Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

Batch to Flow: Recent Advances in Continuous Flow Architectures for the Sustainable Synthesis of Heterocyclic APIs

Nishant Rai[a], Shweta Singh Verma* [a], Mukesh Kumar[a], Ayush Katiyar [a]
[a] School of Pharmaceutical Sciences, Chhatrapati Shahu Ji Maharaj University, Kanpur, 208024
*Corresponding author: Shweta Singh Verma, Assistant Professor, School of Pharmaceutical Sciences, Chhatrapati Shahu Ji Maharaj University, Kanpur, 208024

Received: 12 February 2026 ***Accepted:26 March 2026*** ***Published: 13 April 2026***

KEYWORDS
Continuous,
Batch,
Flow,
Heterocyclic,
E-factor,
PAT, Synthesis.

ABSTRACT:
The pharmaceutical industry is also under the decisive transition of the traditional processing batch system into the continuous manufacturing process production in terms of the growing necessity of safety, sustainability, and intensification of the process. This concise review addresses the advancements of the recent concurrent development of continuous flow architecture of sustainable synthesis of heterocyclic active pharmaceutical ingredient (API), the structural framework of the majority of the small-molecules drugs which are used today. The fundamental differences between batch and flow processing have been discussed where the principal concern is excellent heat and mass exchange, precision in the kinetic control, and high safety since less reactive inventory is utilized and scalability through naturally numbering-up methods. The review systematically surveys key platforms in reactors including micro- and meso-flow reactors, tubular and packed-bed reactors, multiphase reactors and as well as modular telescoped assemblies and parallels the principles of design of said assemblies with specific heterocyclic transformation. Environmental benefits of flow-based synthesis are measured by such types of sustainability measures as process mass intensity (PMI), reduction of E-factor, solvent reduction, energy efficiency, and the life cycle assessment (LCA) processes. The production of such technologies has an industrial relevance as exemplified by the representative case studies of nitrogen-, sulfur-, and oxygen-bearing heterocycles, and marketed APIs which are produced under constant-condition settings. Furthermore, automated catalysts that include process analytical technology (PAT), automations, machine learning-assisted optimization, photochemical and electrochemical flow reactors, in-vitro and in-vivo integrated catalytic and biocatalytic systems are listed as catalysts of the future manufacturing. The overall picture of this review is that continuous flow chemistry is an innovative and future-proof system through which heterocyclic APIs can be made in an efficient, safe, environmentally friendly way, leading to the bridges between the laboratory and the manufacturing of quality-by-design and regulatory-compliant product interpretation.

1. Introduction

The pharmaceutical industry finds itself at a very serious crossroads, and it is shifting to continuous manufacturing (CM) instead of the traditional methodologies of batch-processing [1]. This paradigm shift is predetermined by the fact that there is a critical necessity to intensify the process and ensure the high quality and compliance with the principles of Green Chemistry [2]. In this regard, heterocyclic Active Pharmaceutical Ingredients (APIs) synthesis can be seen as one of the main areas of innovation since these compounds are common in the pharmacotherapy of the present day [3].

1.1. Importance of heterocyclic scaffolds in modern APIs

Small-molecule drugs use the heterocyclic moieties as the structural backbone of the vast majority of small-molecule drugs. Statistical survey of FDA-approved pharmaceuticals shows that more than 85 percent of bioactive small molecules have at least one heterocyclic ring, that nitrogen-based heterocycles (N-heterocycles) are the most common ones [4].

These scaffolds, which are simple five-membered rings, such as pyrroles and imidazole, and complex fused systems, such as quinolines and benzodiazepines (figure 1), are necessary because they provide key physicochemical properties. They promote hydrogen bonding with biological targets,

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

are able to modify lipophilicity (log P) and enhance metabolic stability. The accessibility to a wide range of heterocyclic motifs, in turn, is not just a synthetic problem, but a huge requirement in drug discovery and development. [5].

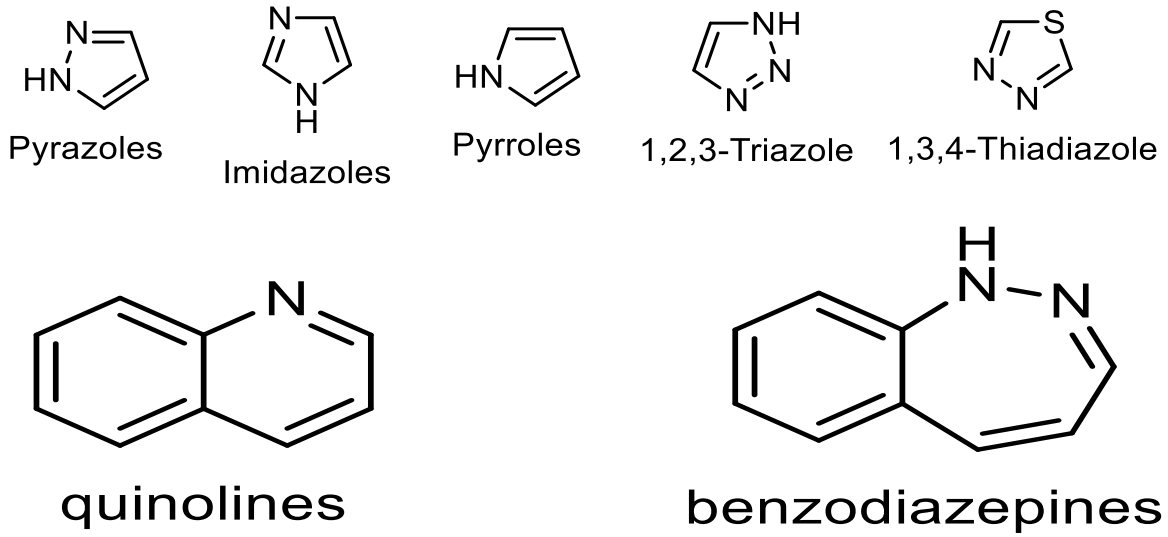

Figure 1. Prevalence of heterocyclic frameworks in small-molecule pharmaceuticals.

1.2. Limitations of conventional batch synthesis in pharmaceutical manufacturing

Heterocyclic API synthesis traditionally has depended on batch reactors (round-bottom flasks or tank reactors) in spite of their dominance [6]. Good in discovery phase synthesis, but inherently limited in scale-up and production, batch processing has its own shortcomings.

- **Limitations in Heat and Mass Transfer At large scale:** Large-scale batch reactors have poor surface-area-volume ratios, resulting in discrete temperature gradients across the reactor (so-called hot spots) and uneven mixing. This especially is harmful when the reaction is fast and highly exothermic like in the formation of heterocycles. [7].
- **Safety Hazards:** Batch A large quantity of high-energy intermediates (e.g., diazonium salts, azides) present in a batch is highly hazardous to explode. [8].
- **Process Inefficiency:** Batch processes are intermittent and the charging, reaction and discharging process thus involve regular start-stop cycles. It leads to high levels of downtime and batch variation in the purity of the API and crystal morphology. [9].
- **Environmental Impact:** With the standard form of synthesis, one will generally need to add very large amounts of reagent and solvent to advance the equilibrium, resulting in high E-factors (mass of waste/mass of product), and poor atom economy [10].

1.3. Emergence of continuous flow chemistry as a paradigm shift

Continuous flow chemistry or micro reaction technology has become a disruptive technology that resolves the inherent defects of batch processing. Flow architectures have high heat and mass transfer coefficients (which are orders of magnitude better than batch vessels) by reacting in narrow channels (micro- or meso-reactors) [11].

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

This very specific control makes it possible to have process windows which are not available in batch mode. As an example, flow systems facilitate safe handling of reactive reagents, can use flash chemistry (reactive intermediates with short lifespans) and can impose extreme temperature/pressure conditions (T > 200°C, P > 100 bar) to increase reaction rates [12]. In addition, the combination of inline purification and Process Analytical Technology (PAT) makes it easy to monitor and guarantee quality in real time and changes the manufacturing philosophy to quality by testing and quality by design (QbD) [13].

2. Batch vs. Continuous Flow in Pharmaceutical Synthesis

The shift towards continuous flow processing is a process that cannot simply be referred to as a simple change of equipment and rather a complete change of the reaction environment. Although batch reactors (usually stir tank reactors) have been the backbone of the pharmaceutical industry throughout the last century, they are becoming more restricted with complex heterocyclic APIs demanding strict control of their kinetics and stringent safety profiles [14].

2.1. Fundamental Differences in Reaction Control and Kinetics

The main difference between the two modes is in the connection between the time and space. A batch reactor, this type of reactor undergoes changes in chemical composition over time in a fixed volume; at any given time, the concentration of reagents remains constant at any point in the vessel provided that the mixture is perfectly mixed. In a continuous flow reactor (here a Plug Flow Reactor (or PFR)) on the other hand, the reaction proceeds as the fluid flows through the length of the channel. Therefore, the batch reaction time is substituted with the flow reaction time (t_R) which is given by the ratio of the reactor volume to the flow rate [15].

This spatial resolution provides a better kinetic control. In flow, the stoichiometry is determined at the mixing point and the product is carried off the reaction zone continuously before over-reaction occurs or the reagents cause the formation of side products due to protracted exposure. It is especially beneficial to competitive consecutive reactions commonly found in functionalizing heterocycles, where termination of the reaction at a specific mono-substituted intermediate is challenging in batch reactions as a result of mixing inhomogeneities [16]. Additionally, flow systems can be used to rapidly synthesize and react unstable intermediates, so-called flash chemistry, which is kinetically inaccessible in conventional batch reactors [17].

2.2. Heat and Mass Transfer Considerations

Continuous flow architectures have the greatest potential engineering advantage which is thermodynamic control. The available specific surface area per unit of the volume (A/V) controls the efficiency of heat exchange.

The A / V ratio of a typical large-scale industrial batch reactor (e.g. 1000 L) is low, typically less than 10 m^{-1}. [18]. This poses a serious dilemma to the exothermic heterocyclic cyclizations, which results into the temperature gradient with the core of the reactor being much hotter than the jacketed walls. Such hot spots have the ability to destroy heat sensitive APIs and change impurity profiles [19].

Conversely, micro- and meso-flow reactors have diameters of the channel of micrometers to millimeters and A/V ratio of 1,000-10,000 m^{-1}. The heat is easily dissipated through this huge surface area. It enables reactions to be run under isothermal conditions with even highly exothermic reactions such as nitrations or organometallic additions, to be run in this manner. Also, diffusion in microchannels causes mass transfer (mixing) in flow or diffusion in larger tubes causes mass transfer (mixing) using a static mixer, which is much faster than the macromixing constraint of a stir tank [20].

2.3. Safety, Scalability, and Reproducibility

The safety profile of continuous flow is in itself better because of the drastic reduction of the so-called reactive inventory. A low amount of hazardous material is stored in the reactor at any particular time. In case of thermal runaway or seal failure, the chances of containment being jeopardized are insignificant with the disastrous possibilities of a 5,000 L batch vessel failure. This allows chemists to use high-energy reagents, including diazomethane, azides and hydrazine, which are vital in building nitrogenous heterocycles

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

but would otherwise be prohibited by large-scale batch plant [21].

In terms of scalability, batch processing has the so-called scale-up effect where the geometry of vessels changes, which influences the heat and mass transfer, and the optimization of the process has to be re-optimized, which is expensive. Flow Chemistry uses numbering up or scale-out strategy. To produce more can be done by operating the reactor over a longer period or by having several units that are of the same reactor, operating in parallel. This makes sure that the conditions of the reaction optimized in the laboratory at gram scale are duplicated at kilogram scale in production ensuring high levels of reproducibility between batches (or actually, over time) [22].

2.4. Regulatory and Industrial Perspectives (QbD, PAT, GMP Relevance)

Regulatory authorities, such as the FDA of the US and the EMA have replaced passive acceptance of Continuous Manufacturing (CM) with active promotion [23]. This is consistent with Quality by Design (QbD) paradigm that promotes the quality development of the process and not the quality testing of the product.

Process Analytical Technology (PAT) is ideally suited to continuous flow [24]. The temperature, pressure and concentration are the Critical Process Parameters (CPPs) that could be measured in real-time with the help of inline sensors (IR, Raman, UV-Vis, HPLC). When a deviation has been identified, the system can automatically divert the non-compliant item to waste without affecting the whole production cycle, and this is referred to as real-time release testing (RTRT). In the case of industrial production of the heterocyclic APIs, it means a more agile, lean manufacturing supply chain with less warehousing and a much smaller environmental footprint [25].

3. Continuous Flow Reactor Architectures

The introduction of continuous flow chemistry is based on a wide range of reactor geometries and material; each being specific to particular kinetic regimes and physicochemical characteristics. Factors like reaction enthalpy, phase homogeneity, residence time that is required, and chemical compatibility determine the choice of the selected architecture [26].

3.1. Microreactors and Meso-flow Reactors

Microreactors (which have been variously called lab-on-a-chip) are usually produced in glass, silicon, or ceramics format, and have channel dimensions of 10 to 500 um. Such equipment is the ultimate in intensifying processes. Because of the very small lateral dimension, the flow regime is laminar only ($Re < 100$) i.e. it is not turbulent. Therefore, diffusion is nearly the sole mechanism of mixing.

The diffusion time (t_{diff}) is an indicator of the mixing efficiency in such systems and is proportional to the square of the channel width (d2).

$$t_{diff} \approx d^2/D$$

D being the diffusion coefficient.

Microreactors also decrease d and allow the mixing times to be in the milliseconds scale, allowing the exact kinetic control of reactions of very high rate, such as direct fluorination, or organolithium exchange [27].

Nonetheless, microchannels are subject to high pressure loss and prone to fouling (clogging) which restrict their application to slurry-based synthesis or high-throughput production. This has given rise to the application of meso-flow reactors, where the channels have a diameter of the millimeter range (1-5 mm). Meso-reactors are more robust at the expense of heat transfer efficiency, so they can operate at higher flow rates with better suspended solids tolerance, making them the best choice to pilot-scale pharmaceutical production [28].

3.2. Tubular Flow Reactors

Flow chemical, the most common, ubiquitous architecture of the region is tubular reactors, namely Coil Flow Inverters (CFIs) or simple coil reactors (SCRs). These reactors are made of tubes coiled around a mandrel or block of heat exchange. Selection of material is vital:

- **Polymeric Tubing (PFA/ETFE):** Photochemistry Transparent: good light penetrator, chemically inert, but have temperature and pressure limits, < 200ºC).

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

- **Metal Tubing (Stainless Steel, Hastelloy):** This is required when there is need of high temperature/high pressure windows (T > 250ºC) like those needed in flash heating or under the supercritical fluid conditions [29].

Dispersion, which is the spreading out of the residence time distribution (RTD), may be a challenging issue in tubular reactors. When fluid is flowing in a tube the velocity is greatest at the centre and zero at the walls (parabolic profile), and this may cause the broadening of bands. The fact that the tube is coiled makes the tube undergo Dean vortices (secondary flows), which enhance radial mixing and confine RTD, which is close to ideal Plug Flow behaviour because it is the only way to ensure consistent product quality [30].

3.3. Packed-Bed and Immobilized Catalyst Reactors

A foundation of heterocyclic synthesis (e.g. Pd-catalysed cross-couplings, hydrogenations) is heterogeneous catalysis. This would demand slurry processing and filtration in batch. Packed-Bed Reactors (PBRs) are used in an elegant manner in flow.

A PBR is a column of a solid stationary phase-commonly a catalyst on the beads of silica, carbon or polymer. The flow of reagents occurs in the void spaces and it interacts with the catalyst surface.

Shutterstock

PBRs have a number of specific benefits to API synthesis:

1. **Catalyst Efficiency:** Efficiency of catalysts is high in high local catalyst concentration resulting in high turnover frequencies (TOF).

2. **Product Purity:** The catalyst is left in the reactor, and a product stream is produced without any metal residue, furthermore, without the need to purify this stream downstream.

3. **Stability:** Catalyst aggregation can be avoided by immobilization.

Nevertheless, engineers have to skilfully balance the pressure drop across the column (determined by the Ergun equation) and watch out the so-called channelling (fluid bypasses the packed bed), so that the conversion efficiency can be lowered [31].

3.4. Multiphase Flow Systems (Gas–Liquid, Liquid–Liquid, Solid–Liquid)

Synthesis of heterocycles often goes through more than one step (e.g., a hydrogenation reaction with H_2 gas, a biphase nucleophilic substitution). Flow chemistry controls such interfaces using a special flow regime.

- **Gas-Liquid Flow:** This is the so-called tube-in-tube reactor, in which the gas is diffused through the liquid phase using gas-permeable membranes (such as Teflon AF-2400), which ensures that no bubbles are formed and that the entire process strictly follows the Henry Saturation Law. The other alternative is called segmented flow (Taylor flow), which adds slugs of gas and liquid alternately. Mass transfer In the case of a batch gas sparger, the mass transfer is far less effective than in the case of internal circulation of the liquid slugs.

- **Liquid-Liquid Flow:** A flow of liquids is carried out in comparable patterns of segmentation flow.

- Solid-Liquid Flow: The solids issue is still thought to be the worst in flow chemistry. Although passive flow can have sedimentation and clogging issues, newer active systems are agitated slurry reactors (CSTR cascades in flow) or oscillatory flow reactors (OFRs) in which the baffles and pulsed flow maintain the suspension of particles [32].

3.5. Modular and Telescoped Flow Platforms

The final development of flow architecture is the telescoped process - connecting one or more modules of reactors in series to deliver multi-step synthesis without any intermediate isolation [33].

The effluent of Reactor A is used as feed in Reactor B in case of telescoped sequence. It is especially useful to safeguard a group or to work with dangerous intermediates (e.g. diazonium salts synthesized in place and immediately used in a cyclization reaction). Less modular designs are now

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

being replaced by more complex modular designs that include inline liquid to liquid separators (membrane-based) and solvent switching units (distillation or membrane pervaporation) between the reactors. This modularity, which is a plug-and-play affair, enables chemists to build a bespoke production line to an intricate heterocyclic API resembling a biological metabolic route on a manufacturing facility [34].

4. Sustainability Metrics in Flow-Based API Synthesis

Sustainability in the pharmaceutical production has ceased to be a backburner to a vital performance measure. The pharmaceutical industry has long had a high environmental impact, and the production of API on a kilogram scale in many cases results in more than 100 kg of waste. Continuous flow manufacturing provides a technical route to match synthesis with the 12 Principles of Green Chemistry, which is based on the process of Process Intensification (PI) [35].

4.1. Green Chemistry Principles Applied to Flow Systems

Flow chemistry is a direct answer to some of the 12 Principles put forward by Anastas and Warner. Most notably:

- **Principle 1 (Prevention):** Flow systems reduce the reactive volume to ensure that side-products are not formed, either due to thermal gradient or inhomogeneity created during mixing, and thus eliminate downstream purification requirement [36].

- **Principle 5 (Safer Solvents and Auxiliaries):** This is due to the capability of operating at high temperatures and pressures so that one can use so-called green solvents (e.g., water, ethanol, supercritical CO2) that may not work in atmospheric reflux in batch [37].

- **Principle 12 (Inherently Safer Chemistry to Prevent Accidents):** As it has been explained in Section 2, the evidence that the inventory of hazardous reagents is negligible can allow the on-demand production of toxic or explosive intermediates (e.g., diazomethane, phosgene) to be inherently safer, since the risks of bulk storage and transportation are eliminated [38].

4.2. Process Mass Intensity (PMI) and E-factor Reduction

To measure sustainability, the industry has also not only been concerned with the simple yield calculations but also with the mass-based measures. The Environment Factor (E-factor) is a powerful measure, as well as Process Mass Intensity (PMI). The ratio of mass of waste produced to the mass of product is termed as E-factor:

E = Mass of Waste (kg)/Mass of Product (kg)

The E-factor, although handy, does not consider water at times and this may give a false impression. As a result, PMI is advocated by the ACS Green Chemistry Institute Pharmaceutical Roundtable (ACS GCIPR):

PMI = Total Mass of Input Materials (kg)/Mass of Product (kg)

Continuous flow architectures also minimize the two metrics considerably using telescoping. Intermediate workups, which otherwise can use large amounts of extraction solvents, drying agents, and wash water, are avoided by linking two or more synthetic steps into one continuous flow. By telescoping, heterocyclic APIs that can necessitate multi-step sequences can be brought down to the industry average of greater than 100 to less than 20, similar to that of bulk commodity chemicals. [39–41].

4.3. Solvent Minimization and Solvent Recycling

Solvents make up about 80-90 per cent of non-aqueous bulk in API production [42]. Flow chemistry has two unique benefits to solvent minimization:

1. **High Concentration Processing:** Reactions that have exotherms or solubility issues were highly diluted (0.1-0.5) in a batch reactor. Flow reactions can be carried out at greatly increased concentrations (1.0-5.0 M) or can be carried out in the neat (solvent-free) state, which results in solvent burden per kilogram of throughput being drastically minimized [43].

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

2. **Superheated Processing:** Solvents may be superheated (through placing a pressure in the system (with back-pressure regulators) to temperatures far higher than their boiling points in the atmosphere. This sharp rise in temperature greatly enhances the dissolution of polar heterocyclic precursors and therefore small amounts of solvent dissolve reactants that would otherwise have to be heavily diluted in batch.

Also, the solvent recycling can be easily implemented in continuous manufacturing. At the end of the line, pervaporation units, based on membranes, or continuous distillation modules could be installed to recover and recycle the solvent over to the reactor inlet to form a closed loop [44,45].

4.4. Energy Efficiency and Waste Reduction

The amount of energy consumed by batch reactors is often not very efficient because of the requirement to reheat and cool the entire thermal mass of the vessel (both the jacket fluid and the vessel walls) many times.

Flow reactors have a much lower thermal mass. It is practically unidirectional energy transfer to the fluid stream. Also, the flow systems can be used in regenerative heat exchange. In this arrangement, the effluent stream leaving the reactor is a hot one, and it flows through the heat exchanger to pre heat the incoming cold feed stream. This results in an autothermal process where the reaction heat itself causes the reaction, which greatly lowers the external energy requirement [46].

Another way of reducing waste is by applying Process Analytical Technology (PAT). Under batch processing, in case quality deviation arises, the whole batch (which can be worth millions of dollars) can be thrown away. Flow This method is suitable in flow because only the small portion of off-spec material can be diverted and the rest of the production run can be preserved with minimal wastage of chemicals [47].

4.5. Life Cycle Assessment (LCA) Considerations

PMI and E-factors would concentrate on the manufacturing phase (gate-to-gate), but to do a serious sustainability analysis, it would be necessary to have a Life Cycle Assessment (LCA), which would gauge the environmental impact on a cradle-to-grave basis [48].

A trade-off is frequently found in LCA studies concerning flow synthesis. Some microreactors (usually made by complex microfabrication of steel or glass) may be more expensive than casting a steel tank in the first place. But the LCA greatly Favours flow at the operation phase (Use Phase). The decreased solvent production upstream (reduced), the removal of the intermediate transport, decreased energy required to power HVAC (smaller facility footprint) lead to a much lower cumulative carbon footprint of the life of the API. With heterocyclic reactions using precious metal catalysts (e.g., Pd, Rh), packed-bed reactors will provide an additional enhancement in the LCA profile, through increased catalyst life and easy recovery of the metal [49].

5. Flow Synthesis of Key Heterocyclic Scaffolds

The process of switching to continuous flow has been especially revolutionary as applied to heterocyclic chemistry. It has made possible access to long process windows (higher T, higher P) and has also enabled reaction with normally hazardous intermediates under conditions safe to scale-up to batch, so-called forgotten chemistries reactions that were once believed too dangerous or too inefficient to scale-up to batch [50].

5.1. Nitrogen-Containing Heterocycles

The FDA Orange Book is dominated by nitrogenous heterocycles, which are found in close to 60 per cent of all of small-molecule drugs. Flow chemistry will solve the main bottleneck in their synthesis, the control of highly exothermic condensation reactions. [51].

5.1.1. Pyridines, Pyrimidines, and Quinolines

Hantzsch dihydropyridine synthesis is a classic multicomponent reaction (MCR) that is commonly subject to lengthy reaction times and challenging workups in batch (Figure 2). This condensation is expedited in flow by superheated solvents. The condensation of aldehydes, 1,3-dicarbonyls, and ammonium acetate may also be done in ethanol at 140°C (far higher than its boiling point) with back-pressure, and reaction times decrease to minutes (t_R < 10 min) [52].

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

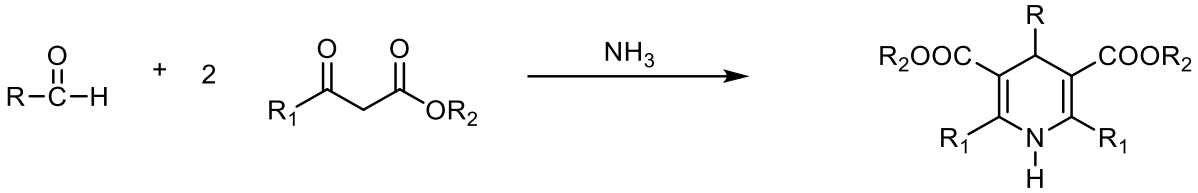

Figure 2.Hantzsch dihydropyridine synthesis accelerated in continuous flow.

On the same note, the Skraup and Friedlander quinoline synthesis (Figure 3) enjoy the advantages of the flash heating of tubular reactors. The Skraup reaction, which is infamously prone to runaways in mixing anilines with glycerol and sulfuric acid, is inherently safe in flow. The large ratio of surface to volume enables quick dissipation of exotherm which develops during the first mixing of acid and amine to prevent charring and enhance yield profiles. [53].

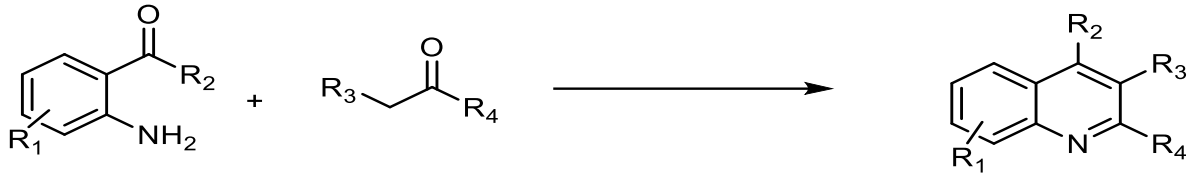

Figure 3. Enhanced safety and efficiency of Skraup and Friedländer quinoline syntheses in flow.

5.1.2. Triazoles, Imidazoles, and Pyrazoles

Perhaps the best-yet killer application of flow chemistry is the synthesis of 1,2,3-triazoles (Figure 4) by the Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC). The organic azides are high power and probably dangerous intermediates. The reactive inventory of azide is insignificant in a flow regime. Reaction streams may be made to produce organic azides in situ (e.g. by reacting halides and sodium azide) and react instantly in a downstream coil with the alkyne and copper catalyst (which is often copper tubing itself). This telescoping can be used to eliminate isolation of the hazardous azide and triazoles can be produced in kilogram scale which would be prohibited in a batch plant (54).

With the case of pyrazoles, the manipulating hydrazine (toxic and unstable) is simplified. Flow protocols make use of T-mixers to mix hydrazine hydrate with 1,3-diketones, after which the mixture is rapidly passed through a hot coil to induce the process of cyclization to prevent the formation of degradation products that are present in long-term batch reflux [55].

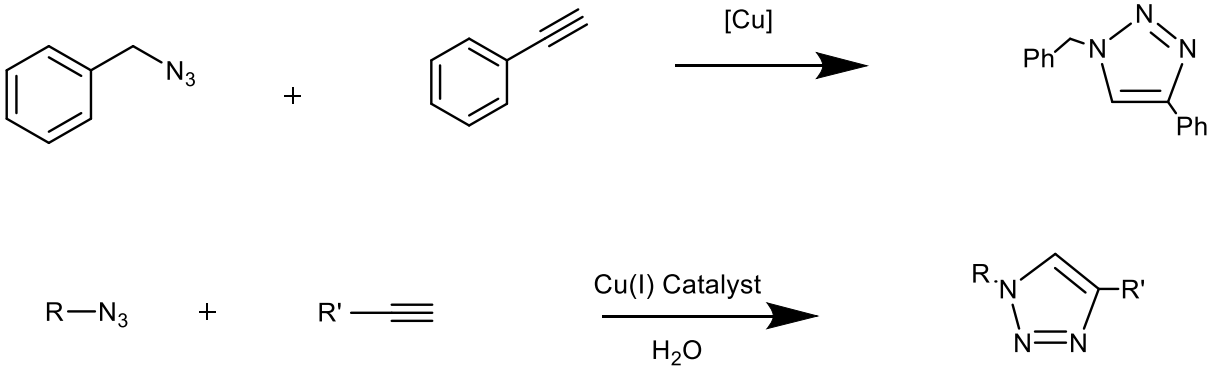

Figure 4. Safe and scalable synthesis of 1,2,3-triazoles and pyrazoles enabled by continuous flow.

5.2. Sulfur- and Oxygen-Containing Heterocycles

Although the S- and O-containing rings are a less predominant bioisosteres in comparison with N-heterocycles, they are essential bioisosteres and control the stability of metabolism and lipophilicity.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

5.2.1. Thiazoles, Thiadiazoles, and Benzothiazoles

One of the processes that are very flowable is the Hantzsch thiazole synthesis (a condensation of thioamides and alpha-haloketones). The reaction usually produces crystalline-intermediate which block batch impellers. During flow, reactors that are ultrasound assisted or agitated slurry systems are used so that the processing is continuous [56].

Continuous flow process intensification has been shown to clearly benefit the 1,2,4-thiadiazole moiety, which is an active pharmacophore in antimicrobial and anticancer investigations. Traditional batch reactivities use harsh oxidants or dehydrating agents (e.g. POCl3, bromine, strong acids) in order to create cyclic thioamides or amidrazones and this exacerbates safety and sustainability concerns. On the contrary, the flow-based oxidative cyclization in heterogeneous packed beds (MnO2, supported hypervalent iodine) provides a better control, safer operating and purification. The electrochemical flow synthesis further enhances this conversion by synthesizing the target oxidative intermediates anodically without using chemical oxidants, synthesizing the core of the 1, 2, 4 -thiadiazole with hydrogen as the only byproduct, which is entirely consistent with the principle of Green Chemistry and continuous manufacturing [57].

5.2.2. Oxazoles and Benzoxazoles

Oxazoles are generally synthesized using strong dehydrating agents ($POCl_3$, H_2SO_4) in the Robinson Gabriel cyclodehydration of 2-acylaminoketones (Figure 5). Flow chemistry in packed-red reactors employing solid acid catalysts such as zeolites or Amberlyst-15 enables this dehydration. This heterogeneous method prevents the necessity to quench large amounts of acidic waste, because the product is eluted out of the column into a neutral organic solvent, which is prepared to either undergo crystallization or functionalization [58].

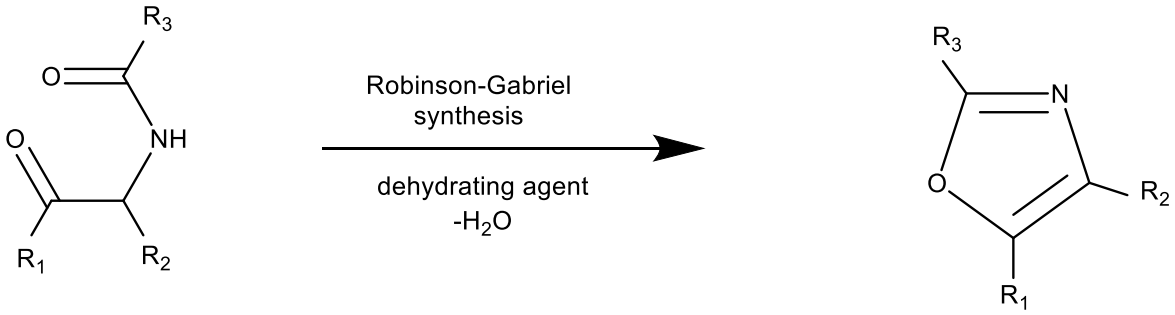

Figure 5. Heterogeneous flow-enabled Robinson–Gabriel cyclodehydration for oxazole synthesis.

5.3. Fused and Polycyclic Heterocycles in Drug Discovery

The tricky systems such as indoles and benzodiazepines in complex forms can be used as scaffolds of privilege in library generation.

Fischer Indole Synthesis (Figure 6) that encompasses rearrangement of arylhydrazones in the presence of acidic conditions needs high temperatures to surmount the barrier of the activation energy. This reaction is driven to completion in seconds in coils heated to 200-250°C (high-boiling solvents or a high-inductivity heating method) in flow. This speed permits kinetic entrapment of delicate intermediates which would be disaggregated by the slow heating rate of a batch mantle [59].

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

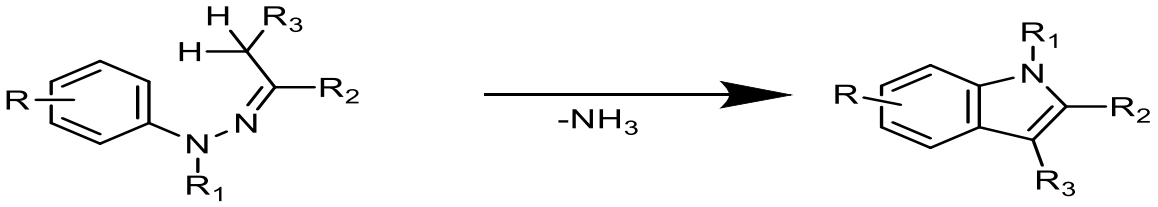

Figure 6. Fischer indole synthesis in flow.

Moreover, flow chemistry helps the preparation of benzodiazepines through step-wise multicomponent reactions (Figure 7). Chemists can carry out an Ugi reaction with a subsequent aza-Wittig cyclization in a single stream by daisy-chaining several reactors, which swiftly construct the seven-membered ring core upon which anxiolytic drugs are built [60].

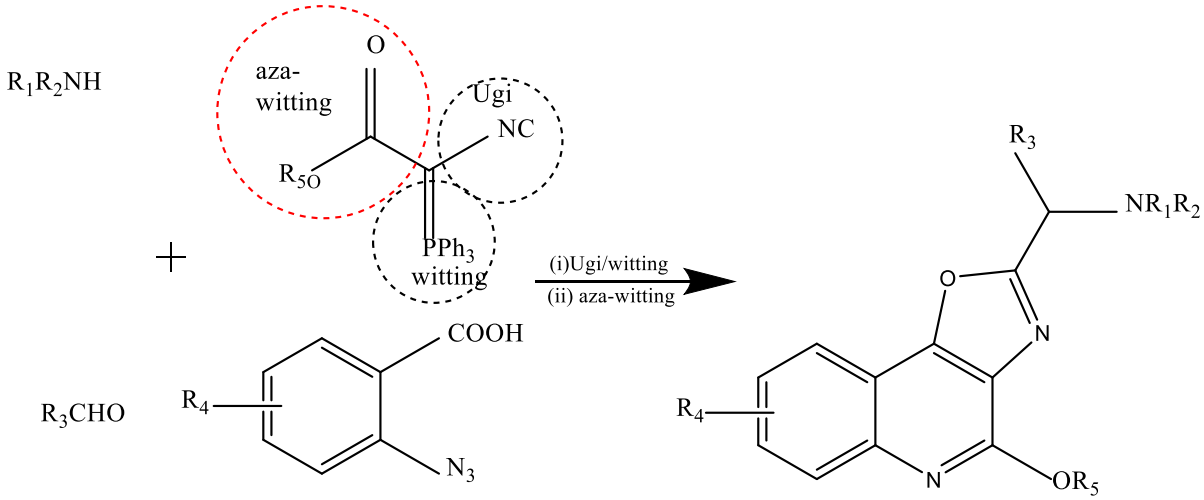

Figure 7.Flow-based multicomponent synthesis of benzodiazepines.

5.4. Case Studies of Marketed APIs Synthesized Under Flow Conditions

The theoretical benefits of flow chemistry are best explained by the success of the method in the high-value Active Pharmaceutical Ingredients (APIs).

Case 1: Rufinamide (Antiepileptic)

Rufinamide includes a triazole ring, which is conventionally formed by the 1,2,3 addition of a lethal azide intermediate (2, 6-difluorobenzyl azide) (Figure 8). It was a ground breaking study that Jamison group developed a fully continuous process and was adopted by later adopters in the industry.

- **Procedure:** The benzyl azide was produced in vivo directly in a flow coil and directly telescoped to a copper reactor (copper tubing was the source of catalyst) to react with a dipolarophile.
- **Impact:** This procedure not only removed the isolation of the explosive azide, but also shortened the overall reaction time by almost a day to less than 15 minutes, as well as making use of the reactor wall itself as the catalyst, eliminating filtration. [61].

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

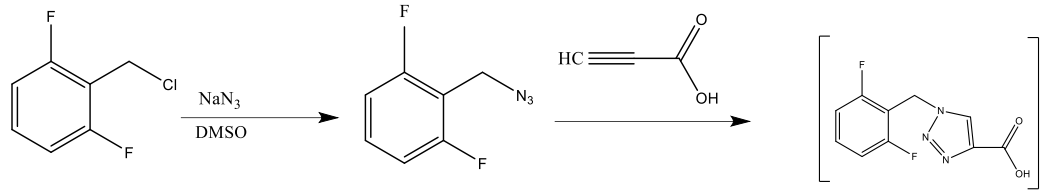

Figure 8. Fully continuous, azide-free synthesis of the triazole core of rufinamide.

Case 2: Efavirenz (Antiretroviral)

Merck and Co. designed a flow process of the synthesis of Efavirenz (Figure 9) in order to enhance the safety of a step in lithiation.

- **Procedure:** One had to lithiate a terminal alkyne (the pyrophoric reagent n-butyllithium) and react the alkyne with a cyclopropyl ketone. This necessitated cryogenic cooling down to -78oC to avoid side reactions in batch.
- **Impact:** With a flow reactor that was more effective in terms of mixing and heat transfer the reaction could be operated at significantly higher temperatures (-10oC to 0oC) without requiring the costly cryogenic infrastructure. The exact amount of residence time control was that it did not allow the decomposition of the lithiated species and yielded more of the intended alcohol intermediate [62].

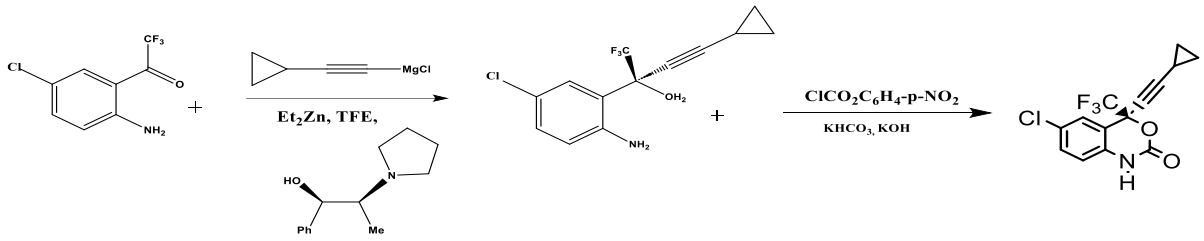

Figure 9. Flow-enabled lithiation step in the synthesis of efavirenz developed by Merck & Co.

Case 3: Imatinib (Anticancer)

A modular flow platform showed the complete synthesis of Imatinib (Figure 10) (Gleevec) by the Ley group.

- **Procedure:** A nucleophilic displacement of an acid chloride with an aniline was done by first coupling the acid chloride with an aniline.
- **Impact:** They would place intermediates in place by purifying using catch-and-release cartridges, which are columns of scavengers on polymer. The impurities were captured by the scavenger column on which the stream passed, and the pure intermediate went into the second reactor. This allowed the production of the final API without any manual treatment, crystallization, or distillation until the last step, the epitome of the end-to-end continuous manufacturing [63].

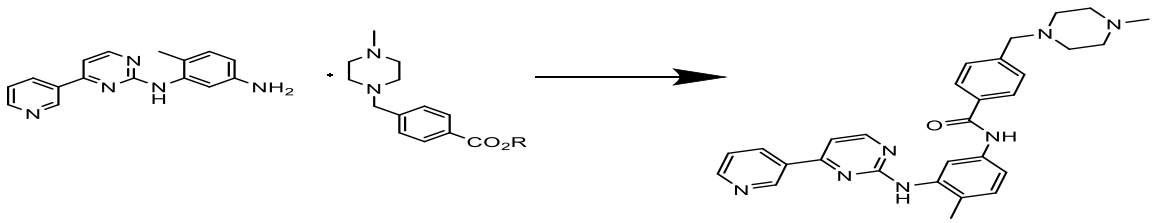

Figure 10.End-to-end continuous-flow synthesis of imatinib using a modular platform developed by the Ley group.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

6. Enabling Technologies for Flow-Based Heterocycle Synthesis

Continuous flow chemistry has a deeper potential than is represented by the simple spatial rearrangement of fluids. It is achieved by incorporation of enabling technologies to make the passive reactor tubes active, responsive manufacturing machine. The combination of all these real-time analysis, automation and alternative energy inputs has been instrumental in breaking the synthetic bottlenecks which had hitherto been a hallmark of complex heterocyclic assembly [64].

6.1. In-line Monitoring and Process Analytical Technologies (PAT)

In classical batch synthesis, reaction monitoring is not continuous (it is based on manual sampling and offline measurements e.g. TLC or HPLC). This snapshot approach has frequently resulted in the loss of transient intermediates or rapid kinetic events. Contrastingly, continuous flow systems allow Process Analytical Technology (PAT) to be incorporated directly into the fluid stream where a continuous data stream provides an indication of the chemical state of the reactor in real-time [65].

IR and Raman - Vibrational Spectroscopy

Flow monitoring workhouses on In-line Infrared (IR) spectroscopy, especially with Attenuated Total Reflectance (ATR) flow cells. ReactIR^{tm} probes are necessary in the heterocyclic synthesis to monitor certain functional group changes. As an example, the disappearance of the typical azide stretch frequency (2100 cm^{-1}) can be used to monitor the cycloaddition of azides to triazoles. Raman spectroscopy is equally a complementary window particularly when one wants to monitor the formation of a carbon-carbon bond or when one wants to observe reactions in aqueous solution where the IR is obscured by the strong water absorption. Using such tools, chemists are able to know when the system has attained steady state, that is, when the concentration of the species at the outlet is not changing with time, which is the precondition necessary to harvest the products.

Flow NMR:

Benchtop NMR spectroscopy has a traditional low-sensitivity and uses deuterated solvents, but flow applications have been renewed recently. More recent flow-NMR instruments take advantage of non-deuterated solvents using solvent-suppression pulse sequences (e.g., WET or PRESAT) to obtain proton spectra of the reaction stream. They are less powerful in the field than the high-field analysis instruments, but can give structural elucidation which is not possible with IR. This is essential in the separation of regioisomers in heterocyclic substitutions, i.e. differentiating between N1- and N2- alkylated pyrazoles, where vibrational spectroscopy can produce overlaps in the signals [66].

MS – Mass Spectroscopy:

To trace impurities or require real-time determination of molecular weight, in-line Mass Spectrometry is unsurpassed. A highly vacuumed MS detector would have to be interfaced with a high-pressure flow stream via a complex interface which would typically be an electrospray ionization (ESI) source connected to a passive splitter to divert a microliter-sized aliquot to the detector. Such an arrangement permits side-products (e.g. an incomplete cyclization or over-oxidation) to be immediately identified, so that the operator can terminate a run before large amounts of starting material have gone to waste [67].

6.2. Automation and Digital Control Systems

The flow reactor is turned into a programmable apparatus as a result of the computerization of the chemical synthesis. In this sense, automation can be described as the centralized control of hardware devices, i.e. pumps, Mass Flow Controllers (MFCs), back-pressure regulators (BPRs), temperature control units (TCUs) through a software interface (e.g., LabVIEW, Python scripts or vendor-specific industrial environments such as Siemens SIMATIC) [68,69].

This link enables fine parameter sweeps. A script can run on the computer monitor the reactor to execute a "gradient" of conditions: increase temperature between 100°C and 150°C, in 10°C steps, and at the same time change the pump flow rate to hold the residence time constant.

In the case of the synthesis of heterocyclic libraries, the automation can be used to process sequentially. It is possible to inject separate slugs of various amine

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

building blocks into a core heterocyclic scaffold stream using an automated liquid handler (autosampler). Every slug is an individual reaction experiment separated by a spacer of solvent. It is called segmented flow library synthesis, where one flow platform can produce dozens of unique analogs each day, which is key to Structure-Activity Relationship (SAR) studies required in early-stage drug discovery [70,71].

6.3. Machine Learning and AI-Assisted Reaction Optimization

PAT and automation have made it possible to develop so called Self-Optimizing Reactors or autonomous discovery platforms. In this closed-loop paradigm, the chemist is substituted in the decision-making loop by an Artificial Intelligence (AI) algorithm.

- Execute: T, P, tR, and stoichiometry are utilized to construct a reaction condition that is employed to run the system.
- **Analyze:** The yield and selectivity are determined by the PAT tool (e.g. HPLC).
- **Decision:** The computer chooses the next set of circumstances to test after evaluating the findings. [72].

This method is especially effective with multicomponent, heterocyclic reactions (e.g., Ugi, Passerini, or Biginelli reactions), whose space of variables is of enormous size and non-linear. It has been shown that AI-driven flow systems are able to find optimal conditions to form complex heterocycles in less than 20 steps, consuming more than 90 percent of material than did the human-driven optimization, known as one-factor-at-a-time (OFAT) optimization [73].

6.4. Photochemical and Electrochemical Flow Reactors

Flow chemistry has renewed the interest in photochemistry and electrochemistry- two reagent-free synthetic modes that are perfectly suited to Green Chemistry but have scaling problems in batch [74].

Photochemical Flow reactor:

Reactions in photochemistry involve absorption of photons which are regulated by the Beer Lambert law (A = elc). The path length (l) in large batch vessels is large, i.e. light only penetrates a few millimeters into the solution; the major part of the reaction mixture is not exposed to light giving rise to long reaction times and side reactions caused by excessive irradiation of surface layer [75].

The microflow reactors with channels depths ranging between 100-500 um are used to ensure that the whole reaction volume is irradiated. This geometric advantage that appears to be simple has opened up new synthetic disconnections of heterocycles. As an illustration, [2+2] cycloadditions to produce azetidines or oxetanes, which are not readily scalable in batch, are quantitatively produced in flow photoreactors [76]. Also, the facile light penetration will allow functionalization of existing heterocyclic cores (e.g., Minisci-type alkylations of pyridines) using photoredox catalysis (Ir or Ru catalysts) without using pre-functionalized precursors, greatly simplifying synthetic pathways. [77].

Electrochemical Flow Reactors:

Electrochemistry provides a sustainable process of conducting oxidations and reductions with the use of electrons as the "reagent" without the use of toxic oxidants (such as Cr (VI)) or reductants (such as Zn dust). Batch electrolysis, however, needs to be supported with conductivity through electrolytes and hence it makes purification more difficult [78].

Continuous flow electrochemical cells have the inter-electrode gap decreased to micrometers. Such close proximity reduces ohmic resistance and in most cases, electrolysis can occur without supportive electrolyte or with minimal support electrolyte. In the case of heterocyclic synthesis, the oxidative cyclizations are being revolutionized with this technology.

With the help of these enabling technologies, the contemporary stakeholder pharmaceutical chemist ceases to be a mere bystander, but rather a participant in the architecture of the assembly of molecules, and has the ability to produce highly complex heterocyclic APIs with unprecedented accuracy, speed, and sustainability [79].

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

7. Catalysis in Continuous Flow Systems

Pharmaceutical synthesis depends on catalysis, and more than 80 percent of complex API production processes include at least one catalytic reaction. A complete shift of these processes to flow mode will necessitate integrating a new approach to the management of catalysts. In batch, the pot is simply loaded with the catalyst; in flow, the catalyst may either move with the stream (homogeneous) or be fixed stationary whilst the stream flows over it (heterogeneous). The synthesis of heterocyclic scaffolds poses engineering issues and opportunities in each approach [80].

7.1. Homogeneous Catalysis in Flow

Homogeneous catalysis, i.e. catalysts and reactants are in a common phase, is much better in terms of atom economy and selectivity because of the extreme accessibility of the active metal centre. In flow chemistry however, it poses a special challenge: solubility [81].

In a tubular flow reactor, catalyst or catalyst-ligand complex precipitation may be disastrous in terms of channel plugging and system over-pressurization. Consequently, the choice of solvent turns into a critical factor, and the solubilizing co-solvents or even ionic liquids may be used, which could be evaded in batch.

These obstacles notwithstanding, homogeneous flow systems have specific kinetic benefits. The high mixing that is a characteristic of microreactors means the catalyst is spread uniformly eliminating any concentration gradient that can cause catalyst deactivation, or hot spot. It is especially useful when quick homogeneous reactions are required, e.g. organocatalytic aldol condensation or Friedel-Crafts alkylation catalyzed by Lewis acids [82].

Moreover, flow makes it possible to dose catalyst via flow with accuracy. The initial loading of a catalyst is fixed in a batch reactor (e.g., 5 mol%). The catalyst solution is pumped into a flow system with the help of a separate pump. This enables the operator to control the catalyst to substrate ratio dynamically throughout the run, to optimize the conversion without halting the reaction process a method referred to as “dynamic optimization” [83].

7.2. Heterogeneous and Immobilized Catalysts

The most natural fit of continuous flow processing is probably heterogeneous catalysis. The separation of the catalyst and product is inherent in the process by fixing the catalyst on a solid support and loading it in a column (Packed-Bed Reactor or PBR). This avoids the filtration or distillation of the reaction products after reaction which is a significant cost driver in the production of a pharmaceutical [84].

Immobilization Strategies:

- **Covalent Tethering:** Ligands are chemically modified on the silica or polymer backbone. This can change the electronic properties of the catalyst, although it is stable.
- **Electrostatic/Adsorption:** An adsorption process onto a porous material such as activated carbon (Pd/C) or alumina. This applies to hydrogenation reactions but may cause leaching, in which the metal is lost to the product stream.
- **Encapsulation:** It is a sol-gel or zeolite that entraps the catalyst physically so that it cannot escape but allows small reagent molecules to pass through [85].

Packed-Bed Reactor (PBR) Engineering:

The pressure drop and mass transfer are to be balanced when designing a PBR to be used in heterocyclic synthesis. Smaller particles are superior as catalysts, which have increased surface area (faster reaction) and induce high back-pressure (Darcys Law). Big particles decrease pressure but could experience some limitation of pore diffusion, with the reagents not able to access the active sites located at the interior of the bead. Turbulent-like mixing is provided by the tortuosity of the path through the bed and this would be ideal in multiphase reactions, including the hydrogenation of nitro-heterocycles to amino-heterocycles with H2 gas and Pd/C [86].

7.3. Metal-Catalyzed Cross-Coupling under Flow

Cross-coupling reactions involving transition metals (Suzuki-Miyaura, Buchwald-Hartwig, Heck, Sonogashira) cannot be done without to build biaryl and aryl-heteroaryl motifs common in modern drugs (e.g. Sartans, kinase inhibitors) [87].

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

Buchwald-Hartwig Amination Pd-Catalyzed:
This reaction contributes greatly in crosslinking C-N bonds in heterocycles (Figure 11) (e.g. to a core of a piperazine to a core of a pyridine). Flow The flow stream can be homogeneous using soluble organic bases (such as DBU or MTBD) instead of inorganic bases (Cs2CO3). Alternatively, it can be run in pre-packed columns of polymer-based Pd catalysts under what can be described as the ligand-free conditions of the mobile phase, which makes the process significantly cheaper.

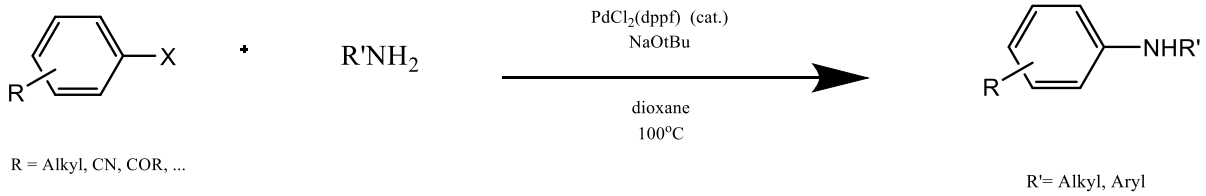

Figure 11.Flow-enabled C–N cross-coupling for heterocycle functionalization.

Suzuki-Miyaura Coupling:
Monolithic catalysts (porous rods of silica, polymer) have been very promising in the synthesis of biaryl heterocycles (Figure 12). In contrast to loose beads, monoliths have a continuous skeleton, which has a high surface area and low pressure drop. They have successfully been employed to make intermediates of drugs such as Valsartan and Boscalid in continuous flow with large Turnover Numbers (TON) and Turnover Frequencies (TOF) relative to batch [88].

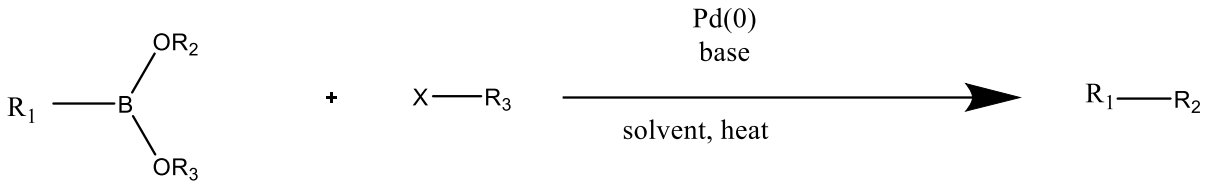

Figure 12.synthesis in flow Monolithic catalysts enabling efficient biaryl heterocycle.

7.4. Biocatalysis and Chemoenzymatic Flow Processes
The Future of Sustainable Synthesis is Flow Biocatalysis the incorporation of enzymes into flow systems. Enzymes provide unmatched regio- and stereoselectivity, which is needed to access the chiral centers present on heterocyclic APIs [89].
Kinetic flow immobilization of the enzyme:
Enzymes are also usually too costly to consume and dispose of (homogeneous batch). Flow enables their re-use through the use of immobilization in PBRs. Common methods include:

- **Cross-Linked Enzyme Aggregates (CLEAs):** Enzymes are cross-linked and thus become solid particles, which can be packed. [90].
- **Carrier-Bound:** Enzymes are bound to resins (e.g. His-tag/Ni-NTA or covalent interaction) [91].

Cofactor Regeneration:
Many enzymes (e.g. ketoreductases, transaminases) utilize the expensive cofactor (NADH, NADPH). Washing away of cofactor would occur in a flow PBR. Some of these solutions are co-immobilization

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

of a recycling enzyme (e.g. glucose dehydrogenase) with the primary enzyme, or using segmented flow to reuse the aqueous cofactor phase and recover the product into an organic phase [92].

Chemoenzymatic Cascades:

The strength of flow is the fact that biological and chemical reactions which cannot be used together in one pot are coupled. As an example, one chemical step may be incompatible with an enzyme (high T, metal catalyst). These steps in flow are spatially separated in other modules [93].

- *Example:* A flow process of Sitagliptin intermediates comprises a chemical step (formation of an enamine) and to follow this is an enzymatic reduction step. The flow arrangement enables an in-line pH change or solvent change between the two modules, in order to get both the chemical catalyst and the biological enzyme to work in their optimum conditions. This is based on this best of both world method to the synthesis of complex chiral heterocycles with high enantiomeric excess (ee > 99%) [94].

8. Scale-Up, Tech Transfer, and Industrial Implementation

The transfer of a synthetic route out of the medicinal chemistry laboratory into a commercial production facility, commonly known as the so-called tech transfer, is notoriously risky. This is done by a complex re-engineering of the synthesis to support the new conditions of large vessels in terms of heat and mass transfer. The fundamental idea behind continuous flow chemistry is that it radically alters this workflow by providing a more smooth road to the industrial implementation by maintaining the reaction environment [95].

8.1. Numbering-up vs. Scaling-up Strategies

Linear scale of manufacture is the hallmark of continuous manufacturing. In batch processing, production scale must be increased with scale: not only by changing the 100 mL flask to a 10L reactor, but then to a 10,000L vessel. Geometric expansion of this type decreases the surface-to-volume ratio (A/V) in which instance reaction conditions are potentially required to be re-optimized entirely in order to prevent thermal runaways or mixing inefficiencies [18].

Flow chemistry has another philosophy called scaling out or numbering-up:-

- **Scale-out (Time Extension):** The most straightforward way of increasing the throughput is to keep the reactor operating longer. A reactor with a capacity of 10 g/hour will yield 240 g per day and 7.2kg in 1 month and there will be no variation in the chemical engineering parameters.

- **Numbering-up (Parallelization):** To reach the metric-ton scale, a central manifold feeds several identical reactor units running in parallel. Both the fluid dynamics and thermal profiles are the same since every parallel unit (or "channel) replicates the scale of the device in the laboratory [96].

The time-to-market is drastically minimized using this method. The so-called pilot plant stage that used to take months of engineering investigation is actually eradicated since the piloit is the production reactor, only to be cloned 10 or 100 times. However, numbering-up creates its own engineering issues, which is mainly flow distribution. It is essential to make channels flow with the same resistance 100 channels in parallel, obstruction in one channel may cause residence time distribution (RTD) and uneven product quality among the array [97].

8.2. Integration of Upstream and Downstream Processing

To be a continuous process, continuous manufacturing requires the synthesis (upstream) to be continuously linked with the workup and isolation (downstream). The holistic thinking of this is commonly referred to as End-to-End (E2E) Manufacturing [98].

Separation and Switching of Solvents:

The solvent required to accomplish synthesis may need to be conducive to both kinetics (e.g., DCM) and reaction kinetics (e.g., THF), which in turn may not be conducive to further crystal growth or biousage. In batch, this is done through distillation

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

and through solvent swaps. Continuous membrane separators are used in flow to fractionate aqueous and organic phases in real-time using hydrophobic/hydrophilic interactions, as an inline separatory funnel. More sophisticated systems are based on membrane pervaporation or continuous vacuum stripping to drive the solvent of the reaction away as well as substituting it with a crystallization solvent (antisolvent) without discontinuity to the flow stream. [99].

Quenching and Scavenging:

The intermediates that are formed must be quenched until isolation. In flow, this is done by blending the stream of reaction with a quenching agent in a static mixer. Alternatively excess reagents can be removed by chemically scavenging of columns of scavengers (packed beds of polymer-supported nucleophiles or electrophiles). As an illustration, a stream of acidic chloride that has excess acid may be subjected to a column of polymer-supported amine which captures the acid chloride but the pure amide product is collected [100].

8.3. Continuous Purification and Crystallization

The last isolation of the API is essential in the regulation of polymorphism, particle size distribution (PSD), and purity [101].

Continuous Crystallization:

The most famous thing about batch crystallization is that it is hard to maintain a batch, and it can easily be affected by variation in the size of the crystals across batches because of unequal cooling rates. A continuous crystalizer, e.g. Mixed Suspension Mixed Product Removal (MSMPR) crystallizer or an Oscillatory Baffled Crystallizer (OBC), provides better control.

- **MSMPR:** It is a CSTR in solids operation whereby slurry is removed continuously.
- **OBC:** Is an oscillatory drive that maintains crystals in a tubular reactor where a slow, constant profile cooling can be done along the tube. This is the exact thermal history that favors the cultivation of homogeneous crystals and makes it possible to selectively crystallize individual polymorphs, which is a very important regulatory need of APIs [102].

Continuous Chromatography:

In situations where crystallization is not adequate to separate complex heterocyclic APIs (ex: separating regioisomers or enantiomers), Simulated Moving Bed (SMB) chromatography is the method of choice in the industry. SMB models the counter-current motion of the stationary phase, solid phase, which maximizes the efficiency of the adsorbent, without consuming a lot of solvent like traditional batch HPLC prep columns [103].

8.4. Industrial Success Stories

Adoption of flow chemistry is no longer a mere theory; it is in use in the large pharmaceutical plants around the globe.

Success Stories:

- **Vertex Pharmaceuticals (Orkambitm):** Vertex became the first company that got the FDA approval of a drug produced through a continuous process. Their plant in Boston uses a continuous production rig which combines the process of synthesis, drying and pressuring pills into one enclosure and it takes up only a fraction of the space that would otherwise be used by a conventional plant [104].
- **Eli Lilly (Prexasertib):** Lilly came up with a cGMP continuous process in Prexasertib lactate, which is a kinase inhibitor. The process consisted of seven chemical reactions, which included: hydrazine (hazardous) and high-pressure hydrogenation. They were able to generate 24 kg of API in a fume hood-sized apparatus by running in flow, and this result shows that it is possible to generate potent compounds safely without a high-containment facility specifically designed [105].
- **Novartis-MIT Center:** It is a partnership that created a factory the size of a refrigerator that can synthesize, purify, and formulate generic drugs (such as ciprofloxacin) in-demand. The proposed solution to this modularity is seen as a method of avoiding the shortage of drugs and decentralization of production [106].

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

9. Regulatory, Economic, and Quality Considerations

The scientific argument that supports continuous flow synthesis of heterocyclic APIs based on safety, efficiency and selectivity is undeniable. Nevertheless, three pragmatic factors, namely, regulatory compliance, economic viability, and quality assurance, are ultimately what controls the mass adoption of this technology into the pharmaceutical sector. With the industry moving out of the static quality control of a snapshot of the batch processing to the dynamic quality control of the continuous manufacturing (CM) a new structure of compliance and business strategy has been created [107].

9.1. Regulatory Acceptance of Continuous Manufacturing

Traditionally, pharmaceutical industry has been conservative and followed the batch processing due to the fact that the pathway to regulations was well worn and predictable. This stalemate started to change drastically in the early 2010s due to the US Food and Drug Administration (FDA) and subsequently the European Medicines Agency (EMA), which started to realize that the variability in the batch processing presented a threat to patient safety.

The turning point in terms of regulations was the ratification of the ICH Q13 Guideline ("Continuous Manufacturing of Drug Substances and Drug Products"). A large ambiguity was the meaning of a batch in a continuous stream, before ICH Q13. In conventional production, a batch is described by the size of the vessel (e.g. all the material in Tank A). ICH Q13 also enables manufacturers to specify a batch in continuous flow either by time-dependent intervals (e.g. all material manufactured between 8:00 AM and 4:00 PM) or by the quantity of output (e.g. every 50 kg of crystallized API). This flexibility can enable manufacturers to unlink lot size and equipment scale, allowing so-called demand-led production in which lot sizes can be modified dynamically to match market changes without re-filing of the regulations.

The regulatory bodies have even put in place special units to help in this transition like the Emerging Technology Team (ETT) of the FDA. Through these units, early interactions are promoted, which means that companies can negotiate their flow control plans (Control Strategy) without a formal New Drug Application (NDA) being submitted. This dialogue plays a critical role in determining the State of Control -a situation whereby a system of controls will always give an assurance of further performance of the process and the quality of the products. In the case of heterocyclic APIs, where such multi-stage reactions are typically complicated and require multiple stages, the essential regulatory need is to show that the system can stabilize to this level of control in the presence of small perturbations (e.g. pump variability) [108].

9.2. Cost–Benefit Analysis for Pharmaceutical Industries

Economic argument of continuous flow is multidimensional, which includes the trade-off of implementing high initial Capital Expenditure (CapEx) against low Operational Expenditure (OpEX).

Capital Expenditure (CapEx):

A continuous flow plant usually necessitates special and sensitive (e.g. Hastelloy microreactors, complex PAT sensor arrays, automated control systems) equipment, which is more costly on a per-unit-volume basis than conventional glass-lined steel batch reactors. This is compensated by the drastic decrease in facility footprint, however. A continuous plant that requires 10 tons of API annually can occupy a typical laboratory module (less than 100 m2), but a batch plant of the same size needs a multi-story pilot hall. This saving in real estate of clean rooms contributes to huge savings in building and HVAC (heating, ventilation and air conditioning) expenditures which are major motivators of CapEx in pharmaceutical facilities.

Operation Expenditure (OpEx):

Flow chemistry provides the best Return on Investment (ROI) in the long-term savings in OpEx.

- **Yield and Purity:** In the case of complex heterocyclic scaffolds, flow chemistry can enhance the yield by 10-20%, preventing side reactions. This yield improvement has a direct impact on the Cost of Goods Sold (COGS) in the environment of high-value

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

APIs (where intermediates may cost $5,000/kg).

- **Inventory Costs:** Batch production implicates monies in "Work in Progress" (WIP) inventory. In between products are made, purified, beat, experimented and stored in weeks before the next step. This WIP is eradicated by continuous processes (telescoped) which transform the raw materials into finished API within hours. This lean production system releases the working capital and enhances the cash flow.

- **Labor:** Flow plants need more skilled operators (usually engineers); however, they need fewer. With automation, it is possible to have lights-out manufacturing (operating 24/7 with minimal oversight), where the amount of labor per kilogram of product is lowered [109].

9.3. Quality Assurance and Real-Time Release Testing (RTRT)

The most radical factor of continuous manufacturing is the change in the principle of Quality by Tests (QbT) to Real time Release Testing (RTRT).

The quality is measured in a backward manner in the traditional batch paradigm. Once a reaction is complete, a sample is collected to the QC lab. When the sample under test fails, it quarantines or destroys the whole batch (which may be worth millions). RTRT inverts this logic. It is based on the assumption that when the Critical Process Parameters (CPPs) temperature, pressure, residence time, stoichiometry are kept within a proven design space the Critical Quality Attributes (CQAs) purity, crystal form, potency, must also be achieved.

This is implemented through large scale integration of online PAT. This can involve: in the case of a heterocyclic synthesis, this can comprise:

- **Reaction Completion:** The loss of a nitrile peak was seen by inline IR.

- **Purity:** Online HPLC after every 15 minutes to measure impurities.

- **Form:** On-line Raman spectroscopy that guarantees the correct polymorph to crystallizing.

More importantly, this system needs a complex knowledge of Residence Time Distribution (RTD). The RTD describes the mixing and dispersion of fluid components on the way they flow through the reactor. When a sensor identifies a transient disturbance (e.g. a temperature spike), then the RTD model is used to determine the precise segment of the fluid stream that was disturbed. A divert valve is then set off automatically to dispose of just that particular "slug" of out of compliance material to waste, leaving the remainder of the production run unaffected. This capability of being able to surgically remove any defects gives a guarantee that the final collection vessel is only filled with compliant material and theoretically the product can be released to be distributed right after it is completed [110].

9.4. Challenges in Regulatory Harmonization

The technological and economical argument is good; however, the global regulation system is still in disarray, which is a big challenge to multinational pharmaceutical firms. This is what is referred to as Regulatory Harmonization.

The ICH guidelines ensure that the three major agencies (FDA, EMA, and the PMDA of Japan) are largely consistent on the principles of continuous manufacturing. Nevertheless, a drug company submits most of the time to more than 100 countries. There are still a lot of emerging markets (e.g., some Latin American countries, southeast Asia, and Africa) in which there are not yet designated any guidelines or assessors of continuous manufacturing [111].

10. Current Challenges and Knowledge Gaps

Continuous flow chemistry has not become as industrial as a need, but it is not a panacea, even though it has grown out of an academic interest. This has been accompanied by different physicochemical and operational limits which characterize the present knowledge gaps in the field due to the implementation of flow architectures of heterocyclic synthesis. These restrictions should be recognized to make a sound and fair scientific evaluation.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

10.1. Handling Solids and Clogging Issues

The weakest point of microfluidics is still the manipulation of solids, be it as reagents, catalysts, or precipitates. Overhead stirring is easy to use in batch reactors in the management of slurries. Particulate matter forms different failure modes in flow channels (with a channel width of less than 1 mm) namely bridging (particles interlocked over the channel width), settling (sedimentation by the laminar velocity profiles in the flow), and fouling (progressively developed layers along the walls).

In the case of heterocyclic synthesis, this is objectionable since most classical cyclizations (e.g. the insoluble hydrochloride formation of amine-acid chloride couplings) produce solids. Although encouraging promises have been made with engineering solutions such as Oscillatory Flow Reactors (OFRs) and acoustic (ultrasonic) irradiation, these further complicate and increase the cost. Future technologies include liquid-walled reactors, which are in the early research phase, which is based on a ferrofluid sheath to ensure that there is no contact between the mixture and the solid wall. At present, the process window is determined by the "solubility limit" which, more often than not, requires chemists to adopt non-ideal, costly solvents to ensure homogeneity [112–114].

10.2. Limited Substrate Scope in Complex Heterocycles

Flow chemistry typically boasts of being universal but in reality, complex heterocycles have a more restricted range of substrates compared to batch. This is mostly because of limitations of solubility. Unstable heterocyclic intermediates (typical of late-stage functionalization of APIs) are in many cases poorly soluble in common flow solvents (MeCN, MeOH, THF) [115].

In addition, even the residence time distribution (RTD) in tubular reactors may be counterproductive to reactions with very long kinetic times (> 5 hours). Although this can be obtained by low flow rates, this can generally result in Taylor dispersion, which will cause band broadening and low selectivity. Therefore, even slow-reacting heterocycle reactive structures (such as some transition-metal catalyzed C-H activations) remain typically more effective in batch form, since to obtain the required residence-time in flow would require prohibitively long coils of reactors (> 100 meters) or very slow flow rates which would impair the mixing efficiency [116].

10.3. Catalyst Deactivation and Reactor Fouling

The first knowledge gap in the field of heterogeneous catalysis (Packed-Bed Reactors) is long-term stability of catalyst. In contrast to batch, a flow PBR has to work hundreds of hours with new catalyst being introduced after each run.

Deactivation Mechanisms:

- **Leaching:** The active metal (e.g., Pd, Rh) moves out of the active component into the mobile phase. The conversion profile can shift due to even low-ppm levels of leaching that deplete the bed in weeks.
- **Sintering:** Nanoparticle catalysts can aggregate under a high thermal stress commonly used in the flow to produce faster kinetics and thereby eliminate surface area.
- **Poisoning/Fouling:** Active sites in heterocyclic synthesis are highly susceptible to catalyst poisons (e.g. nitrogen and sulfur) which irreversibly interact with the active site.

The "breakthrough point" is the exact point at which the catalyst bed fails and this is determined by complex predictive modeling that is poorly developed at the moment. The majority of campaigns are based on empirical stress tests as opposed to ab initio lifetime predictions [117].

11. Conclusion:

Future Perspectives

With the pharmaceutical industry no longer in the early stages of validation of flow chemistry, the theme is changing to unit operations versus system integration. The coming decade will probably see the development of continuous flow as a specialized instrument to the nervous system of the contemporary drug production.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2873 - 2900

End-to-End Continuous API Manufacturing

The final path is achievement of the fully End-to-End (E2E)-manufacturing systems, i.e. accepting raw starting materials at one end, and at the other end, the release of the formulated drug product (tablets or injectables) with zero human participation. Though only a few examples of such architectures are possible now (e.g. Orkambitm by Vertex), the architecture of the future will regularly telescope complex heterocyclic syntheses directly into continuous crystallization, wet granulation, and tableting modules. This integrative interconnectedness will eradicate the hold times that characterize the batch supply chains, as time will decrease as months to days between the raw material and the patient [118].

Integration with Precision Medicine and On-Demand Synthesis

Flow chemistry has a unique opportunity to facilitate the so-called Pharmacy on Demand or decentralized production. In comparison to large scale batch plants that are dependent on the economies of scale, compact flow modules may be implemented in hospitals or remote areas (economies of scope). This can be used in the paradigm of precision medicine, in which batches of orphan drugs can be synthesized on-site in small batches, or doses can be tailored to an individual. Smaller-than-a-suitcase-sized factories of the future would be able to produce unstable, short-half-life radiopharmaceuticals or even tailored chemotherapies right before administration and avoid the cold-chain logistics process altogether [119].

References

1. Helal NA, Elnoweam O, Eassa HA, Amer AM, Eltokhy MA, Helal MA, et al. Integrated Continuous Manufacturing in Pharmaceutical Industry: Current Evolutionary Steps Toward Revolutionary Future. Pharm Pat Anal. 2019 Jul 29;8(4):139–61. doi:10.4155/ppa-2019-0011
2. Boodhoo K, Harvey A, editors. Process Intensification for Green Chemistry. Wiley; 2013. doi:10.1002/9781118498521
3. Baumann M, Baxendale IR. The synthesis of active pharmaceutical ingredients (APIs) using continuous flow chemistry. Beilstein Journal of Organic Chemistry. 2015 Jul 17;11:1194–219. doi:10.3762/bjoc.11.134
4. Aatif M, Raza MA, Javed K, Nashre-ul-Islam SMohd, Farhan M, Alam MW. Potential Nitrogen-Based Heterocyclic Compounds for Treating Infectious Diseases: A Literature Review. Antibiotics. 2022 Dec 3;11(12):1750. doi:10.3390/antibiotics11121750
5. Rusu A, Moga IM, Uncu L, Hancu G. The Role of Five-Membered Heterocycles in the Molecular Structure of Antibacterial Drugs Used in Therapy. Pharmaceutics. 2023 Oct 29;15(11):2554. doi:10.3390/pharmaceutics15112554
6. Bogdan AR, Dombrowski AW. Emerging Trends in Flow Chemistry and Applications to the Pharmaceutical Industry. J Med Chem. 2019 Jul 25;62(14):6422–68. doi:10.1021/acs.jmedchem.8b01760
7. Lovato K, Fier PS, Maloney KM. The application of modern reactions in large-scale synthesis. Nat Rev Chem. 2021 Jun 22;5(8):546–63. doi:10.1038/s41570-021-00288-z
8. Donnelly K, Baumann M. Advances in the Continuous Flow Synthesis of 3- and 4-Membered Ring Systems. Chemistry – A European Journal. 2024 Jun 6;30(32). doi:10.1002/chem.202400758
9. Hyer A, Gregory D, Kay K, Le Q, Turnage J, Gupton F, et al. Continuous Manufacturing of Active Pharmaceutical Ingredients: Current Trends and Perspectives. Adv Synth Catal. 2024 Feb 19;366(3):357–89. doi:10.1002/adsc.202301137
10. Pandit B, Saha P. Eco-friendly alternatives to conventional solvents: Innovations and applications in pharmaceutical

manufacturing. Sustainable Chemistry for Climate Action. 2025 Dec;7:100140. doi:10.1016/j.scca.2025.100140

11. Wiles C, Watts P. Continuous Flow Reactors, a Tool for the Modern Synthetic Chemist. European J Org Chem. 2008 Apr 12;2008(10):1655–71. doi:10.1002/ejoc.200701041
12. Fitzpatrick DE, Battilocchio C, Ley S V. Enabling Technologies for the Future of Chemical Synthesis. ACS Cent Sci. 2016 Mar 23;2(3):131–8. doi:10.1021/acscentsci.6b00015
13. Rathore AS, Kapoor G. Application of process analytical technology for downstream purification of biotherapeutics. Journal of Chemical Technology & Biotechnology. 2015 Feb 30;90(2):228–36. doi:10.1002/jctb.4447
14. Atapalkar RS, Kulkarni AA. Batch and continuous flow mechanochemical synthesis of organic compounds including APIs. React Chem Eng. 2024;9(1):10–25. doi:10.1039/D2RE00521B
15. Plouffe P, Macchi A, Roberge DM. From Batch to Continuous Chemical Synthesis—A Toolbox Approach. Org Process Res Dev. 2014 Nov 21;18(11):1286–94. doi:10.1021/op5001918
16. Demaerel J, Bieliūnas V, De Borggraeve WM. Functionalization of Heteroarenes Under Continuous Flow. In. 2018. p. 237–317. doi:10.1007/7081_2018_22
17. Hone CA, Kappe CO. Towards the Standardization of Flow Chemistry Protocols for Organic Reactions. Chemistry–Methods. 2021 Nov 13;1(11):454–67. doi:10.1002/cmtd.202100059
18. Yang J, Lu C, Stasny B, Henley J, Guinto W, Gonzalez C, et al. Fed-batch bioreactor process scale-up from 3-L to 2,500-L scale for monoclonal antibody production from cell culture. Biotechnol Bioeng. 2007 Sep 9;98(1):141–54. doi:10.1002/bit.21413
19. Royer J, Bonin M, Micouin L. Chiral Heterocycles by Iminium Ion Cyclization. Chem Rev. 2004 May 1;104(5):2311–52. doi:10.1021/cr020083x
20. Gill KK, Gibson R, Yiu KHC, Hester P, Reis NM. Microcapillary film reactor outperforms single-bore mesocapillary reactors in continuous flow chemical reactions. Chemical Engineering Journal. 2021 Mar;408:127860. doi:10.1016/j.cej.2020.127860
21. Gutmann B, Cantillo D, Kappe CO. Continuous-Flow Technology—A Tool for the Safe Manufacturing of Active Pharmaceutical Ingredients. Angewandte Chemie International Edition. 2015 Jun 18;54(23):6688–728. doi:10.1002/anie.201409318
22. Raby-Buck SE, Devlin J, Gupta P, Battilocchio C, Baumann M, Polyzos A, et al. Continuous flow chemistry for molecular synthesis. Nature Reviews Methods Primers. 2025 Jul 17;5(1):44. doi:10.1038/s43586-025-00414-x
23. Alemie AA, Siraj EA, Yayehrad AT, Tafere C, Tessema TA, Belete A. Continuous pharmaceutical manufacturing and its contemporary regulatory insights. Discover Applied Sciences. 2025 Sep 26;7(10):1057. doi:10.1007/s42452-025-07712-9
24. Price GA, Mallik D, Organ MG. Process Analytical Tools for Flow Analysis: A Perspective. J Flow Chem. 2017 Jul 30;7(3–4):82–6. doi:10.1556/1846.2017.00032
25. Adak S. Advances in the Synthesis and Optimization of Pharmaceutical APIs: Trends and Techniques. Universal Journal of Pharmacy and Pharmacology. 2025 Jan 9;4(1):1–6. doi:10.31586/ujpp.2025.1239
26. Noël T, Su Y, Hessel V. Beyond Organometallic Flow Chemistry: The Principles Behind the Use of Continuous-Flow Reactors for Synthesis. In. 2015. p. 1–41. doi:10.1007/3418_2015_152
27. Bojang AA, Wu HS. Design, Fundamental Principles of Fabrication and Applications of Microreactors. Processes. 2020 Jul 25;8(8):891. doi:10.3390/pr8080891

28. Le TNQ, Tran QD, Tran NN, Priest C, Skinner W, Goodsite M, et al. Critical elements: opportunities for microfluidic processing and potential for ESG-powered mining investments. Green Chemistry. 2022;24(23):8879–98. doi:10.1039/D2GC02214A
29. Bobers J, Grühn J, Höving S, Pyka T, Kockmann N. Two-Phase Flow in a Coiled Flow Inverter: Process Development from Batch to Continuous Flow. Org Process Res Dev. 2020 Oct 16;24(10):2094–104. doi:10.1021/acs.oprd.0c00152
30. Monge F, Aranda V, Millera A, Bilbao R, Alzueta MU. Tubular Flow Reactors. In. 2013. p. 211–30. doi:10.1007/978-1-4471-5307-8_9
31. Hatridge TA, Liu W, Yoo C, Davies HML, Jones CW. Optimized Immobilization Strategy for Dirhodium(II) Carboxylate Catalysts for C−H Functionalization and Their Implementation in a Packed Bed Flow Reactor. Angewandte Chemie International Edition. 2020 Oct 26;59(44):19525–31. doi:10.1002/anie.202005381
32. Wright SF, Zadrazil I, Markides CN. A review of solid–fluid selection options for optical-based measurements in single-phase liquid, two-phase liquid–liquid and multiphase solid–liquid flows. Exp Fluids. 2017 Sep 2;58(9):108. doi:10.1007/s00348-017-2386-y
33. Murray PRD, Browne DL, Pastre JC, Butters C, Guthrie D, Ley S V. Continuous Flow-Processing of Organometallic Reagents Using an Advanced Peristaltic Pumping System and the Telescoped Flow Synthesis of (*E/Z*)-Tamoxifen. Org Process Res Dev. 2013 Sep 20;17(9):1192–208. doi:10.1021/op4001548
34. Capaldo L, Wen Z, Noël T. A field guide to flow chemistry for synthetic organic chemists. Chem Sci. 2023;14(16):4230–47. doi:10.1039/D3SC00992K
35. Cravotto G. Reshaping Chemical Manufacturing Towards Green Process Intensification: Recent Findings and Perspectives. Processes. 2025 Feb 8;13(2):459. doi:10.3390/pr13020459
36. Green Chemistry: Principles, Applications, and Disadvantages. Chemical Methodologies. 2020 Jun 1;4(4):408–23. doi:10.33945/SAMI/CHEMM.2020.4.4
37. Ivanković A. Review of 12 Principles of Green Chemistry in Practice. International Journal of Sustainable and Green Energy. 2017;6(3):39. doi:10.11648/j.ijrse.20170603.12
38. DeVierno Kreuder A, House-Knight T, Whitford J, Ponnusamy E, Miller P, Jesse N, et al. A Method for Assessing Greener Alternatives between Chemical Products Following the 12 Principles of Green Chemistry. ACS Sustain Chem Eng. 2017 Apr 3;5(4):2927–35. doi:10.1021/acssuschemeng.6b02399
39. Sheldon RA. The E factor 25 years on: the rise of green chemistry and sustainability. Green Chemistry. 2017;19(1):18–43. doi:10.1039/C6GC02157C
40. Hu C, Testa CJ, Born SC, Wu W, Shvedova K, Sayin R, et al. E-factor analysis of a pilot plant for end-to-end integrated continuous manufacturing (ICM) of pharmaceuticals. Green Chemistry. 2020;22(13):4350–6. doi:10.1039/D0GC01397H
41. Zhang P, Weeranoppanant N, Thomas DA, Tahara K, Stelzer T, Russell MG, et al. Advanced Continuous Flow Platform for On-Demand Pharmaceutical Manufacturing. Chemistry – A European Journal. 2018 Feb 21;24(11):2776–84. doi:10.1002/chem.201706004
42. Chakravarty P, Famili A, Nagapudi K, Al-Sayah MA. Using Supercritical Fluid Technology as a Green Alternative During the Preparation of Drug Delivery Systems. Pharmaceutics. 2019 Nov 25;11(12):629. doi:10.3390/pharmaceutics11120629
43. Gawande MB, Bonifácio VDB, Luque R, Branco PS, Varma RS. Solvent-Free and Catalysts-Free Chemistry: A Benign Pathway to Sustainability. ChemSusChem.

2014 Jan 4;7(1):24–44. doi:10.1002/cssc.201300485

44. Voros V, Drioli E, Fonte C, Szekely G. Process Intensification via Continuous and Simultaneous Isolation of Antioxidants: An Upcycling Approach for Olive Leaf Waste. ACS Sustain Chem Eng. 2019 Nov 18;7(22):18444–52. doi:10.1021/acssuschemeng.9b04245
45. García-Lacuna J, Baumann M. Inline purification in continuous flow synthesis – opportunities and challenges. Beilstein Journal of Organic Chemistry. 2022 Dec 16;18:1720–40. doi:10.3762/bjoc.18.182
46. Galle M, Agar DW, Watzenberger O. Thermal N2O decomposition in regenerative heat exchanger reactors. Chem Eng Sci. 2001 Feb;56(4):1587–95. doi:10.1016/S0009-2509(00)00386-9
47. Mulholland KL, Dyer JA. Process analysis via waste minimization: Using DuPont's methodology to identify process improvement opportunities. Environmental Progress. 2001 Jul 20;20(2):75–9. doi:10.1002/ep.670200209
48. Cespi D, Beach ES, Swarr TE, Passarini F, Vassura I, Dunn PJ, et al. Life cycle inventory improvement in the pharmaceutical sector: assessment of the sustainability combining PMI and LCA tools. Green Chemistry. 2015;17(6):3390–400. doi:10.1039/C5GC00424A
49. Kressirer S, Protasova LN, de Croon MHJM, Hessel V, Kralisch D. Removal and renewal of catalytic coatings from lab- and pilot-scale microreactors, accompanied by life cycle assessment and cost analysis. Green Chemistry. 2012;14(11):3034. doi:10.1039/c2gc35803d
50. Hessel V. Novel Process Windows – Gate to Maximizing Process Intensification via Flow Chemistry. Chem Eng Technol. 2009 Nov 29;32(11):1655–81. doi:10.1002/ceat.200900474
51. Taylor RD, MacCoss M, Lawson ADG. Rings in Drugs. J Med Chem. 2014 Jul 24;57(14):5845–59. doi:10.1021/jm4017625
52. Lavanya G, Abdul Khadar Iynoon Jariya S bee, Sasikala M, Kalpana V, Padmanaban A, Wang J, et al. Recent Advances in the Synthesis of Dihydropyridine and Their Corresponding Fused Systems via Multi-Component Hantzsch Reaction Using Catalytic Nanomaterials. ChemistrySelect. 2024 Nov 11;9(43). doi:10.1002/slct.202403664
53. Frecentese F, Sodano F, Corvino A, Schiano ME, Magli E, Albrizio S, et al. The Application of Microwaves, Ultrasounds, and Their Combination in the Synthesis of Nitrogen-Containing Bicyclic Heterocycles. Int J Mol Sci. 2023 Jun 27;24(13):10722. doi:10.3390/ijms241310722
54. de Souza MVN, da Costa CF, Facchinetti V, Gomes CRB, Pacheco PM. Advances in Triazole Synthesis from Copper-catalyzed Azide-alkyne Cycloadditions (CuAAC) Based on Eco-friendly Procedures. Curr Org Synth. 2019 Mar 26;16(2):244–57. doi:10.2174/1570179416666190104141454
55. Plutschack MB, Pieber B, Gilmore K, Seeberger PH. The Hitchhiker's Guide to Flow Chemistry. Chem Rev. 2017 Sep 27;117(18):11796–893. doi:10.1021/acs.chemrev.7b00183
56. Patel M, Bambharoliya T, Shah D, Patel K, Patel M, Shah U, et al. Emerging green synthetic routes for thiazole and its derivatives: Current perspectives. Arch Pharm (Weinheim). 2024 Feb 27;357(2). doi:10.1002/ardp.202300420
57. Baumann M, Baxendale IR. A continuous flow synthesis and derivatization of 1,2,4-thiadiazoles. Bioorg Med Chem. 2017 Dec;25(23):6218–23. doi:10.1016/j.bmc.2017.01.022
58. da Silva FM, Junior JJ, Hernández Muñoz JA. The Chemistry of Aldehydes and Ketones in the Synthesis of Heterocycles - Historical Reactions with a New and Green Perspective. Curr Org Chem. 2024 Jul;28(13):1023–45.

doi:10.2174/0113852728295534240223044735

59. Bosch C, López-Lledó P, Bonjoch J, Bradshaw B, Nieuwland PJ, Blanco-Ania D, et al. Fischer Indole Reaction in Batch and Flow Employing a Sulfonic Acid Resin: Synthesis of Pyrido[2,3-a]carbazoles. J Flow Chem. 2016 Jul 1;6(3):240–3. doi:10.1556/1846.2016.00016
60. Farhid H, Khodkari V, Nazeri MT, Javanbakht S, Shaabani A. Multicomponent reactions as a potent tool for the synthesis of benzodiazepines. Org Biomol Chem. 2021;19(15):3318–58. doi:10.1039/D0OB02600J
61. Borukhova S, Noël T, Metten B, de Vos E, Hessel V. From alcohol to 1,2,3-triazole via a multi-step continuous-flow synthesis of a rufinamide precursor. Green Chemistry. 2016;18(18):4947–53. doi:10.1039/C6GC01133K
62. Correia CA, Gilmore K, McQuade DT, Seeberger PH. A Concise Flow Synthesis of Efavirenz. Angewandte Chemie International Edition. 2015 Apr 13;54(16):4945–8. doi:10.1002/anie.201411728
63. Di Filippo M, Baumann M. Continuous Flow Synthesis of Anticancer Drugs. Molecules. 2021 Nov 19;26(22):6992. doi:10.3390/molecules26226992
64. Baumann M, Moody TS, Smyth M, Wharry S. A Perspective on Continuous Flow Chemistry in the Pharmaceutical Industry. Org Process Res Dev. 2020 Oct 16;24(10):1802–13. doi:10.1021/acs.oprd.9b00524
65. Talicska CN, O'Connell EC, Ward HW, Diaz AR, Hardink MA, Foley DA, et al. Process analytical technology (PAT): applications to flow processes for active pharmaceutical ingredient (API) development. React Chem Eng. 2022;7(6):1419–28. doi:10.1039/D2RE00004K
66. Zhang Y, Su WK. A Review of Inline Infrared and Nuclear Magnetic Resonance Applications in Flow Chemistry. Pharmaceutical Fronts. 2023 Dec 1;05(04):e209–18. doi:10.1055/s-0043-1776906
67. Browne DL, Wright S, Deadman BJ, Dunnage S, Baxendale IR, Turner RM, et al. Continuous flow reaction monitoring using an on-line miniature mass spectrometer. Rapid Communications in Mass Spectrometry. 2012 Sep 15;26(17):1999–2010. doi:10.1002/rcm.6312
68. Kitson PJ, Marie G, Francoia JP, Zalesskiy SS, Sigerson RC, Mathieson JS, et al. Digitization of multistep organic synthesis in reactionware for on-demand pharmaceuticals. Science (1979). 2018 Jan 19;359(6373):314–9. doi:10.1126/science.aao3466
69. Maier MC, Valotta A, Hiebler K, Soritz S, Gavric K, Grabner B, et al. 3D Printed Reactors for Synthesis of Active Pharmaceutical Ingredients in Continuous Flow. Org Process Res Dev. 2020 Oct 16;24(10):2197–207. doi:10.1021/acs.oprd.0c00228
70. Kappe CO. Controlled Microwave Heating in Modern Organic Synthesis. Angewandte Chemie International Edition. 2004 Nov 26;43(46):6250–84. doi:10.1002/anie.200400655
71. Lange PP, James K. Rapid Access to Compound Libraries through Flow Technology: Fully Automated Synthesis of a 3-Aminoindolizine Library via Orthogonal Diversification. ACS Comb Sci. 2012 Oct 8;14(10):570–8. doi:10.1021/co300094n
72. He C, Zhang C, Bian T, Jiao K, Su W, Wu KJ, et al. A Review on Artificial Intelligence Enabled Design, Synthesis, and Process Optimization of Chemical Products for Industry 4.0. Processes. 2023 Jan 19;11(2):330. doi:10.3390/pr11020330
73. Liu C, Chen Y, Mo F. Transforming organic chemistry research paradigms: moving from manual efforts to the intersection of automation and artificial intelligence

[Internet]. 2023 Nov 26. Available from: http://arxiv.org/abs/2312.00808
74. Leadbeater NE. Flow Chemistry as an Enabling Technology for Synthetic Organic Chemistry. In. 2022. p. 489–526. doi:10.1007/978-1-0716-1579-9_14
75. Casasanta G, Falcini F, Garra R. Beer–Lambert law in photochemistry: A new approach. J Photochem Photobiol A Chem. 2022 Nov;432:114086. doi:10.1016/j.jphotochem.2022.114086
76. Mizuno K, Nishiyama Y, Ogaki T, Terao K, Ikeda H, Kakiuchi K. Utilization of microflow reactors to carry out synthetically useful organic photochemical reactions. Journal of Photochemistry and Photobiology C: Photochemistry Reviews. 2016 Dec;29:107–47. doi:10.1016/j.jphotochemrev.2016.10.002
77. Holmberg-Douglas N, Nicewicz DA. Photoredox-Catalyzed C–H Functionalization Reactions. Chem Rev. 2022 Jan 26;122(2):1925–2016. doi:10.1021/acs.chemrev.1c00311
78. Botte GG. Electrochemical Manufacturing in the Chemical Industry. Interface magazine. 2014 Jan 1;23(3):49–55. doi:10.1149/2.F04143if
79. Klement WJN, Savino E, Rooijmans S, Mulder PPMFA, Lynn NS, Browne WR, et al. Electrochemical Flow Reactors: Mass Transport, iR Drop, and Membrane-Free Performance with In-Line Analysis. ACS Electrochemistry. 2025 Apr 3;1(4):504–15. doi:10.1021/acselectrochem.4c00167
80. Akhter M, Alam MM. Catalysis. In: Physical Pharmacy and Instrumental Methods of Analysis. Cham: Springer Nature Switzerland; 2023. p. 97–107. doi:10.1007/978-3-031-36777-9_7
81. Cole-Hamilton DJ, Tooze RP. Homogeneous Catalysis — Advantages and Problems. In. 2006. p. 1–8. doi:10.1007/1-4020-4087-3_1
82. Peña LF, Parte LG, Díez-Poza C, Guerra J, López E. Homogeneous catalysis in continuous flow integrating photocatalysis, electrocatalysis, and automation technologies. Commun Chem. 2025 Nov 7;8(1):336. doi:10.1038/s42004-025-01725-6
83. Srinivasan B, Palanki S, Bonvin D. Dynamic optimization of batch processes. Comput Chem Eng. 2003 Jan;27(1):1–26. doi:10.1016/S0098-1354(02)00116-3
84. Zhang C, Luo J, Xie B, Liu W, Zhang J. Green and continuous aerobic oxidation of ethylbenzene over homogeneous and heterogeneous NHPI in a micro-packed bed reactor. Chemical Engineering Journal. 2023 Jul;468:143674. doi:10.1016/j.cej.2023.143674
85. McMorn P, Hutchings GJ. Heterogeneous enantioselective catalysts: strategies for the immobilisation of homogeneous catalysts. Chem Soc Rev. 2004;33(2):108. doi:10.1039/b200387m
86. Afandizadeh S, Foumeny EA. Design of packed bed reactors: guides to catalyst shape, size, and loading selection. Appl Therm Eng. 2001 Apr;21(6):669–82. doi:10.1016/S1359-4311(00)00072-7
87. Han FS. Transition-metal-catalyzed Suzuki–Miyaura cross-coupling reactions: a remarkable advance from palladium to nickel catalysts. Chem Soc Rev. 2013;42(12):5270. doi:10.1039/c3cs35521g
88. Takale BS, Kong FY, Thakore RR. Recent Applications of Pd-Catalyzed Suzuki–Miyaura and Buchwald–Hartwig Couplings in Pharmaceutical Process Chemistry. Organics. 2022 Jan 18;3(1):1–21. doi:10.3390/org3010001
89. Britton J, Majumdar S, Weiss GA. Continuous flow biocatalysis. Chem Soc Rev. 2018;47(15):5891–918. doi:10.1039/C7CS00906B
90. Sheldon RA. Cross-linked enzyme aggregates (CLEA®s): stable and recyclable biocatalysts. Biochem Soc Trans. 2007 Dec 1;35(6):1583–7. doi:10.1042/BST0351583
91. Wang M, Qi W, Su R, He Z. Advances in carrier-bound and carrier-free immobilized

nanobiocatalysts. Chem Eng Sci. 2015 Oct;135:21–32. doi:10.1016/j.ces.2015.03.051

92. Liu W, Wang P. Cofactor regeneration for sustainable enzymatic biosynthesis. Biotechnol Adv. 2007 Jul;25(4):369–84. doi:10.1016/j.biotechadv.2007.03.002
93. Losada-Garcia N, Cabrera Z, Urrutia P, Garcia-Sanz C, Andreu A, Palomo JM. Recent Advances in Enzymatic and Chemoenzymatic Cascade Processes. Catalysts. 2020 Oct 30;10(11):1258. doi:10.3390/catal10111258
94. Patel RN. Pharmaceutical Intermediates by Biocatalysis: From Fundamental Science to Industrial Applications. In: Applied Biocatalysis: From Fundamental Science to Industrial Applications. Wiley; 2016. p. 367–403. doi:10.1002/9783527677122.ch16
95. Butters M, Catterick D, Craig A, Curzons A, Dale D, Gillmore A, et al. Critical Assessment of Pharmaceutical ProcessesA Rationale for Changing the Synthetic Route. Chem Rev. 2006 Jul 1;106(7):3002–27. doi:10.1021/cr050982w
96. Lévesque F, Rogus NJ, Spencer G, Grigorov P, McMullen JP, Thaisrivongs DA, et al. Advancing Flow Chemistry Portability: A Simplified Approach to Scaling Up Flow Chemistry. Org Process Res Dev. 2018 Aug 17;22(8):1015–21. doi:10.1021/acs.oprd.8b00063
97. Hurley S, Tantuccio A, Escotet-Espinoza MS, Flamm M, Metzger M. Development and Use of a Residence Time Distribution (RTD) Model Control Strategy for a Continuous Manufacturing Drug Product Pharmaceutical Process. Pharmaceutics. 2022 Feb 3;14(2):355. doi:10.3390/pharmaceutics14020355
98. Schmidt A, Hengelbrock A, Strube J. Continuous biomanufacturing in upstream and downstream processing. Physical Sciences Reviews. 2024 Oct 29;9(10):3167–222. doi:10.1515/psr-2022-0106
99. White LS. Development of large-scale applications in organic solvent nanofiltration and pervaporation for chemical and refining processes. J Memb Sci. 2006 Dec;286(1–2):26–35. doi:10.1016/j.memsci.2006.09.006
100. Hosaka S, Obuki M, Nakajima J, Suzuki M. Comparative study of antioxidants as quenchers or scavengers of reactive oxygen species based on quenching of MCLA-dependent chemiluminescence. Luminescence. 2005 Nov 20;20(6):419–27. doi:10.1002/bio.867
101. Lu J, Rohani S. Polymorphism and Crystallization of Active Pharmaceutical Ingredients (APIs). Curr Med Chem. 2009 Mar 1;16(7):884–905. doi:10.2174/092986709787549299
102. Orehek J, Teslić D, Likozar B. Continuous Crystallization Processes in Pharmaceutical Manufacturing: A Review. Org Process Res Dev. 2021 Jan 15;25(1):16–42. doi:10.1021/acs.oprd.0c00398
103. O'Brien AG, Horváth Z, Lévesque F, Lee JW, Seidel-Morgenstern A, Seeberger PH. Continuous Synthesis and Purification by Direct Coupling of a Flow Reactor with Simulated Moving-Bed Chromatography. Angewandte Chemie International Edition. 2012 Jul 9;51(28):7028–30. doi:10.1002/anie.201202795
104. Di Filippo M, Baumann M. Continuous Flow Synthesis of Anticancer Drugs. Molecules. 2021 Nov 19;26(22):6992. doi:10.3390/molecules26226992
105. Rogers L, Jensen KF. Continuous manufacturing – the Green Chemistry promise? Green Chemistry. 2019;21(13):3481–98. doi:10.1039/C9GC00773C
106. Adak S. Advances in the Synthesis and Optimization of Pharmaceutical APIs: Trends and Techniques. Universal Journal of Pharmacy and Pharmacology. 2025 Jan 9;4(1):1–6. doi:10.31586/ujpp.2025.1239
107. Alemie AA, Siraj EA, Yayehrad AT, Tafere C, Tessema TA, Belete A. Continuous

pharmaceutical manufacturing and its contemporary regulatory insights. Discover Applied Sciences. 2025 Sep 26;7(10):1057. doi:10.1007/s42452-025-07712-9

108. Mendoza Suarez F, Tatarchuk B. Comparative economic analysis of batch vs. continuous manufacturing in catalytic heterogeneous processes: impact of catalyst activity maintenance and materials costs on total costs of manufacturing in the production of fine chemicals and pharmaceuticals. J Flow Chem. 2025 Mar 13;15(1):21–38. doi:10.1007/s41981-024-00342-z
109. Mendoza Suarez F, Tatarchuk B. Comparative economic analysis of batch vs. continuous manufacturing in catalytic heterogeneous processes: impact of catalyst activity maintenance and materials costs on total costs of manufacturing in the production of fine chemicals and pharmaceuticals. J Flow Chem. 2025 Mar 13;15(1):21–38. doi:10.1007/s41981-024-00342-z
110. Yang S, Hu X, Zhu J, Zheng B, Bi W, Wang X, et al. Aspects and Implementation of Pharmaceutical Quality by Design from Conceptual Frameworks to Industrial Applications. Pharmaceutics. 2025 May 8;17(5):623. doi:10.3390/pharmaceutics17050623
111. Kanďárová H, Pôbiš P. The “Big Three” in biocompatibility testing of medical devices: implementation of alternatives to animal experimentation—are we there yet? Frontiers in Toxicology. 2024 Jan 8;5. doi:10.3389/ftox.2023.1337468
112. K. Kashani S, Sullivan RJ, Andersen M, Newman SG. Overcoming solid handling issues in continuous flow substitution reactions through ionic liquid formation. Green Chemistry. 2018;20(8):1748–53. doi:10.1039/C8GC00618K
113. Banakar VV, Sabnis SS, Gogate PR, Raha A, Saurabh. Ultrasound assisted continuous processing in microreactors with focus on crystallization and chemical synthesis: A critical review. Chemical Engineering Research and Design. 2022 Jun;182:273–89. doi:10.1016/j.cherd.2022.03.049
114. Mata A, de Fraipont C, Hervieux C, Giacchetti L, Hadj-Sassi O, Bogicevic A, et al. Nonclogging Liquid-Walled Continuous Flow Reactors. Org Process Res Dev. 2025 Feb 21;29(2):472–8. doi:10.1021/acs.oprd.4c00459
115. Li H, Guo H, Fang Z, Aida TM, Smith RL. Cycloamination strategies for renewable N-heterocycles. Green Chemistry. 2020;22(3):582–611. doi:10.1039/C9GC03655E
116. Nagy KD, Shen B, Jamison TF, Jensen KF. Mixing and Dispersion in Small-Scale Flow Systems. Org Process Res Dev. 2012 May 18;16(5):976–81. doi:10.1021/op200349f
117. Sádaba I, López Granados M, Riisager A, Taarning E. Deactivation of solid catalysts in liquid media: the case of leaching of active sites in biomass conversion reactions. Green Chemistry. 2015;17(8):4133–45. doi:10.1039/C5GC00804B
118. Hyer A, Gregory D, Kay K, Le Q, Turnage J, Gupton F, et al. Continuous Manufacturing of Active Pharmaceutical Ingredients: Current Trends and Perspectives. Adv Synth Catal. 2024 Feb 19;366(3):357–89. doi:10.1002/adsc.202301137
119. Rodriguez GYG, Díaz CMG, Dahiya S. Personalized medicine: perspectives on innovations and challenges in 3D printing, continuous manufacturing and on-demand production. Discover Pharmaceutical Sciences. 2025 Jul 10;1(1):10. doi:10.1007/s44395-025-00011-7