting-edge technology like artificial intelligence and machine learning, it showcases novel techniques including biocatalysis, solvent-free reactions, and continuous-flow chemistry. The conversation highlights that no single technology is completely environmentally friendly and that attaining sustainability necessitates a thorough assessment of the effects of materials, energy, and life cycles while maintaining the quality and safety of pharmaceuticals.

INTRODUCTION

Therapeutic performance, cost, manufacturability, quality, and safety have historically been given top priority in pharmaceutical development. This model now includes resource consumption, waste production, greenhouse gas emissions, solvent hazards, water use, packaging, and the environmental fate of pharmaceutical residues due to growing environmental pressures. A preventive framework for creating chemical products

and processes that minimise or completely eradicate waste and hazardous materials at the source is provided by green chemistry. The idea has developed into a more comprehensive life-cycle perspective in the pharmaceutical industry, where sustainability is taken into account at every stage of drug discovery, route design, synthesis, formulation, analytical testing, manufacturing, distribution, use, and disposal.

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Sustainable pharmaceutical development should take into account both upstream production impacts and downstream environmental exposure because the environmental burden of pharmaceuticals is not limited to manufacturing; APIs and transformation products can enter environmental compartments through manufacturing discharges, wastewater, patient excretion, improper disposal of unused medicines, and veterinary use. The increasing body of research on pharmaceutical pollution and environmental risk further supports the necessity of incorporating environmental considerations into drug design and stewardship

A published green-pharmaceutical review must avoid confusing "green" with "natural," "bio-based," or "low toxicity." Only after taking into account the pertinent boundary conditions, hazard profile, resource use, energy demand, process performance, and end-of-life effects can a solvent, excipient, extraction technique, or nanomaterial be deemed greener. Sustainability needs

to be quantitatively proven; recent critical work comparing batch and flow API synthesis similarly demonstrates that technological replacement alone does not guarantee a lower overall environmental effect.[1]

2. Environmental Footprint Across the Pharmaceutical Life Cycle

The production of raw materials, drug discovery and design, chemical or biotechnological synthesis, purification and isolation, formulation, analytical quality control, packaging, distribution, patient use, wastewater treatment, and end-of-life management are all interrelated steps in the pharmaceutical life cycle. Products and processes have different environmental hotspots. Solvents control mass intensity and waste production in many synthetic pathways; in other systems, energy use, water consumption, starting materials, refrigeration, fermentation, or downstream purification might be more significant.[2]

Life-cycle stage	Major environmental concerns	Representative greener strategies
Drug discovery	Large screening libraries, synthesis of low-value candidates, animal and laboratory burden	CADD, virtual screening, AI/ML prioritization, predictive toxicology
Route design and synthesis	Hazardous reagents, solvents, waste, energy	Atom economy, catalysis, biocatalysis, solvent minimization, flow chemistry
Formulation	Material sourcing, non-biodegradable polymers, energy and water use	Renewable/biodegradable excipients, solvent-minimized processing, QbD
Analytical testing	Organic solvents, sample preparation, energy, laboratory waste	GAC, miniaturization, direct analysis, greener LC, PAT
Manufacturing	High solvent/water/energy demand, batch waste, deviations	Continuous manufacturing, PAT, digital control, process intensification
Packaging/distribution	Plastic, secondary packaging, transport emissions	Right-sized packaging, recyclable materials, supply-chain optimization
Use/end-of-life	API release, unused medicines, wastewater and packaging waste	Take-back systems, environmental risk assessment, responsible disposal

3. Green Chemistry Principles Relevant to Pharmaceuticals

The conceptual basis for more environmentally friendly pharmaceutical development is provided by the 12 principles of green chemistry. When the principles are presented as quantifiable design decisions rather than as discrete definitions, their medicinal relevance is at its highest.

3.1 Waste prevention

Waste should be prevented at the source rather than treated or disposed of after it has formed. This comprises lowering protecting-group stages, avoiding pointless isolation, minimising work-up, raising reaction concentration, and enhancing solvent recovery in pharmaceutical synthesis.[3]

3.2 Atom economy

The efficiency with which reactant atoms are integrated into the intended product is measured by atom economy. Although high atom economy is ideal, it does not



fully account for the effects of solvent, energy, catalyst, toxicity, or work-up.[4,5]

3.3 Less hazardous synthesis

When appropriate substitutes are available, synthetic pathways should minimize inherent hazard and steer clear of compounds that are poisonous, persistent, bioaccumulative, carcinogenic, mutagenic, highly combustible, or otherwise troublesome.[6]

3.4 Designing safer chemicals

When it is scientifically possible, molecular design should take into account ecotoxicity, environmental permanence, degradability, and therapeutic activity. Human safety evaluation should be supplemented, not replaced, by this new "environmental fate-aware" method.

3.5 Safer solvents and auxiliaries

Pharmaceutical process mass is frequently dominated by solvents. Toxicity, flammability, volatility, environmental fate, recovery, recyclability, process performance, and energy needed for separation should all be taken into account when choosing a solvent.[7]

3.6 Energy efficiency

When their entire process footprints are favorable, lower-temperature reactions, quicker reaction times, effective heat transfer, photochemistry, microwave processing, and continuous flow may lower energy consumption.[8]

3.7 Renewable feedstocks

Renewable feedstocks can lessen reliance on fossil fuels, but before making sustainability claims, their effects on agricultural inputs, land use, water demand, processing, and end-of-life should be assessed.

3.8 Catalysis

Catalysts can lower stoichiometric waste and increase selectivity. In sustainable synthesis, biocatalysts, heterogeneous catalysts, and reusable catalytic systems are especially crucial.

3.9 Design for degradation

After therapeutic use, controlled environmental transformation can be taken into account in pharmaceutical and formulation design, provided that degradation does not jeopardize patient safety or product stability.

3.10 Real-time analysis for pollution prevention

Rejected batches, reprocessing, and material waste can be decreased by using PAT and real-time analytical data to detect process abnormalities early.

3.11 Inherently safer chemistry

Through safer reagents, reduced stockpiles, and increased process control, process design should lessen the risk of fires, explosions, uncontrolled exotherms and worker exposure.

3.12 Reduce accident potential

When properly built and evaluated, flow systems, contained processing, automation, and enhanced process monitoring can lessen the effects of dangerous reactions.

4. Quantitative Metrics for Greener Pharmaceutical Processes

Since qualitative terms like "eco-friendly" or "green" are insufficient for objective comparison, quantitative criteria are crucial. E-factor, Process Mass Intensity (PMI), Reaction Mass Efficiency (RME), atom economy, and life-cycle assessment (LCA) are examples of common process metrics. GAPI, NEMI, Analytical Eco-Scale, AGREE, and similar instruments offer supplementary data for analytical techniques. A multi-criteria evaluation is better as no single statistic can account for every aspect.[9- 12]

Metric/tool	What it evaluates	Important limitation
E-factor	Mass of waste generated per mass of product. Lower values are generally preferable.	Useful for process waste comparison; system boundary must be stated.
PMI	Total mass of inputs divided by mass of product.	Captures solvents and water more comprehensively than atom economy.



Metric/tool	What it evaluates	Important limitation
RME	Mass efficiency reflecting stoichiometry and yield.	Useful for reaction-level comparison.
Atom economy	Theoretical fraction of reactant atoms incorporated into product.	Does not include solvents or actual yield.
LCA	Life-cycle assessment of environmental impacts across defined boundaries.	Most comprehensive but data-intensive.
AGREE / GAPI / NEMI / Eco-Scale	Tools for analytical-method greenness.	Should be used alongside analytical performance and validation.

5. Green Drug Discovery and Design

5.1 Computer-Aided Drug Design and Virtual Screening

The number of compounds that must be manufactured and tested experimentally can be decreased by using computer-aided drug design (CADD), molecular docking, pharmacophore modeling, molecular dynamics, quantitative structure–activity relationships (QSAR), and virtual screening. Thus, these methods can minimize material use in the early stages of discovery. When computational prioritizing is paired with strong experimental validation instead than being utilized in place of evidence, their sustainability value is at its highest.[13]

5.2 Artificial Intelligence and Machine Learning in Molecular Design

AI/ML can help in molecular creation, property prediction, reaction prediction, route planning, catalyst selection, solvent selection, and the prioritization of compounds with attractive potency and safety profiles. Recent work involves developing molecules and processes with sustainability aims in mind. Potential benefits include fewer failed tests, better route selection, and early hazardous material discovery. However, there are still a number of serious problems, including model bias, a lack of training data, ambiguity, interpretability, and reproducibility.[14, 15]

5.3 Predictive Toxicology and Environmental Considerations

Prioritizing chemicals prior to production is possible with in silico toxicology, which may also lessen the burden of experiments. New methods also take ecotoxicity, biodegradation, and environmental persistence into account. These forecasts ought to be

regarded as decision-supporting instruments and suitably verified by experimental data.[16]

6. Greener Pharmaceutical Synthesis

The synthesis of active pharmaceutical ingredients (APIs) can significantly increase the environmental impact of pharmaceutical products due to the usage of solvents, the need for raw materials, energy consumption, the need for several reaction and purification stages, and the production of organic and aqueous waste. Therefore, redesigning synthetic pathways to minimize material use, toxic compounds, energy demand, waste generation, and life-cycle impacts is a goal of greener pharmaceutical synthesis in addition to maximizing chemical output. Solvent minimization, solvent-free processing, synthesis assisted by microwaves and ultrasounds, continuous-flow chemistry, process intensification, and biocatalysis are significant strategies [17-22].

When assessing these methods, it's crucial to remember that no artificial technology is intrinsically green. The entire process, including reaction concentration, solvent type and quantity, energy consumption, purification, catalyst production, waste treatment, process safety, and system boundaries utilized for evaluation, determines environmental performance [19–21, 23–25]. Similar emphasis is placed on quantitative, multi-dimensional evaluation rather than technology-based presumptions in recent work comparing batch and flow API synthesis [25].

6.1 Solvent-Minimized and Solvent-Free Reactions

In pharmaceutical synthesis, solvents can make up a significant portion of the material input. Solvent waste, emissions, occupational exposure, storage needs, and downstream separation burdens can be reduced by lowering solvent volume, raising reaction



concentration, substituting safer solvents for hazardous ones, recovering and recycling solvents, or removing reaction solvents when technically possible [22]. As a result, early research stages of industry-oriented solvent-selection methodologies have integrated safety, health, environmental, and process-performance concerns [26, 27].

When high substrate concentration does not impair mixing, heat transfer, selectivity, safety, or product separation, solvent-free processing may be appealing. However, a procedure is not always more environmentally friendly just because there is no solvent. The apparent benefit could be countered by increased viscosity, challenging heat control, less selectivity, or a more complicated purification process. Thus, process mass intensity (PMI), E-factor, reaction mass efficiency (RME), solvent intensity, energy demand, and, when relevant, life-cycle assessment (LCA) should be used to analyze solvent minimization.

Solvent selection is placed within an integrated framework that takes into account feedstock supply, catalyst selection, process intensification, and end-to-end life-cycle performance, according to recent greener-by-design viewpoints. Comparing "solvent-free" to "green" is not as scientifically sound as this method.

6.2 Microwave-Assisted Pharmaceutical Synthesis

Through selective interaction of microwave energy with the reaction media and volumetric heating, microwave irradiation is used in microwave-assisted organic synthesis to heat reaction mixtures. Microwave irradiation can provide quick heating, reduce reaction times, and enhance conversion or selectivity in appropriate systems when compared to traditional conductive heating.

In a recent study published in 2026, Zhang et al.[28] evaluated the use of microwave technology in drug synthesis and emphasized its potential to reduce by-product generation, shorten reaction times, boost target-product yield or selectivity, and cut energy demand in suitable systems. The mechanistic and process-development foundation for controlled microwave heating and its evolution from a lab curiosity to a useful synthetic technology were built by Kappe's earlier work.

However, rather than being taken for granted, the sustainability benefit of microwave processing should be proven. When comparing microwave-assisted and conventionally heated processes, factors including electrical energy consumption, equipment efficiency, reaction scale, vessel design, solvent selection, repeatability, and downstream purification should be taken into account. Therefore, the best way to characterize microwave-assisted synthesis is as a potentially greener process-intensification technique whose environmental performance depends on the process.[28, 29]

6.3 Ultrasound-Assisted Processing

The sound waves and cavitation phenomena are used in ultrasound-assisted processing to improve extraction, mass transfer, mixing, and certain chemical transformations. Ultrasound can shorten processing times, promote reactions at milder circumstances, and, in appropriate systems, lower solvent requirements in pharmaceutical production and related processing.

Improved mass transfer, shorter reaction times or temperatures, and less solvent consumption are some of the possible sustainability advantages. However, the environmental performance of sonication is dependent on acoustic power, processing time, reactor design, size, reaction yield, solvent volume, and downstream purification. Sonication also requires electrical energy. Cavitation behavior and acoustic-field distribution may alter with reactor shape and operating scale, making scale-up difficult. Therefore, energy and material-intensity measurements rather than reaction time alone should be used to evaluate ultrasound-assisted processing [30, 31].

6.4 Flow Chemistry and Process Intensification

One significant platform for intensifying pharmaceutical processes is continuous-flow chemistry. In addition to enabling telescoped multistep sequences and safer handling of extremely reactive or hazardous intermediates, flow reactors offer regulated mixing, heat and mass transfer, residence duration, temperature, and reaction inventory

Particularly relevant is recent quantitative findings. In their study, Ferlin et al. used E-factor, reaction mass efficiency, solvent safety and hazard, solvent utilization, and space-time yield to critically compare flow



and batch techniques for API synthesis. The analysis revealed that flow often provides benefits in terms of productivity and solvent consumption, but it also shown that enhanced sustainability is not universal and heavily depends on concentration, solvent management, and downstream activities.

The seven-step continuous-flow synthesis of the anti-hepatitis-B nucleoside analog entecavir is a relatively recent example. Wang et al. [32,33] demonstrated the possibility of compact integration of several transformations for a structurally complex API by reporting sequential flow operations that delivered entecavir in 41% isolated overall yield with a total residence time of 111.5 minutes.

For thermal, photochemical, electrochemical, asymmetric, and other transformations pertinent to fine chemicals and medicines, continuous-flow processing has also been proven. However, flow in conjunction with high concentration, decreased solvent exchange, telescoping, continuous separations, effective heat management, and suitable product isolation increases the likelihood of sustainability benefits. Therefore, rather than being viewed as an inherently green technology, flow chemistry should be evaluated as a platform for process intensification.

PMI or E-factor, reaction mass efficiency, solvent quantity and hazard, energy consumption, space-time yield, process safety, number of isolation steps, and, when possible, LCA and techno-economic indicators should be used to compare flow and batch methods for a robust evaluation [32–37].

6.5 Biocatalysis and Enzyme Engineering

Enzymes or entire cells are used in biocatalysis to catalyze chemical reactions with strong chemo-, regio-, and stereoselectivity, often in moderate environments. These features can lessen the need for purification, harsh reaction conditions, protective groups, and side reactions.

The altered transaminase technique employed in the production of sitagliptin is one of the seminal examples in pharmaceuticals. In order to replace a rhodium-catalyzed pathway and show the economic potential of designed biocatalysis, Savile et al. demonstrated that protein engineering and directed evolution converted

an initially insufficient enzyme into a useful catalyst for asymmetric amination

Enzyme engineering, directed evolution, computational protein design, genome mining, immobilization, and enhanced cofactor-regeneration techniques are some of the more recent advancements that have broadened the application of biocatalysis. The importance of enzyme discovery, protein engineering, high-throughput screening, and tailored catalytic cascades in contemporary chemical synthesis is highlighted in a 2024 Chemical Society Reviews tutorial.[38,39] Applications to API and advanced-intermediate synthesis, such as highly selective redox reactions and other challenging transformations, are also described in recent reviews with a pharmaceutical focus.

Even so, a biocatalytic process's sustainability needs to be evaluated throughout. Enzyme production, catalyst loading, cofactor requirement and regeneration, reaction medium, substrate concentration, enzyme stability, immobilization, catalyst lifetime, reuse, downstream purification, and waste treatment are important factors. Therefore, a biological catalyst should not be labeled green just because it is enzyme-based; instead, its overall process performance should be compared with an appropriate chemical alternative [38–42].

6.6 Integrated Biocatalysis and Continuous-Flow Processing

The combination of modified or immobilized enzymes with continuous-flow reactors is becoming a more appealing approach. While flow operation offers controlled residence time, substrate delivery, temperature, and product collection, immobilized enzymes can be stored and utilized again. High catalytic selectivity, catalyst reuse, enhanced transportation, decreased reaction inventory, and continuous production are all possible benefits of the combined platform [43].

Enzyme deactivation, mass-transfer constraints, substrate loading, fouling, catalyst lifetime, cofactor regeneration, pressure drop, and downstream purification are the main development obstacles. Therefore, before scaling up, integrated biocatalysis-flow platforms should be assessed using both quantitative sustainability criteria and chemical performance.



6.7 Comparative Sustainability Assessment

Approach	Potential advantage	Key limitation / assessment
Solvent minimization / solvent substitution	Lower solvent waste, emissions and separation burden	Mixing, selectivity, hazard, recovery and scale-up must be assessed [22]
Solvent-free synthesis	Very low reaction-solvent consumption	Viscosity, heat/mass transfer and purification may offset gains [22]
Microwave-assisted synthesis	Rapid heating and shorter reaction times in suitable reactions	Electrical energy, equipment efficiency and scale-up require assessment [28,29]
Ultrasound-assisted processing	Enhanced mass transfer and potentially shorter processing	Sonication energy and scale-up effects must be quantified [30,31]
Flow chemistry	High process control, productivity, safety and potential solvent/waste reduction	Benefit depends on concentration, solvent management and downstream integration [25,32-36]
Biocatalysis	High selectivity, mild conditions and potential reduction of protecting-group chemistry	Enzyme production, cofactors, stability and purification affect total impact [37-41]
Immobilized biocatalysis in flow	Catalyst reuse with continuous processing	Mass transfer, catalyst lifetime and fouling can limit performance [34,37-39]

7. Sustainable Solvents

Instead than focusing only on labels like "green," "bio-based," or "natural," solvent selection should be supported by evidence. In certain applications, water, ethanol, and certain bio-based solvents might be advantageous. Supercritical carbon dioxide has use in specialized extraction and processing. Although the properties of ionic liquids and deep eutectic solvents can be adjusted, they shouldn't be categorized as green without further consideration of persistence, toxicity, synthesis burden, and recovery.[44]

7.1 Natural Deep Eutectic Solvents (NaDES)

NaDES extraction, solubilization, and pharmaceutical processing have drawn more and more attention. Naturally occurring metabolites or similar components can frequently serve as the basis for their composition. However, prior to industrial implementation, viscosity, downstream separation, environmental destiny, reproducibility, and residual solvent factors should be evaluated. NaDES for pharmaceutical applications was the subject of a 2025 review that emphasized both their potential and the necessity of critical assessment. [45]

8. Green Analytical Chemistry

Solvents, reagents, water, energy, and disposable materials are all consumed in analytical labs. Therefore,

Green Analytical Chemistry (GAC) aims to maintain analytical quality while minimizing occupational and environmental effects. Direct analysis, minimal sample size, in situ measurement, automation, miniaturization, decreased derivatization, low waste, multi-analyte techniques, energy reduction, safer reagents, and operator safety are all highlighted by the 12 GAC principles.[46]

8.1 Green Liquid Chromatography

Although solvent usage can be significant, HPLC is nevertheless essential to pharmaceutical quality control. Reduced flow rates, shorter columns, miniaturization, greener mobile phases, effective sample preparation, and quantitative greenness assessment are all highlighted in recent green-LC work. NEMI, GAPI, Analytical Eco-Scale, AGREE, and other composite techniques are examples of current evaluation tools. By taking resource recovery and reuse into account, circular analytical chemistry expands on the idea.

8.2 AQbD and Green Analytical Method Development

Sustainability goals and method performance standards can be combined with Analytical Quality by Design (AQbD). Method robustness can be increased and repeated trials can be decreased by defining an analytical



target profile, identifying crucial method parameters, and optimizing within a design space. In addition to resolution, accuracy, precision, and sensitivity, replies may contain sustainability metrics.[47]

8.3 Miniaturization and Alternative Instrumentation

Sustainability goals and method performance standards can be combined with Analytical Quality by Design (AQbD). Method robustness can be increased and repeated trials can be decreased by defining an analytical target profile, identifying crucial method parameters, and optimizing within a design space. In addition to resolution, accuracy, precision, and sensitivity, replies may contain sustainability metrics.[47]

9. Green Formulation Development

9.1 Renewable and Biodegradable Excipients

In some formulations, the use of biodegradable excipients and renewable polymers can lessen reliance on petrochemical feedstocks. Alginate, chitosan, cellulose derivatives, starch-based polymers, and other polysaccharide systems are a few examples. "Natural" does not always equate to sustainable; factors including sourcing, processing, purification, water and land use, batch variability, and biodegradation products need to be taken into account.[48]

9.2 Green Extraction of Pharmaceutical and Herbal Ingredients

Solvent toxicity or extraction time may be decreased using pressurized liquid extraction, water-based extraction, ethanol–water systems, ultrasound-assisted extraction, microwave-assisted extraction, and other enhanced methods. Instead than focusing only on yield, process optimization should take into account extraction yield, selectivity, energy demand, solvent recovery, and repeatability.[49]

9.3 Nanoformulations and Green Nanopharmaceuticals

Solubility, distribution, and controlled release can all be enhanced by nanotechnology, however the creation of nanomaterials may raise new environmental and safety issues. Therefore, a full life-cycle approach, encompassing nanoparticle creation, purification,

stability, biological fate, and end-of-life behavior, should be used to assess green synthesis.[50]

10. Green Manufacturing and Process Intensification

10.1 Continuous Manufacturing

Continuous manufacturing can enhance process control, lower hold-up volumes, and provide real-time quality monitoring. It may lower solvent, energy, and waste intensity when combined with effective reactions and separations. However, it is necessary to take into account the complexity of the equipment, process development, control strategy, and regulatory issues.[51]

10.2 Process Analytical Technology (PAT)

Critical material and process properties can be monitored in real-time or almost real-time thanks to PAT. Particle-size monitoring, Raman, NIR, UV/Vis, and multivariate models can help with process comprehension and control. PAT can improve resource efficiency by lowering failed batches and needless sampling.[52]

10.3 Quality by Design (QbD)

QbD offers a methodical framework for establishing quality goals, determining essential quality characteristics, and comprehending the connections between process parameters and material characteristics. Quality, productivity, and environmental performance can all be optimized at the same time by combining QbD with green measures.[47]

10.4 Digital Manufacturing and Digital Twins

Process models and real-time production data can be connected via digital twins to facilitate deviation control, optimization, and prediction. Reduced experimentation, better energy management, predictive maintenance, and less material loss could all contribute to their sustainability. Interoperability, model verification, and data governance are still crucial prerequisites. [53, 54]

11. AI-Assisted Sustainable Pharmaceutical Analysis and Manufacturing

Recent research published in 2026 describes the growing integration of AI/ML with chromatographic optimization, impurity profiling, predictive stability



evaluation, PAT, and continuous manufacturing. Instead of "AI everywhere," the emerging trend is targeted deployment in areas with sufficient data, validated models, and a clear analytical or process benefit. [55]

11.1 AI for Analytical Method Development

mobile-phase composition optimization, and experimental condition identification can be aided by machine-learning algorithms. When applied inside a predetermined design space, AI can minimize the number of experimental trials. Nevertheless, final procedures must prove their suitability for their intended use and go through traditional analytical validation. [56]

11.2 AI for Predictive Stability and Impurity Assessment

Impurity-risk assessment and stability trend analysis can be aided by predictive models. High-quality historical datasets, suitable model design, external validation, and transparent uncertainty estimation are all necessary for their utility. Instead of being automatically accepted as regulatory conclusions, AI outputs should be viewed as supporting evidence. [57]

11.3 AI-QbD-PAT Integration

Risk assessment, experimental design, real-time measurements, and adaptive process control can all be connected by an integrated AI-QbD-PAT framework. Strong data integrity, cybersecurity, model lifecycle management, and regulatory monitoring are necessary for such systems to minimize material loss and speed up process improvement. [47]

12. Sustainable Packaging and Distribution

Pharmaceutical packaging needs to safeguard patient safety, stability, sterility, and product quality. Therefore, it is important to promote sustainability without sacrificing compatibility, barrier qualities, or shelf life. Appropriate size, lightweighting, recyclable materials, responsible use of recycled content when appropriate, less secondary packing, and enhanced transport efficiency are some strategies.

Life-cycle thinking should be used to assess packaging sustainability. If more processing is needed or product protection is compromised, a material with a high

recycled content does not necessarily have the least overall impact. In a similar vein, biodegradable materials need appropriate end-of-life circumstances and shouldn't be presumed to biodegrade quickly in every setting. [59, 60]

13. Pharmaceutical Waste Management and Ecopharmacology

Analytical waste, contaminated materials, manufacturing wastes, and unused or expired medications are all considered pharmaceutical waste. Prevention, segregation, recovery when possible, and safe destruction via legally permissible means are the top priorities of sustainable management. Programs for household take-back help lessen the improper disposal of unneeded medications. [61]

13.1 Pharmaceutical Residues in the Environment

Environmental pharmaceutical contamination is becoming recognized as a cross-sector issue that impacts households, manufacturing, wastewater treatment, healthcare, and agriculture. When assessing environmental risks, parent chemicals, metabolites, persistence, mobility, bioaccumulation, and ecotoxicity should all be considered. Therefore, ecopharmacology and pharmacoenvironmentology complement standard pharmaceutical safety assessment by considering the environmental effects of pharmaceutical use and disposal. [62]

14. Regulatory and Quality Considerations

Greener pharmaceutical procedures must continue to adhere to applicable regulatory requirements and good manufacturing practices. Without sacrificing individuality, strength, purity, quality, safety, or efficacy, sustainability should be incorporated. Validated control strategies and suitable data integrity should support QbD, PAT, continuous manufacturing, and advanced analytics.

Current regulatory thinking places more emphasis on creation, validation, and lifecycle management of analytical processes that are grounded in science and risk. Therefore, rather than taking the place of validation requirements, green analytical method development should be positioned as a means of increasing resource



efficiency while maintaining analytical performance and regulatory fitness.

15. Challenges and Research Gaps

- The term "green" for pharmaceutical operations and products lacks a universally accepted definition.
- Research comparability is hindered due to the use of numerous system constraints and sustainability indicators.
- Insufficient life-cycle data for nanomaterials, excipients, solvents, and emerging digital technologies.
- Potential trade-offs between solvent safety, energy use, recovery, cost, and extraction efficiency.
- Limited scale-up data for laboratory-based green synthesis and extraction methods.
- Problems with natural and renewable raw resource standardization and unpredictability.
- AI limitations related to data quality, cybersecurity, explainability, reproducibility, bias, and regulatory acceptance.
- It is necessary to have standardized sustainability standards that work with pharmaceutical quality systems.

16. Recent and Emerging Approaches (2024–2026)

AI-assisted green route and solvent selection

Route ranking, solvent selection, reaction prediction, and process optimization are among the areas where AI/ML is being researched more and more. Validated, comprehensible models connected to quantifiable sustainability endpoints are the primary research need.

AI-assisted pharmaceutical analysis

AI for chromatographic optimization, impurity profiling, prediction stability, and PAT-supported continuous manufacturing is highlighted in recent 2026 literature. Although these applications show promise, they still rely on validated and high-quality data.

Green liquid chromatography and circular analytical chemistry

Green solvents, smaller sample preparation, energy-efficient equipment, and coupled greenness metrics like GAPI, AGREE, Eco-Scale, and NEMI with

circular analytical concepts are all highlighted in recent studies.

Natural deep eutectic solvents

NaDES are being studied for pharmaceutical processing, extraction, and solubilization; however, case-specific assessment is necessary for toxicity, persistence, viscosity, recovery, and life-cycle implications.

Digital twins and predictive process control

To enhance process comprehension, predictive maintenance, and resource efficiency, digital twins can connect real-time data, mechanistic models, and artificial intelligence.

Circular pharmaceutical systems

Recovering solvents, water, and materials, reducing waste, and redesigning supply chains and packaging around reuse and recycling where quality and safety allow are all goals of emerging circular approaches.

Environmental-fate-aware drug design

In addition to potency, ADME, and human safety, biodegradability and environmental persistence may be considered in early candidate selection in future medicinal chemistry.

16. Recent Updates in Green Pharmaceutical Development (2024–2026)

A change from discrete green-chemistry interventions to integrated, statistically evaluated pharmaceutical sustainability is seen in recent research released between 2024 and 2026. AI-assisted route and solvent selection, environmentally friendly liquid chromatography and circular analytical chemistry, natural deep eutectic solvents (NaDES), mechanochemistry, quantitative comparison of batch and continuous-flow API synthesis, digital twins and digitalized quality systems, and life-cycle assessment (LCA) used earlier in process development are some significant advancements. There is growing agreement that a technology shouldn't be called "green" only because it makes use of digital tools, water, biomass, enzymes, or flow reactors. It is necessary to evaluate the entire system boundary, which includes raw materials, utilities, solvent



recovery, downstream processing, energy source, danger, quality, cost, and end-of-life [63–70].

16.1 AI/ML-assisted sustainable route and analytical development

Ranking synthetic routes, predicting reactions, choosing solvents, optimizing chromatographic settings, identifying impurity hazards, and supporting predictive process control are all increasingly being done with AI and machine learning. Faster exploration of huge design spaces and fewer pointless experimentation are the practical benefits. AI can help with retention prediction and mobile-phase optimization in pharmaceutical analysis, but traditional validation and fitness-for-purpose proof are still needed for the final analytical process. Uncertainty, explainability, cybersecurity, sparse or non-representative training data, model bias, and regulatory acceptability continue to be significant drawbacks. Therefore, rather than acting as an independent substitute for experimental evidence, AI is best applied as a decision-support layer within a proven QbD/PAT architecture [71,72,73,74].

Practical example: Prior to laboratory testing, a chromatographic-development procedure might screen potential mobile-phase compositions using historical retention data. While the chosen method is subsequently verified for specificity, accuracy, precision, robustness, and system appropriateness, this can minimize the number of trial runs, solvent use, and analyst time.

16.2 Quantitative sustainability assessment of flow versus batch

A significant advancement in 2026 is a more thorough comparison of batch and flow API synthesis. Instead of assuming that flow is inherently greener, Ferlin et al. compared methods using E-factor, reaction mass efficiency, solvent safety/hazard, and space–time yield. Flow can minimize reaction inventory, enhance heat and mass transmission, enable telescoping, and prevent intermediate isolation; nevertheless, additional loads may be introduced by pumps, tubing, back-pressure management, solvent switching, and energy consumption. Therefore, a multi-criteria comparison that incorporates hazard, energy, techno-economic, and life

cycle data with mass measurements is the most defensible method [72,75].

Practical example: Continuous-flow synthesis of artemisinin has demonstrated how intensified photochemical processing can combine rapid reaction control with a compact manufacturing footprint. Similarly, recent reviews identify flow routes for APIs such as diazepam and other high-value compounds as useful case studies for telescoping and process intensification [76,77].

16.3 Mechanochemistry as a solvent-reduction strategy

Because, pharmaceutical solid-form transformations and reactions can be carried out with little to no bulk solvent, mechanochemistry is gaining attention again. In comparison to a solvent-based approach, kilogram-scale mechanochemical pathways produced favorable aggregate green-metric performance, according to a 2026 life-cycle assessment of rac-ibuprofen–nicotinamide cocrystallization. However, the same study demonstrated that the source of electricity matters: renewable electricity can significantly lessen the effects of global warming, whereas fossil-intensive electricity can counteract certain benefits. The most important lesson is that reduced life-cycle impact does not always follow from solvent elimination [78].

An example of a viable route for solvent-minimized pharmaceutical solid-state manufacturing is the manufacture of ibuprofen–nicotinamide cocrystals by milling or hot-melt extrusion, with renewable electricity enhancing the overall sustainability profile [78].

16.4 Natural deep eutectic solvents (NaDES) and deep eutectic systems

NaDES are becoming multipurpose media for formulation, extraction, synthesis, and solubilization. They are used as solvents, excipients, cofactors, catalysts, solubilization promoters, and stabilizers in pharmaceutical synthesis, extraction, drug delivery, and nanotechnology, according to the 2025 Green Chemistry critical evaluation. Benefits include the potential for low volatility, easy preparation, variable polarity, and the use of naturally derived components. High viscosity, challenging downstream separation, composition-dependent toxicity, stability problems, residual solvent



concerns, and unclear environmental fate are some drawbacks. Therefore, rather than relying solely on the term "natural," NaDES should be chosen by comparing recovery, toxicity, life-cycle burden, and process performance with conventional options [79,80,81].

Some examples of practical applications include the extraction of phenolic or other bioactive chemicals from plant material using choline-chloride/polyol or organic-acid-based NaDES, as well as the improvement of the solubility of weakly water-soluble APIs following appropriate purification or formulation controls [80, 81].

16.5 Green analytical chemistry and circular analytical chemistry

Simple solvent replacement is giving way to miniaturization, direct analysis, decreased sample preparation, microextraction, lower-flow chromatography, alternative detectors, and quantitative greenness assessment in green analytical chemistry. While more recent work addresses circular analytical chemistry, resource recovery, and reuse, recent pharmaceutical LC evaluations highlight instruments like NEMI, GAPI, Analytical Eco-Scale, and AGREE. Reducing solvent, sample, and disposable material usage without sacrificing analytical quality is the primary benefit. The absence of universal harmonization across greenness measurements, method-transfer difficulties, matrix effects, validation needs, and instrument constraints are some of the drawbacks [82, 83,84–87].

Practical example: AGREE/GAPI/Eco-Scale can be used in conjunction with standard validation parameters to assess a pharmaceutical impurity method that is redesigned from traditional high-flow HPLC to a shorter column, lower flow rate, reduced sample volume, and a less hazardous mobile phase. This offers a numerical foundation for determining if the more environmentally friendly approach is indeed better.

16.6 Life-cycle assessment, solvent recovery and early sustainability decisions

LCA is being used earlier in the pharmaceutical process development process. Simplifying the microbiological manufacturing process reduced environmental implications across all studied categories, whereas switching to renewable electricity improved certain impacts but

raised others, according to recent research on citicoline production. A 2026 study on pharmaceutical crystallization found that solvent recovery can also outperform cremation on larger scales. These findings corroborate a basic principle of sustainable pharmaceutical engineering, which states that optimization should concentrate on the process as a whole rather than just one variable [88,89].

Practical example: When selecting an API route, teams can examine two routes using PMI/E-factor, solvent hazard, energy consumption, carbon footprint, water use, and recovery rates. A route may be preferable to one with a marginally lower reaction yield if it eliminates a dangerous solvent, reduces the number of purification steps, and uses much less material and energy overall.

16.7 Continuous biomanufacturing and end-to-end process intensification

Monoclonal antibody manufacturing while lowering facility and material. Additionally, continuous bioprocessing is going beyond the creation of tiny molecules. In comparison to an optimal fed-batch benchmark, a recent evaluation of end-to-end continuous monoclonal antibody manufacturing revealed possible savings in annual production cost, facility footprint, plastic waste, and CO₂ emissions. Higher productivity, increased chromatography, automation, and fewer equipment/facility requirements all contribute to the practical sustainability benefit; however, implementation calls for complex control, comprehension of the process, evaluation of single-use materials, and robust lifecycle management [90].

For example, computerized process control, multicolumn chromatography, and perfusion culture can all facilitate continuous intensity. The environmental impact of utilities, upstream raw materials, and single-use plastics should still be compared to the sustainability claim.

16.8 Digital twins and smart pharmaceutical manufacturing

Digital twins facilitate prediction, optimization, maintenance, and deviation control by linking process models with real-time production data. Digitalization is positioned in recent pharmaceutical sustainability



literature as a cross-life-cycle tool that spans supply chains, manufacturing, quality control, and discovery. Benefits include reduced physical experimentation, early deviation identification, enhanced asset use, and better energy management. Data-quality standards, interoperability, model upkeep, cybersecurity, computing infrastructure, and the possibility that digitalization may only transfer environmental costs to data and hardware systems are some of the drawbacks [91].

Practical example: By combining PAT data with a mechanistic model, a digital twin of a continuous API crystallization step can forecast supersaturation and crystal-size distribution, enabling process conditions to be modified prior to the production of an off-specification batch.

16.9 Sustainable packaging, distribution and end-of-life

Even when the API process is streamlined, packaging and distribution can still constitute significant environmental hotspots, according to recent life-cycle research. Therefore, without sacrificing barrier qualities, sterility, stability, or patient safety, sustainable packaging should make use of proper sizing, lightweighting, suitable recycled/recyclable materials, and transport optimization. For instance, a 2025 aspirin life cycle assessment (LCA) revealed that packaging significantly contributed to the system's overall environmental impact, indicating that sustainability shouldn't end at API manufacturing [92].

Practical example: Rather than choosing packaging based just on recycled content, a tablet maker can assess blister designs or bottle systems by taking into account material mass, product-protection requirements, transport weight, recyclability, and end-of-life paths.

16.10 Advantages and disadvantages of major green approaches

Approach	Main advantages	Main disadvantages / risks	Practical pharmaceutical application
Biocatalysis	High chemo-/regio-/stereoselectivity; mild conditions; fewer protecting groups	Enzyme cost/stability; cofactor regeneration; aqueous processing and downstream burden	Sitagliptin manufacture using an evolved transaminase [93]
Continuous-flow chemistry	Small reaction inventory; excellent heat/mass transfer; telescoping; safer hazardous chemistry	Equipment/control complexity; fouling; scale-up and residence-time constraints	API synthesis and telescoped multistep processing [75–77]
Mechanochemistry	Little/no bulk solvent; high atom economy for solid-state processes	Electricity demand; scale-up/equipment wear; heat/mass-transfer differences	Ibuprofen–nicotinamide cocrystallization [78]
NaDES/DES	Low volatility; tunable properties; extraction and solubilization potential	Viscosity; recovery; composition-dependent toxicity and environmental fate	Natural-product extraction and drug-delivery systems [80,81]
Green LC / GAC	Lower solvent and waste use; miniaturization; quantitative greenness assessment	Validation and transfer challenges; metric non-harmonization	Pharmaceutical impurity and assay testing [82,83,84–87]
AI/ML	Fewer experiments; route/solvent/chromatography optimization; predictive monitoring	Bias; data scarcity; uncertainty; cybersecurity; regulatory validation	Route selection, analytical development and PAT [63,68,73,91]
QbD/PAT	Early risk control; real-time monitoring; fewer rejected batches	Instrumentation and model-validation burden; data integrity requirements	Continuous manufacturing and real-time release [94–96]

Approach	Main advantages	Main disadvantages / risks	Practical pharmaceutical application
LCA / PMI / E-factor	Makes sustainability measurable and comparable	Data-intensive; results depend strongly on system boundary and data quality	API route selection, solvent recovery and process redesign [63,70,88,89]
Sustainable packaging	Reduces material and transport burden	Barrier/sterility requirements can limit substitutions	Right-sized bottles/blisters and optimized secondary packaging [92]

16.11 Practical implementation framework for pharmaceutical organizations

Eight steps make up a practical implementation pathway: (1) define the system boundary and sustainability objective; (2) establish baseline PMI, E-factor, solvent use, energy and water consumption; (3) identify hotspots using hazard and LCA screening; (4) generate alternatives using safer solvents, catalysis, biocatalysis, flow, mechanochemistry, or digital tools; (5) evaluate alternatives using multiple metrics; (6) confirm pharmaceutical quality, process capability, and analytical validation; (7) pilot and scale under the proper GMP/QbD/PAT controls; and (8) monitor lifecycle performance after commercialization. Technology-driven decisions that assume a new process is green without quantitative evidence are prevented by this sequence [63,97,98].

A helpful guideline is that a green intervention is only considered practically successful if it results in a quantifiable decrease in pertinent environmental or safety burdens while maintaining quality, patient safety, efficacy, supply reliability, and acceptable economics. This aligns with the present orientation of regulatory thought and pharmaceutical sustainability literature [99, 94–96].

17. Future Perspectives

It is anticipated that isolated "green" interventions will give way to integrated decision-making over the entire life cycle in the next stage of green pharmaceutical research. Molecular design, reaction prediction, solvent selection, analytical greenness, production data, and environmental assessment can all be connected through digital platforms. When potency, safety, cost, manufacturability, and environmental performance are all taken into account at the same time, AI may help with multi-objective optimization.

Quantitative proof is the most crucial future necessity. When possible, researchers should disclose material inputs, solvent volumes, energy consumption, waste generation, yields, recovery rates, and pertinent greenness indicators. Traditional laboratory performance data should be supplemented more and more by life-cycle assessment and techno-economic analysis. Reproducibility would be enhanced, technology comparison would be made easier, and business would be assisted in identifying sustainable advances that are still both commercially and scientifically feasible.

CONCLUSION

Green pharmaceutical development is better viewed as a life-cycle approach rather than a single technology. Green chemistry principles constitute the foundation, while CADD, AI/ML, biocatalysis, flow chemistry, safer solvents, green analytical chemistry, QbD, PAT, continuous production, sustainable formulation, packaging optimization, and responsible waste management provide useful application pathways. Recent data shows rapid advancements in AI-assisted pharmaceutical analysis, sustainable analytical chemistry, and quantitative comparison of flow versus batch synthesis. However, no technology should be considered fundamentally green without specifying the system boundaries and evaluating its implications on the environment, safety, quality, and economy. Future developments will require integrated measurements, validated digital technologies, open reporting, regulatory harmonization, and early environmental considerations in pharmaceutical design. Therefore, research can support a green strategy that can be demonstrated to minimize resource use, hazard, or waste while maintaining pharmaceutical quality, patient safety, therapeutic performance, and practical manufacturability.



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