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Research Article

Integrated Green Strategies for Pharmaceutical Intermediate Synthesis

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ABSTRACT

The pharmaceutical industry remains one of the most solvent- and reagent-intensive branches of chemical manufacturing, generating an environmental factor (E-factor) far higher than that of bulk chemicals. This paper synthesises current evidence on how green chemistry is reshaping the synthesis of pharmaceutical intermediates — the multistep chemical building blocks from which active pharmaceutical ingredients (APIs) are constructed. Drawing on peer-reviewed literature spanning catalysis, biocatalysis, green solvent systems, mechanochemistry, microwave- and ultrasound-assisted synthesis, continuous-flow processing, multicomponent and click chemistry, photoredox and electrochemical methods, nanocatalysis, and artificial-intelligence-assisted route design, the paper evaluates each strategy against established sustainability metrics — atom economy, E-factor, and Process Mass Intensity (PMI). The analysis shows that no single technique is sufficient on its own; the greatest reductions in waste and energy use arise when catalytic, biocatalytic, and flow-based methods are combined into integrated production systems. Industrial evidence from major pharmaceutical manufacturers is examined alongside economic feasibility considerations, and the paper concludes by outlining the principal barriers to industrial adoption — capital cost, scale-up risk, enzyme stability, and inconsistent sustainability reporting — before proposing directions for future research, including standardised green metrics, life-cycle assessment integration, and AI-guided retrosynthesis.

INTRODUCTION

1.1 Background and Rationale

Green chemistry has developed, over roughly three decades, from a set of academic principles into a working framework for pharmaceutical process design. The field is generally traced to the twelve principles articulated by Anastas and Warner [1], which reframed pollution as a design failure to be prevented at the molecular level rather than a by-product to be treated after the fact. For the pharmaceutical sector, this reframing is unusually consequential: the synthesis of active pharmaceutical ingredients typically proceeds

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through several discrete intermediates, each requiring its own reagents, solvents, and purification steps. Sheldon's widely cited analysis puts the E-factor of pharmaceutical manufacturing — the mass of waste generated per unit mass of product — in the range of 25 to 100 [2], considerably higher than the corresponding figure for bulk or fine chemicals. This waste burden is a direct consequence of low atom economy, heavy reliance on volatile organic solvents, and multistep sequences that require repeated isolation and purification.

The historical emphasis in pharmaceutical process chemistry was almost entirely on yield, purity, and time-to-market, with environmental performance treated, at best, as a secondary consideration addressed through end-of-pipe waste treatment. Over the past two decades this emphasis has shifted considerably. Rising costs of hazardous-waste disposal, tightening regulatory limits on solvent emissions and effluent toxicity, greater public and investor scrutiny of corporate environmental performance, and a growing scientific recognition that pollution prevention is cheaper than pollution treatment have together made green chemistry a commercial as well as an ethical priority for pharmaceutical manufacturers.

1.2 The Pharmaceutical Waste Problem

Pharmaceutical manufacturing is distinguished from bulk and fine chemical manufacturing by the complexity of its synthetic routes. A single active pharmaceutical ingredient may require anywhere from six to more than twenty discrete synthetic steps, each involving reagents, solvents, catalysts, and work-up procedures. Because yield losses compound across steps, and because each step typically requires its own solvent volume for reaction and purification, the cumulative material footprint of a finished API can be many times its own mass. Solvents alone are consistently reported to account for the majority of the mass used in a typical pharmaceutical process, a finding echoed across multiple industry solvent-selection studies [3,4]. This solvent burden, combined with the toxicological and regulatory profile of many traditional process solvents such as benzene, chloroform, dichloromethane, and carbon tetrachloride, makes solvent management one of the single most consequential levers available for improving pharmaceutical sustainability.

1.3 Scope and Objectives of the Study

This paper focuses specifically on pharmaceutical intermediates rather than on finished APIs, because intermediates account for the majority of the reaction steps, solvent volume, and energy input in a typical synthetic route [5]. Improving the sustainability of intermediate synthesis therefore has a disproportionately large effect on the overall environmental and economic profile of drug manufacturing. The specific objectives of the study are: (i) to review and classify the principal green chemistry strategies applied to pharmaceutical intermediate synthesis; (ii) to evaluate the reported sustainability performance of each strategy against atom economy, E-factor, and Process Mass Intensity; (iii) to compare conventional and green synthetic routes across representative reaction classes; (iv) to examine industrial adoption evidence and the practical barriers that slow scale-up; and (v) to identify promising directions for future research and industrial investment.

1.4 Significance of the Study

The significance of this review lies in its integrative approach. Much of the existing literature treats individual green chemistry techniques — biocatalysis, flow chemistry, solvent substitution — as separate research streams, each with its own community of practice

and its own metrics [6]. This paper instead evaluates these techniques side by side, using a common set of sustainability indicators, in order to identify which combinations of interventions are most likely to deliver measurable, reproducible improvements in industrial pharmaceutical manufacturing. In doing so, it aims to be useful both to academic researchers designing new synthetic methodology and to process chemists and engineers responsible for translating laboratory-scale green chemistry into commercial production.

1.5 Foundational Principles of Green Chemistry

Two ideas anchor almost all subsequent work in this field. The first is atom economy, introduced by Trost [7], which measures the proportion of reactant mass that ends up in the desired product rather than in by-products. Reactions with inherently high atom economy — cycloadditions, rearrangements, and catalytic additions — are preferred synthetic strategies precisely because they minimise waste at the design stage rather than requiring it to be treated afterward. The second is the E-factor, formalised by Sheldon [2], which extends the same logic to an entire process rather than a single reaction, and which remains the most widely quoted single indicator of pharmaceutical process sustainability. A related, and arguably more complete, metric, Process Mass Intensity (PMI), was proposed by Curzons and co-workers to capture the total mass of all materials — including solvents, water, and auxiliaries — consumed per unit of product, addressing a known blind spot of the E-factor [8]. Anastas and Eghbali later reviewed the practical uptake of these principles across industry, concluding that environmentally benign synthetic methods could simultaneously improve productivity and profitability rather than trading one off against the other [9].

1.6 Catalysis and Atom Economy

Catalysis forms the backbone of modern green pharmaceutical chemistry. Homogeneous catalysts, heterogeneous catalysts, and organocatalysts improve reaction rates and selectivity while reducing reagent consumption and waste formation relative to stoichiometric methods. Transition-metal-catalysed cross-coupling reactions — including Suzuki, Heck, Sonogashira, Negishi, and Buchwald–Hartwig couplings — have become indispensable tools for constructing the carbon–carbon and carbon–heteroatom bonds that recur throughout pharmaceutical intermediate synthesis. Li and Trost demonstrated that catalytic carbon–carbon bond-forming reactions are central to minimising synthetic steps while maximising atom economy [10], and more recent literature extends this principle to earth-abundant metal catalysis, in which iron, copper, nickel, and cobalt catalysts substitute for costlier and more toxic noble-metal systems. Advances in catalyst recycling, immobilisation on solid supports, and single-atom catalysis further improve the recyclability and selectivity of catalytic pharmaceutical synthesis.

1.7 Green Solvent Systems

Solvent use is consistently identified as the single largest contributor to pharmaceutical process waste. Constable, Jiménez-González and Henderson, in an influential industry perspective [3], and later Henderson and colleagues in the GSK solvent selection guide [4], showed that solvents can account for the majority of the total mass used in a typical pharmaceutical process, and proposed structured selection criteria based on toxicity, flammability, and end-of-life fate. Byrne and colleagues subsequently developed practical

solvent-selection tools that weigh environmental, safety, and economic criteria together, moving solvent choice from an informal judgement to a documented decision process [11]. This body of work underlies the now-common substitution of chlorinated and aromatic solvents with water, ethanol, 2-methyltetrahydrofuran, ionic liquids, and deep eutectic solvents. Welton's review of ionic liquids highlights their negligible vapour pressure and tunable polarity, which make them attractive reaction media, though cost and biodegradability remain open questions [12]. Abbott and colleagues introduced deep eutectic solvents — typically prepared from choline chloride and a hydrogen-bond donor such as urea or a carboxylic acid — as a lower-cost, more readily biodegradable alternative that has since been applied across a range of pharmaceutical intermediate syntheses [13]. Clarke and colleagues provide a comprehensive review of these and other alternative solvent classes, including supercritical carbon dioxide and bio-derived solvents such as ethyl lactate, concluding that no single alternative solvent is universally superior and that selection must be matched to the specific reaction and downstream processing requirements [14]. Solvent choice is increasingly considered alongside feedstock renewability: Sheldon's review of green and sustainable chemical manufacture from biomass argues that solvent substitution and bio-based feedstocks are complementary rather than competing strategies for reducing the overall environmental footprint of a synthetic route [15].

1.8 Biocatalysis and Enzymatic Synthesis

Biocatalysis has emerged as one of the most environmentally attractive approaches to pharmaceutical intermediate synthesis, particularly for compounds containing chiral centres. Sheldon and Woodley's review documents the growing industrial use of lipases, nitrilases, oxidases, transaminases, ketoreductases, and monooxygenases for the stereoselective synthesis of chiral intermediates, an application area where conventional chemical synthesis struggles to match enzymatic selectivity without resorting to costly resolution steps or chiral auxiliaries [16]. Enzymatic reactions typically proceed under mild temperature and pressure, avoid the need for protecting groups, and generate few by-products, all of which translate directly into lower E-factor and PMI values. Reetz's work on directed evolution shows how enzyme performance — substrate scope, thermal stability, and activity — can be systematically improved through iterative mutagenesis and screening, expanding the range of pharmaceutical transformations accessible to biocatalysis [17]. Sheldon and Brady's later analysis is more cautious, noting that enzyme stability under industrial process conditions, the cost of enzyme production, and the engineering required for immobilisation and reuse remain genuine limits on how far biocatalysis can be pushed without further investment in protein engineering and process design [18]. A 2025 update to this literature, by Bayer and colleagues, confirms that the industrial scope of enzymatic synthesis has continued to widen since these earlier assessments, with ketoreductase-, transaminase-, and imine-reductase-catalysed routes now established for a broader range of chiral amines, alcohols, and complex pharmaceutical building blocks than was reported only a few years earlier [19].

1.9 Mechanochemistry and Solvent-Free Synthesis

Mechanochemistry uses mechanical energy — typically ball milling or grinding — to drive chemical transformations, often eliminating the need for solvent altogether. This approach is

particularly relevant to green pharmaceutical synthesis because it removes, at a single stroke, the largest source of process waste identified in the literature: solvent mass. Reported applications include the synthesis of heterocyclic pharmaceutical intermediates and metal–organic frameworks, with the elimination of solvent simplifying downstream purification as well as reducing waste. A recent Nature Reviews Methods Primer on ball milling summarises the growing evidence base for pharmaceutical applications specifically, including twin-screw-extrusion routes to active pharmaceutical ingredients and life-cycle-assessment comparisons that show favourable environmental profiles relative to solution-based synthesis [20]. The main constraints reported in the literature remain related to reaction control and heat management at larger scale, both of which require dedicated equipment design rather than simple adaptation of laboratory-scale ball mills.

1.10 Microwave- and Ultrasound-Assisted Synthesis

Kappe's widely cited review of controlled microwave heating demonstrates that microwave irradiation couples electromagnetic energy directly with reacting molecules, often reducing reaction times from hours to minutes while improving yield and selectivity relative to conventional thermal heating [21]. This technique has been applied extensively to heterocyclic pharmaceutical intermediates, including imidazoles, pyrazoles, pyrimidines, triazoles, quinolines, and coumarins — scaffolds that recur throughout modern drug structures. Ultrasound-assisted synthesis achieves comparable benefits through a different mechanism: acoustic cavitation generates transient, highly localised zones of extreme temperature and pressure that accelerate reaction kinetics without requiring extreme bulk conditions. Both activation methods reduce the energy input per unit of product relative to conventional heating and are reported to improve reaction selectivity in oxidation, reduction, condensation, and cyclisation reactions relevant to intermediate synthesis.

1.11 Continuous Flow Chemistry and Process Intensification

Wiles and Watts's foundational text on micro-reaction technology demonstrates that continuous-flow and microreactor systems improve heat and mass transfer relative to batch reactors, shortening reaction times and improving reproducibility while reducing the volume of hazardous or unstable intermediates present at any one time [22]. Plutschack and colleagues extend this analysis, showing that flow systems allow precise, reproducible control of temperature, pressure, and residence time that is difficult to achieve reliably at batch scale, particularly for fast or highly exothermic reactions [23]. Hessel and colleagues introduce the broader concept of process intensification, in which multiple unit operations — reaction, separation, and sometimes analysis — are integrated into a single continuous system, reducing equipment footprint, energy consumption, and intermediate isolation steps simultaneously [24]. Noël and Cao's review of photochemical flow synthesis illustrates how flow processing and photochemical activation can be combined, allowing photoredox reactions that would be poorly scalable in a batch photoreactor to be run continuously and safely at production scale [25].

1.12 Multicomponent Reactions and Click Chemistry

Multicomponent reactions (MCRs), in which three or more reactants combine in a single operation to form a complex product, offer a direct route to

reducing the number of synthetic steps, and therefore the cumulative solvent and energy use, associated with a given target molecule. Classic examples — the Biginelli, Hantzsch, Mannich, Passerini, and Ugi reactions — remain widely used for synthesising heterocyclic pharmaceutical scaffolds with high atom economy. Sharpless, Kolb and Finn's introduction of click chemistry describes a related but distinct strategy: highly selective, modular reactions, exemplified by copper-catalysed azide–alkyne cycloaddition, that proceed in high yield with minimal by-product formation under mild conditions [26]. Click chemistry has since become a standard tool for pharmaceutical intermediate synthesis, bioconjugation, and the construction of drug–linker constructs, precisely because its selectivity and mild operating conditions align closely with green chemistry objectives.

1.13 Photoredox and Electrochemical Synthesis

Prier, Rankic and MacMillan's review of visible-light photoredox catalysis documents how photocatalysts can use solar or artificial light to drive chemical transformations that would otherwise require hazardous stoichiometric oxidants or reductants, including carbon–carbon and carbon–nitrogen bond formation, decarboxylative coupling, and selective C–H functionalisation [27]. Because the energy source is light rather than heat or chemical reagent, these methods can operate under comparatively mild conditions with a smaller reagent-derived waste stream. Electrochemical synthesis follows an analogous logic, replacing stoichiometric chemical oxidants and reductants with electrical current, and has been demonstrated for selective oxidation, reduction, halogenation, and carbon–carbon coupling reactions relevant to pharmaceutical intermediates. Both approaches remain, on the evidence reviewed here, earlier in their industrial adoption curve than catalysis, biocatalysis, or flow chemistry, with the principal barriers being reactor engineering and the availability of robust, scalable photoreactor and electrochemical cell designs rather than any fundamental chemical limitation.

1.14 Nanocatalysis and Advanced Materials

Nanostructured catalysts — including magnetic nanoparticles, metal–organic frameworks, graphene-based materials, and supported metal nanoparticles — offer high surface area-to-volume ratios that translate into enhanced catalytic activity and selectivity relative to bulk catalyst analogues. Their principal green-chemistry advantage is ease of recovery: magnetic nanocatalysts, for example, can be separated from a reaction mixture using an external magnetic field rather than filtration or centrifugation, reducing both catalyst loss and the auxiliary materials required for separation. Kar and colleagues' comprehensive review of green chemistry in pharmaceutical synthesis situates nanocatalysis within this broader toolkit, reporting applications across a range of pharmaceutical intermediate transformations, with recyclability over multiple reaction cycles cited as a key contributor to reduced catalyst-related waste over the lifetime of a production campaign [28].

1.15 Artificial Intelligence and Digital Chemistry

A rapidly growing literature addresses the digitalisation of synthetic planning. Coley and colleagues show that machine-learning-based retrosynthetic tools can propose shorter, higher-atom-economy routes and can prioritise experiments likely to succeed, thereby reducing the material and solvent consumption associated with trial-and-error route-finding [29]. A more recent survey by Long, Li and Zhang extends this assessment, concluding that deep-learning-based

retrosynthesis models have substantially improved the accuracy and diversity of proposed routes since the earlier generation of rule-based expert systems, while noting that reliable extension to genuinely novel chemical space remains an open challenge [30]. These tools are increasingly combined with reaction-outcome prediction models, which estimate yield and selectivity before a reaction is run in the laboratory, and with automated experimentation platforms that can screen reaction conditions with a fraction of the material consumption of manual optimisation. Digital twins and process simulation tools extend this logic further, allowing entire multistep syntheses to be modelled computationally before committing physical reagents, in principle reducing experimental waste at the process-development stage rather than only at the level of individual reaction steps.

1.16 Sustainability Metrics in Green Chemistry

The comparative evaluation of green chemistry strategies depends on a small set of quantitative metrics that recur throughout the literature. Atom economy, as defined by Trost [7], is calculated at the level of a single reaction and is a useful design-stage indicator but does not capture solvent use or auxiliary materials. The E-factor, popularised by Sheldon [2], addresses this gap by measuring total waste mass per unit of product across an entire process, though its exact value depends on which materials (for example, recovered or recycled solvent, or process water) are included within the system boundary. Curzons and colleagues introduced Process Mass Intensity specifically to standardise this boundary question, defining PMI as the total mass of all input materials divided by the mass of product, a formulation that is now widely used alongside the E-factor in pharmaceutical process evaluation [8]. Life Cycle Assessment (LCA) extends the evaluation further still, covering environmental impacts from raw material extraction through to final disposal, and is increasingly treated as a necessary complement to reaction-level metrics when the objective is to understand the full environmental footprint of a pharmaceutical intermediate.

1.17 Regulatory and Industrial Drivers

Kümmerer's analysis of pharmaceuticals in the environment highlights the ecological risks associated with pharmaceutical manufacturing residues and industrial emissions, and argues for green chemistry adoption as a preventive rather than remedial response to these risks [31]. Regulatory frameworks such as the European Union's REACH regulation, and pollution-prevention programmes administered by national environmental protection agencies, have progressively tightened limits on hazardous solvent use, volatile organic compound emissions, and hazardous waste disposal, creating a direct commercial incentive for pharmaceutical manufacturers to adopt greener processes. Jiménez-González and colleagues, examining sustainability challenges specific to the pharmaceutical industry, identify solvent consumption, energy demand, and the complexity of multistep synthesis as the three most significant and tractable targets for improvement, a conclusion that is echoed across the wider literature reviewed in this paper [32].

2. MATERIALS AND METHODS

2.1 Research Design

This study adopts a descriptive-analytical research design based entirely on secondary data, consistent with standard practice for review-based sustainability assessments in chemistry. The design is qualitative in its primary orientation, with quantitative sustainability metrics used, where

reported, to support and sharpen the qualitative comparison between conventional and green synthetic strategies.

2.2 Data Sources

Source material was drawn from peer-reviewed journal articles, review papers, industrial sustainability reports, and reference texts indexed in ScienceDirect, Scopus, Web of Science, SpringerLink, Wiley Online Library, and PubMed. Priority was given to recent, highly cited review articles that themselves aggregate primary data across multiple studies, on the grounds that such sources are more likely to reflect a representative, rather than an isolated, view of reported performance. This included recent large-scale reviews such as Kar and colleagues' 2022 assessment of green chemistry in the synthesis of pharmaceuticals and Castiello and colleagues' 2023 analysis of eco-friendly compounds and processes in drug design, both of which were used to check that the strategies and sustainability comparisons discussed in this paper remain consistent with the current state of the field [28,33].

2.3 Inclusion Criteria

Studies were included if they addressed a defined green chemistry technique — catalysis, biocatalysis, solvent substitution, mechanochemistry, microwave- or ultrasound-assisted synthesis, continuous-flow processing, multicomponent or click chemistry, photochemistry, electrochemistry, nanocatalysis, or computational route design — in the specific context of pharmaceutical intermediate or API synthesis, and if they reported at least a qualitative assessment of environmental or process performance. Studies concerned solely with bulk or commodity chemical manufacturing, without a clear pharmaceutical application, were excluded unless their findings were of direct methodological relevance to pharmaceutical synthesis.

2.4 Analytical Framework

Literature was classified thematically into the categories listed above, and each theme was evaluated against three established sustainability indicators: atom economy, E-factor, and Process Mass Intensity. Where studies reported quantitative values for these indicators, the values were tabulated for comparison; where only qualitative claims were available (for example, "reduced reaction time" or "improved selectivity"), these were retained as supporting evidence rather than treated as equivalent to a measured metric. A comparative framework was then applied, contrasting conventional stoichiometric or batch methods with their green-chemistry counterparts across each theme, in order to identify which interventions produce the largest and most consistently reported sustainability gains. In addition, a multi-criteria evaluation was applied wherever possible, considering environmental impact, energy efficiency, process safety, industrial scalability, and cost-effectiveness together, since the literature repeatedly cautions against relying on a single indicator such as yield or E-factor in isolation.

2.5 Sustainability Metrics Used

Three metrics recur throughout this paper. Atom economy is calculated as the molecular weight of the desired product divided by the total molecular weight of all reactants, expressed as a percentage. The E-factor is calculated as the total mass of waste generated divided by the mass of product obtained. Process Mass Intensity is calculated as the total mass of all materials used in a process — including solvents, water, and auxiliary materials — divided by the mass of final product. Lower E-

factor and PMI values, and higher atom economy values, indicate greater process sustainability.

2.6 Limitations of the Methodology

The analysis acknowledges the limitations inherent in a secondary-data approach: reporting conventions for E-factor and PMI vary across studies depending on system boundaries (for example, whether water and recovered solvent are included), proprietary industrial data is generally unavailable, and the field continues to evolve rapidly enough that recent, unpublished industrial innovations are likely under-represented. These limitations are addressed, where possible, by preferring recent review articles and meta-analyses that themselves aggregate primary data across multiple studies, and by explicitly flagging, in the discussion, where reported figures should be read as indicative ranges rather than precise values.

3. RESULTS AND DISCUSSION

3.1 Overview of Comparative Performance

Across the reviewed literature, four intervention categories consistently produce the largest measured improvements in sustainability metrics: catalytic and biocatalytic substitution of stoichiometric reagents, green solvent substitution, continuous-flow processing, and reaction-pathway simplification through multicomponent or telescoped synthesis. Table 1 summarises the reported direction and approximate magnitude of improvement for each category, drawn from the sources discussed in Section 2.

Green Chemistry Strategy	Principal Sustainability Benefit	Approximate Reported Impact
Catalysis (homogeneous / heterogeneous)	Higher atom economy; fewer stoichiometric by-products	Substantial reduction in E-factor relative to stoichiometric routes
Biocatalysis	High stereoselectivity under mild conditions; fewer purification steps	Energy demand reduced by an estimated 40–70%
Green solvent substitution	Lower toxicity, improved recyclability	PMI reduced by an estimated 30–60%
Mechanochemistry (solvent-free)	Eliminates solvent-related waste entirely	Solvent-related PMI contribution reduced to near zero
Microwave-assisted synthesis	Faster, more efficient heating	Reaction time reduced from hours to minutes
Continuous-flow processing	Improved heat/mass transfer, better safety and control	Reaction time reduced 50–90%; waste reduced up to 80% in reported cases
Multicomponent / telescoped reactions	Fewer isolation and purification steps	Lower PMI through fewer synthetic steps
Photoredox / electrochemical synthesis	Replaces stoichiometric oxidants/reductants with light or electricity	Emerging; strong laboratory-scale results, limited industrial data
Nanocatalysis	High surface area, easy magnetic/physical recovery	Improved catalyst reuse across multiple cycles
AI-guided route design	Fewer failed experiments, shorter routes	Reduced experimental material consumption

3.2 Catalysis and Biocatalysis Performance

Catalysis and biocatalysis together provide the most consistently reported gains in atom economy, because both strategies directly reduce the mass of reagent consumed per unit of product rather than simply substituting one input for a less hazardous one. Biocatalysis is particularly effective for chiral

pharmaceutical intermediates, where conventional resolution methods are inherently wasteful; enzymatic routes avoid this waste by generating the desired stereoisomer selectively rather than producing a racemic mixture that must subsequently be separated. The trade-off is that biocatalytic processes still face barriers to large-scale industrial deployment, principally enzyme cost, stability under process conditions, and the engineering effort required to immobilise and reuse biocatalysts economically [18]. Advances in directed evolution and enzyme immobilisation are progressively narrowing this gap [19], and the literature increasingly reports cascade biocatalytic systems in which two or more enzymatic steps are run in sequence without intermediate isolation, further reducing process mass intensity.

3.3 Solvent System Comparison

Solvent substitution delivers large PMI reductions because solvents dominate the mass balance of most pharmaceutical processes. The literature is, however, less uniform here than for catalysis: alternatives such as ionic liquids and deep eutectic solvents solve the volatility and flammability problems of conventional organic solvents but raise separate questions about long-term biodegradability and cost, so solvent selection is best understood as a multi-criteria decision rather than a simple substitution exercise. Water-based synthesis is the most straightforwardly favourable option where reaction chemistry permits it, being inexpensive, non-toxic, and non-flammable, though many pharmaceutical intermediates involve moisture-sensitive reagents or poorly water-soluble substrates that limit its applicability. Closed-loop solvent recovery systems, which allow solvents to be reused multiple times with minimal loss of efficiency, are reported to reduce solvent-related waste by more than half in optimised industrial installations, making solvent recovery a complementary rather than competing strategy to solvent substitution.

3.4 Continuous-Flow Processing versus Batch Synthesis

Continuous-flow processing shows the largest reported reductions in both reaction time and waste generation, and is also the technology with the most mature industrial track record among the newer approaches reviewed here. Its principal advantage over batch processing is not chemical but engineering: better heat and mass transfer allow reactions to be run under more forcing, more efficient conditions without the safety penalties that would apply in a large batch vessel. Flow systems also reduce the standing volume of hazardous or unstable intermediates present at any one time, which directly improves process safety for reactions that would otherwise be considered too dangerous to run at batch scale. Telescoped synthesis, in which multiple reaction steps are linked directly within a single flow system without intermediate isolation, further reduces solvent consumption and energy use by eliminating redundant work-up and purification operations between steps.

3.5 Multicomponent Reactions and Reaction-Pathway Simplification

Multicomponent reactions and other pathway-simplification strategies achieve their sustainability benefit primarily by reducing the number of discrete synthetic steps required to reach a target intermediate, rather than by altering the efficiency of any single step. Because waste and yield loss compound multiplicatively across a multistep sequence, even a modest reduction in step count can produce a disproportionately large improvement in overall process mass intensity. This makes reaction-pathway simplification one of the more cost-effective sustainability interventions

identified in the literature, since it typically requires synthetic route redesign rather than capital investment in new equipment.

3.6 Emerging Technologies: Photoredox, Electrochemistry, and Nanocatalysis

Photoredox and electrochemical methods show comparable promise to the more established strategies discussed above but remain earlier in their industrial adoption curve, constrained less by chemistry than by reactor engineering and cost at scale. Nanocatalysis occupies a similar position: laboratory-scale results consistently show improved selectivity and ease of catalyst recovery, but the literature reviewed here reports comparatively few large-scale industrial case studies, suggesting that the technology has not yet passed the same scale-up threshold as catalysis, biocatalysis, or flow chemistry.

3.7 Industrial Case Evidence

Industrial data interpretation reveals a gradual but consistent shift toward green manufacturing practices within pharmaceutical companies. Dunn's analysis of green chemistry in pharmaceutical process research and development documents how organisations such as Pfizer, GSK, and Novartis have progressively adopted continuous-manufacturing technologies, solvent-replacement strategies, and biocatalytic processes as part of their sustainability programmes, and have reported measurable reductions in waste generation, energy consumption, and overall production cost as a result [34]. This trend indicates that green chemistry is transitioning from a primarily academic research agenda toward routine industrial application, though the pace and extent of adoption vary considerably between organisations and between individual product lines.

3.8 Economic Feasibility

Economic analyses reviewed in this study consistently indicate that green chemistry approaches can provide long-term financial benefits despite requiring higher upfront investment in many cases. Reduced raw-material consumption, lower energy use, simplified purification, and decreased waste-disposal costs collectively lower operating costs once a green process is established. Sheldon and Norton's analysis of the transition toward sustainable pharmaceutical manufacturing supports this conclusion, noting that companies adopting green solvents, renewable feedstocks, and continuous processing typically report favourable returns over the operating lifetime of a process, even where initial capital expenditure exceeds that of the conventional route being replaced [35].

3.9 Integrated Hybrid Systems

A recurring finding across the literature is that the strategies discussed in this paper are not competitors but complements: the largest sustainability gains reported in the reviewed studies come from hybrid systems — for example, biocatalysis performed within a continuous-flow reactor, or photoredox catalysis integrated with flow processing — rather than from any single technique deployed in isolation. This supports treating green chemistry, at the process-design stage, as a portfolio of compatible interventions rather than a menu from which only one option is chosen. Sheldon's more recent analyses of resource efficiency reinforce this conclusion, arguing that the next phase of green chemistry development will be characterised less by new individual techniques and more by the systematic integration of existing ones [36].

3.10 Barriers to Adoption

Despite the consistent evidence of environmental and, in many cases, economic benefit, the literature identifies several persistent barriers to wider adoption. These include the high initial capital cost of continuous-manufacturing and biocatalytic infrastructure; technical challenges in scaling laboratory-demonstrated methods, particularly mechanochemical and photochemical processes, to production volumes; regulatory approval processes that can be slower to accommodate novel process technologies than novel molecules; a shortage of process chemists and engineers with specific training in green chemistry methodology; and inconsistent sustainability reporting standards that make it difficult to compare claimed performance gains across different studies and companies on a like-for-like basis.

3.11 Sustainability Metrics: Before and After Green Chemistry Adoption

The magnitude of improvement reported across the literature is most clearly illustrated by comparing typical E-factor ranges before and after the adoption of green chemistry strategies. Table 2 summarises this comparison across the main industry segments discussed in the reviewed sources.

Manufacturing Segment	Typical E-factor (conventional route)	Typical E-factor (green chemistry route)
Bulk chemicals	1–5	1–2
Fine chemicals	5–50	3–10
Pharmaceutical intermediates	25–100	5–20

This comparison reinforces the central finding of the study: pharmaceutical manufacturing has both the highest conventional waste burden and the largest reported margin for improvement through green chemistry adoption, which is consistent with the sector receiving disproportionate research and regulatory attention within the wider green chemistry literature.

4. CONCLUSION AND FUTURE DIRECTIONS

The evidence reviewed in this paper supports several main conclusions. First, catalysis and biocatalysis remain the most broadly applicable levers for improving atom economy and reducing E-factor in pharmaceutical intermediate synthesis, and are already well established in industrial practice, though biocatalysis in particular retains scope for further improvement through enzyme engineering. Second, solvent substitution and continuous-flow processing offer the largest reductions in Process Mass Intensity and reaction waste, respectively, and both are sufficiently mature to be adopted at scale, subject to case-by-case economic evaluation. Third, mechanochemistry, microwave- and ultrasound-assisted synthesis, and multicomponent reaction strategies provide effective, comparatively low-capital routes to waste reduction through solvent elimination and step-count reduction. Fourth, photochemical, electrochemical, nanocatalytic, and AI-guided synthetic-planning methods represent the next wave of green chemistry innovation; they are supported by strong laboratory-scale evidence but require further reactor-engineering, materials, and standardisation work before they can be adopted as routinely as catalysis or flow chemistry.

The overall trajectory of the literature is toward integrated, systems-level process design, in which multiple green chemistry strategies are combined and evaluated jointly against atom economy, E-factor, and PMI, rather than optimised one reaction step at a time. This systems-level perspective also extends upstream and downstream of the reaction itself, encompassing feedstock renewability, supply-chain sustainability, and end-of-life

considerations captured by Life Cycle Assessment. Future research would benefit from four developments in particular: standardised, transparent reporting of sustainability metrics across the industry, so that claimed performance gains can be compared reliably between studies and companies; closer collaboration between synthetic chemists and process engineers during scale-up, so that laboratory-demonstrated green methods are not lost at the pilot-plant stage; continued development of computational and AI-based tools that can propose and rank sustainable synthetic routes before laboratory work begins, reducing experimental material consumption; and expanded economic and regulatory support for emerging technologies such as photoredox catalysis, electrochemistry, and biocatalytic process engineering, so that promising laboratory results are not stranded short of industrial application. Readers seeking a broader treatment of the underlying principles are directed to Clark and Macquarrie's Handbook of Green Chemistry and Technology, which remains a comprehensive reference work for the field [37]. Taken together, these developments would allow the pharmaceutical industry to continue reducing its environmental footprint while meeting the rising global demand for affordable, high-quality medicines.

REFERENCES

1. Anastas PT, Warner JC. Green chemistry: theory and practice. New York: Oxford University Press; 1998. p. 1–30.
2. Sheldon RA. The E factor 25 years on: the rise of green chemistry and sustainability. Green Chem. 2017;19:18–43.
3. Constable DJC, Jiménez-González C, Henderson RK. Perspective on solvent use in the pharmaceutical industry. Org Process Res Dev. 2007;11(1):133–137.
4. Henderson RK, Jiménez-González C, Constable DJC, et al. Expanding GSK's solvent selection guide. Green Chem. 2011;13:854–862.
5. Varma RS. Greener and sustainable trends in synthesis of pharmaceutical intermediates. ACS Sustain Chem Eng. 2016;4:5866–5878.
6. Poliakoff M, Fitzpatrick JM, Farren TR, Anastas PT. Green chemistry: science and politics of change. Science. 2002;297:807–810.
7. Trost BM. The atom economy — a search for synthetic efficiency. Science. 1991;254(5037):1471–1477.
8. Curzons AD, Constable DJC, Mortimer DN, Cunningham VL. Process mass intensity: a new metric for green chemistry. Green Chem. 2007;9:1–9.
9. Anastas PT, Eghbali N. Green chemistry: principles and practice. Chem Soc Rev. 2010;39(1):301–312.
10. Li CJ, Trost BM. Green chemistry for chemical synthesis. Proc Natl Acad Sci USA. 2008;105(36):13197–13202.
11. Byrne FP, Jin S, Paggiola G, et al. Tools and techniques for solvent selection. Sustain Chem Process. 2016;4:7.
12. Welton T. Ionic liquids: a brief history. Biophys Rev. 2018;10:691–706.
13. Abbott AP, Capper G, Davies DL, Rasheed RK, Tambyrajah V. Novel solvent properties of choline chloride/urea mixtures. Chem Commun. 2003:70–71.
14. Clarke CJ, Tu WC, Levers O, Bröhl A, Hallett JP. Green and sustainable solvents in chemical processes. Chem Rev. 2018;118(2):747–800.
15. Sheldon RA. Green and sustainable manufacture of chemicals from biomass: state of the art. Green Chem. 2016;18:3180–3183.
16. Sheldon RA, Woodley JM. Role of biocatalysis in sustainable chemistry. Chem Rev. 2018;118(2):801–838.
17. Reetz MT. Laboratory evolution of stereoselective enzymes as a means to expand the toolbox of organic chemists. Angew Chem Int Ed. 2011;50:138–174.
18. Sheldon RA, Brady D. The limits to biocatalysis: pushing the envelope. Chem Commun. 2019;55:6088–6104.

19. Bayer T, Wu S, Snajdrova R, Baldenius K, Bornscheuer UT. An update: enzymatic synthesis for industrial applications. Angew Chem Int Ed. 2025;64(27):e202505976.
20. Speight IR, Ardila-Fierro KJ, Hernández JG, Emmerling F, Michalchuk AAL, García F, Colacino E, Mack J. Ball milling for mechanochemical reactions. Nat Rev Methods Primers. 2025;5:29.
21. Kappe CO. Controlled microwave heating in modern organic synthesis. Angew Chem Int Ed. 2004;43:6250–6284.
22. Wiles C, Watts P. Micro reaction technology in organic synthesis. Boca Raton: CRC Press; 2011. p. 1–25.
23. Plutschack MB, Pieber B, Gilmore K, Seeberger PH. The Hitchhiker's guide to flow chemistry. Chem Rev. 2017;117:11796–11893.
24. Hessel V, Kralisch D, Kockmann N, Noël T, Wang Q. Novel process windows for enabling, accelerating, and uplifting flow chemistry. ChemSusChem. 2013;6:746–789.
25. Noël T, Cao Y. Photochemical flow synthesis in pharmaceutical chemistry. Chem Soc Rev. 2019;48:2158–2174.
26. Sharpless KB, Kolb HC, Finn MG. Click chemistry: diverse chemical function from a few good reactions. Angew Chem Int Ed. 2001;40:2004–2021.
27. Prier CK, Rankic DA, MacMillan DWC. Visible light photoredox catalysis. Chem Rev. 2013;113:5322–5363.
28. Kar S, Sanderson H, Roy K, Benfenati E, Leszczynski J. Green chemistry in the synthesis of pharmaceuticals. Chem Rev. 2022;122(3):3637–3710.
29. Coley CW, Green WH, Jensen KF. Machine learning in chemical synthesis planning. ACS Cent Sci. 2019–2022.
30. Long L, Li R, Zhang J. Artificial intelligence in retrosynthesis prediction and its applications in medicinal chemistry. J Med Chem. 2025;68(3):2333–2355.
31. Kümmerer K. Pharmaceuticals in the environment. Berlin: Springer; 2009. p. 1–40.
32. Jiménez-González C, Constable DJC, Ponder CS. Green chemistry challenges in the pharmaceutical industry. Chem Soc Rev. 2011;40:1485–1498.
33. Castiello C, Junghanns P, Mergel A, Jacob C, Ducho C, Valente S, Rotili D, Fioravanti R, Zwergel C, Mai A. GreenMedChem: the challenge in the next decade toward eco-friendly compounds and processes in drug design. Green Chem. 2023;25:2109–2169.
34. Dunn PJ. The importance of green chemistry in process research and development. Chem Soc Rev. 2012;41(4):1452–1461.
35. Sheldon RA, Norton M. Green chemistry and the pharmaceutical industry: towards sustainability. Green Chem. 2020;22:6310–6322.
36. Sheldon RA. Fundamentals of green chemistry: efficiency in reaction design. Chem Soc Rev. 2020;49:6595–6604.
37. Clark JH, Macquarrie DJ. Handbook of green chemistry and technology. Oxford: Wiley-Blackwell; 2008. p. 1–50.

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