Chemical Synthesis in Flow Systems: Modern Approaches in the Pharmaceutical Industry

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Review
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Abstract

Chemical synthesis in flow systems has emerged as one of the most transformative approaches in modern pharmaceutical manufacturing, offering a shift from traditional batch processing toward safer, more efficient, and sustainable production. This article provides a comprehensive overview of recent advances in continuous-flow systems, with particular emphasis on their practical implementation in the synthesis of active pharmaceutical ingredients (APIs) and key intermediates. The fundamental principles of chemical synthesis in flow systems are outlined, highlighting precise control over reaction conditions, improved reproducibility, and enhanced safety, especially for hazardous or highly exothermic reactions. The role of micro- and millireactors is discussed in the context of process intensification, enabling superior heat and mass transfer compared to conventional systems. Special attention is given to multiphase reactions, where flow-based systems significantly improve phase contact and mass transfer, thereby enabling reaction pathways that are difficult or unsafe in batch processes. Selected industrial case studies illustrate how these systems can overcome scale-up challenges, reduce production time, and increase process robustness. In addition, the integration of mathematical modelling and real-time analytical tools is examined as a key factor in optimising reactor design and accelerating process development. Finally, the contribution of these approaches to green chemistry is evaluated, including reduced waste generation, improved energy efficiency, and the potential use of environmentally friendly solvents such as natural deep eutectic solvents (NADES).

Overall, this review demonstrates that chemical synthesis in flow systems is not only an alternative but an enabling technology shaping the future of chemical synthesis in the pharmaceutical industry.

Keywords

Chemical synthesis in flow systems, continuous manufacturing, pharmaceutical industry, microreactors, process intensification, green chemistry, NADES

1 Introduction

The pharmaceutical industry is undergoing significant changes in the manufacturing of drug substances and drug products, driven by the need for safer, more efficient, and environmentally sustainable processes.[1] Among the most transformative advancements is continuous manufacturing, which replaces traditional batch production with faster, more cost-effective, and flexible continuous systems.[2] The importance of implementing continuous manufacturing in the pharmaceutical sector was highlighted by the American Chemical Society (ACS) Green Chemistry Institute (GCI) Pharmaceutical Roundtable, established in 2005 in collaboration with several leading pharmaceutical companies. The Roundtable identified continuous processing and process intensification to be among the ten most critical green engineering research areas to promote long-term sustainability in pharmaceutical development.[3]

Significant focus has been placed on flow chemistry methodologies for the preparation of active pharmaceutical ingredients (APIs), leading to a growing number of organic synthesis reactions being performed in flow reactors.[4] Flow chemistry enables precise control over key reaction parameters such as temperature, pressure, and residence time which results in improved product quality, reproducibility, and safety, particularly for hazardous or exothermic transformations.[2] As the technology matures, its integration into pharmaceutical R&D and production is expanding with numerous case studies showcasing its practical benefits from companies like GlaxoSmithKline and Novartis.[5,6]

In this review paper, the current state-of-the-art in flow chemistry within the pharmaceutical sector will be explored with emphasis on continuous micro- and milli-reactors and a focus on several additional key themes. These include phase transfer in multiphase flow systems, process intensification, and the role of mathematical modelling and simulation as an

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essential tool for reactor design and optimisation. Finally, the contribution of flow systems to green chemistry and the potential use of green solvents is discussed.

2 Flow chemistry: Principles and advantages

Flow chemistry refers to the process of conducting chemical reactions in a continuously flowing stream through channels or tubing. This technique is very flexible and offers a set of components that can be configured and adapted to suit a wide variety of processes. A typical continuous-flow setup for synthetic applications consists of several basic components arranged in sequence: fluid and reagent delivery, mixing, reactor, quenching, pressure regulation, product collection, analysis, and purification (Fig. 1).

Initially, a precise fluid and reagent delivery system (typically a pump) introduces the reactants into the flow system. These streams are then combined using specialised mixing devices before entering the reactor unit where the chemical reaction takes place. One of the fundamental distinctions between batch and continuous systems lies in how reactant concentration changes over time and space. In batch reactions, the concentration of reactants decreases throughout the reactor volume over time. In a continuous-flow reactor, the concentration of the starting material decreases gradually along the length of the reactor. Under ideal plug-flow conditions, the concentration at any point along the reactor corresponds to a steady-state position and is determined by the residence time as a key parameter in continuous-flow systems. Residence time, defined as the time between the entry and exit of a substance from the reactor, depends on the flow rate and reactor volume. Additionally, the downstream quenching module can provide precise control over the overall reaction time by rapidly stopping the reaction upon leaving the reactor.

Flow systems also allow straightforward operation under elevated pressures, which can be achieved using pressure regulators typically placed before the collection module. Analytical tools and inline purification units can be integrated directly into the system, enabling real-time monitoring and product refinement. The modular nature of flow chemistry allows each component to be arranged, repeated, or replaced, resulting in an unlimited number of configurations tailored to specific reaction requirements. Interchangeability and connectivity of components are simplified by standardised connections, which typically involve chemically resistant tubing and fittings such as nuts and ferrules. The material and dimensions of the tubing are critically important. Systems operating at pressures up to 30 bar commonly use chemically resistant polymers such as polytetrafluoroethylene (PTFE), perfluoroalkoxy alkane (PFA), polyether ether ketone (PEEK), or fluorinated ethylene propylene (FEP). In contrast, high-pressure operations such as reactions conducted far above the solvent's boiling point require robust materials like stainless steel or high-performance alloys.

This high level of control over reaction parameters such as time, temperature, pressure, and stoichiometry in flow chemistry offers enhanced safety, particularly for exothermic reactions or those involving hazardous compounds. It also enables greater reproducibility and scalability, which are essential for industrial production while offering the potential to perform reactions not feasible in batch processes, such as ultrafast lithiations and photochemical processes.[7]

Moreover, flow chemistry has proven particularly beneficial for biphasic systems, such as gas-liquid and liquid-liquid reactions. In these systems, flow reactors and mass-flow controllers enable precise dosing and enhanced phase contact, leading to improved efficiency. Furthermore, photochemical transformations have seen renewed interest due to the compatibility of flow reactors with light-driven processes, facilitated by short path lengths and uniform irradiation.[8]

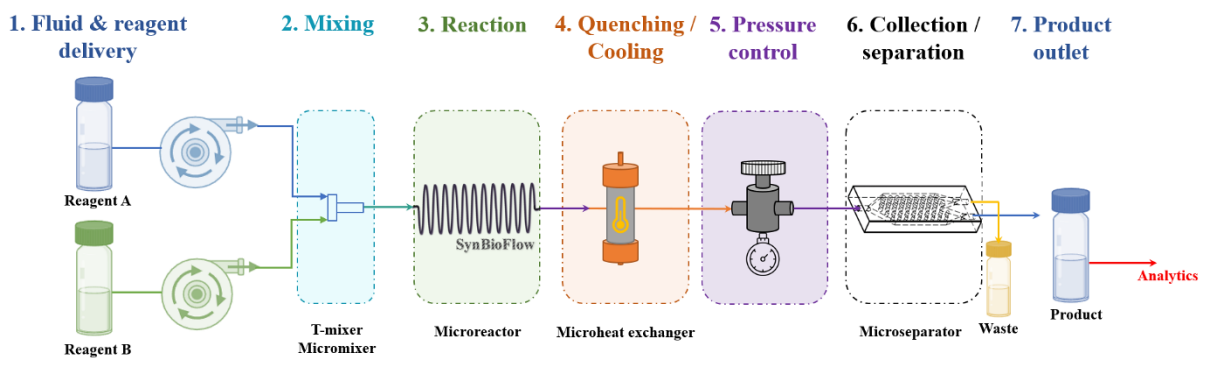


Fig. 1 – Basic parts of a standard continuous-flow setup with two inlets (inspired by [7])

Slika 1 – Osnovni dijelovi standardnog protočnog sustava s dva ulaza (inspirirano s [7])

Advances in automation and process analytics are also driving the development of self-optimising flow systems, where inline or online analytical feedback enables real-time optimisation of reaction conditions. These platforms not only accelerate reaction development but also provide valuable kinetic and mechanistic insights.

Despite their many advantages, continuous technologies still face several practical challenges that currently limit their broader application. One of the most critical issues in such systems is clogging, which can arise from particle accumulation, product crystallisation, equipment corrosion, or fouling during chemical reactions. Furthermore, the reliable delivery of solids into any flow system is particularly problematic, as it not only increases the risk of clogging but also requires complex dosing equipment. Consequently, solid-handling reactions are still often avoided in continuous-flow setups and represent an important area for further research. In addition, the design of flow systems introduces the possibility of leakage at connection points, requiring careful attention to fittings and seals to ensure process reliability.

Taken together, these advances demonstrate that flow chemistry is revolutionising chemical synthesis by providing advanced control, scalability, and versatility, making it a powerful tool in both academic and industrial pharmaceutical research. Nevertheless, several practical challenges remain, highlighting the need for continued engineering innovations to broaden the range of reactions that can be successfully transferred to continuous-flow systems.[7]

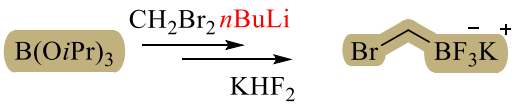
3 Applications in the pharmaceutical industry

In recent years, major regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have recognised the need for innovation in drug manufacturing, and have begun promoting continuous processing technologies because of their potential to improve product quality, process control, and manufacturing efficiency. These agencies encourage the adoption of advanced technologies, such as continuous-flow processing, to support modern pharmaceutical production. However, regulatory approval requires a thorough understanding of the manufacturing process and evidence that product quality remains consistent throughout production. Encouraging pharmaceutical companies to develop and implement such technologies forms part of a broader initiative to promote safer, more efficient, and environmentally sustainable production. In line with these efforts, the adoption of flow chemistry in pharmaceutical research, development, and manufacturing is steadily increasing. By offering greater process control, improved efficiency, and alignment with green chemistry principles, flow chemistry supports long-term sustainability and has shown clear practical advantages in numerous case studies.[2]

3.1 Flow synthesis of a Suzuki-Miyaura coupling intermediate

An excellent example of a safer and more efficient production using flow chemistry to overcome the challenges associated with the Suzuki-Miyaura coupling was reported by *Broom et al*.[5] at GlaxoSmithKline. The Suzuki-Miyaura coupling is a well-established method for forming carbon-carbon bonds. It has been adapted for coupling aryl halides with functionalised methylene groups (*e.g.*, amines, ethers, thioethers) using methylboronates, which are typically derived from potassium bromomethyltrifluoroborate. During the development of a multikilogram synthesis route for a drug candidate at GSK, the team needed to produce this reagent on a substantially larger scale than was commercially available. Although the published synthesis (Scheme 1) yielded good quality material, it presented significant scale-up limitations: the highly exothermic butyllithium step required −78 °C, which is difficult to maintain on a large scale, while the associated solvent requirements became impractical.

To overcome the limitations of batch synthesis, the team developed a continuous-flow process that provided improved heat control, enhanced safety when handling unstable intermediates, and accelerated halogen-metal exchange. This scalable method enabled the production of high-quality potassium bromomethyltrifluoroborate on a scale ranging from grams to kilograms while using significantly fewer resources than the traditional batch route. At the production site, a team of three successfully manufactured approximately 100 kg of the product in under four weeks. This approach demonstrated that using potassium bromomethyltrifluoroborate and its derivatives in multikilogram-scale Suzuki–Miyaura couplings can be both practical and cost-effective when combined with the appropriate process technology.[5]



Scheme 1 – Synthesis of potassium bromomethyltrifluoroborate[5]

Shema 1 – Sinteza kalijeva brom-metiltrifluorborata[5]

3.2 Continuous synthesis of a key benzoaxazole building block

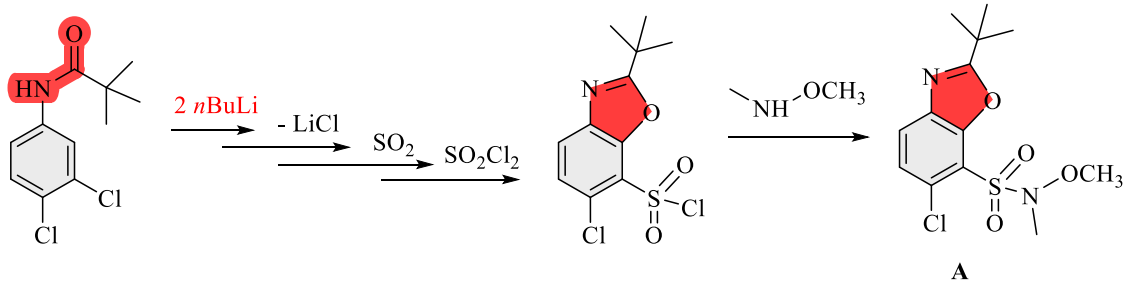
Another interesting case of flow chemistry improving both yield and process robustness was reported by *Susanne et al*.[6] at Novartis Pharma, where flow chemistry was applied to optimise the synthesis of a key benzoxazole intermediate **A** (Scheme 2). This compound was required in the development of a squaramide CXCR2 receptor antagonist for the treatment of chronic obstructive pulmonary disease (COPD). All proposed synthetic routes relied on benzoxazole **A** as a starting material. Owing to both high production costs and an unreliable external supply chain, Novartis initiated in-house process development to improve its synthesis. The target transformation involved a sequence of base-mediated deprotonation, *ortho*-lithiation, and intramolecular cyclisation of 3-halo-*N*-acyl anilines to form unstable lithiated benzoxazoles, which were then trapped with electrophiles (Scheme 2).

Although the method was effective in batch mode, challenges associated with solids formation, heat removal, and by-product formation at cryogenic temperatures made it ideal for continuous-flow processing. Tubular reactors equipped with precooling loops enabled improved control of exothermic reactions and minimised holding times. During process development, Novartis applied kinetic modelling and process analytical technologies (PAT) to identify the critical quality attributes of each step in the synthesis. Batch, semi-batch, and flow reactors were rationally allocated throughout the process, with continuous stirred-tank reactors (CSTRs) selected for low-temperature operations involving solids formation. This hybrid approach enabled a robust and scalable flow synthesis, culminating in a successful mini-plant campaign that delivered 17 kg of benzoxazole **A** with improved yield and product quality. Importantly, the continuous manufacturing approach increased the overall yield from 34 % for the original batch process to approximately 65 %, while also reducing the projected manufacturing costs by about 35 %. This work highlights how continuous-flow processing can enable safer, more reliable, and cost-effective pharmaceutical manufacturing.[6]

3.3 Advanced flow technologies: Photochemical case studies

In addition to conventional flow-based reactions applied in pharmaceutical manufacturing, continuous-flow technology has enabled the implementation of photochemical transformations, providing access to unique reaction pathways under mild and highly controlled conditions using photons as reagents. In batch photochemical systems, light penetration is often poor, resulting in inefficient irradiation and scale-up challenges due to light attenuation within larger reaction volumes. In contrast, the inherent features of flow reactors, particularly micro- and millireactors, including efficient mass and heat transfer, and precise residence-time control, ensure short optical path lengths and uniform irradiation of the reaction mixture. This enables more efficient photon utilisation, improved reaction control, and safer handling of reactive intermediates, making these reactors ideal platforms for implementing photochemical technologies at both laboratory and industrially relevant scales.[8]

A widely cited industrial example of flow photochemistry is the development of a continuous-flow, visible-light-induced benzylic bromination step in the synthesis of the anticancer drug belzutifan (MK-6482). In this case, the implementation of flow photochemistry enabled the replacement of a traditional thermal radical process that relied on hazardous initiators and was prone to side reactions. This approach allowed operation under milder conditions and provided precise control over irradiation and residence time, resulting in improved selectivity and reduced formation of by-products.



Scheme 2 – Synthesis of benzoxazole **A** from *N*-pivaloyl 3,4-dichloro aniline[6]

Shema 2 – Sinteza benzoksazola **A** iz *N*-pivaloil-3,4-dikloranilina[6]

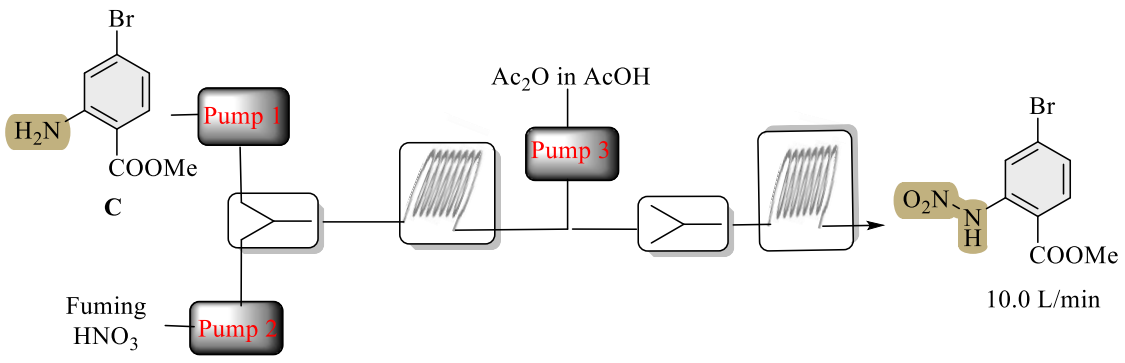
The flow photochemical process was successfully scaled from kilogram to manufacturing scale, converting 50 kg of starting material in 32 h with a productivity of 38 kg day^{-1}. Further reactor numbering-up increased productivity to more than 100 kg day^{-1} while maintaining high assay yields of approximately 93–94 % and low levels of over-bromination impurities. Importantly, the process was successfully translated to larger scale and therefore selected for manufacturing, representing one of the first examples of a photochemical transformation implemented at an industrial level in pharmaceutical production. This case highlights how continuous-flow photochemistry can enable safer, more robust, and scalable processes, which is difficult to achieve under conventional batch conditions.[9]

4 Process intensification

Flow chemistry is often discussed in the context of process intensification, a rapidly growing field that is driving innovation in the chemical industry including the pharmaceutical sector. Process intensification is a well-established concept in chemical engineering aimed at improving efficiency, safety, and sustainability by rethinking conventional processing methods. The concept encompasses innovative reactor and process design strategies that offer benefits such as reduced energy consumption, lower capital and operating costs, improved product quality, and reduced environmental impact. Process intensification has also enabled highly exothermic reactions and processes involving explosive substances or include immiscible reactants to be conducted safely and effectively.[10,11]

The core principles of process intensification include maintaining uniform process conditions, maximising driving forces and specific surface areas, enhancing synergy between unit operations, and optimising time and energy through the application of advanced technologies. These principles have become central to modern reactor design, where compact, integrated systems are replacing traditional large-scale units, simplifying process control and enabling more efficient heat and mass transfer. Equipment designs aligning with process intensification principles include miniaturisation, structured reaction chambers, incorporation of mixing elements and static mixers, and multifunctional reactors.[10,12]

All the key design characteristics supporting process intensification can be embodied in flow chemistry equipment, with continuous micro- and milli-reactors recognised as particularly powerful tools.[13] Flow systems classified as microreactor systems have dimensions between 10–500 μm, while milli-reactors have dimensions ranging from 500 μm up to a few millimetres. Microreactors offer an exceptionally high surface-to-volume ratio due to their small internal diameters, enabling superior mass and heat transfer compared with conventional batch reactors. These enhanced transport phenomena result from the short diffusion distances and efficient heat dissipation inherent to microscale channels. However, the same small channel dimensions that provide these advantages also make microreactors more susceptible to clogging. Even small amounts of precipitated product, suspended particles, or fouling layers may partially or completely block the channels, leading to increased pressure drop and interruption of continuous operation. Thus, the tendency to clog is not contradictory to the enhanced transport performance but rather a direct consequence of reactor miniaturisation. Millireactors have therefore emerged as a practical compromise between process intensification and operational robustness. Their larger channel dimensions reduce the risk of clogging and lower pressure drops while still providing substantially improved heat and mass transfer compared with conventional batch reactors.



Scheme 3 – Nitration of 2-amino-4-bromo-benzoic acid methyl ester **C** under continuous flow[15]

Shema 3 – Nitriranje metilnog estera 2-amino-4-brombenzojeve kiseline **C** u kontinuiranom protoku[15]

Consequently, millireactors are often preferred for reactions involving precipitates, highly viscous media, or multiphase systems where long-term stable operation is required. Additionally, flow-through design of micro- and millireactors allows for accurate process control and straightforward scale-up using a numbering-up strategy and adding multiple identical units in parallel. Furthermore, such continuous systems can be integrated with downstream continuous units, enabling the development of fully continuous and efficient production processes.[14]

Examples of process intensification by implementing milli- and microreactors are numerous and can also be found in API production in pharmaceutical industry. As previously mentioned, milli- and microflow technology offer a safer and more efficient alternative for highly exothermic reactions, such as the nitration reactions, which pose a thermal runaway risk in batch processes. At Novartis, three nitration reactions were successfully scaled up using commercial flow equipment and millireactors within just one to two weeks, including screening. In particular, the nitration of methyl 2-amino-4-bromobenzoate **C** showed poor reproducibility and significant byproduct formation (25–35 %) in batch mode. In contrast, the continuous-flow setup (Scheme 3) enabled precise control over stoichiometry and residence time, eliminating side-products and delivering an 84 % yield at a production rate of 70 g h^{-1} on a 123 g scale.[15]

In another example, a continuous synthesis platform was tested for synthesis of a potent δ-opioid receptor agonist *N,N*-diethyl-4-(3-fluorophenylpiperidin-4-ylidenemethyl) benzamide developed by AstraZeneca. The system combined a series of microreactors with flow-purification modules based on solid-supported reagents and in-line infrared (IR) analysis for real-time monitoring of the final feed stream. This coupling of synthesis, purification, and analytics within a single continuous process highlights the potential of microreactor platforms to streamline pharmaceutical manufacturing.[13]

5 Mass transfer in two-phase systems

Many important chemical reactions involve two or more phases, such as gas–liquid, liquid–liquid, solid–liquid, or even three-phase systems like solid–liquid–gas. As the rate of mass transfer across phase boundaries often limits reaction performance, achieving efficient reactivity in these systems depends greatly on effective phase mixing. As a result, a multiphase reactor design becomes a critical factor in ensuring sufficient mixing and interfacial contact to improve the mass transfer. Enhancing transport processes typically relies on increasing interfacial surface area and minimising diffusion distances.[16]

Micro- and millireactors offer a distinct advantage in this area because their small dimensions lead to a high surface-area-to-volume ratio, enhancing mass transfer rates in multiphase flow systems. This makes them especially useful for intensifying two-phase reactions and overcoming limitations commonly encountered in batch setups.[7,16] The interfacial area within micro- and millireactors, and thus mass transfer efficiency, is strongly influenced by the flow regime, which is determined by factors such as flow rates, fluid viscosities, and the surface properties of the reactor. Therefore, understanding the hydrodynamics within such systems is essential for the successful design of a multiphase reactor.[7,17]

5.1 Gas-liquid systems

As previously mentioned, flow reactors offer significant benefits compared to batch reactors when it comes to safely and efficiently conducting multiphase reactions, especially those involving gases. Reactions with gaseous substrates in batch setups are often limited by low interfacial areas, poor gas diffusion into the reaction media, and safety risks due to gas accumulation in the headspace. These factors restrict the operating conditions, such as pressure and temperature, and often limit the stoichiometric use of reactive gaseous compounds. Consequently, the most atom-efficient and sustainable synthetic routes that frequently require reactive, low-molecular-weight gases are avoided in many laboratories due to the hazardous nature of those gases. As a result, chemists often resort to longer, less efficient synthetic pathways, increasing waste and reducing overall process efficiency.

Continuous-flow technology offers a promising solution to the challenge of the safe and effective use of reactive gases in pharmaceutical synthesis. In micro- and millireactor systems, the high surface-area-to-volume ratio and consequently enhanced interfacial area between the gas and liquid phases ensure significantly improved heat and mass transfer rates. Efficient heat and mass transfer is critical for gas–liquid reactions and enables reactions that are difficult or unsafe in batch processes to proceed smoothly. Flow regimes that can be obtained in microreactors and millireactors with diameters of up to 1 mm and determine the interfacial area are shown in Fig. 2.[18,19]

Additionally, the solubility of gases, often limited by pressure and temperature constraints in batch processes, can be better managed under flow conditions, where internal pressures can be precisely controlled. Since flow reactors often withstand higher pressures than the corresponding batch vessels, gas solubility can be significantly improved according to Henry's law, which states that the concentration of a gas in a solution depends on the partial pressure of that gas. Furthermore, gas dosing can be finely tuned together with convenient quenching of toxic gases.

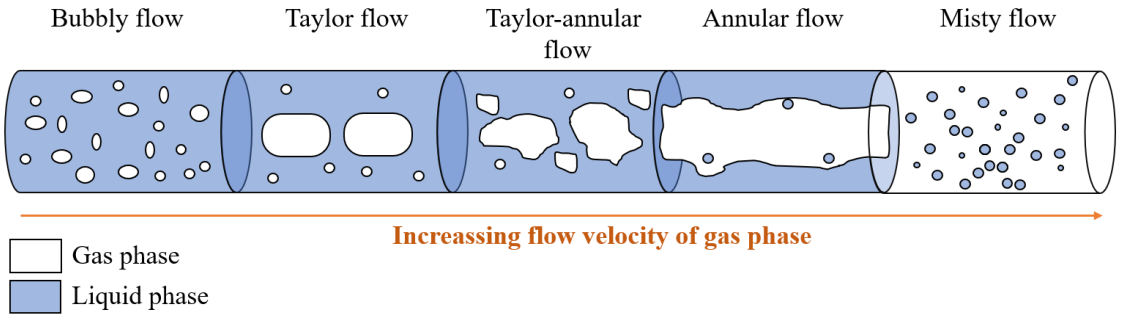


Fig. 2 – Flow regimes in a flow reactor for a gas-liquid mixture
Slika 2 – Profili strujanja u cijevnom reaktoru za sustav plin-kapljevina

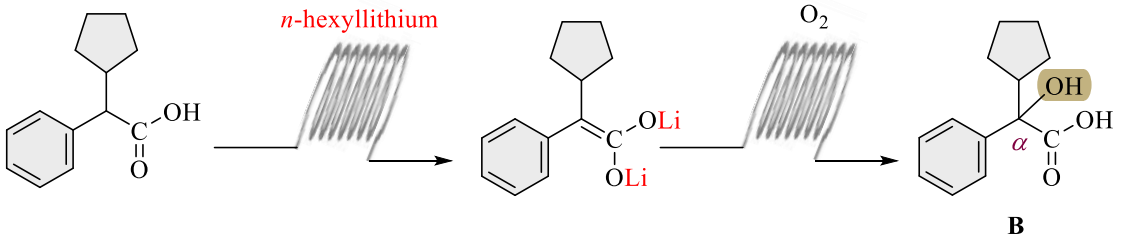
Collectively, these advantages make continuous flow a powerful tool for incorporating gaseous reagents into pharmaceutical manufacturing in a safer, more sustainable, and cost-effective manner.[7,18,19]

An example of overcoming the safety challenges of gas use is highlighted in the work of *De Angelis et al*.[20] They demonstrated the safe use of molecular oxygen in a multistep continuous-flow synthesis of cyclopentylmandelic acid **B** as a main building block of an API (Scheme 4). In batch reactors, large volumes of oxygen and organic vapours accumulate in the headspace, creating a flammable and potentially explosive environment. This risk limits the use of pure oxygen, requiring diluted forms that can slow down reactions and reduce selectivity. In contrast, continuous-flow systems minimise the volume of reactive gases at any time, greatly reducing explosion risk and allowing the safe use of pure oxygen, which improves reaction rates and product quality, as demonstrated in the given example. This makes continuous-flow processing a safer and more efficient alternative for aerobic oxidations, even at large production scales.[20]

Furthermore, continuous-flow processing offers solutions for handling highly hazardous reagents such as elemental fluorine, which is extremely toxic, corrosive, and reactive. Even minor exposure to fluorine gas can result in severe injury or fatal outcomes, making its use impractical in standard laboratory and manufacturing settings. However, *Znidar et al*.[21] have emphasised that using F_2 directly in synthesis is the most atom-economic and cost-effective route to fluorinated pharmaceuticals. They developed a safe and controlled continuous-flow system for delivering 10 % fluorine in nitrogen. By detailing appropriate reactor configurations and safety protocols, this work highlights how continuous-flow technology enables the safe on-site use of highly reactive gases and opens more direct, efficient synthetic routes for drug development.[21]

5.2 Liquid-liquid systems

Liquid-liquid processes in flow systems benefit significantly from the enhanced interfacial area and phase mixing provided by the small dimensions of micro- and millireactors. Many different flow regimes can occur in liquid–liquid systems, but laminar and slug flow are the most commonly observed in micro- and millireactors (Fig. 3).



Scheme 4 – Continuous-flow synthesis of cyclopentylmandelic acid **B** as a key API intermediate using molecular oxygen[20]
Shema 4 – Kontinuirana sinteza ciklopentil-mandelične kiseline **B** kao ključnog API međuprodukta uporabom molekulskog kisika[20]

Slug flow is more common and can be generated using devices like T-mixers where one liquid phase enters perpendicularly and plugs the channel. As pressure builds behind the plug, a droplet breaks off so that alternating segments of each liquid phase are formed. In this way, interfacial contact is enhanced and mass transfer between the phases is improved.[7,22,23]

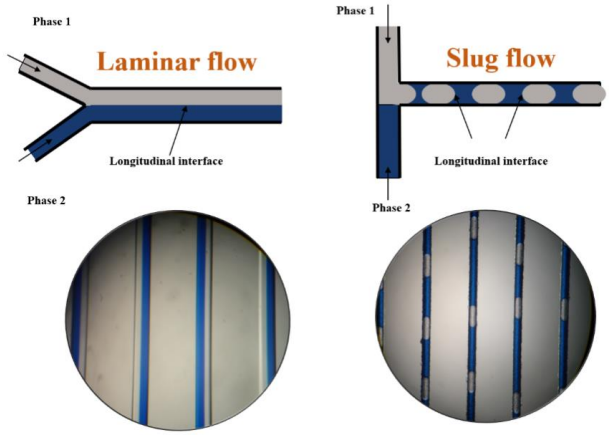


Fig. 3 – Flow regimes in a flow reactor for a liquid-liquid mixture

Slika 3 – Profili strujanja u cijevnom reaktoru za sustav kapljevina-kapljevina

At lower flow rates, various flow patterns provide comparable mass transfer efficiencies. However, as flow rates increase, reactor geometry becomes more critical. In such cases, elements such as static mixers can induce turbulence in flow paths, thereby increasing the liquid–liquid interfacial area and improving mass transfer. Additionally, in some reactions, a phase-transfer catalysis (PTC) approach is applicable, meaning that the mass transfer between immiscible phases can be enhanced by using phase-transfer catalysts. In PTC, the catalyst helps reactants move from one liquid phase to another, allowing the reaction to proceed faster and more efficiently.[7,23]

A notable example of PTC implementation is the Wittig reaction, which usually requires dry, aprotic conditions due to the moisture sensitivity of ylide formation. PTC allows the use of aqueous sodium hydroxide, enabling the reaction between immiscible phases by transferring phosphonium salts between them.[24] *Šinkovec et al*.[25] performed such a reaction in a microreactor under stable slug flow and achieved higher conversions in less time compared to the batch reaction due to the enhanced interfacial area. For example, after 1 min of reaction time, the conversion of *p*-methoxybenzaldehyde reached 35.5 % in the microreactor compared to 18 % in the batch reactor, while 50 % conversion was achieved after 180 s and 300 s, respectively. Similarly, 90 % conversion of *o*-methoxybenzaldehyde was obtained after 500 s in the microreactor, whereas 900 s were required in the batch reactor. Flow chemistry has improved mass transfer significantly with its superior mixing and hydrodynamic control, demonstrating the benefits of flow processing for mass transfer-limited PTC reactions.

5.3 Solid-liquid and gas-liquid-solid systems

Solid-liquid systems in flow chemistry present unique challenges and opportunities, depending on the nature of the solid involved. Reactions in which product precipitation drives conversion to completion are typically better suited for batch setups, as solids tend to clog the units in continuous-flow systems. Although there are specialised tools to manage such clogging, no universal solution exists, while troubleshooting often requires significant engineering expertise. Similarly, accurately delivering suspensions when using insoluble reagents remains a complex task. In such cases, batch processing offers more reliability and control.

However, when solid catalysts are involved, continuous-flow systems become preferable, particularly when using packed-bed reactors. Enhanced interfacial contact in those systems significantly improves mass transfer, which allows for efficient processing even under gas–liquid–solid conditions in transformations such as hydrogenations. Heterogeneous catalysis in continuous flow is particularly attractive due to the simplicity of separating solid catalysts from the reaction mixture and the ability to integrate reaction and separation into a single step. Packed-bed reactors not only maintain high catalyst loading but also often extend catalyst lifetime by minimising environmental exposure. Continuous-flow setups also allow for rapid and efficient screening of reaction parameters, accelerating process optimisation. Compared to conventional packed-bed reactors, packed-bed microreactors offer enhanced heat and mass transfer due to their small dimensions and high surface-area-to-volume ratio, leading to improved temperature control, reduced concentration gradients, increased reaction rates, and often higher selectivity and safety, particularly for highly exothermic reactions.[7]

A representative case of heterogeneous catalysis in a packed-bed microreactor involves the immobilisation of (*R*)-2-(1-piperazinyl)-1,1,2-triphenylethanol onto a polystyrene-based Merrifield resin for use in asymmetric synthesis. This chiral catalyst was applied in the enantioselective ethylation of aromatic aldehydes with diethylzinc, achieving quantitative conversions and enantioselectivities of up to 93 %. While both batch and continuous-flow processes delivered similar selectivity and enantioselectivity, the continuous-flow reactions were faster by a factor of 10 to 28, which highlighted the enhanced efficiency achievable with flow-based heterogeneous catalysis.[26]

6 Mathematical modelling

Mathematical modelling plays a vital role in understanding and optimising chemical processes. It enables the prediction of steady-state behaviour of the system and possibly the dynamic responses to process disturbances that may occur.[27] An essential component of this approach is mechanistic modelling, which captures physical and chemical transformations occurring under specific process conditions. Such models provide a detailed, science-based framework, which describes complex interactions within reactors and unit operations. In process development, mechanistic models offer multiple advantages. They enable improved interpretation of experimental results, identification of key process characteristics, and more informed decision-making during development with less experimentation. With the aid of computer-based design and simulation tools, mathematical modelling has become a valuable tool in industries like pharmaceuticals, where accuracy and efficiency are of extreme importance.[28]

When considering mathematical modelling of continuous-flow reactors, it is important to note that these systems are considered open systems, meaning that matter is exchanged with the surroundings. Under steady-state operating conditions, concentrations vary spatially along the reactor but do not change with time. Therefore, to mathematically describe such a system, it is necessary to establish material balances for each substance in a series of volume elements (Fig. 4).[29] These elements are considered to be in steady state across the reactor; therefore, the mass balance equation for each element contains no accumulation term. This means that the input of the material is equal to its output combined with change in concentration caused by chemical reaction.[30]

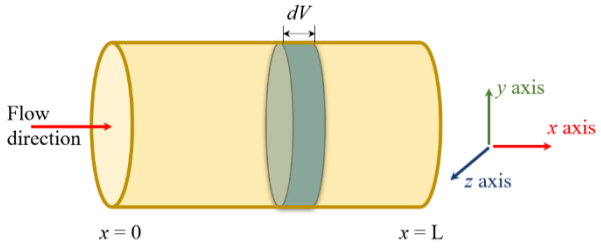


Fig. 4 – Volume element d*V* in a tubular reactor
Slika 4 – Volumni element d*V* u cijevnom reaktoru

With these characteristics in mind, a differential mass balance for substance A, whose concentration (c_A) varies due to chemical reaction and is dissolved in B, can be derived from the component mass balance equation combined with Fick's law of diffusion. In that case, the reaction space is an element d*V* with a volume close to 0 that is a part of a continuous-flow reactor where there is convective flow in axial direction and dispersion in all three directions (Eq. (1)):

$$u_x \frac{\partial c_A}{\partial x} - D_{AB}\left(\frac{\partial^2 c_A}{\partial x^2} + \frac{\partial^2 c_A}{\partial y^2} + \frac{\partial^2 c_A}{\partial z^2}\right) + r_A = 0 \quad (1)$$

where u_x is linear velocity in x-direction, D_{AB} is a diffusion coefficient of substance A in a solvent B, and r_A is a rate of the chemical reaction, which is usually a function of concentration and temperature with required knowledge on the corresponding kinetic model.[30–32]

While the presented 3D model provides the most comprehensive description of concentration changes in all directions, it is often computationally demanding and not always necessary. In many practical cases, concentration gradients in one direction can be neglected, making a 2D model sufficient to capture the key transport and reaction phenomena. This simplification reduces computational costs while still enabling accurate predictions of reactor performance. Therefore, the 3D model can be simplified into a commonly used 2D model for a one-phase system in a tubular reactor (Eq. (2)):

$$u_x \frac{\partial c_A}{\partial x} - D_{AB}\left(\frac{\partial^2 c_A}{\partial x^2} + \frac{\partial^2 c_A}{\partial y^2}\right) + r_A = 0 \quad (2)$$

which includes convection in the flow direction and dispersion in two directions and corresponding boundary conditions.

Further simplification of the model equation is possible. By assuming uniform concentration across the reactor cross-section, radial concentration gradients can be neglected, resulting in a 1D axial dispersion model. In this case, convection and axial dispersion are considered only in the flow direction. An additional simplification leads to the plug-flow reactor model, a commonly used 1D approximation for continuous-flow systems. Here, axial dispersion is neglected and transport is assumed to be dominated by convection (Eq. (3)):

$$u_x \frac{dc_A}{dx} + r_A = 0 \quad (3)$$

which describes mass transport only in the flow direction due to convection.[33]

The chemical reaction that takes place in a flow system must also be mathematically described to be incorporated into a mathematical model. This involves determining the reaction kinetics, which define the rate of the chemical transformation and its dependence on parameters such as temperature, pressure, concentrations of compounds, solvent properties, and the physical state of the compounds involved. Such kinetic descriptions are fundamental not only for understanding the intrinsic

behaviour of a chemical reaction but also for scaling up laboratory processes to industrial size.[30] In flow chemistry, where reaction conditions can be precisely tuned and monitored, kinetic data become particularly valuable for optimising yields, enhancing selectivity, and improving safety. The development of accurate kinetic models is often supported by experimental techniques, such as *in situ* spectroscopy, which allow continuous monitoring of the reaction under operating conditions.[7]

When considering two-phase systems undergoing a chemical reaction in a tubular reactor, it becomes essential to account for diffusion across the interfacial surface, since that is often where the reaction occurs. The mathematical description of such a system must incorporate not only the intrinsic kinetics of the reaction but also the mass transport phenomena at the phase boundary. A key factor in this case is the flow regime, which dictates the size and dynamics of the interfacial surface. For instance, laminar flow produces limited interfacial area, whereas slug flow significantly enhances contact between phases, leading to improved mass transfer. Consequently, mathematical models for such systems require setting up separate material balances for each phase, while incorporating additional diffusion terms and boundary conditions to describe interphase transport. Modelling two-phase systems is challenging due to the interplay of kinetics, hydrodynamics, and mass transfer, but advanced methods like computational fluid dynamics (CFD) help improve predictive accuracy and reactor design.[33,34]

An illustrative example of practical application of mathematical modelling is a study on the continuous manufacturing of an active pharmaceutical ingredient (API) in an industrial setting by *Diab et al*.[35] In this work, a system model was developed to simulate both steady-state and dynamic reactor behaviour. This approach enabled the researchers to minimise the number of experimental trials, accelerate process optimisation, and gain a deeper understanding of the reactor's performance across a range of operating conditions. Moreover, the predictive power of the model supported scale-up and contributed to greater process robustness and reliability. The study demonstrates how mathematical modelling is not only a theoretical tool but also a practical asset in pharmaceutical flow chemistry, where it enhances efficiency, reduces costs, and mitigates risks associated with process development.

The second example focuses on the application of mathematical modelling and simulations for the continuous manufacturing of ibuprofen. The study integrates both mechanistic and data-driven approaches to model reaction kinetics, transport phenomena, and unit operations involved in the synthesis and purification of ibuprofen. These models were then combined into a comprehensive simulation to predict steady-state behaviour, optimise operating conditions, and evaluate process dynamics under disturbances. The results demonstrated that mathematical modelling provides significant benefits by accelerating process understanding and scale-up, reducing experimental burden, supporting control strategy development, and ensuring robust and efficient production of pharmaceutical compounds.[36]

Recent advances in flow chemistry have also introduced machine-learning and artificial intelligence as tools for reactor design and process optimisation. *Savage et al*.[37] developed a machine-learning-assisted approach that combined computational fluid dynamics (CFD) simulations with Bayesian optimisation to identify improved flow reactor designs. The method enabled efficient exploration of a large design space and led to the discovery of reactor geometries with enhanced mixing and plug-flow performance. Experimental validation showed that the optimised designs outperformed conventional coiled-tube reactors, demonstrating the potential of AI-driven approaches to support mathematical modelling, reduce development time, and improve continuous manufacturing processes.

7 Green chemistry

Flow chemistry has shifted chemical process design toward process intensification and is widely considered a green methodology. It is increasingly recognised as a powerful tool that supports several of the twelve principles of Green Chemistry (Fig. 5), which aim to make chemical manufacturing more sustainable, safe, and efficient. These twelve principles serve as "design rules" to guide chemists toward the goal of sustainability. Green Chemistry emphasises the careful planning of synthetic routes and molecular design to minimise waste, avoid hazardous substances, and reduce environmental and health impacts throughout the lifecycle of a chemical process.[38–40]

Among the most directly addressed principles is Principle 1: Pollution Prevention, as flow processes often minimise waste generation by improving reagent utilisation and reaction control, reducing the need for downstream purification. Principle 2: Atom Economy is also supported through the high selectivity and precision of flow reactions, enabling more efficient use of starting materials and reducing by-products. Additionally, Principle 3: Less Hazardous Chemical Syntheses and Principle 12: Inherently Safer Chemistry for Accident Prevention are particularly relevant in flow chemistry, as the precise control and, in the cases of micro- and millireactors, small reactor volumes reduce risks associated with exothermic reactions, hazardous gases (e.g., oxidising gases such as O_2 or F_2), and toxic intermediates. These features make hazardous chemistries feasible and safer even at industrial scales. Furthermore, flow chemistry enhances energy efficiency (Principle 6: Design for Energy Efficiency) by allowing for better heat

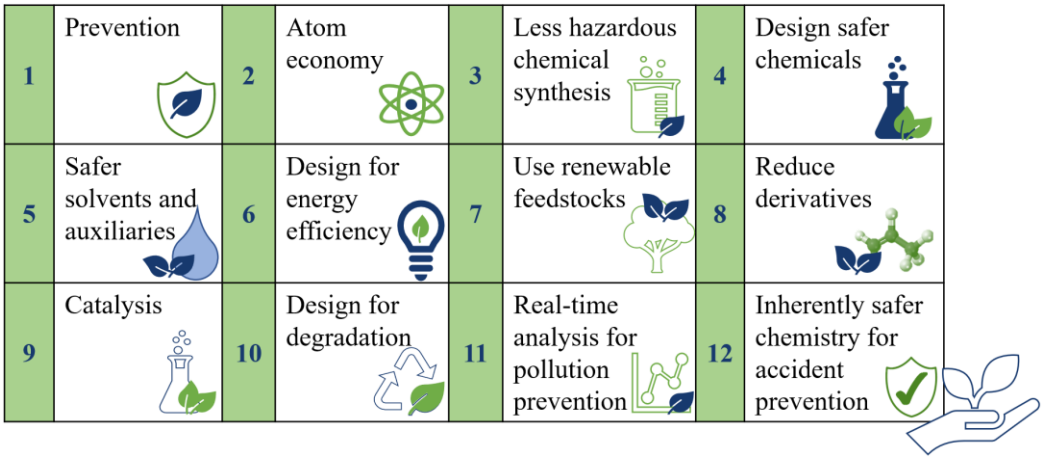


Fig. 5 – Principles of Green Chemistry
Slika 5 – Načela zelene kemije

management and often eliminating the need for heating or cooling large reactor volumes.

Some of the principles can also be additionally implemented by modifying the reaction itself or the system setup. The modularity of flow setups supports Principle 9: Catalysis, enabling efficient use of both homogeneous and heterogeneous catalysts, including immobilised systems in packed-bed reactors that allow catalyst recovery and reuse. In terms of Principle 8: Reduce Derivatives, flow systems often eliminate the need for protective groups and multiple synthetic steps, owing to in-line purification or telescoped reactions. Continuous flow also aligns with Principle 11: Real-Time Analysis for Pollution Prevention, as it is compatible with in-line monitoring tools (*e.g.*, IR, NMR, or MS) that allow for immediate detection of deviations, ensuring optimal reaction conditions are maintained.[39]

A great example of a process becoming "greener" by flow chemistry implementation is the Pharmacy on Demand (PoD) platform, developed under DARPA's Battlefield Medicines initiative with MIT and Novartis. It is a compact continuous manufacturing system that enables on-demand production of multiple APIs and reduces supply chain complexity and drug stockpiling. By integrating continuous multistep synthesis, in-line purification, crystallisation, and real-time monitoring into a small, reconfigurable unit, it demonstrated the efficient and flexible production of WHO-listed essential medicines such as diphenhydramine, diazepam, lidocaine, and fluoxetine. PoD highlights the green advantages of flow chemistry, including reduced solvent use, energy savings, waste minimisation, and improved safety. With the addition of portable tableting units, it also prevents overproduction and unnecessary waste, illustrating how flow chemistry can make pharmaceutical manufacturing more sustainable and aligned with the twelve principles of Green Chemistry.[41]

7.1 Green solvents

One Green Chemistry approach that is not yet used often in flow chemistry but is gaining importance over time is the implementation of Principle 5: Safer Solvents and Auxiliaries.[42] It is addressed by the ability to perform flow reactions with minimal or no solvent, or in safer solvents.[39] In the pharmaceutical industry, especially in API synthesis, the use of solvents hazardous to humans and the environment is often seemingly inevitable. However, various bio-based solvents have recently gained attention in terms of replacement of hazardous solvents like *N*,*N*-dimethylformamide, *N*-methyl pyrrolidone, and dichloromethane. One of them is Cyrene, a bio-based polar aprotic solvent derived from cellulose as an environmentally friendly alternative. Its low toxicity, biodegradability, and favourable safety profile make it highly attractive for pharmaceutical applications. Alongside Cyrene, other next-generation bio-based solvents such as γ-valerolactone (GVL), 2-methyltetrahydrofuran (2-MeTHF), and propylene carbonate have gained attention due to their renewable origins, reduced environmental impact, and versatile applicability across synthesis and formulation processes.

Other options include solvent classes such as supercritical fluids, ionic liquids, and deep eutectic solvents (DESs) as a potential alternative to hazardous solvents. Of these, although they are still rarely applied beyond lab demonstration, the greatest potential for pharmaceutical application can be noticed in NADESs as a special class of DESs due to their traits. They are formed by mixing natural primary metabolites such as organic acids, sugars, and amino acids, which results in liquids with melting points lower than those of the individual pure components. Due to the wide variety of possible components and their polarity ranges, the physicochemical properties of NADESs can be ad-

justed, making them highly versatile for different applications. Beyond their tunability, NADESs offer important practical advantages such as low cost, simple preparation, biodegradability, and non-toxicity, which position them as attractive and sustainable alternatives to conventional organic solvents. These properties make NADESs especially promising in fields like pharmaceuticals, where both efficiency and environmental safety need to be maximised.[42]

An illustrative example of NADES application in continuous organic synthesis of APIs and their intermediates is its use in the Wittig reaction. In the research by *Ljubić et al*.[14] it has been demonstrated that natural deep eutectic solvents could effectively replace conventional organic solvents in the synthesis of hydroxylated stilbenes in a millireactor. By employing a suitable NADES as the reaction medium, comparable yields were achieved while reducing the environmental impact, highlighting the practicality and sustainability of NADES in modern synthetic methodologies. Nonetheless, potential drawbacks such as their often high viscosity, which can lead to clogging or slowing down the mass transfer in flow systems, remain important challenges that need to be addressed for their wider application in the future.

8 Conclusions and future perspectives

Flow chemistry has emerged as more than a mere alternative to batch synthesis. It is a technology that enables safer, more efficient, and more sustainable pharmaceutical manufacturing. By integrating precise control of reaction parameters with modular, scalable reactor designs, it has already demonstrated clear industrial impact in the synthesis of APIs and key intermediates. Case studies from companies such as GSK, Novartis, and AstraZeneca highlight its capacity to overcome traditional challenges, particularly in handling hazardous chemistries. The combination of flow chemistry with process intensification and mathematical modelling has made it even more useful, helping scientists to better understand reactions, scale them up more reliably, and design reactors more effectively. In addition, flow chemistry fits well with the principles of Green Chemistry, which brings clear environmental benefits.

However, several limitations in the flow chemistry field remain. Microreactors, as a process intensification tool, while offering exceptional control, face issues of clogging and limited throughput, restricting their industrial use. Green solvents such as NADESs are promising, but still rarely applied at scale, raising questions about their industrial viability in long-term production. Likewise, mathematical modelling often struggles with multiphase or highly complex reaction systems, highlighting the gap between theoretical potential and practical reliability. Addressing these challenges requires not only engineering solutions but also cross-disciplinary collaboration among chemists, chemical engineers, and data scientists.

Looking forward, the future is likely to be defined by advances in automation, real-time monitoring, and new modelling approaches that combine mechanistic knowledge with obtained data. Collectively, these advances could accelerate the transition toward autonomous flow platforms. Furthermore, the need for sustainability enhancement will make the integration of green solvents and energy-efficient process intensification strategies necessary. Finally, portable and modular flow systems initiatives, such as the Pharmacy on Demand platform, may fundamentally change supply chains and make drug production more flexible and reliable.

These developments suggest that flow chemistry will not only complement but increasingly redefine how pharmaceuticals are manufactured. Its success, however, will depend on overcoming engineering challenges, demonstrating scalability and robustness under regulatory assessment, and building sustainability into the design. In conclusion, for researchers in this field, the central task should be to not only prove what flow chemistry can do, but to critically determine what it should do in order to drive the pharmaceutical industry toward a safer, greener, and more reliable future.

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SAŽETAK

Kemijska sinteza u protočnim sustavima: suvremeni pristupi u farmaceutskoj industriji

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Kemijska sinteza u protočnim sustavima jedan je od najznačajnijih suvremenih pristupa u farmaceutskoj proizvodnji, omogućujući prijelaz s klasičnih šaržnih na sigurnije, učinkovitije i održivije procese. Ovaj pregledni rad donosi uvid u najnovija dostignuća protočnih sustava s naglaskom na njihovu primjenu u sintezi djelatnih tvari (API) i ključnih intermedijara. Opisani su temeljni principi kemijske sinteze u protočnim sustavima, uključujući preciznu kontrolu reakcijskih uvjeta, bolju ponovljivost i povećanu sigurnost, osobito kod opasnih ili egzotermnih reakcija. Uloga mikro i milireaktora razmotrena je u kontekstu intenzifikacije procesa gdje se postiže znatno učinkovitiji prijenos topline i tvari u odnosu na klasične sustave. Posebna pažnja posvećena je višefaznim sustavima u kojima protočni sustavi omogućuju bolji međufazni kontakt i otvaraju mogućnost provođenja reakcija koje su u šaržnim uvjetima ograničene ili nesigurne. Kroz odabrane industrijske primjere pokazano je kako takvi sustavi omogućuju lakše uvećanje procesa, kraće vrijeme proizvodnje i veću robusnost. Također je istaknuta uloga matematičkog modeliranja i analitičkih metoda u stvarnom vremenu u optimizaciji i razvoju procesa. Na kraju se razmatra doprinos tih pristupa principima zelene kemije, uključujući smanjenje otpada i primjenu ekološki prihvatljivih otapala poput prirodnih eutektičkih otapala (NADES-a).

Ovaj rad pokazuje da kemijska sinteza u protočnim sustavima nije samo alternativa već ključna tehnologija budućnosti kemijske sinteze u farmaceutskoj industriji.

Ključne riječi

Kemijska sinteza u protočnim sustavima, kontinuirana proizvodnja, farmaceutska industrija, mikroreaktori, intenzifikacija procesa, zelena kemija, NADES

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