CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.22047192

Available online at: http://www.iajps.com Review Article

GREEN CHEMISTRY IN PHARMACEUTICAL DRUG DISCOVERY: SUSTAINABLE SYNTHETIC STRATEGIES, CATALYSIS, AND FUTURE PERSPECTIVES

Omkar Rai[1*], Soma Sekhar Pulamarasetti[1], Manish Gupta[1], Kovvada Vandana[2], Vishva Prakash[3]

[1] Department of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur, Madhya Pradesh, India (PIN: 458001)

[2] AU College of Pharmaceutical Sciences (AUCOPS), Andhra University, Visakhapatnam, Andhra Pradesh, India

[3] Department of Pharmacy, Central University of Rajasthan, NH-8, Bandarsindri, Ajmer District, Rajasthan, India (PIN: 305817)

Abstract:

In pharmaceutical discovery, potency, selectivity, pharmacokinetics, safety and manufacturability have traditionally been optimized, with environmental performance often considered later in process development. But this separation is becoming increasingly untenable, as discovery routes can consume large quantities of solvents and reagents, produce large amounts of waste, and depend on rare or hazardous materials. Green chemistry is a proactive strategy designed to reduce waste, hazards, energy requirements, and resource consumption at the molecular and reaction-design levels rather than after pollution has been generated. This review formulates an integrated view on sustainable pharmaceutical drug discovery with a focus on catalysis, biocatalysis, safer solvents, solvent minimization, one-pot and multicomponent synthesis, continuous-flow processing, photochemistry, electrochemistry, mechanochemistry, microwave-assisted synthesis, renewable feedstocks, green purification and life-cycle assessment. It also proposes a Sustainable Synthesis-to-Process (S2P) framework linking molecular design to retrosynthetic planning, reaction optimization, process intensification, quantitative green metrics, and scale-up. Special emphasis is placed on process mass intensity (PMI), E-factor, atom economy, reaction mass efficiency, energy intensity, carbon footprint and life-cycle assessment. Recent literature also supports the use of artificial intelligence and automated experimentation to multi-objectively optimize yield and sustainability. The review argues that the most important transition is conceptual: green chemistry should be factored in as a design variable in drug discovery, rather than as a downstream manufacturing correction .

Keywords: *green chemistry; pharmaceutical synthesis; drug discovery; sustainable catalysis; biocatalysis; green solvents; flow chemistry; process intensification; mechanochemistry; photocatalysis; electrochemistry; PMI; life-cycle assessment; artificial intelligence.*

Corresponding author:

Omkar Rai,

Department of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur, Madhya Pradesh, India.

Mobile: +91-9792279812

Email Id: *omkarrai274304@gmail.com*

QR CODE

Please cite this article in press Omkar Rai et al., Green Chemistry In Pharmaceutical Drug Discovery: Sustainable Synthetic Strategies, Catalysis, And Future Perspectives. Indo Am. J. P. Sci, 2026; 13(08).

1. INTRODUCTION:

The pharmaceutical industry occupies a distinctive position in sustainable chemistry. Unlike bulk chemical manufacturing, pharmaceutical synthesis often produces high-value products in comparatively small quantities, but the molecular complexity of active pharmaceutical ingredients (APIs) can require numerous synthetic operations, protecting-group manipulations, excess reagents, solvent-intensive work-ups, and chromatographic purification. Consequently, a process can have an excellent isolated yield while still generating a large environmental burden. Green chemistry reframes this problem by asking how the desired molecule can be produced with less material, lower hazard, lower energy demand, and fewer downstream operations [1–7].

The original green-chemistry principles established prevention, atom economy, catalysis, safer solvents, energy efficiency, renewable feedstocks, and inherently safer synthesis as design principles rather than end-of-pipe controls [1,2]. For pharmaceuticals, these principles have particular relevance because the route chosen during discovery can influence the environmental and economic trajectory of a molecule for years. Modern reviews emphasize that green synthesis is not simply the replacement of one solvent or reagent; it requires holistic optimization from raw material selection through API isolation and manufacturing [7,8].

Recent literature backs up this change . Pharmaceutical green chemistry is more and more associated with quantitative sustainability metrics, process development, continuous manufacturing, catalytic synthesis, biocatalysis and alternative reaction media [9–14]. Solvent selection, catalytic methods, biocatalysis, flow chemistry, microwave methods and process intensification are also major areas of current development as highlighted in a recent review of pharmaceutical synthesis [15]. Thus a modern review should integrate medicinal chemistry, process chemistry, chemical engineering and sustainability science, rather than treating them in isolation.

Table 1. Major sustainability pressures in pharmaceutical drug discovery and their design responses

Pressure point	Typical consequence	Green-chemistry response	Useful metric / indicator
Multistep synthesis	Cumulative waste and yield loss	Route compression, telescoping, one-pot chemistry	Step count; PMI; E-factor
Large solvent volumes	High material demand and waste	Concentration, safer solvents, solvent recovery	Solvent intensity; PMI
Stoichiometric reagents	Salt/by-product generation	Catalysis, catalytic redox, biocatalysis	Atom economy; RME
Protecting groups	Extra steps and purification	Chemoselective chemistry; direct functionalization	Step economy; PMI
Chromatographic purification	High solvent consumption	Crystallization, precipitation, direct isolation	Solvent mass; PMI
Hazardous intermediates	Worker and process risk	Flow processing, safer reagents, in situ generation	Hazard assessment
High energy demand	Higher operating footprint	Milder conditions, flow, photochemical/electrochemical alternatives	Energy intensity
Scarce catalysts	Resource and supply-chain risk	Base metals, immobilized catalysts, recovery	Catalyst loading; criticality

2. Why Green Chemistry Must Enter Drug Discovery Early

An unusual synthetic workload comes from drug discovery Series of analogs are frequently synthesized by medicinal chemists to investigate structure–activity relationships, physicochemical properties, selectivity and metabolic stability. Now speed and molecular diversity can power the decision making process. But if a promising scaffold ends up requiring an inefficient or unsafe route, the cost of redesign escalates substantially in later development. Incorporation of sustainability considerations at the discovery stage can help prevent route lock-in and find chemistry that is both biologically effective and process-ready [16–20].

The distinction between “green reaction chemistry” and “green drug-discovery chemistry” is important. The first asks if a reaction is efficient, the second asks if the whole sequence from building blocks to purified API is resource efficient. A reaction with 95% yield might be less sustainable than a reaction with 85% yield if the former requires excess protecting groups, toxic solvent, multiple extractions, chromatography, and large aqueous washes. This systems view is consistent with the pharmaceutical green-metrics literature, which integrates the mass, energy, environmental, health, and

safety dimensions [21–24]. A practical discovery workflow should thus record at least reaction yield, stoichiometric excess, solvent volume, catalyst loading, purification method, reaction time, temperature and waste generated. This data can be used later to support PMI and life-cycle analysis. This type of documentation is especially useful in high-throughput medicinal chemistry, where the aggregation of many small individual experiments across thousands of compounds is important [25–27].

3. The Sustainable Synthesis-to-Process (S2P) Framework

We propose a Sustainable Synthesis-to-Process (S2P) framework as a conceptual model to integrate green chemistry into pharmaceutical discovery. The first layer is the molecular design, where synthetic accessibility and structural complexity are taken into account with the potency. The second layer is retrosynthetic planning, which ranks routes by the number of reactions, atom economy, protecting-group loadings, catalyst criticality, and predicted PMI. The third layer is reaction optimization where yield is optimized with solvent, energy, catalyst and waste metrics simultaneously [28–32].

The process intensification is the fourth layer. One-pot sequences, telescoped operations, continuous flow, in situ separation and catalytic cascades allow to avoid intermediate isolation steps. The fifth layer is the quantitative assessment using PMI, E-factor, energy use, carbon footprint and LCA. The final layer is scale-up and circularity, including solvent recovery, catalyst recycling, renewable electricity, waste valorization and recovery of valuable materials. Thus, the framework does not view sustainability as a one-time assessment at the end of development, but as a feedback loop.

Table 2. Decision matrix for selecting a greener synthetic route during discovery

Decision criterion	Route characteristic to prefer	Why it matters	Related metric
Step count	Fewer isolated steps	Reduces cumulative losses and work-up	PMI; E-factor
Atom economy	Higher	Less theoretical waste	Atom economy
Catalysis	Catalytic over stoichiometric	Reduces reagent-derived waste	RME; PMI
Solvent burden	Lower volume / safer solvent	Solvents can dominate material use	Solvent intensity
Purification	Crystallization/direct isolation	Avoids chromatography	PMI
Energy	Mild, efficient conditions	Lowers process energy demand	Energy intensity
Waste	Fewer, less hazardous streams	Simplifies treatment and disposal	E-factor
Scale-up	Robust and controllable	Improves manufacturing translation	STY; LCA

4. Green Metrics: From Yield to Life-Cycle Thinking

One of the simplest ways to evaluate how efficiently reactant atoms become product atoms is still atom economy [33]. It is very useful to compare transformations such as addition, coupling, substitution, protection/deprotection and redox processes. However atom economy is a theoretical concept and does not consider the yield, solvents, work-up materials or energy. It should thus be combined with reaction mass efficiency and process-level metrics [34–37].

The E-factor is the amount of waste per mass of product. PMI is the total material input (mass) per mass of product. In pharmaceutical process development, PMI is particularly useful as it can include solvents, water, reagents, catalysts, and processing aids. Life-cycle assessment extends the analysis beyond the manufacturing gate to include upstream raw-material production, energy sources, emissions, water, and end-of-life impacts [38–41]. Recent pharmaceutical metrics literature highlights that no one metric is sufficient and that the environmental, health, safety, resource and energy dimensions need to be considered together [42,43].

The major practical lesson is that metrics should be used prospectively. If PMI is calculated only after a route has been finalized, it is mostly diagnostic. Early inclusion of PMI in the route scouting process can help chemists eliminate inefficient routes before being locked into development. Such calculations could be increasingly automated by digital instruments and structured electronic laboratory records [44-46].

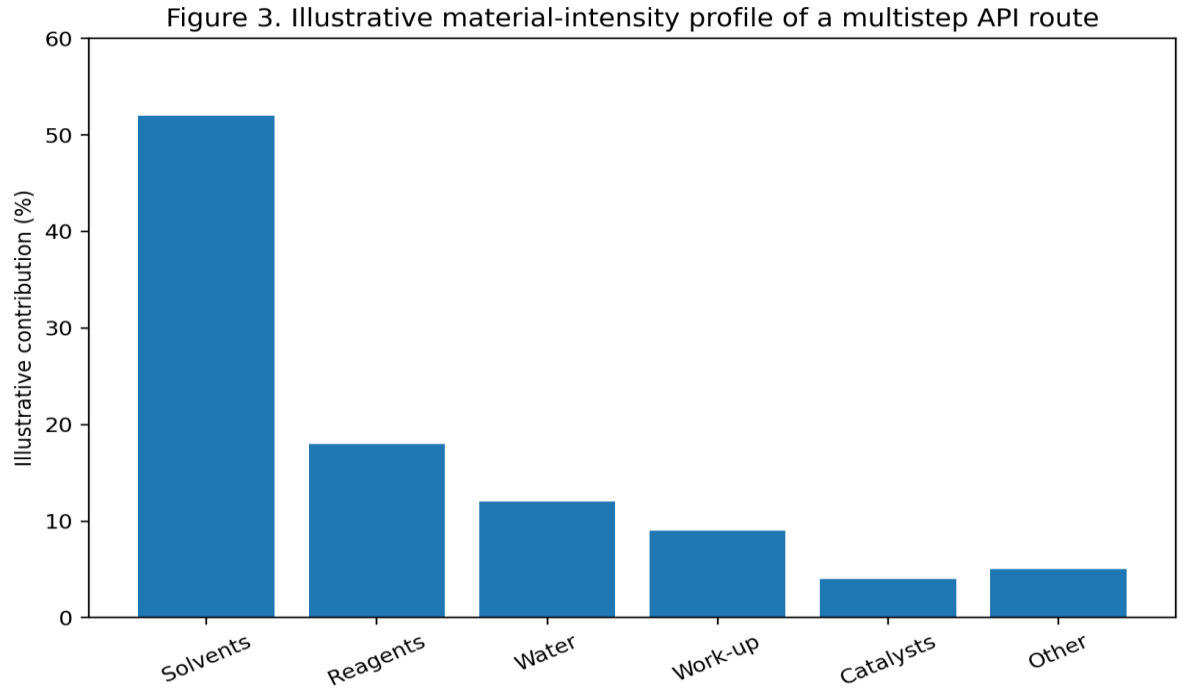

Figure 3. Illustrative material-intensity profile of a multistep API route. Values are conceptual and should not be interpreted as a universal pharmaceutical average.

5. Catalysis as the Central Engine of Sustainable Synthesis

Catalysis is one of the most powerful tools to implement green chemistry because catalysts can lower activation barriers, enhance selectivity, reduce reagent stoichiometry and allow milder reaction conditions. Catalytic hydrogenation, oxidation, carbon–carbon coupling, carbon–heteroatom bond formation, asymmetric catalysis, and organocatalysis have transformed the synthesis of pharmaceuticals [47–50].

Transition-metal catalysis, particularly palladium-catalyzed cross-coupling reactions, has become an indispensable tool in medicinal chemistry. But low catalyst loading does not a catalytic sustainability make. Metal criticality, mining impacts, ligand synthesis, toxicity, residual-metal specifications, catalyst recovery and purification must be taken into account. Base-metal catalysts, heterogeneous catalysts, supported catalysts and metal-free organocatalysis are appealing alternatives, as long as they retain the required selectivity and robustness [51–54].

Catalysis also offers opportunities for route compression. A resolution could be replaced by a catalytic asymmetric step, a few isolated intermediates could be replaced by a catalytic cascade. In this sense, the number of downstream operations that the catalyst eliminates should be used as a criterion for catalyst design, in addition to the turnover number and selectivity.

6. Biocatalysis and Chemoenzymatic Synthesis

Biocatalysis is particularly compelling for pharmaceutical chemistry because enzymes frequently offer exceptional chemo-, regio-, and stereoselectivity under relatively mild conditions. Modern protein engineering has expanded the substrate scope and operational stability of enzymes, while directed evolution can optimize catalytic performance for synthetic applications [55–58].

The strongest sustainability advantage often arises when biocatalysis replaces a sequence of protection, activation, and stereochemical-control operations. Enzymatic transaminations, ketoreductions, hydrolyzes, oxidations and amide-forming transformations are becoming more and more important in the synthesis of APIs. Enzyme cascades can also minimize solvent exchange and intermediate isolation by coupling multiple transformations in one pot [59–62].

However, biocatalysis is not sustainable by definition. The process footprint includes enzyme production, co-factors, buffering agents, water use, downstream isolation and enzyme disposal. A realistic comparison should therefore be made of the whole process and not just the reactor. Chemoenzymatic pathways are particularly promising as they combine the broad reaction space of synthetic chemistry with the selectivity of enzymes [63,64].

Table 3. Sustainable catalytic and biocatalytic strategies relevant to pharmaceutical synthesis

Strategy	Representative use	Sustainability advantage	Main limitation
Transition-metal catalysis	C–C / C–N coupling	High selectivity and lower reagent excess	Metal residues; criticality
Base-metal catalysis	Hydrogenation / coupling / oxidation	Potentially lower criticality	Catalyst development
Organocatalysis	Asymmetric synthesis	Metal-free option	Catalyst loading
Biocatalysis	Ketoreduction / transamination	Excellent selectivity under mild conditions	Enzyme stability/cofactors
Chemoenzymatic cascades	Sequential chemical + enzymatic steps	Route compression	Step compatibility
Immobilized catalysts	Catalytic synthesis	Recovery and reuse	Mass transfer
Catalytic cascades	Multiple transformations	Fewer isolated intermediates	Condition compatibility

7. Green Solvents and Solvent Minimization

Solvents are usually the largest material inputs in pharmaceutical synthesis. Thus, solvent selection guides have become useful tools for medicinal and process chemists. The guides take into account parameters such as human toxicity, environmental hazard, volatility, flammability, reactivity and waste treatment [65–68]. Commonly preferred solvents include water, ethanol, ethyl acetate and some alternative ethers, but suitability depends strongly on the chemistry and the full life cycle of the solvent [69].

The goal should not be just to change solvents. Benefits can be greater solvent volume reduction, increased reaction concentration, elimination of solvent exchange, solvent recycling and avoiding chromatography. Other recent work stresses that "green," "renewable," and "low-carbon" are not synonymous terms, and that solvent feedstock origin, intrinsic hazard, and life-cycle emissions should be considered separately [70,71]. Ionic liquids and deep eutectic solvents provide tailor-made physical properties, low vapor pressure, but the sustainability of their application has to be critically assessed. Their apparent advantages may be offset by toxicity, persistence, viscosity, preparation, purification, recovery and end-of-life behavior. However deep eutectic solvents are an important research platform, as many can be prepared by simple mixing of components and can be tailored for catalysis, extraction and synthesis [72–74].

8. One-Pot, Telescoped, and Multicomponent Synthesis

Any isolated intermediate also introduces solvent exchange, extraction, drying, concentration, purification, analytical testing, and material loss. One-pot and telescoped synthesis minimize these operations by passing an intermediate directly to the next transformation, Multicomponent reactions have the capacity to generate considerable molecular complexity from a handful of simple precursors in one step [75].

Telescoping is especially valuable in pharmaceutical discovery where unstable intermediates are hard to isolate, or purification can be postponed until the final step. When the telescoping process is combined with catalytic reactions and direct crystallization, the sustainability gain can be further enhanced. The problem is that the pH, temperature, catalysts, impurities and solvent requirements of the consecutive reactions have to be compatible with one another.

Table 4. Comparison of conventional and intensified pharmaceutical processing

Feature	Batch	Flow / intensified processing	Potential sustainability effect
Reaction inventory	Larger instantaneous inventory	Small reactor inventory	Improved safety
Heat transfer	Can become limiting at scale	High surface-to-volume ratio	Better thermal control
Reaction time	Often longer	Precisely controlled residence time	Potential productivity gain
Intermediate isolation	Often separate	Telescoping possible	Less solvent and waste
Photochemistry	Light penetration can limit scale	Thin channels improve illumination	Better photon utilization
Gas reactions	Separate gas handling	Controlled gas–liquid contact	Improved mass transfer
Automation	Discrete sampling	Inline analytics possible	Data-rich optimization
Scale-up	Larger vessels	Numbering-up / scale-out	Potentially controlled translation

9. Continuous-Flow Chemistry and Process Intensification

Continuous-flow chemistry enables precise control of the reaction time, heat transfer, mass transfer and the addition of reagents. It can minimize the inventory of hazardous intermediates and is especially attractive for exothermic, gas–liquid, photochemical, and electrochemical reactions. Flow processing also enables automation and rapid optimization of parameters [26–31].

Process intensification is a major sustainability benefit. A compact reactor can provide high productivity with less equipment footprint and better heat transfer. Telescoping, inline analytics and continuous crystallization can also be enabled by flow. However, sustainability should be considered throughout the whole process, as flushing, dilution, tubing, pumps and solvent consumption can be an issue at low throughput. The correct question therefore is not Is flow green? but Does the flow configuration reduce the total environmental burden of this particular route?

10. Photochemistry and Photocatalysis

Photoredox chemistry has opened up reactivity pathways that are otherwise difficult to access by conventional two-electron chemistry. Visible-light photoredox catalysis can produce radicals under relatively mild conditions and has facilitated C–C, C–N, C–O and other bond-forming transformations of relevance to medicinal chemistry [34,35]. Photochemistry can reduce the need for harsh reagents and perhaps enable direct activation of otherwise inert substrates from a sustainability perspective. Limitations are photon efficiency, light penetration, reactor geometry, photocatalyst cost and electricity demand. Thin reaction channels are of interest for flow photochemistry as they facilitate light penetration and heat management [36].

11. Electrochemical Synthesis

Electrosynthesis replaces some stoichiometric oxidants and reductants by electrical current. It can reduce waste generated from reagents and provide tunable redox control. Therefore, electrochemistry is attractive for oxidation, reduction, cross-coupling and functionalization chemistry [37–39].

The sustainability of electrochemistry is directly connected with the source of electricity. Renewable electricity can improve the climate profile substantially, and carbon-intensive electricity can erode the advantage. Important process parameters are current efficiency, electrode lifetime, electrolyte selection, mass transfer, cell design and downstream electrolyte removal. Continuous electrochemical reactors allow for integration of reaction, heat management and automation.

12. Mechanochemistry and Solvent-Free Synthesis

Mechanochemistry uses mechanical energy to drive chemical transformations, often with little or no bulk solvent. Ball milling, extrusion, grinding and similar methods can lower solvent intensity and sometimes speed up reactions. Pharmaceutical applications involve synthesis of APIs, salt formation, cocrystal preparation, coupling chemistry and late-stage functionalization [40–46].

The field is promising, but needs more focus on scale-up, reproducibility, energy accounting, lifetime of equipment and product isolation. Extrusion-based processing in particular may provide a pathway for scaling continuous mechanochemistry from laboratory demonstration to manufacturing. Another growing trend is mechanochemical biocatalysis, which combines enzyme selectivity and lower solvent requirements.

13. Microwave-Assisted and Alternative-Energy Synthesis

Microwave irradiation can accelerate many organic reactions due to effective energy delivery and rapid heating. In medicinal chemistry this can decrease reaction time and sometimes improve yields. Ultrasound and other alternate energy sources may also affect mass transfer and reaction kinetics. However, a short reaction time does not automatically correspond to a lower environmental footprint, as the total electricity use, the solvent volume and the scale-up behavior have to be measured [47].

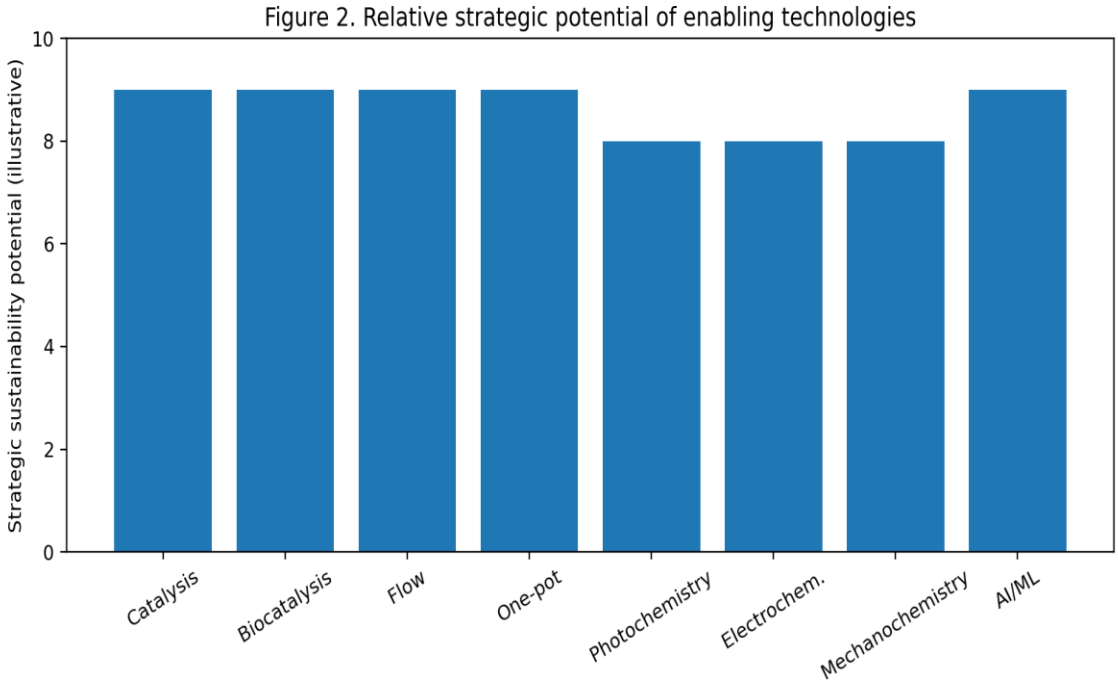

Figure 2. Relative strategic potential of enabling technologies. Scores are illustrative and intended for conceptual comparison, not experimental measurements.

14. Renewable Feedstocks and Circular Carbon

Environmentally responsible production of renewable feedstocks can reduce our dependence on fossil carbon . Potential substrates include carbohydrates, lignocellulosic biomass, glycerol, fermentation products, amino acids, and bio-based platform chemicals [48].

Circular carbon is a more general idea than the substitution of petroleum by biomass. A circular pharmaceutical process is designed to reduce the use of virgin material, recover solvents, recycle catalysts, valorize side streams , and minimize waste . Life-cycle assessment is important, as cultivation, land use, water consumption, fertilizer use, transport and biomass processing can influence the overall environmental profile.

15. Green Purification: The Often-Ignored Bottleneck

Purification can contribute significantly to PMI as chromatography and repeated extraction may require a lot more solvent than the reaction itself. This is especially important in medicinal chemistry where fast purification of small amounts can enable routine use of silica chromatography. A route that eliminates a solvent-intensive reaction but still requires repeated chromatography may only provide a modest overall improvement [7,9,15].

Crystallization, precipitation, direct phase separation, minimization of aqueous work-up, selective extraction, and reusable separation media can offer more sustainable alternatives. The design of molecules and intermediates with desirable solid-state properties could thus be incorporated into green process design. Often the synthetic route with the highest reaction yield is not the best one, but the one that yields a material that is easy to isolate.

16. Green Medicinal Chemistry: Beyond Potency

The traditional focus of medicinal chemistry is on optimization of biological properties, but sustainable medicinal chemistry should add synthetic complexity and environmental burden as additional dimensions. A practical multi-objective profile can include potency, Selectivity, Physicochemical Properties, Synthetic Accessibility, Number of Steps, PMI, Solvent Hazard, Catalyst Criticality, Energy Demand and Purification Burden [9,10,16].

This approach does not mean that environmental performance must come at the expense of therapeutic value. Instead, sustainability can help to distinguish among biologically similar candidates. If two compounds are similar in efficacy and developability, the compound that is easier to synthesize, safer to make, and less resource intensive may be selected. This kind of thinking can also inspire the design of molecular scaffolds that are easier to assemble and recycle.

Table 5. AI-enabled opportunities for sustainable pharmaceutical synthesis

AI / automation task	Input data	Green objective	Potential output
Retrosynthetic planning	Target structure + reaction data	Minimize steps, PMI and hazard	Ranked sustainable routes
Solvent recommendation	Reaction + solvent descriptors	Reduce hazard and solvent burden	Solvent shortlist
Condition optimization	Catalyst, solvent, T, time	Optimize yield and sustainability together	Pareto-optimal conditions
Catalyst selection	Substrate + catalyst descriptors	Lower loading / criticality	Catalyst ranking
Process monitoring	Inline analytical data	Detect deviations early	Adaptive control
LCA prediction	Material and energy inputs	Estimate impact early	Route sustainability score
Autonomous experimentation	Model + experiments	Minimize material and experiments	Self-optimizing platform

17. Artificial Intelligence, Automation, and Green Route Design

Artificial intelligence and machine learning are becoming more and more relevant to sustainable synthesis. Predicting reaction yields, planning retrosynthetic steps, selecting catalysts, recommending solvents, optimizing reaction conditions and automatically mining the literature can reduce the experimental search. The next step is to embed sustainability goals directly in these models [10,44-46].

A green retrosynthesis engine could rank candidate routes according to a composite objective comprising chemical yield, step count, PMI, solvent hazard, catalyst criticality, predicted energy demand and carbon footprint. Then, Bayesian optimization and active learning could be used to select experiments that maximize the information gain while minimizing the material consumption. Recent literature has stressed the rise of AI and quantum-chemical approaches as elements of green organic synthesizing in drug discovery [10].

18. High-Throughput Experimentation and Self-Optimizing Chemistry

Automated experimentation can turn green chemistry from a largely manual optimization process into a data-driven control loop. Miniaturization of reactions lowers material consumption during condition screening, and inline analytics offer rapid feedback. Bayesian optimization can point to promising conditions with fewer experiments than exhaustive grids. When sustainability variables are incorporated into the objective function, the system is able to optimize yield and environmental performance together.

The problem is data quality. Sustainability models require accurate information on the quantities of solvents, energy use, catalyst preparation, waste treatment and upstream material production. Therefore, the importance of standardized electronic laboratory records and machine-readable reaction descriptions will be equal to sophisticated algorithms.

19. Industrial Translation and Case-Based Lessons

Industrial experience demonstrates that green chemistry can provide environmental and economic benefits . Examples of pharmaceutical process development include solvent substitution , aqueous micellar catalysis , process intensification and continuous manufacturing, where PMI is applied as a practical optimization metric [9,14]. Reviews of pharmaceutical green chemistry also highlight that successful industrial examples tend to combine catalytic efficiency, improved solvent selection, fewer steps and better isolation rather than a single innovation [6,15].

An important lesson from industry is that sustainability needs to be incorporated with quality-by-design and GMP requirements. A greener route still needs to meet impurity specifications, reproducibility, robustness, stability and regulatory expectations. Consequently, the most successful green processes are those where environmental performance is enhanced alongside process control, cost, safety and product quality [9].

20. Challenges and Research Gaps

There are still a number of hurdles. First, green metrics are not yet standardized across discovery labs universally. Second, many promising laboratory techniques lack data on scaling up. Third, toxicity or life-cycle information for solvent and catalyst alternatives may not be complete. Fourth, regulatory and analytical requirements may be a challenge to process simplification. Fifth, renewable feedstocks and novel solvents may introduce upstream burdens that are not visible if only the reaction vessel is considered [21–24,70–74].

Another gap is the absence of integrated datasets that link reaction conditions to environmental outcomes. The majority of reaction databases are focused on yield and selectivity, with data on PMI, solvent mass, energy requirements and waste disposal being reported less consistently. Thus, academia and industry should focus primarily on building up high quality sustainability datasets.

Table 6. Integrated technology roadmap for next-generation green pharmaceutical synthesis

Technology	Discovery-stage role	Process-stage role	Maturity / trend	Priority research need
Catalysis	Rapid analogue synthesis	Scalable API synthesis	High	Critical-metal reduction and recovery
Biocatalysis	Selective chiral building blocks	Large-scale asymmetric synthesis	High / growing	Enzyme engineering and cofactor recycling
Green solvents	Early route screening	Manufacturing solvent systems	High	Closed-loop recovery and LCA data
Flow chemistry	Reaction screening	Continuous API manufacture	High / growing	Quantitative LCA and purification integration
Photochemistry	Late-stage functionalization	Continuous photochemical production	Growing	Photon efficiency and scale-out
Electrochemistry	Alternative redox screening	Reagent-minimized manufacturing	Growing	Electrolyte recovery and renewable power
Mechanochemistry	Solvent-minimized discovery	Potential continuous processing	Emerging	Scale-up and energy accounting
AI/ML	Green retrosynthesis	Optimization and process control	Rapidly growing	Standardized sustainability datasets
Circularity	Building-block selection	Solvent/catalyst/material recovery	Emerging	Closed-loop process models

21. FUTURE PERSPECTIVES:

The future of pharmaceutical green chemistry will likely be defined by convergence rather than by a single breakthrough technology. AI-assisted retrosynthesis can identify low-impact routes; biocatalysis can deliver selective transformations; flow reactors can intensify hazardous or photochemical operations; renewable electricity can support electrochemistry; mechanochemistry can reduce solvent use; and digital LCA can provide continuous environmental feedback. Together these technologies could create a new paradigm of "sustainability-by-design" [10,15].

A particularly attractive future model is the autonomous green laboratory. In such a system, a target structure is entered, candidate routes are generated, environmental metrics are predicted, experiments are performed automatically at microscale, analytical results are fed back to a model, and the best route is selected according to a multi-objective function. This could dramatically reduce the amount of material required to discover and optimize synthetic processes.

22. CONCLUSION:

Green chemistry is transitioning from a set of environmentally preferred reactions to a holistic design philosophy for drug discovery and manufacturing. The best opportunities come when sustainability is factored in before a route is decided. The distinctive potentials of catalysis, biocatalysis, green solvents, one-pot synthesis, flow chemistry, photochemistry, electrochemistry, mechanochemistry, renewable feedstocks, green purification, and AI are outlined. Their greatest value is when embedded in a quantitative, lifecycle decision framework.

The S2P framework proposed is a useful conceptual bridge between medicinal and process chemistry. Pharmaceutical research can shift from "less harmful synthesis" to truly sustainable drug development through the integration of molecular design, reaction selection, process intensification, green metrics, LCA and circularity. The basic idea is simple: the greenest pharmaceutical process is usually not the result of a single green reaction, but rather the optimization of the whole synthesis-to-process system.

25. REFERENCES:

1. Anastas PT, Kirchhoff MM. Origins, current status, and future challenges of green chemistry. Accounts of Chemical Research. 2002;35:686–694. DOI: 10.1021/ar0100657
2. Poliakoff M, Licence P. Green chemistry: science and politics of change. Nature. 2007;450:810–812. DOI: 10.1038/450810a
3. Wiles C, Watts P. Continuous flow reactors: a perspective. Green Chemistry. 2012;14:38–54. DOI: 10.1039/C1GC16022B
4. Jensen KF, Reizman BJ, Newman SG. Tools for chemical synthesis in the 21st century: continuous-flow chemistry. Lab on a Chip. 2014;14:3206–3212. DOI: 10.1039/C4LC00330F
5. Simić S, Zukić E, Schmermund L, Faber K. Shortening synthetic routes to small molecule active pharmaceutical ingredients employing biocatalytic methods. Chemical Reviews. 2022;122. DOI: 10.1021/acs.chemrev.1c00574

6. Usutani H. Lessons learned in developing a manufacturing facility for flow chemistry. Organic Process Research & Development. 2025;29(6):1486–1494. DOI: 10.1021/acs.oprd.5c00082
7. Hughes DL. Highlights of the recent patent literature: continuous chemistry in the pharmaceutical industry. Organic Process Research & Development. 2024;28(5):1272–1287. DOI: 10.1021/acs.oprd.3c00438
8. Hughes DL. Applications of flow chemistry in the pharmaceutical industry—highlights of the recent patent literature. Organic Process Research & Development. 2020;24(10):1850–1860. DOI: 10.1021/acs.oprd.0c00156
9. Baumann M, Moody TS, Smyth M, Wharry S. A perspective on continuous flow chemistry in the pharmaceutical industry. Organic Process Research & Development. 2020;24(10):1802–1813. DOI: 10.1021/acs.oprd.9b00524
10. Bogdan AR, Organ MG. Emerging trends in flow chemistry and applications to the pharmaceutical industry. Journal of Medicinal Chemistry. 2019;62(14):6422–6468. DOI: 10.1021/acs.jmedchem.8b01760
11. Anastas PT, Warner JC. Green Chemistry: Theory and Practice. Oxford University Press; 1998.
12. Anastas P, Eghbali N. Green chemistry: principles and case studies. Chemical Society Reviews. 2010;39:301–312. DOI: 10.1039/B918763B
13. Trost BM. The atom economy—a search for synthetic efficiency. Science. 1991;254:1471–1477. DOI: 10.1126/science.1962206
14. Constable DJC, Curzons AD, Cunningham VL. Metrics to 'green' chemistry—which are the best? Green Chemistry. 2002;4:521–527. DOI: 10.1039/B206169B
15. Sheldon RA. The E Factor: fifteen years on. Green Chemistry. 2007;9:1273–1283. DOI: 10.1039/B713736M
16. Sheldon RA. The E factor 25 years on. Green Chemistry. 2017;19:18–43. DOI: 10.1039/C6GC02157C
17. Jiménez-González C, Constable DJC, Ponder CS. Evaluating the "greenness" of chemical processes and products in the pharmaceutical industry. Chemical Society Reviews. 2012;41:1485–1498. DOI: 10.1039/C1CS15215G
18. Henderson RK, et al. Green Chemistry Metrics. Wiley-VCH; 2010. DOI: 10.1002/9783527629688.ch2
19. ACS Green Chemistry Institute Pharmaceutical Roundtable. Green chemistry and engineering metrics.
20. Becker J, Manske C, Randl S. Green chemistry and sustainability metrics in the pharmaceutical manufacturing sector. Current Opinion in Green and Sustainable Chemistry. 2022;33:100562. DOI: 10.1016/j.cogsc.2021.100562
21. Richardson P, Bryan MC, Diorazio L, et al. Solvent Sustainability in Drug Discovery: Where Are We Now, and How Can We Improve? Journal of Medicinal Chemistry. 2025. DOI: 10.1021/acs.jmedchem.5c01220
22. Li J, Simmons EM, Eastgate MD. A data-driven strategy for predicting greenness scores and benchmarking PMI outcomes. Green Chemistry. 2017;19:127–139. DOI: 10.1039/C6GC02359B
23. Prat D, Hayler J, Wells A. A survey of solvent selection guides. Green Chemistry. 2014;16:4546–4551. DOI: 10.1039/C4GC01149J
24. Henderson RK, et al. Expanding GSK's solvent selection guide. Green Chemistry. 2011;13:854–862. DOI: 10.1039/C0GC00918K
25. Prat D, Wells A, Hayler J, et al. CHEM21 selection guide. Green Chemistry. 2016;18:288–296. DOI: 10.1039/C5GC01008J
26. Sheldon RA. Green solvents for sustainable organic synthesis. Green Chemistry. 2005;7:267–278. DOI: 10.1039/B418069K
27. Hansen BB, Spittle S, Chen B, et al. Deep Eutectic Solvents. Chemical Reviews. 2021;121:1232–1285. DOI: 10.1021/acs.chemrev.0c00385
28. Zhang Q, De Oliveira Vigier K, Royer S, Jérôme F. Deep eutectic solvents. Chemical Society Reviews. 2012;41:7108–7146. DOI: 10.1039/C2CS35178A
29. Perna FM, Vitale P, Capriati V. Deep eutectic solvents and their applications. Current Opinion in Green and Sustainable Chemistry. 2020;21:27–33. DOI: 10.1016/j.cogsc.2019.09.004
30. Rosenthal K, Lütz S. Recent developments and challenges of biocatalytic processes. Current Opinion in Green and Sustainable Chemistry. 2018;11:58–64. DOI: 10.1016/j.cogsc.2018.03.015
31. Britton J, Majumdar S, Weiss GA. Continuous Flow Biocatalysis. Chemical Society Reviews. 2018;47:5891–5918. DOI: 10.1039/C7CS00906B
32. Bornscheuer UT, Hauer B, Jaeger KE, Schwaneberg U. Directed evolution empowered redesign of natural proteins. Angewandte Chemie. 2019;58:36–40. DOI: 10.1002/anie.201807495
33. Sheldon RA, Brady D. The limits to biocatalysis. Chemical Communications. 2018;54:6088–6104. DOI: 10.1039/C8CC02434G
34. Sheldon RA, Woodley JM. Role of biocatalysis in sustainable chemistry. Chemical Reviews. 2018;118:801–838. DOI: 10.1021/acs.chemrev.7b00203
35. Wu S, et al. Biocatalysis: enzymatic basics and applications. Angewandte Chemie. 2021;60:88–119. DOI: 10.1002/anie.202006648
36. Rogers L, Jensen KF. Continuous manufacturing—the Green Chemistry promise? Green Chemistry. 2019;21:3481–3498. DOI: 10.1039/C9GC00773C
37. Ferlin F, Lanari D, Vaccaro L. Sustainable flow approaches to active pharmaceutical ingredients. Green Chemistry. 2020;22:5937–5955. DOI: 10.1039/D0GC02404J
38. Plutschack MB, Pieber B, Gilmore K, Seeberger PH. The Hitchhiker's Guide to Flow Chemistry.

Chemical Reviews. 2017;117:11796–11893. DOI: 10.1021/acs.chemrev.7b00183
39. Gutmann B, Cantillo D, Kappe CO. Continuous-flow technology for safe manufacturing of APIs. Angewandte Chemie. 2015;54:6688–6728. DOI: 10.1002/anie.201409694
40. Porta R, Benaglia M, Puglisi A. Flow chemistry and pharmaceutical products. Organic Process Research & Development. 2016;20:2–25. DOI: 10.1021/acs.oprd.5b00369
41. Baxendale IR. Integration of flow reactors into synthetic organic chemistry. Chemical Engineering Technology. 2013;36:230–240. DOI: 10.1002/ceat.201200607
42. Burange AS, Osman SM, Luque R. Understanding flow chemistry for API production. iScience. 2022;25:103892. DOI: 10.1016/j.isci.2022.103892
43. Nicewicz DA, MacMillan DWC. Merging photoredox catalysis with organocatalysis. Science. 2008;322:77–80. DOI: 10.1126/science.1161976
44. Prier CK, Rankic DA, MacMillan DWC. Visible light photoredox catalysis. Chemical Reviews. 2013;113:5322–5363. DOI: 10.1021/cr300503r
45. Romero NA, Nicewicz DA. Organic photoredox catalysis. Chemical Reviews. 2016;116:10075–10166. DOI: 10.1021/acs.chemrev.6b00057
46. Photocatalysis in the Life Science Industry. Chemical Reviews. 2022;122:2907–2980. DOI: 10.1021/acs.chemrev.1c00416
47. Yan M, Kawamata Y, Baran PS. Synthetic Organic Electrochemical Methods Since 2000. Chemical Reviews. 2017;117:13230–13319. DOI: 10.1021/acs.chemrev.7b00397
48. Kingston C, et al. A survival guide to electrosynthesis. Accounts of Chemical Research. 2020;53:72–83. DOI: 10.1021/acs.accounts.9b00586
49. Francke R, Little RD. Redox catalysis with electrochemical methods. Chemical Society Reviews. 2014;43:2492–2521. DOI: 10.1039/C3CS60464K
50. Ghosh A, Parida VK, Banerjee D. Sustainable electrochemical transformations for pharmaceuticals. Green Chemistry. 2024;26:5770–5789. DOI: 10.1039/D3GC04881K
51. Mechanochemical and Mechanoenzymatic Synthesis of Pharmacologically Active Compounds. ACS Sustainable Chemistry & Engineering. 2020;8:8881–8893. DOI: 10.1021/acssuschemeng.0c01645
52. Arfelis S, et al. Linking mechanochemistry with the green chemistry principles. Heliyon. 2024;10:e34655. DOI: 10.1016/j.heliyon.2024.e34655
53. Naidu BR, et al. Catalyst-free mechanochemistry as a versatile tool. Green Chemistry. 2023;25:6120–6148. DOI: 10.1039/D3GC01229H
54. Mechanochemistry: A Green Approach in the Preparation of Pharmaceutical Cocrystals. Pharmaceutics. 2021;13:790. DOI: 10.3390/pharmaceutics13060790
55. Mechanochemical C–X/C–H Functionalization. European Journal of Organic Chemistry. 2022. DOI: 10.1002/ejoc.202101440
56. Mechanochemical Strategies Applied to Late-Stage Modifications of Pharmaceutically Active Compounds. Angewandte Chemie. 2025. DOI: 10.1002/anie.202503061
57. Starvaggi J, Ettari R. Microwave-Assisted Organic Synthesis. Pharmaceuticals. 2025;18:1692. DOI: 10.3390/ph18111692
58. Sheldon RA. Green and sustainable manufacture of chemicals from biomass. Green Chemistry. 2014;16:950–963. DOI: 10.1039/C3GC41935E
59. Sheldon RA. The E factor 25 years on. Green Chemistry. 2017;19:18–43. DOI: 10.1039/C6GC02157C
60. Jiménez-González C, et al. Green metrics in pharmaceutical development. Current Opinion in Green and Sustainable Chemistry. 2022;33:100564. DOI: 10.1016/j.cogsc.2021.100564
61. Green synthesis interventions of pharmaceutical industries for sustainable development. Current Research in Green and Sustainable Chemistry. 2021;4:100174. DOI: 10.1016/j.crgsc.2021.100174
62. Green Chemistry Approaches in Pharmaceutical Synthesis: Sustainable Methods for Drug Development. AppliedChem. 2025. DOI: 10.3390/appliedchem5020013
63. Solvent Eco-Impact Metric. Organic Process Research & Development. 2025. DOI: 10.1021/acs.oprd.4c00546
64. Becker J, Manske C, Randl S. Green chemistry and sustainability metrics in pharmaceutical manufacturing. Current Opinion in Green and Sustainable Chemistry. 2022;33:100562. DOI: 10.1016/j.cogsc.2021.100562
65. Continuous manufacturing – the Green Chemistry promise? Green Chemistry. 2019;21:3481–3498. DOI: 10.1039/C9GC00773C
66. Sustainable flow approaches to active pharmaceutical ingredients. Green Chemistry. 2020;22:5937–5955. DOI: 10.1039/D0GC02404J
67. Deep Eutectic Solvents and their applications as green solvents. Chemical Society Reviews. 2012;41:7108–7146. DOI: 10.1039/C2CS35178A
68. Quintana AA, et al. Enabling Sustainable Chemistry with Ionic Liquids and Deep Eutectic Solvents. Angewandte Chemie. 2022;61:e202205609. DOI: 10.1002/anie.202205609
69. Calvo-Flores FG. Deep Eutectic Solvents and Multicomponent Reactions. ChemistryOpen. 2021;10:815–829. DOI: 10.1002/open.202100137
70. Bornscheuer UT. The fourth wave of biocatalysis is approaching. Philosophical Transactions B. 2018;373:20170068. DOI: 10.1098/rstb.2017.0068
71. Turner NJ, O'Reilly E. Recent advances in biocatalytic retrosynthesis. Current Opinion in Chemical Biology. 2013;17:283–289. DOI: 10.1016/j.cbpa.2013.01.006

72. Sheldon RA, Brady D. Broadening the scope of biocatalysis. Chemical Communications. 2018. DOI: 10.1039/C8CC04753H
73. Romero NA, Nicewicz DA. Organic photoredox catalysis. Chemical Reviews. 2016;116:10075–10166. DOI: 10.1021/acs.chemrev.6b00057
74. Prier CK, Rankic DA, MacMillan DWC. Visible light photoredox catalysis. Chemical Reviews. 2013;113:5322–5363. DOI: 10.1021/cr300503r
75. Kingston C, et al. A survival guide to electrosynthesis. Accounts of Chemical Research. 2020;53:72–83. DOI: 10.1021/acs.accounts.9b00586
76. Trost BM. The atom economy—a search for synthetic efficiency. Science. 1991;254:1471–1477. DOI: 10.1126/science.1962206
77. Constable DJC, et al. Metrics to green chemistry. Green Chemistry. 2002;4:521–527. DOI: 10.1039/B206169B
78. Sheldon RA. Green solvents for sustainable organic synthesis. Green Chemistry. 2005;7:267–278. DOI: 10.1039/B418069K
79. Prat D, et al. CHEM21 solvent selection guide. Green Chemistry. 2016;18:288–296. DOI: 10.1039/C5GC01008J
80. Henderson RK, et al. GSK solvent selection guide. Green Chemistry. 2011;13:854–862. DOI: 10.1039/C0GC00918K
81. Rogers L, Jensen KF. Continuous manufacturing. Green Chemistry. 2019;21:3481–3498. DOI: 10.1039/C9GC00773C
82. Ferlin F, Lanari D, Vaccaro L. Sustainable flow approaches to APIs. Green Chemistry. 2020;22:5937–5955. DOI: 10.1039/D0GC02404J
83. Gutmann B, Cantillo D, Kappe CO. Continuous-flow technology. Angewandte Chemie. 2015;54:6688–6728. DOI: 10.1002/anie.201409694
84. Plutschack MB, Pieber B, Gilmore K, Seeberger PH. Flow Chemistry guide. Chemical Reviews. 2017;117:11796–11893. DOI: 10.1021/acs.chemrev.7b00183
85. Hansen BB, et al. Deep eutectic solvents. Chemical Reviews. 2021;121:1232–1285. DOI: 10.1021/acs.chemrev.0c00385