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Continuous microreactor technology to container-scale manufacturing: A blueprint for the next generation pharma industry

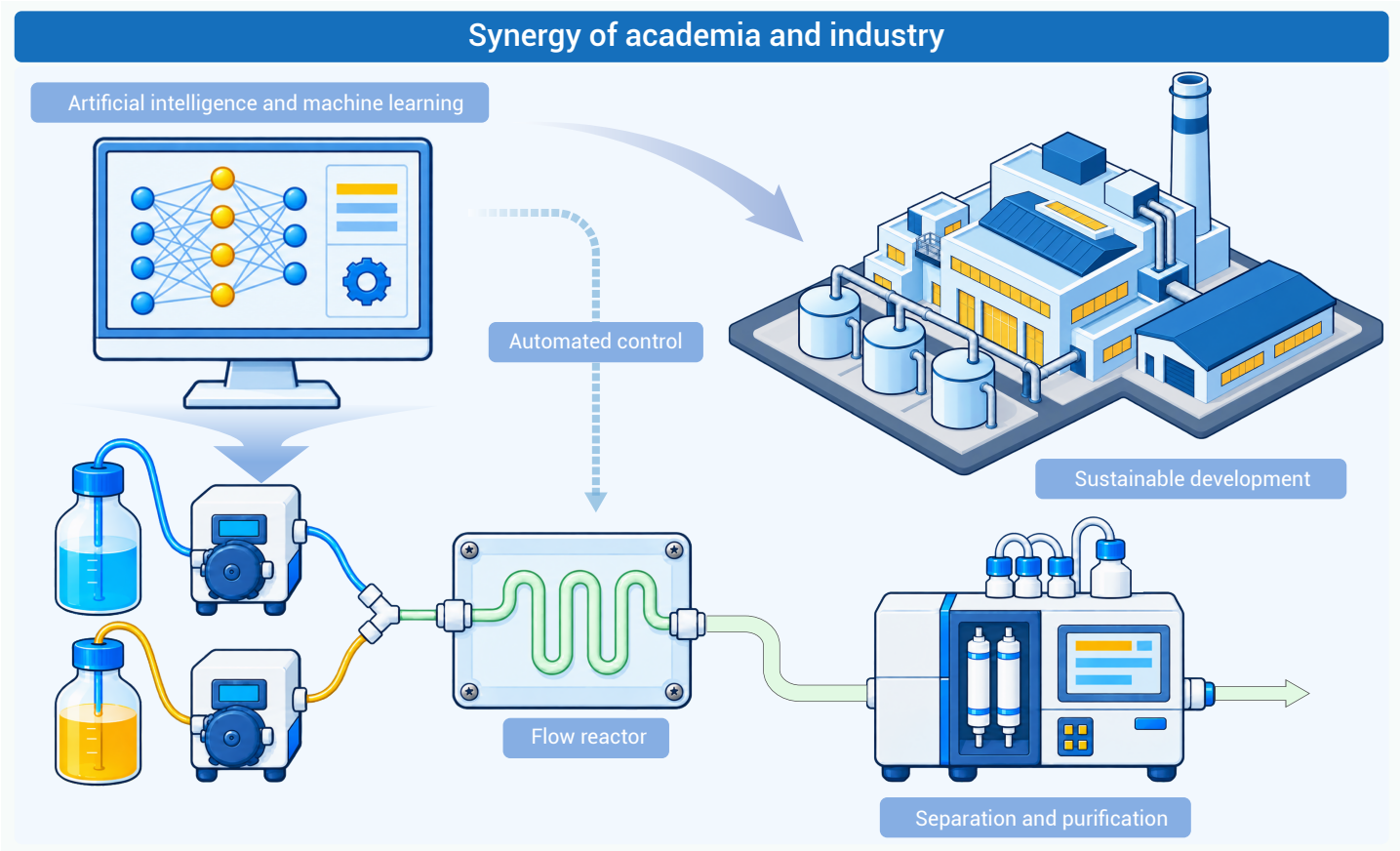
Maxim Oshchepkov,[1] Konstantin Kochetkov,[2] Pavel Pavlov,[1] Mikhail Il'in,[2] and Alexander Oshchepkov[3,4,*]

*Correspondence: alexander.oshchepkov@chemie.uni-halle.de

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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Integrated flow purification combines separation and isolation with continuous synthesis.
- Artificial intelligence and real-time monitoring support data-driven process optimization.
- Integrated purification helps reduce waste, solvent use, and intermediate processing steps.
- Industrial flow platforms combine reaction, purification, and product isolation in one process.
- Modular plants offer flexible production, from active ingredients to distributed manufacturing.

REVIEW Chemical Engineering

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Continuous microreactor technology to container-scale manufacturing: A blueprint for the next generation pharma industry

Maxim Oshchepkov,[1] Konstantin Kochetkov,[2] Pavel Pavlov,[1] Mikhail Il'in,[2] and Alexander Oshchepkov[3,4,*]

[1]Mendeleev University of Chemical Technology of Russia, Miusskaya pl. 9, Moscow 125047, Russia

[2]Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, Moscow 119991, Russia

[3]Max Planck Institute for the Science of Light, Department of Physics, Erlangen D-91058, Germany

[4]Martin Luther University Halle-Wittenberg, Faculty of Natural Sciences II, Institute of Chemistry, Organic Chemistry Kurt-Mothes-Straße 2, Halle 06120, Germany

*Correspondence: alexander.oshchepkov@chemie.uni-halle.de

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Continuous flow chemistry and microfluidic technologies are presently regarded as a pivota platform for the technological transformation of the pharmaceutical and fine-chemical sectors, facilitating the transition from conventional batch manufacturing to intelligent, sustainable, and fully integrated production systems. In this review, recent advances in the continuous synthesis of active pharmaceutical substances (APIs) and bioactive molecules such as amino acids and peptides are systematically organized, with particular emphasis on the utilization of microfluidic reactors, multistage flow platforms, and modular production complexes. Contemporary strategies for scale-up, notably numbering-up, the integration of Process Analytical Technology (PAT), and the deployment of artificial intelligence (AI) and machine learning (ML) algorithms for autonomous synthesis optimization, predictive quality control, and the implementation of self-optimizing reactors, are examined. Special attention is given to inline purification and isolation techniques, including liquid–liquid extraction, membrane-based separations, scavenger systems, continuous chromatography, and microfluidic crystallization. Emerging trends toward modular and container-based "mini-plants" are analyzed as the foundation of distributed manufacturing concepts and "pharmaceuticals-on-demand" paradigms. The synthesis of these elements demonstrates that the convergence of flow chemistry, digitalization, automation, and AI-driven control establishes a new paradigm of sustainable, flexible, and decentralized chemical-pharmaceutical production. Overall, the reviewed studies indicate that continuous microfluidic technologies constitute one of the most promising avenues for the next generation of the pharmaceutical industry.

INTRODUCTION

Synergy of academia and industry

Over the past two decades, the co-development of emerging synthetic technologies has been increasingly facilitated by systematic collaborations between academic research groups and the fine chemical industry.[1] A substantial number of high impact case studies now demonstrate that such partnerships often lead to results that would be difficult to achieve by either sector alone, particularly in the context of continuous flow chemistry.[2] Current research in the domain of flow synthesis is organized around four fundamental concepts: (a) alternative modes of physicochemical activation of chemical reactions; (b) the scaling of flexible, distributed-synthesis platforms (i.e., containerized factories); (c) additive design of reactors; and (d) the automation of processes through artificial intelligence.

Continuous processes have long been central to the chemical industry, where multitone scale production must satisfy stringent economic constraints, rigorous environmental regulations, comprehensive safety requirements, and intense market competition.[3] Under these conditions, the industry seeks synthetic routes that are atom-economical, intrinsically safe, and economically advantageous.[2] Microfluidics address these objectives by providing enhanced mass and heat transfer, precise control of residence time,temperature,pressure,andstoichiometry,scalabilitythroughnumbering-up, and integrated inline analytical capabilities.[4,5] Together, these features can improve reaction efficiency, increase product yield, and reduce the inventory of hazardous reagents, and allow some hazardous or demanding reactions to be performed more safely at scale.[6-9]

It is important to distinguish continuous-flow chemistry from microfluidic technology. Continuous-flow chemistry refers primarily to the mode of process operation, in which reactants are continuously introduced into a reactor and products are continuously withdrawn, whereas microfluidics describes a class of small-scale fluidic systems characterized by confined dimensions and specific transport phenomena. Microreactors may therefore be operated under continuous-flow conditions, but continuous-flow processing is not necessarily microfluidic. In this review, the term "continuous-flow" is used for the broader process concept, while "microfluidic" or "microreactor" is reserved for systems in which the device scale and architecture are specifically relevant.

In the pharmaceutical sector, continuous manufacturing is being promoted by regulatory authorities as a strategy to enhance product quality, supply-chain robustness, and cost-effectiveness.[3] The United States Food and Drug Administration (FDA) has issued guidance documents that delineate expectations for validation, control strategies, and data integrity in continuous processes. The simultaneous adoption of Quality-by-Design (QbD) principles and PAT tools enables manufacturers to design robust processes, monitor critical quality attributes (CQAs) and critical process parameters (CPPs) in real time, and support regulatory compliance while shortening process development.[4] Modern processes for developing innovative pharmaceuticals are based on the synthesis of small molecules, biopolymers (peptides), and therapeutic nucleic acids (mRNA), and the shift from traditional batch processes to automated continuous flow systems.[10,11] Recent literature reviews document a progressive increase in peer-reviewed reports describing continuous flow routes to active pharmaceutical ingredients (APIs); the proportion of contributions originating from industrial practitioners has risen markedly, indicating a trend toward greater transparency and knowledge exchange.[1]

Despite these advances, dissemination of detailed process information remains limited. Corporate confidentiality policies frequently restrict industrial chemists from publishing comprehensive experimental data, resulting in the confinement of many innovative developments to the patent literature.[12] This restriction hampers the broader scientific community's ability to evaluate, reproduce, and build upon industrial breakthroughs, potentially retarding the overall pace of technological progress.

APPLICATIONS OF FLOW CHEMISTRY IN THE PHARMACEUTICAL INDUSTRY / SYNTHESIS OF BIOACTIVE COMPOUNDS

Scope and boundaries of flow chemistry

Despite its substantial advantages, continuous-flow processing is not a universal replacement for batch manufacturing. Its applicability depends on reaction kinetics, phase behaviour, rheology, heat and mass transfer, solids formation, residence time, and long-term process stability.[13-15] Continuous flow should therefore be regarded as a complementary process-intensification strategy whose benefits depend on the physicochemical characteristics of the transformation and the requirements of the overall process.[16]

A major limitation is encountered in reactions involving suspended solids or generating significant amounts of insoluble material. Solids can increase pressure drop, promote wall deposition, disturb flow distribution, and ultimately cause reactor blockage.[17] These problems are particularly important when

precipitation is unpredictable or when particle concentration, size, or morphology changes during operation.[18] Although segmented flow, active mixing, optimized reactor geometries, and dedicated solids-handling strategies can mitigate these effects, they generally increase process complexity.[18,19] Highly viscous and non-Newtonian reaction mixtures present another challenge. Increased viscosity can raise pressure drop and reduce mixing efficiency, while viscosity changes during polymerization, crystallization, or concentration may alter the hydrodynamic regime during operation. Consequently, reactor geometry, flow regime, mixing, and residence-time distribution must be considered together during process design.[20,21]

Very slow reactions can also reduce the practical advantages of continuous processing. Long residence times may require larger reactor volumes or multiple reactors in parallel, partially offsetting the benefits of intensified heat and mass transfer and precise process control.[21-23] Thus, reaction kinetics should be considered at an early stage of technology selection.

Additional challenges arise from fouling, uncontrolled precipitation, and changing multiphase behaviour. These phenomena can progressively increase pressure drop, modify heat transfer and residence-time distribution, and cause process drift during prolonged operation.[18,24] Accordingly, robust continuous manufacturing requires effective process monitoring and control, with PAT increasingly serving as an essential component of long-term process stability and reproducibility.[16,24,25]

For pharmaceutical manufacturing, these considerations are particularly important because process robustness must be demonstrated over extended operation rather than only during individual experiments. Industrial-scale studies show that successful continuous manufacturing depends on coordinated control of unit operations, process monitoring, residence-time management, and integration of upstream and downstream steps.[26,27] Moreover, continuous reaction does not automatically eliminate downstream bottlenecks such as separation, crystallization, filtration, solvent exchange, or product isolation. Increasingly, therefore, continuous synthesis is being integrated with PAT and downstream processing within unified manufacturing platforms.[13,16,17] Continuous manufacturing may also require additional investment in specialized reactors, pumps, sensors, control systems, and PAT infrastructure. Nevertheless, reduced reactor inventory can provide important safety benefits for highly exothermic or hazardous reactions.[16,23] Economic assessment should therefore consider the performance and requirements of the entire process rather than the reactor alone.

Overall, the selection between batch and continuous manufacturing should consider reaction kinetics, phase behaviour, rheology, heat and mass transfer, solids formation, safety, residence time, throughput, downstream processing, PAT, equipment complexity, and economics.[15,17] Continuous flow is most advantageous when its intrinsic benefits: enhanced heat and mass transfer, precise process control, reduced hazardous inventory, and process integration -translate directly into improved manufacturing performance.

Thus, the most realistic industrial strategy is not the complete replacement of batch processing, but the selective implementation of continuous flow for transformations compatible with stable and sustained operation. Advances in reactor engineering, solids handling, PAT, and automation continue to expand its applicability, while technology selection remains fundamentally dependent on the characteristics of the individual chemical process.

Overview of microreactor technology market

In recent years there has been a steady growth in the industrial use of microreactor technologies and continuous microflow synthesis within the chemical and pharmaceutical sectors. Analytical market studies estimate that the global micro-reactor market reached approximately USD 597.9 million in 2024 and is projected to grow to about USD 1.4 billion by 2033, corresponding to an average annual growth rate of roughly 10% (Figure S1). The largest share of microreactor implementation is found in the pharmaceutical sector (≈ 45%), where continuous synthesis technologies are used to produce APIs and intermediates. The second-most significant segment is the production of specialty chemicals, encompassing aromatic compounds, functional monomers, agrochemicals, and fine organic reagents.[28]

The principal application domains are pharmaceutical manufacturing and the synthesis of fine organic chemicals, where microreactors offer superior selectivity, safety, and process controllability compared with conventional batch reactors.[29-31]

Currently, more than 780 industrial microreactor installations are operating worldwide for the production of chemicals, and over 250 chemical companies have integrated microflow technologies into their manufacturing processes. Notable adopters include Novartis, Lonza, Merck, DSM, Snapdragon Chemistry, among others. In addition, approximately 670 laboratory-scale and pilot-scal e microreactor systems are employed for the development of new synthetic routes and the optimisation of reactions.[32] At several Chinese facilities, specifically Nanjing Refinery Co., Ltd. and Zhejiang Weihua New Material Co., large-scale continuous production lines equipped with glass modules are employed for nitration and diazotisation reactions. The annual throughput of these lines ranges from 10 000 to 20 000 tonnes.[33]

In 2005 the American Chemical Society (ACS) Green Chemistry Institute (GCI) and a consortium of leading multinational pharmaceutical firms: AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Hoffmann-La Roche (together with its U.S. subsidiary Genentech), Merck, Novartis, Pfizer, and DSM established the ACS-GCI Roundtable.[34] The Roundtable explicitly designated continuous processing as a priority research theme for the sector.

Since that inception, virtually all innovative large-scale pharmaceutical manufacturers have initiated programmes aimed at the development and implementation of continuous-manufacturing technologies.[35] As a direct outcome, several drug products have entered the market that are manufactured, at least partially, by continuous processes approved by regulatory agencies. Representative examples include darunavir (Johnson & Johnson), lumacaftor, ivacaftor, and tezacaftor (Vertex), abemaciclib (Eli Lilly), and glasdegib (Pfizer).[36-38]

Moving from batch to continuous production is a long and capital-intensive process, requiring comprehensive research and development. Nevertheless, the economic advantages of continuous manufacturing have been demonstrated unequivocally.[12,39] Continuous evaluation of the applicability of extant technologies, together with the conception of novel continuous routes that have not yet received regulatory approval, remains imperative. In addition, a systemic shift in corporate culture and the systematic training of specialists in configuration management are prerequisites, each demanding considerable time and resources.[38]

The transition from laboratory-scale microreactors to industrial manufacturing therefore requires not only reactor scale-up and numbering-up, but also increasingly sophisticated process monitoring and control. Once reaction and separation modules are transferred to continuous operation, the resulting high-dimensional process data create an opportunity for automated optimization and adaptive control. These aspects are considered separately in the following section.

From laboratory to industrial technology

Microflow synthesis has progressed from a laboratory curiosity to an established industrial technology. After laboratory installations that are capable of producing up to 1 L of product, scale up on a pilot plant unit generally enables the attainment of a productivity of several liters per hour.[40] The development of continuous manufacturing processes also follows a staged strategy: starting from a batch mode protocol, progressing to a laboratory scale continuous flow setup, and finally transferring the technology to an industrial environment.[41]

For microfluidic devices, three principal routes are employed to increase material throughput: a) increasing the number of channels or the number of devices, b) extending the operating time, and c) raising the linear flow velocity through the device (Figure 1).[40,42]

The most straightforward approach is the internal multiplication of channel count, a strategy that has been the focus of numerous investigations.[43] A particularly illustrative case is the use of the DSM micro-structured reactor for the Ritter reaction.[44] Initial laboratory experiments were conducted in a cyclonic mixer coupled to a microchannel heat exchanger. The production scale reactor comprised four cyclonic mixers arranged in parallel, followed by several hundred parallel microchannels to ensure adequate heat transfer. Subsequent studies addressed the uniform distribution of liquid among the channels, thereby enabling large scale production within a single unit while achieving high volumetric productivity.[45,46]

In recent years, Lonza's microflow technology has moved from research

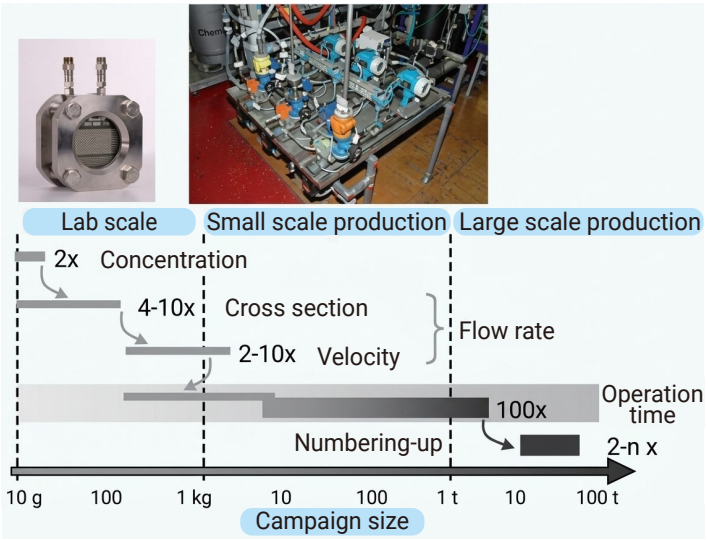


Figure 1. Scaling parameters for continuous-flow microfluidic reactors (Lonza FlowPlate™).[40]

development to commercial implementation for major pharmaceutical companies. The assembly of the microreactors in the form of modular plates inside scalable container blocks allows Lonza to reduce the time to market the drug by 30-50%.[47,48]

Corning has developed a plate-type glass reactor, the Advanced-Flow™ system, whose scale up is achieved by parallel connection of individual reaction modules.[49] This modular arrangement enables a substantial increase in the productivity of continuous nitration and other highly exothermic reactions. An analogous "number-up" strategy is employed in other industrial continuous-flow platforms, including microreactor and microfluidic configurations where appropriate, wherein parallelization of reactors augments total throughput without compromising heat- and mass-transfer performance (Figure S2).[50,51] It has been demonstrated that microreactors afford precise hydrodynamic control, high heat-transfer intensities, and enhanced safety when processing chemically reactive and potentially hazardous substances.[52]

Another article provides a detailed analysis of the migration of the nitration reaction from a laboratory flask to the industrial pilot plant Corning AFR-G1, which comprises five standard modules.[53] The authors show that productivity can be scaled to the kilogram per hour (kg/h) range on a single line while maintaining selectivity (the isolated yield of mono-nitroxylenes was 94.6%–97.6%). This quantitative result substantiates the transition to multi-tonnage G4/G5 modules. The latter two reactor configurations are currently deployed in production lines for diazotization and nitration with capacities of 10–20 kt/yr at facilities in China (Nanjing Refinery Co., Ltd.; Zhejiang Weihua New Material Co., Ltd.).[54-56]

The introduction of Ehrfeld Mikrotechnik GmbH's micro- and millireactor platforms into commercial process lines over the past five years exemplifies a successful paradigm shift in the chemical industry—from periodic batch operations to continuous, automated manufacturing (Continuous Manufacturing).[57] At large-scale facilities such as the Shaoxing Eastlake High-Tech plant, the integration of scalable millichannel systems from the Miprowa® series has enabled the conversion of intrinsically hazardous, highly exothermic continuous polymerization and ethoxylation of organic intermediates into safe, plug-flow regimes. By minimizing the reaction volume and achieving a heat-transfer coefficient exceeding 2 000 W m^{-2} K^{-1}, these systems provide precise temperature control and suppress side reactions, thereby allowing a productivity of more than 10 000 t yr^{-1} of the target product per equipment unit.[58,59]

Modular micro- and millireactor platforms (MMRS and FlowPlate®) have become the de-facto standard for executing kinetically rapid, highly sensitive, and stoichiometrically demanding transformations in fine-organic and pharmaceutical synthesis. Ehrfeld's technological solutions have demonstrated particular efficacy in continuous photochemical ozonolysis,[60] the synthesis of organic peroxides, and multistage organometallic reactions.[61] Notably, continuous C-glycosylation strategies[62] have been adopted on an industrial scale for the manufacture of the antiviral agent remdesivir, and a flow-based acetylation of 4-fluoro-2-methoxy-aniline—a pivotal building block in the synthesis of the anticancer drug ozimeritinib.[63]

The transition from laboratory-scale flow chemistry to industrial pharmaceutical manufacturing is illustrated by several commercial and cGMP-scale examples. In Italy, Sanofi implemented the industrial production of semisynthetic artemisinin at its Garessio site, reaching approximately 50–60 tonnes per year; although the final photochemical process was semi-batch, it demonstrated the successful industrial scale-up of an intensified API synthesis.[64,65] In the United States, Eli Lilly demonstrated an integrated eight-operation continuous-flow process for prexasertib monolactate monohydrate, producing 24 kg under cGMP conditions at approximately 3 kg/day.[66] In Spain, Medichem, together with Corning, implemented commercial-scale continuous-flow production of an organometallic API under cGMP conditions using an Advanced-Flow™ reactor.[67] In Japan, Takasago International Corporation has operated commercial continuous-flow manufacturing at its Iwata facility since 2015, reporting more than 100 tonnes of continuous-flow production and GMP manufacturing of pharmaceutical intermediates.[68,69] In China, Raybow Pharmaceutical has reported continuous-flow API production exceeding 140 tonnes in a single reactor in 2019.[70] These cases demonstrate the progressive transition of flow chemistry from laboratory and pilot-scale development to kilogram- and tonne-scale pharmaceutical manufacturing, providing an industrial foundation for the modular, automated, and scalable continuous-manufacturing platforms discussed below. The increasing regulatory acceptance of continuous manufacturing is reflected in FDA guidance Q13, which provides specific scientific and regulatory considerations for continuous manufacturing of drug substances and drug products.[71]

Despite these advantages, industrial scale-up of microreactors is not simply a matter of increasing the number of channels. Numbering-up introduces challenges associated with uniform flow distribution, pressure drop, manifold design, residence-time distribution, and thermal management across parallel channels. Long-term operation may also be limited by fouling, precipitation, channel blockage, corrosion, or incompatibility between reactor materials and aggressive reagents. These problems become particularly important for pharmaceutical streams containing suspended solids, highly viscous materials, or multiphase mixtures. Consequently, successful industrial scale-up requires validated hydraulic and thermal performance, robust materials of construction, reliable blockage detection, and maintenance strategies capable of preserving stable operation over extended production campaigns.

The integration of Artificial Intelligence and Machine Learning into microfluidic platforms

Rather than serving only as predictive tools, AI and machine-learning methods are increasingly being incorporated into closed-loop experimental systemsinwhichprediction,experimentation,measurement,anddecision-making form a continuous cycle. A representative example is AlphaFlow, a self-driven fluidic platform in which reinforcement learning was coupled with a modular microfluidic reactor and in situ spectral monitoring to autonomously explore complex multistep reaction spaces. The system was able to optimize reaction sequences involving a large number of experimental parameters, illustrating how AI can move from predicting experimental outcomes to actively selecting the next experiment (Figure 2).[72-74] A second important development is the integration of AI with PAT and mechanistic process models. In such a rchitectures, inline IR, NMR, Raman, UV–Vis, or chromatographic measurements provide continuous information on the reaction state, while machine-learning models update predictions of conversion, selectivity, or impurity formation.[75] Hybrid approaches that combine kinetic or transport models with machine-learning components are particularly attractive because mechanistic constraints can improve extrapolation and provide a moreinterpretablerepresentationoftheprocessthanpurelydata-drivenmodels.[76] Recent self-driving laboratory platforms further demonstrate that Bayesian optimization, automated experimentation, and real-time analytical feedback can be combined into closed-loop workflows for autonomous reaction optimization.[77,78]

However, several limitations currently restrict the deployment of AI/ML in pharmaceutical synthesis. Chemical datasets are often small, heterogeneous,

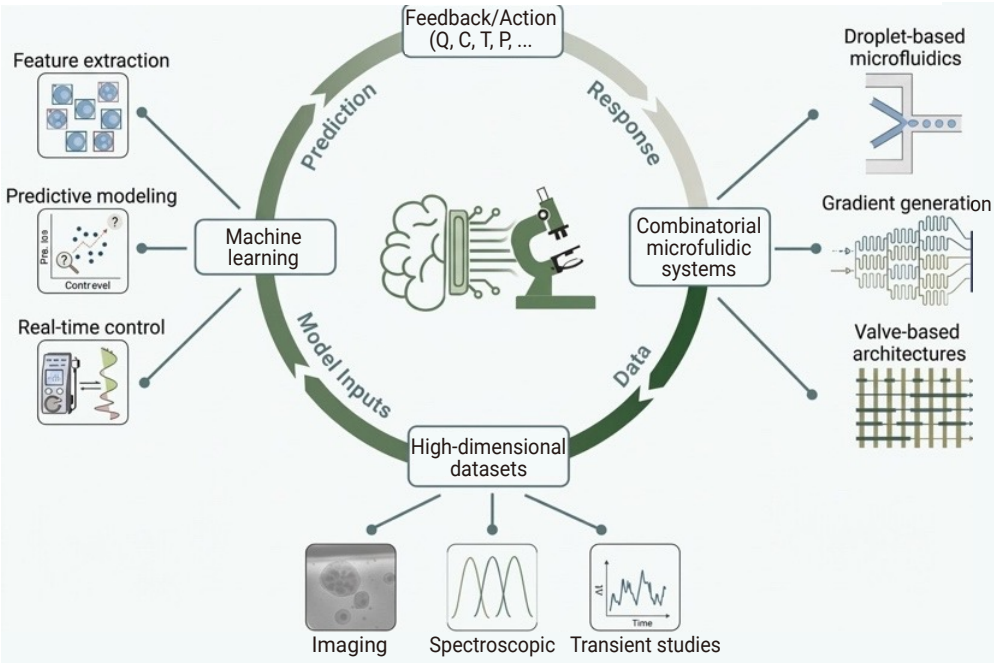


Figure 2. Closed-loop optimization strategy harnessing synergies between CMFs and ML promotes development of intelligent microfluidic workflows Q: flow rate, C: concentration, T: temperature, P: pressure.[77]

and biased toward successful experiments, whereas failed experiments and negative results are rarely reported. Consequently, a model may perform well within its training domain but fail when applied to new substrates, reaction regimes, reactor geometries, or operating windows. Additional challenges include uncertainty quantification, model interpretability, sensor drift, data synchronization, differences between laboratory and manufacturing equipment, and the need to demonstrate model robustness under changing raw-material and process conditions. For pharmaceutical manufacturing, AI should therefore be regarded not as a replacement for mechanistic process understanding but as a complementary layer that combines experimental data, physical constraints, and real-time process measurements.

In the pharmaceutical and fine chemical sectors, the combination of AI and microfluidics is particularly transformative. AI models can predict and reduce common industrial failures such as channel clogging and thermal runaway, making them invaluable for the synthesis of complex molecules and nanomaterials. Deep learning architectures, including Convolutional Neural Networks (CNNs)[79] and Physics-Informed Neural Networks (PINNs),[80] are being employed for real-time quality control, enabling inline monitoring of product purity and droplet consistency at rates up to kilohertz, thereby supporting more consistent product quality. PINNs are increasingly integrated to incorporate fluid dynamics and reaction kinetics directly into the ML architecture, addressing the need for mechanistic.

Beyond drug development, AI-microfluidics is revolutionizing industrial cooling for high-performance computing. Microfluidic heat sinks can be optimized through generative design to manage the extreme thermal loads of modern AI hardware, thereby enhancing sustainability and operational efficiency.[81]

Despite challenges such as the "black box" nature of deep learning and the need for standardized data formats, the adoption of AI-integrated microfluidics is accelerating the development of green chemistry and shortening the time-to-market for new therapeutics.[82,83] A major hurdle is model interpretability–the "black box" problem–where deep neural networks fail to provide mechanistic insights into why specific reaction conditions succeed. Additionally, current AI models are hindered by data bias in published literature, which overwhelmingly reports successful reactions while omitting the negative results essential for unbiased ML training.

Moreover, the integration of AI with microfluidics bridges the gap in handling massive, multidimensional datasets generated from high-resolution imaging and real-time sensor data, which often exceed the analytical capacity of traditional methods.[84] AI algorithms, particularly machine learning and deep learning, automate complex tasks such as cell segmentation and predictive modeling, significantly accelerating processes like drug discovery and enhancing the accuracy of phenotypic drug discovery (PDD).[82]

Overall, the integration of AI and microfluidics represents a revolutionary leap in technology, enabling the solution of complex data challenges in biomedical research and paving the way for more sustainable, efficient, and personalized solutions in the pharmaceutical and chemical industries.[74,83] The topic of combinatorial microfluidics and machine learning is discussed in greater detail in the review article.[77]

Amino acids and peptide synthesis

The historical development of automated synthesis predates modern AI- and microfluidic-based platforms. In 1965, an automated solid-phase peptide synthesizer was reported for the preparation of peptides such as bradykinin and angiotensin II, demonstrating that repetitive synthetic operations could already be automated with limited operator intervention.[85] Although this early system lacked modern feedback control and machine-learning capabilities, it established an important conceptual precedent for the automated synthesis platforms discussed below.

The 1965 system represents an early form of programmable chemical automation in which predefined sequences of operations were executed without adaptive feedback (Figure S3).[85] Modern automated synthesis platforms retain this fundamental concept but extend it through continuous-flow processing, inline analytical monitoring, and machine-learning algorithms capable of using experimental data to optimize subsequent synthesis cycles. This evolution from predefined automation to data-driven closed-loop control provides the conceptual link between early automated peptide synthesis and the contemporary platforms illustrated in Figures 3 & 4.

Half a century later the objective remains the same: to cut the time spent on repetitive operations. What has changed is the power of contemporary computing, which now enables far more sophisticated levels of automation and performance gains.[86]

The synthesis of amino acids and peptides has been transformed by the adoption of microfluidic and continuous-flow technologies, which have now enables more precise control of short-lived intermediates and complex synthetic sequences of transient intermediates and the construction of intricate molecular architectures.[87] In contrast to conventional batch reactors, microfluidic platforms afford superior control over mass and heat transfer—which is particularly useful when working with thermolabile amino acid derivatives, because their high surface-area-to-volume ratios enable exothermic processes such as mixed anhydride formation or the deployment of energetic coupling agents (e.g., thionyl chloride, triphosgene) to be performed under strictly isothermal conditions.[88] This capability is especially valuable for handling unstable species in situ; for example, the rapid generation of α-aminonitriles within the Strecker pathway can be achieved with only seconds of residence time, thereby facilitating the automated production of carbon-11-labeled sarcosine and methionine for clinical PET imaging.[89] Solid-phase peptide synthesis of large, homogeneous peptides has been difficult due to inefficient coupling and side reactions. In peptide assembly, modern flow-based automated systems operate under low-pressure environments and complete a single coupling cycle in several minutes, accelerating the convergent N-C ligation that has enabled total synthesis of large, biologically active proteins such as Barnase (113 residues) and DARPin pE59 (130 residues).[90] In 2020, Hartrampf et al. used an automated platform to optimize fast-flow peptide synthesis, enabling the production of fully synthetic single-domain proteins, including proinsulin, barnase, and a version of HIV-1 protease with noncanonical amino acids.[91] Refolded peptides were

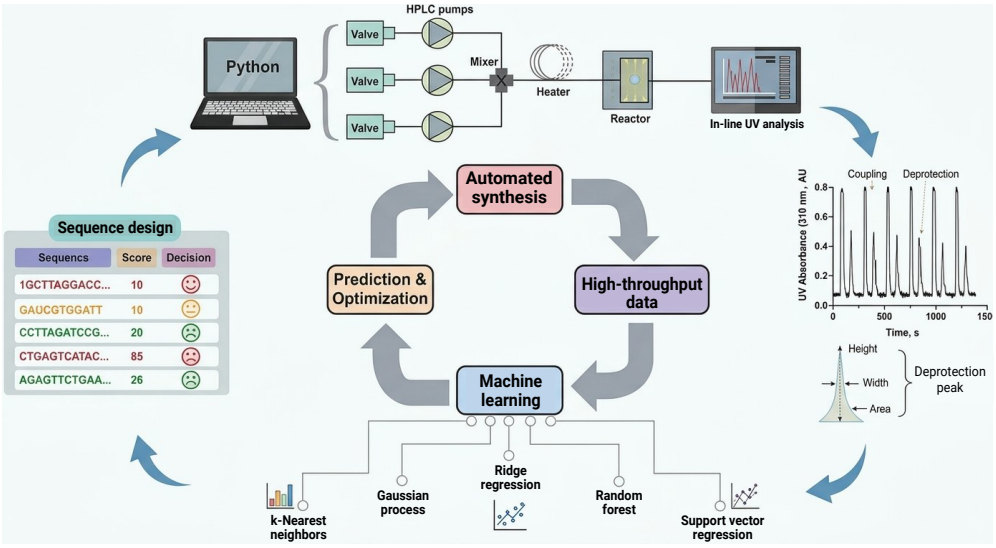


Figure 3. Combining machine learning with automated synthesis technology delivers a design-build-test-learn cycle for PNA (Peptide nucleic acids) sequence design A Python program-controlled automated oligonucleotide synthesizer is used to synthesize PNAs, with a real time UV-Vis trace monitoring all coupling and deprotection reactions. ML was applied over the integral peak areas calculated from the deprotection steps in the experimental data. A trained and optimized ML model makes prediction on the synthesis efficiency for any arbitrary PNA sequences, and therefore, enables informed sequence design.[93]

nearly identical to recombinant proteins, and synthesized enzymes had activity close to their ribosomally synthesized counterparts.

To mitigate challenges associated with resin swelling and aggregation in solid-phase peptide synthesis, variable-bed flow reactors have been implemented to dynamically adjust reaction volumes, preserving low back-pressure even for recalcitrant sequences like poly-L-alanine.[92] Real time analytical feedback such as inline UV-Vis monitoring of Fmoc deprotection provides immediate insight into coupling efficiency and chiral integrity, effectively suppressing epimerization (Figure 3).[93,94] Moreover, microfluidics supports the directed self-assembly of short peptides into functional nanostructures; heterochiral tripeptide hydrogels exhibiting distinctive optical waveguiding have been generated by controlling diffusion at laminar interfaces.

Industrial translation of these technologies follows the paradigm of "numbering-up," wherein multiple identical microreactors are operated in parallel rather than enlarging a single unit, thus preserving the advantageous mass and heat transfer characteristics while scaling throughput. The following trends in the development of peptide synthesis in the industry can be anticipated. First, microfluidic production of N-carboxyanhydrides (NCAs) a pivotal class of monomers for polyamino acids benefits from microfluidic cooling during phosgenation, allowing safe, large-scale synthesis with high purity and reduced solvent consumption; the resulting NCAs feed into polypeptide-based drug delivery platforms.[95,96] Second, flow-based Boc/Fmoc chemistry has been adopted for the preparation of the antidiabetic and specific proteins, where elevated temperatures and short contact times minimize deletion sequences and improve overall yield relative to the batch solid phase synthesis.[97,98] Third, modular flow skids now enable on-demand, decentralized manufacture of patient-specific peptide neoantigen vaccines for cancer immunotherapy; these compact systems integrate continuous synthesis with automated purification, dramatically lowering the E-factor by limiting the inventory of reactive material and employing machine-learning-driven PAT to maintain consistent quality under a quality-by-design framework (Figure 4).[99-101]

The transition from laboratory to industrial scale is achieved without compromising the intrinsic advantages of microfluidic control through parallelized microreactor arrays, continuous crystallizers, and membrane-based solvent-exchange modules that together constitute an end-to-end platform for peptide APIs.[102] This intensification reduces solvent waste and energy consumption, aligning with green chemistry objectives, and the inherently small reaction volumes enhance safety when handling hazardous reagents. Advanced control architectures, incorporating real-time PAT and AI-enabled optimization, ensure reproducible product quality across parallel units, thereby facilitating the adoption of these protocols in large-scale manufacturing while preserving atom-economical and highly controllable processes for complex biogenic molecules.[95] Collectively, the microfluidic peptide synthesis represents a decisive evolution from traditional batch solid-phase peptide synthesis, delivering a miniaturized, highly controllable environment that exploits laminar flow and rapid mass/heat transfer to accelerate reaction, minimize reagent consumption, and enable scalable production of both linear and functional peptide constructs.[103]

Microfluidic platform for mRNA synthesis and purification

Messenger RNA (mRNA) is an intermediary macromolecule that conveys genetic information from DNA to ribosomes for protein biosynthesis; consequently, it plays a pivotal role in gene expression.[104] Until the mid-2000s, the widespread exploitation of mRNA was hampered by its intrinsic instability and its propensity to elicit a strong innate-immune response. Chemical modification of mRNA nucleotides can substantially reduce recognition by innate immune sensors and thereby attenuate unwanted innate immune activation, while maintaining the desired translational activity of the mRNA. This discovery was recognized with the Nobel Prize in Physiology or Medicine in 2023. Since the late 2010s, mRNA has been employed therapeutically for a variety of diseases. The most prominent examples are the SARS-CoV-2 vaccines Comirnaty (Pfizer/BioNTech) and Spikevax (Moderna) which encode a non-pathogenic spike protein of the virus. Beyond vaccination, mRNA is being investigated for oncology (personalized neo-antigen vaccines), autoimmune disorders (temporary reprogramming of T cells, e.g., the Descartes-08 platform), and congenital diseases.[105,106]

Microfluidic synthesis is an emerging approach to the production of therapeutic mRNA. The process is based on in vitro transcription (IVT) carried out within microfluidic reactors that provide a continuous stream of reactants.[107] Compared with conventional batch-mode IVT, the microflow methodology offers superior control of critical parameters, including temperature, residence time, and mixing intensity. This heightened control translates into improved reproducibility and product quality. Owing to the exceptionally efficient heat and mass transfer inherent to microfluidic geometries, RNA degradation is minimized and the formation of undesired side-products, most notably immunogenic double-stranded RNA (dsRNA) contaminants, is substantially reduced. Consequently, microfluidic platforms enable the manufacturing of high-purity mRNA suitable for clinical applications.[108,109]

Continuous IVT and microreactor-Based mRNA synthesis

The principal advantage of microreactor-based continuous IVT lies in the ability to control reaction conditions at a well-defined spatial and temporal scale. Continuous feeding of the transcription mixture enables precise regulation of temperature, residence time, reagent ratios, and mixing conditions, which are critical parameters for RNA synthesis. The high surface-to-volume ratio of small-scale reactors facilitates rapid thermal equilibration and efficient mixing, while continuous operation provides a defined residence-time environment for the transcription reaction. These characteristics may improve process reproducibility and reduce degradation associated with prolonged exposure of RNA to suboptimal reaction conditions. For example, the AMO-IVT platform generated 3.3-fold more messenger RNA (mRNA) than a conventional reactor within a 1 h reaction, while reducing toxic impurities (e.g., double-stranded RNA, dsRNA) by 65%.[110]

Downstream operations such as clarification, removal of double-stranded RNA impurities, membrane-based concentration and buffer exchange, tangential-flow filtration, and chromatographic purification represent separate separation and purification functions.[111] These operations are therefore

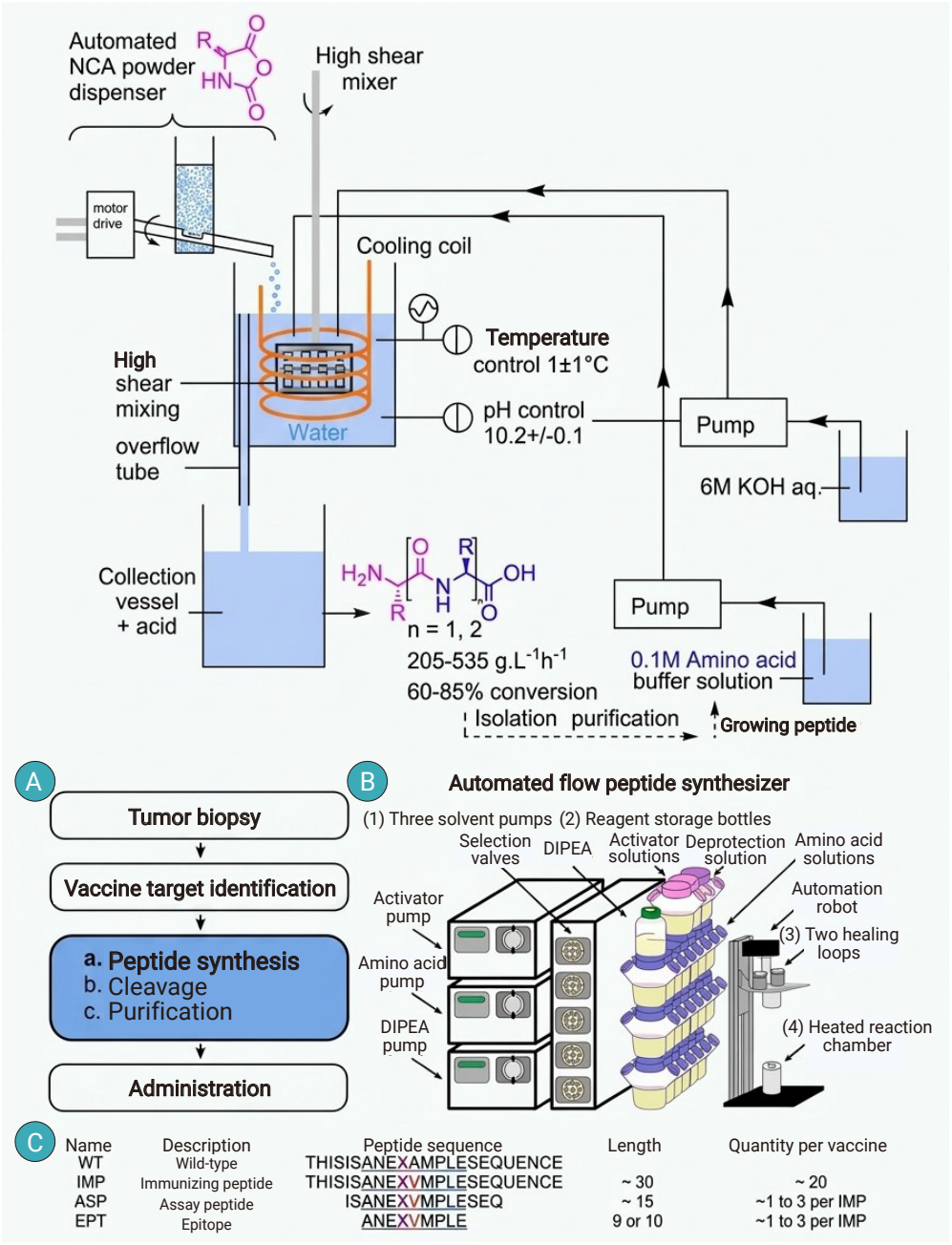


Figure 4. (UP) Diagram of the continuous stirred tank reactor setup used, showing high shear mixer, continuous solids addition system, internal cooling coil, and pumps.[95] (DOWN) Peptide design and production for a personalized neoantigen vaccine (A) Workflow for the design and production of neoantigen vaccines. (B) Example peptide sequences for a wildtype (WT), immunizing (IMP), immune monitoring assay (ASP), and epitope (EPT) peptides. (C) Schematic illustration of an automated flow peptide synthesizer (without connective capillary tubing and UV-vis module).[100]

considered in Section 3 rather than being treated as intrinsic components of the IVT reaction itself.

A particularly illustrative case is the integrated microfluidic system developed at POSTECH, which unites an in vitro transcription (IVT) module, a microfluidic fragmentation and clarification block (μFD), multimodal chromatography (MMC), and high-flux tangential flow filtration (HF-TFF) (Figure S4).[111] The system incorporates a biocatalytic membrane functionalized with immobilized DNA-ase I, enabling simultaneous removal of the DNA template and residual IVT components while preserving full-length mRNA. Process control is fully automated through embedded pH and conductivity sensors, ensuring reproducibility and further decreasing dsRNA levels.

The platform delivered a productivity of ≈1.2 mg of mRNA per cycle of ≈2 h, more than twofold higher than the conventional approach (641 μg). Because the architecture is modular, the process can be scaled by parallelizing reaction modules, making such platforms promising for rapid manufacturing of mRNA vaccines and personalized therapeutic agents.[111]

Complex multistage syntheses under microfluidic (flow) conditions

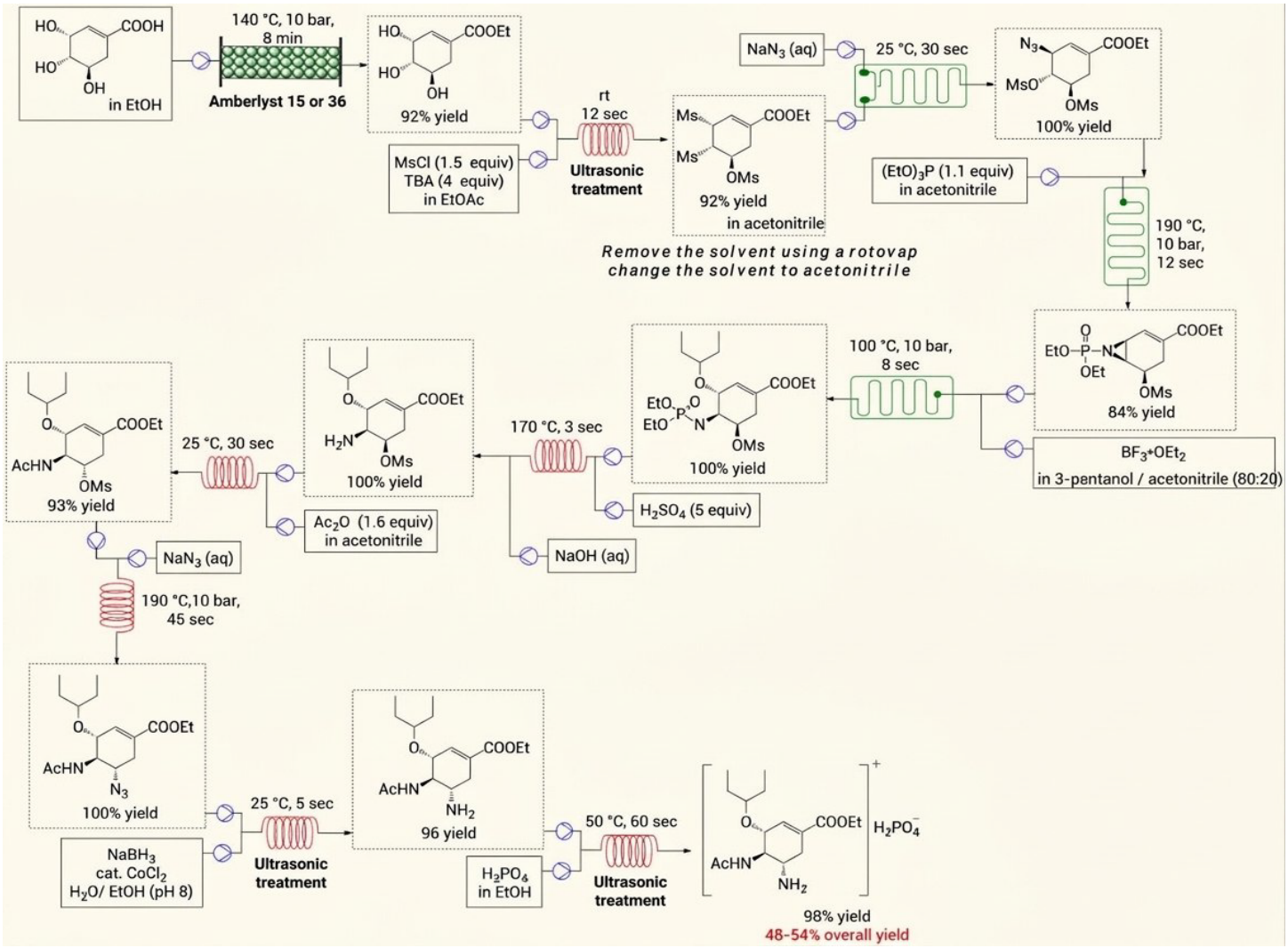
Increasing attention in recent years has been directed toward the development of multistage, technologically sophisticated organic syntheses carried out under microfluidic conditions. In the early studies (2012–2016), the primary emphasis lay on demonstrating the principle of operation for continuous synthesis of pharmaceutically relevant molecules. For instance, a 2016 review[112] already listed the continuous preparations of rac-oxomaritidine (a cytotoxic alkaloid of the Amaryllidaceae family), the antimalarial agent artemisinin, the antipsychotic olanzapine (Zyprexa), the nonsteroidal anti-inflammatory drug (NSAID) ibuprofen, and the enantioselective synthesis of the anti-inflammatory agent (R)-rolipram. A central requirement for modern continuous pharmaceutical manufacturing is the seamless integration of multi-step chemical transformations, PAT, inline purification, and modular hardware skids into a single continuous sequence.

For example, the synthesis of linezolid, in contrast to conventional procedures that require more than 60 h and labor intensive purification of intermediates, can be performed by a micro-fluidic approach that constitutes a fully continuous seven-step process.[113] In this protocol, for the first time, solvent exchanges and intermediate purification are avoided throughout all stages. The entire sequence is completed in only 27 min, affording the target linezolid in an isolated yield of 73%.

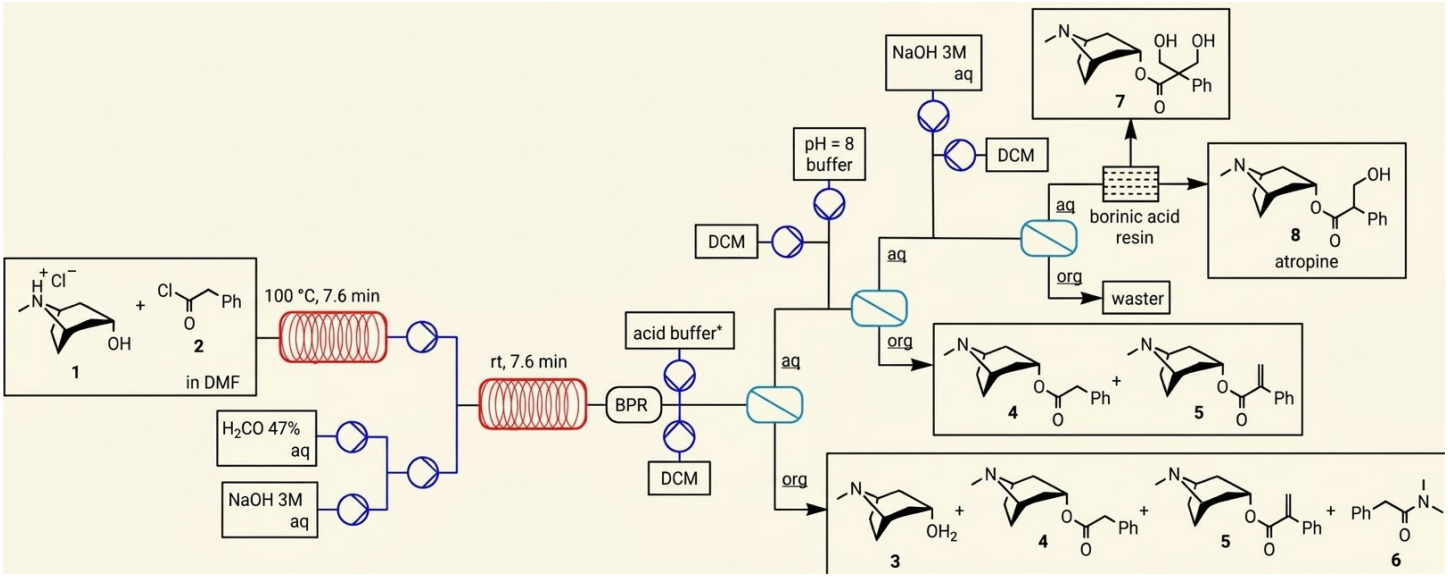
The ten step synthesis of oseltamivir (Tamiflu) is illustrated in Scheme 1.[114-117] This route delivers the product with an overall yield of 58% and is characterized by an exceptionally short residence time of the reagents in the system—3.5 min.[116] The sequence begins with the esterification of natural shikimic acid (6) with ethanol in the presence of a catalyst (Amberlyst 15 or $SOCl_2$). The synthesis is concluded by treating oseltamivir (3) with phosphoric acid to obtain the final salt, oseltamivir phosphate (4).

Beyond these pioneering achievements, the field has progressed toward automated and robotically driven platforms, as illustrated by the continuous synthesis of Sonidegib on a system guided by computer-assisted synthetic planning. Crucially, to maintain such telescoped processes within validated operating windows, PAT tools–including inline IR, NMR, UV-Vis, Raman spectroscopy, and automated HPLC–are integrated at intermediate stages to provide real-time feedback control.

Contemporary publications are characterized by a pronounced increase in the complexity of microfluidic process architectures, a higher number of integrated stages, and a shift toward fully automated synthetic platforms. This evolution mirrors the general trend in continuous flow chemistry from proof of concept demonstrations to technologically mature solutions. Representative examples include an eight-stage synthesis of oligosaccharides employing a "catch and release" strategy in a microflow reactor,[118] a six-step synthesis of prexasertib,[119] and a three stage automated synthesis of the anticancer agent sonidegib that utilizes a computer-assisted synthetic



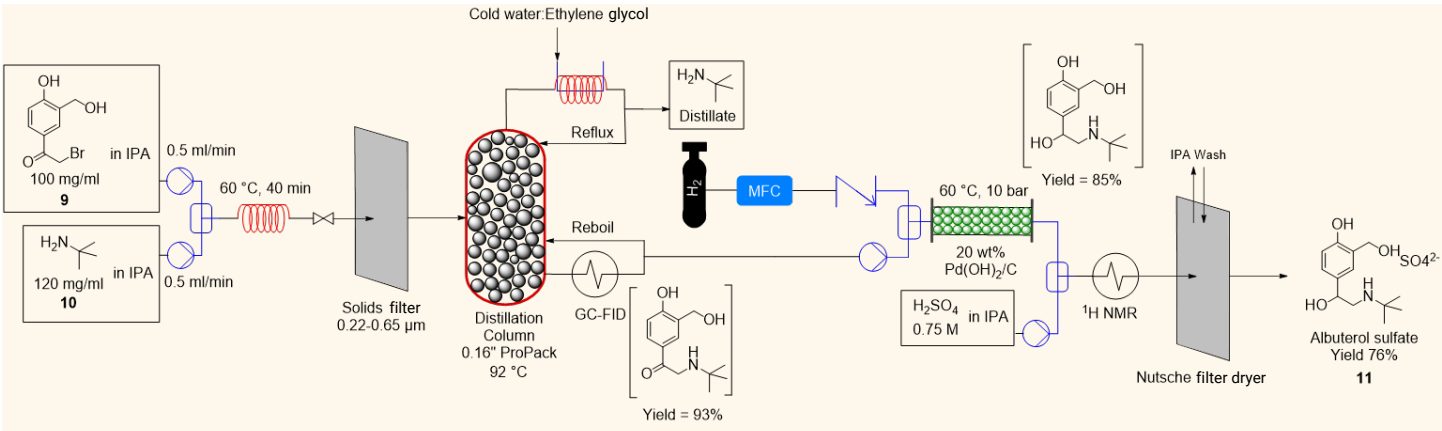
Scheme 1. Continuous synthesis of oseltamivir in a multistage continuous process.



Scheme 2. Continuous-flow synthesis of atropine (adopt. from ref.[123]).

planning system on a modular robotic platform for flow synthesis equipped with integrated process-analytical technology.[120]

To date, the literature reports approximately one hundred APIs whose synthesis has been at least partially realized under continuous flow conditions. Table 1 (at the end of the review) summarizes the current state of the art in multistage continuous synthesis, isolation, and analysis of pharmaceutically active compounds. The dataset encompasses representatives of diverse therapeutic classes: antimalarials, anticancer



Scheme 3. Continuous-flow synthesis of albuterol sulfate (adopt. from ref.[124]).

agents, anti-inflammatory drugs, antivirals, anxiolytics, antipsychotics, local anesthetics, and cardiology medicines underscoring the universality of the approach and its growing industrial relevance.

Most of the reviewed processes include the implementation of PAT concepts and the transition to real time analytical control. The most frequently employed online monitoring techniques are infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy, ultraviolet (UV) spectroscopy, Raman spectroscopy, high-performance liquid chromatography (HPLC), including using chiral columns and refractometry.[121,122] Notably, recent works increasingly combine several analytical modalities within a single flow line, enabling continuous quality control at each synthetic stage and markedly enhancing process reproducibility.

In earlier investigations, for instance in the study by Dai et al. (2015), a continuous-flow synthesis of atropine was implemented together with sequential inline purification (Scheme 2).[123] To separate structurally related impurities, a cascade of continuously operating liquid-liquid extractors equipped with pH control was integrated. This configuration eliminated the need for energy intensive column chromatography, enabling the isolation of a pure product directly from the flow stream.

In more recent work, such as the investigation by Gregory et al. (2026), an advanced continuous-flow platform for the synthesis of albuterol sulfate was proposed, incorporating a multistage downstream purification system for both intermediates and the final API (Scheme 3).[124] A tangential-flow filter was employed to remove side-product salts of tert-butylamine and oligomeric impurities directly from the reaction stream. Excess volatile amine reagent was efficiently purged from the process line by means of an in-line continuous distillation unit operating at 92 °C. Qualitative and quantitative monitoring of the composition of the process stream at intermediate stages was performed in real time using an integrated 80 MHz nuclear magnetic resonance (NMR) spectrometer. The final isolation of the high-purity target compound from the suspension was carried out in a semi-periodic stage using an automated nut-type filter-dryer, thereby delivering a pharmaceutically acceptable product that consistently meets ICH quality specifications.

Equally important is the advancement of integrated downstream-processing methodologies. The most commonly applied techniques include continuous liquid-liquid extraction, membrane-based liquid-liquid separation, continuous crystallization, and continuous filtration. The expansion of the repertoire of built-in isolation and purification steps indicates a move toward fully integrated continuous manufacturing lines a critical prerequisite for the industrial uptake of flow chemistry in pharmaceutical production.

Consequently, the data compiled in Table 1 convincingly demonstrate the transition of continuous API synthesis from laboratory scale investigations to the realization of comprehensive, automated platforms capable of delivering high efficiency, reproducibility, and scalability for pharmaceutical processes.

The examples discussed above demonstrate that the industrial relevance of continuous-flow pharmaceutical synthesis does not depend solely on the continuous reaction step. As the number of sequential transformations increases, the overall process must also incorporate intermediate separation, purification, analytical monitoring, and process control. Thus, continuous synthesis should be considered as the first component of an integrated manufacturing sequence in which reaction, separation, purification, and analytics are interconnected rather than operated as isolated unit operations. This integrated perspective provides the basis for the inline purification strategies discussed in Section 3. Purification technologies in microflow and, ultimately, for their implementation within modular and containerized manufacturing platforms discussed in Section 4. Transition to modular and container based chemical manufacturing

PURIFICATION TECHNOLOGIES IN MICROFLOW

In an integrated continuous pharmaceutical process, purification is not a separate downstream activity but a functional extension of the continuous synthesis platform. The incorporation of separation and purification steps directly into the process stream enables intermediate handling to be minimized and creates a continuous pathway from reaction to isolated product. Therefore, the development of inline purification technologies is a critical step toward translating multistage continuous synthesis into an end-to-end manufacturing process.

Short overview

Accordingly, many peer-reviewed studies now addresses all stages of the pharmaceutical value chain, from API synthesis to the production of final dosage forms. The emergence of continuous flow chemistry has provoked a renewed attention to both synthesis and downstream processing, including purification, isolation, and product separation.

In contrast to batch schemata, wherein purification frequently represents a process bottleneck, microfluidic flow systems permit the seamless integration of reaction, separation, and analytical modules within a single continuous platform.[125] The principal technical merits of microflow technology are: shortened diffusion pathways, resulting in accelerated mass transfer rates; elevated interfacial surface area per unit volume, facilitating intensified phase contact; precise hydrodynamic regulation, enabling reproducible residence-time distributions and temperature profiles. Collectively, these attributes lead to increased reaction kinetics, reduced purification residence times, and enhanced chemoselectivity.[126] Recent research has placed particular emphasis on the incorporation of in-line purification techniques into multistep continuous syntheses, which can simplify scale-up and reduce, or altogether obviating, the need for intermediate isolation of reaction intermediates.[127]

Beyond the retrofitting of conventional batch unit operations for continuous execution, entirely new continuous technologies are under active investigation. To fully capitalize on the benefits of continuous flow, unit operations that have historically been developed in isolation must be integrated into end-to-end platforms, extending from raw material feed to the final drug product.[127] Even the coupling of two consecutive unit operations remains technically challenging. The design of such integrated systems therefore demands a rigorous mechanistic understanding of individual steps combined with a holistic, systems level approach to process development and optimisation.[38]

Effective purification strategies must be based on the physicochemical properties of the target compound rather than on trial-and-error

Table 1. Representative multistage continuous flow routes, separations, and process-analytical monitoring for active pharmaceutical ingredients.

Name	Publication year	Drug class	Number of stages (full synthesis, partial synthesis)	Flow analysis method	Continuous Flow separation method	Ref.
Ibuprofen	2009, 2015, 2019	nonsteroidal anti-inflammatory drug (NSAID)	full synthesis	IR and NMR spectroscopy		148,149,191
Artemisinin	2012	Antimalarial drug	full synthesis	IR and NMR spectroscopy	Liquid-liquid extraction	192
Olanzapine	2013	atypical antipsychotic (or second-generation antipsychotic)	full synthesis	UV spectroscopy	liquid-liquid extraction	193
Imatinib	2013, 2019	tyrosine kinase inhibitor (TKI)	full synthesis	UV spectroscopy		194,195
Tamoxifen	2013, 2023	Selective Estrogen Receptor Modulator (SERM)	full synthesis	IR and NMR spectroscopy		196,197
Atropine	2015, 2017	M-cholinergic antagonists	full synthesis	IR and NMR spectroscopy	Liquid-liquid extraction	123,198
Diazepam	2016	Benzodiazepine drug class, anxiolytic	full synthesis	IR spectroscopy	liquid-liquid membrane separation, crystallization, filtration	199
Lidocaine hydrochloride	2016	amide-type local anesthetic and a Class IB antiarrhythmic agent	full synthesis	IR and NMR spectroscopy		199
Ribociclib	2016	cyclin-dependent kinase (CDK) inhibitor	Hybrid synthesis (intermediate stages)	UV spectroscopy	liquid-liquid extraction	200
Captopril	2017	ACE inhibitor	full synthesis		Liquid-liquid extraction	201
Prexasertib	2017	investigational, small-molecule checkpoint kinase 1 and 2 (CHK1/CHK2) inhibitor	Hybrid synthesis	HPLC and refractometry	liquid-liquid membrane separation, crystallization, filtration	66
Acetylsalicylic acid	2018	non-steroidal anti-inflammatory drug (NSAID)	full synthesis	Raman and IR spectroscopy		202
Hydroxychloroquine	2018	Antimalarial drug	piperazine formation stage	IR and NMR spectroscopy	liquid-liquid membrane separation	203
Lomustine	2019	nitrosourea-class alkylating agent	Hybrid synthesis		Liquid-liquid extraction	204
Mesalazine	2021	aminosalicylate class	full synthesis	UV, IR, and NMR spectroscopy and HPLC (in-line analytical methods)	liquid-liquid membrane separation	121
Remdesivir	2023	antiviral compound (SARS-CoV-2)	full synthesis	IR and NMR spectroscopy	gas–liquid separation, filtration, liquid–liquid membrane separator, annular centrifugal extractor, fixed-bed reactor	205
Fluconazole	2026	Antifungal agent	full synthesis	UV spectroscopy	liquid-liquid extraction	206

experimentation. Hydrophobicity and acid-base character (pK_a) dictate the success of liquid-liquid extraction: multistage counter-current cascades and membrane-based phase separators exploit pK_a differences to selectively partition ionised actives from neutral impurities. Molecular weight and molecular dimensions are critical parameters for nanofiltration in organic solvents, enabling facile separation of catalysts from low-molecular-weight products. Specific affinity for functional groups is harnessed in solid-phase sorbent cartridges: thiol-functionalised silica efficiently captures metals such as palladium and copper, whereas basic resins neutralise acidic species. Solubility and supersaturation kinetics underpin continuous microfluidic crystallisation; rapid micromixing with an antisolvent or precise temperature control generates uniform supersaturation, allowing deliberate control of polymorphism and particle-size distribution.

Based on the current literature, extraction and purification techniques suitable for continuous manufacturing can be categorised (Table S1).[125] In the present review these categories are examined systematically, with emphasis on recent technological advances, persisting knowledge gaps, and prospective research directions.

Physically driven separation methods

To date, microfluidic technologies offer a wide range of tools for the manipulation of particles and cells including transport, separation, capture, and enrichment by exploiting hydrodynamic, acoustic, electric, optical, and magnetic phenomena.[128]

Electrophoresis and dielectrophoresis (DEP) constitute the principal electric field-based strategies for handling micro-objects in micro streaming conditions. These techniques are routinely employed to separate uncharged microparticles (e.g., polymeric microspheres, biological microparticles), cells, nanoparticles, and organic aggregates within chip-integrated platforms.[129,130] However, because of their complexity, these techniques are used only in selected cases. For example, an electrophoresis system capable of analyzing and isolating optically active amino acids from the surface of Mars was installed on the rover.[131]

Acoustophoretic manipulation uses standing ultrasonic waves that generate acoustic radiation forces, driving particles toward pressure nodes or antinodes depending on their density and compressibility. This approach is particularly valuable for the gentle fractionation of delicate organic particulates and bio-organic systems, as it preserves structural integrity.[128]

Inertial separation in spiral microchannels relies on the interplay of centrifugal forces and secondary (Dean) flows that arise under laminar conditions in curved geometries.[132] The resultant size- and density-dependent lateral focusing enables continuous downstream isolation of reaction products, removal of solid by-products, and scalable stream purification in flow chemistry settings, while offering high throughput and seamless

integration with microreactor modules.[133]

Magnetic fields serve as an efficient post-reaction purification and product-separation tool by directing the motion of magnetic nanoparticles and functionalized catalysts within the flow. In practice, Fe_3O_4 nanoparticles conjugated to a catalyst or target compound are extracted from the reaction mixture under the influence of an external, non-uniform magnetic field without halting the process.[134] This strategy permits truly continuous flow-mode clean up, reducing the number of conventional sample preparation steps and reducing or eliminating the need for extraction or filtration.[135]

Nevertheless, despite their demonstrated versatility, these physically driven separation methods based on external force fields are currently scarcely applied in the context of organic synthesis.

Sequential stages for purification and isolation

In general, the techniques employed for purification and isolation can be subdivided into three sequential stages: primary processing, intermediate purification, and final purification. The selection of a continuous purification strategy should be based primarily on the physicochemical differences between the target API and the impurity population. Liquid–liquid extraction is favored when differences in polarity, ionization state, pKa, or partition coefficient provide sufficient phase selectivity. Membrane processes are more appropriate when molecular size, solvent compatibility, and membrane–solute interactions permit selective retention or permeation. Scavenger systems rely on specific chemical or coordinative interactions between functional groups on the sorbent and the impurity, making them particularly effective for trace metals and reactive residues. Chromatography is preferred when structurally similar compounds, regioisomers, or enantiomers require high selectivity that cannot be achieved by bulk phase separation. In contrast, crystallization becomes attractive when differences in solubility, supersaturation, nucleation kinetics, or solid-state properties can be exploited to selectively isolate the desired API. Thus, the optimal purification train is determined by the molecular properties of the product and impurities, rather than by the nominal availability of a particular separation technology.

Primary processing. Primary processing encompasses extraction and phase separation operations. Liquid-liquid extraction (LLE) remains one of the most versatile primary processing methodologies for reactive mixtures in continuous-flow microfluidic systems. It is routinely applied for reaction quenching, removal of inorganic impurities and catalysts, and phase switching, thereby conditioning the stream for downstream synthetic steps, simplifying subsequent purification, and markedly reducing the burden on chromatographic separations.[125,136,137] Nevertheless, the efficiency of LLE is governed by thermodynamic distribution coefficients and is often limited by kinetic phenomena such as the formation of stable emulsions and sluggish phase coalescence, particularly under microfluidic flow conditions.[138]

Although microchannel chips constitute the most common implementation, the literature also reports alternative reactor configurations. For instance, a Taylor–Couette microreactor has been employed to intensify liquid–liquid mass transfer.[139] Reported mass transfer coefficients are an order of magnitude higher than those obtained with conventional mixers, enabling extraction of reaction products on the time scale of seconds. Such systems are suitable for the continuous neutralisation of reaction streams following nitration or Friedel–Crafts processes, where rapid removal of acids and salts is required.

Intermediate purification. Intermediate purification includes scavenger cartridges and membrane-based techniques. Scavenger systems are typically realised as packed-bed reactors containing functionalised polymeric media that selectively bind contaminants. In microflow environments they provide continuous solid phase purification, allowing the removal of excess reagents, side products, and trace metals. The principal mechanism is either chemisorption or coordinative binding at the surface of the functional groups.[140] The high specific surface area and short diffusion paths afford rapid adsorption kinetics, making operation feasible at very short residence times. Specialized scavenger materials (e.g., silica gels functionalised with thiol, amino, or phosphine ligands for Pd/Cu removal play a particularly important role.[141,142]

Implementation of solid-phase carriers yields a distinct performance profile: high product purity can be achieved without recourse to chromatography, albeit with a modest decline in overall yield.[143] For example, in the synthesis of triazoles a sequence of four scavenger cartridges afforded a 55% isolated yield with 95% purity.[144] The principal limitations of this approach are sorbent saturation, fouling, and limited selectivity when separating closely related species. Despite these constraints, scavenger-based platforms are widely deployed as intermediate purification steps in multistage flow processes, especially within the context of pharmaceutical synthesis.

Recent review articles have demonstrated that the coupling of membrane technologies with microfluidic platforms creates novel opportunities for the continuous separation and purification of reactive streams.[145,146] Membranes can be directly incorporated into micro-fluidic chips, yielding compact "react-separate" modules capable of removing homogeneous or heterogeneous catalysts (e.g., Pd, Grubbs-type complexes), concentrating the desired product, and recycling organic solvents.

The membrane operations most frequently employed in this context are organic-solvent nanofiltration (OSN) and pervaporation. Both techniques enable catalyst recovery, product concentration, and solvent reclamation without interrupting the flow or resorting to energy intensive distillation. A particularly illustrative case is the work of Noël`s group, in which OSN was used to recover the photocatalyst tetrabutylammonium decatungstate (TBADT) within a microreactor.[147] The authors showed that the membrane-based recovery strategy makes it possible to translate TBADT mediated photochemistry from laboratory scale to industrial production without incurring additional catalyst cost.

Membrane-based downstream processes, especially OSN and membrane-assisted crystallisation have already been deployed successfully for pharmaceutical intermediates and APIs such as ibuprofen, erythromycin, and various steroids.[148,149] Reported benefits include a 40–70% reduction in solvent consumption, a marked decrease in the number of chromatographic steps, and the attainment of pharmaceutically acceptable purities. These findings support the potential of membrane-based isolation for both advanced flow synthesis (AFS) and conventional organic drug manufacture.[150] Nevertheless, widespread adoption is hampered by the challenges associated with fabricating chemically robust membranes and by the generally lower selectivity of membrane separations relative to high-performance chromatography.[151]

Final purification: continuous chromatography and crystallisation. The terminal purification stage traditionally relies on chromatography and crystallisation. Continuous chromatography remains one of the most versatile but technically demanding separation methods. In microflow environments, miniature columns or liquid-liquid counter-current chromatography (CPC) systems are used for continuous product separation.[152] Continuous chromatographic methods consistently deliver the highest degree of purification, routinely achieving analytical grade product specifications (≥ 98–99% purity).[153] This performance cements chromatography's status as the "gold standard" of selectivity.

However, the superior purity is often accompanied by significant drawbacks: isolated yields frequently drop to 50–60% due to extensive product-streaming across the column, and the operation demands careful flow synchronization, specialized hardware, and detailed optimization of operating parameters (e.g., gradient profiles, residence times, temperature control).[154] Consequently, continuous chromatography is preferentially applied to the most challenging separations, such as the resolution of closely related isomers or the enantio-selective purification of chiral compounds, where alternative technologies cannot meet the required selectivity.[155]

Crystallisation in microflow

Crystallization is one of the most frequently used methods for purifying substances in a microflow. It is an effective way to control phase transitions, exploiting microchannel reactors whose characteristic dimensions range from a few tens to several hundreds of micrometres.[156] Unlike conventional, macroscale periodic devices, microfluidic platforms afford precise control over supersaturation, hydrodynamics, and residence time—parameters that are important for controlling nucleation and crystal growth.[157] The diminutive channel dimensions yield elevated heat- and mass transfer coefficients, enabling rapid and spatially uniform supersaturation build up while suppressing local concentration and temperature gradients.[158]

In microflow, a crystallisation can be implemented in a variety of operational modes, including continuous-flow, slug-flow, droplet-based systems, and

specialised vortex reactors such as Taylor-vortex or spinning-disc devices.[125,159] The most widely adopted configuration is antisolvent crystallisation, wherein a solution of the target solute is rapidly mixed with an immiscible or partially miscible antisolvent phase, triggering instantaneous supersaturation and nucleation. Owing to intense micromixing characterised by diffusion times on the order of 10^{-3}–10^{-2} s one can achieve a narrow particle-size distribution (PSD) and high process reproducibility (Figure 5).[160]

The kinetics of crystallisation are governed primarily by channel length and flow velocity. For example, microchannel systems have been shown to enable the efficient production of low molecular weight crystals such as acetaminophen,[161] β-alanine,[162] and 1,1-diamino-2,2-dinitroethylene (FOX-7)[163] with well controlled morphology and size. Moreover, the synthesis and crystallisation of metal organic frameworks (MOFs) in microflow afford crystals possessing tunable defect populations and enhanced sorption capacities when compared with those obtained by conventional batch methods.[164,165]

Another promising configuration for industrial-scale crystallisation is the plug-flow crystalliser, which operates by engendering discrete plugs (or segments) of two immiscible phases within a tubular conduit.[166] In the idealised case, each individual plug functions as an autonomous, periodically acting crystallisation zone (Figure 6).[159] Because the plugs flow as coherent bodies with minimal internal turbulence, mechanical attrition of the nascent crystals is greatly reduced.[167] This plug-flow strategy has been modelled for L-alanine,[168] and successfully employed for the crystallisation of glycine,[169] and a range of low-molecular-weight pharmaceutical compounds.

The foremost advantage of microfluidic crystallisation is the decoupling of nucleation and growth. In segmented flow devices, each droplet or slug operates as an autonomous micro-reactor with spatially uniform conditions, permitting precise regulation of the number of nuclei that form and effectively suppressing secondary nucleation. Taylor vortex reactors generate ordered vortex structures that provide intense radial mixing while maintaining minimal axial dispersion, further contributing to the production of a narrow particle size distribution.[170] Likewise, thin-film platforms such as spinning-disc reactors and vortex fluidic devices (VFDs) achieve exceptionally high rates of heat removal and mass transfer, which are critical for rapid crystallisation processes.

From a mechanistic viewpoint, microflow influences crystallisation through four principal factors: (a) accelerated attainment of supersaturation via vigorous micromixing; (b) suppression of concentration and temperature gradients within the reaction zone; (c) narrow residence time distribution (RTD) that ensures a well-defined exposure time for each crystallising element; and d) enhanced stability of the hydrodynamic regime, reducing fluctuations that could trigger uncontrolled nucleation.[171]

These interrelated effects enable not only tight control over crystal size and morphology but also deliberate manipulation of polymorphism—an issue of particular significance for APIs.[171] Consequently, the microfluidic crystallisation has emerged as a cornerstone of intensified chemical process technology, delivering high selectivity, reproducibility, and controllability in solid phase formation.[172,173]

Chromatography in flow-based and microfluidic technologies

During the development of flow-based and microfluidic processes, chromatography retains a dual function. On the one hand, it serves as a highly selective analytical tool for monitoring the composition of the reaction mixture, product purity, impurity profile, and stereochemical composition. On the other hand, chromatography remains one of the most versatile preparative -purification techniques, especially when the separation of structurally closely related impurities, isomers, or enantiomers is required.

In the analytical domain, the most widely employed techniques are high-performance liquid chromatography (HPLC), ultra high performance liquid chromatography (UHPLC), chiral HPLC, gas chromatography (GC), and related methods. In contrast to spectroscopic techniques, which can often be integrated directly into the process stream, chromatographic analysis generally necessitates sample withdrawal, dilution, occasional quenching of the reaction in the sample, filtration, and subsequent injection into the chromatograph. Consequently, HPLC in flow systems is more appropriately regarded not as an instantaneous real-time monitoring method, but as an automated online or nearline technique with a finite analytical delay.[151]

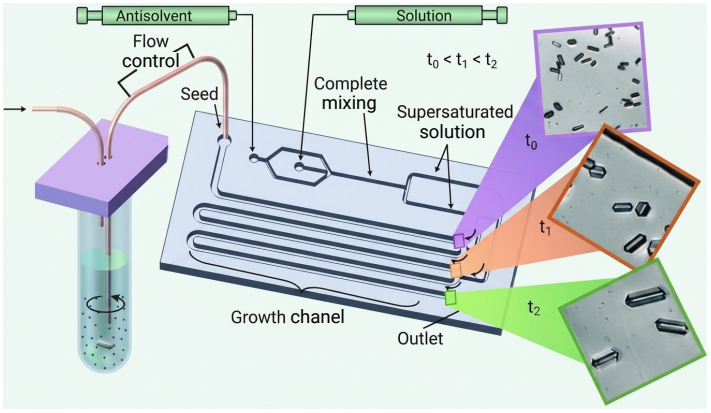


Figure 5. Schematic diagram of a microflow system with crystallisation in the presence of an antisolvent.[160]

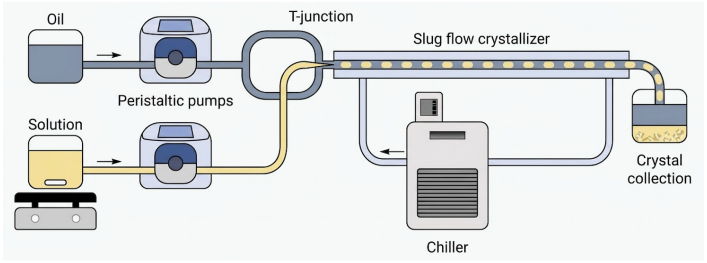


Figure 6. Schematic diagram of a slug-flow (segmented) micro crystalliser.[159]

Microflow chromatography has emerged as one of the most promising tools for the purification of APIs in continuous manufacturing. Such systems typically employ columns with diameters ranging from 0.1 to 1.0 mm and mobile phase flow rates of 1–100 μL min^{-1}, thereby markedly reducing solvent consumption and enhancing detection efficiency relative to conventional HPLC. The principal advantage of microflow systems lies in improved mass transfer characteristics and reduced analyte dilution. In recent years, a variety of continuous chromatography configurations have been developed, including multicolumn chromatography, simulated moving bed chromatography, periodic counter current chromatography, liquid-liquid counter current chromatography, and other related approaches.[144,152] Their common benefit is a more efficient utilisation of both the stationary phase and the solvent compared with a single periodic column, making these methods particularly valuable for separating closely related substances where extraction, membrane processes, or crystallisation fail to provide sufficient selectivity.

As an illustrative example, the study reported by Sivo et.al employed biphenyl, obtained via a Suzuki–Miyaura coupling of bromobenzene and phenylboronic acid, as a model compound (Figure S5).[174] A periodic chromatography process on a C18 resin was devised for its purification. Preliminary dynamic binding capacity experiments revealed a breakthrough of 1% product after loading 34 mL of the crude reaction mixture, corresponding to a loading capacity of 48.5 mg biphenyl per millilitre of resin. Based on this value, the periodic separation protocol was defined as follows: after sample loading, the column was washed with an aqueous Na_2CO_3 solution to remove polar impurities, followed by elution with acetonitrile. HPLC analysis of the collected fractions indicated a product purity of approximately 86%, an isolated yield of 51%, and a process productivity of 17 g h^{-1} L^{-1} of resin. The reduced yield was attributed to product losses incurred during the loading and washing steps required to achieve the desired purification level.

The transition from conventional analytical columns (inner diameter 2.1 mm) to microflow columns (inner diameter 0.3 mm) can dramatically enhance the sensitivity of mass spectrometric detection. Geller and co-workers reported up to a 49 fold increase in signal intensity depending on the analyte, with an average enhancement of 2-4 times relative to standard analytical flow rates.[175]

Representative studies on the continuous synthesis and purification of

ibuprofen illustrate how microflow chromatography can be coupled with reaction steps to improve overall process efficiency. Snead and Jamison described a three-minute, fully continuous synthesis-purification sequence, highlighting the integration of product isolation with rapid reaction kinetics.[148] Lee, Kim and co-authors later demonstrated a three step flow synthesis of ibuprofen from p-xylene using a unified sequence of chemoselective C-H metalations, again emphasizing the seamless combination of synthesis and downstream purification.[149]

While chromatography remains the workhorse for high-selectivity separations, recent advances in membrane technologies, particularly organic-solvent nanofiltration, show that a subset of tasks traditionally handled by chromatography can be transferred to operations with a considerably lower solvent footprint. Wen Z. et al. employed membrane-based recovery of the tetra-tert-butyl-hydroxydiphenylamine (TBADT) photocatalyst to increase the sustainability of continuous flow hydrogen atom transfer (HAT) transformations.[147] Similarly, Xiao H., Feng Y., Goundry W.R.F., and Karlsson S. reviewed the application of organic solvent nanofiltration to pharmaceutical processes, underscoring its potential to replace or augment chromatographic steps.[150]

A further advantage of microflow systems is their excellent compatibility with mass spectrometry. Reviews of microflow LC-MS have shown that reducing the eluent flow rate from 500 μL min^{-1} to 10 μL min^{-1} can improve ionisation efficiency by roughly a factor of seven, leading to overall sensitivity gains of 10-20 times compared with conventional analytical flows.[176]

Despite these benefits, the adoption of microflow chromatography is constrained by several technical challenges. Individual microcolumns exhibit relatively low loading capacities and are highly susceptible to extra column dead volumes, which can erode performance. Scale-up from laboratory scale devices to industrial production remains nontrivial, and the specialized hardware required for microflow operation incurs substantial capital costs. Nevertheless, the combination of low solvent consumption, high separation efficiency, and facile integration with continuous synthesis renders microflow chromatography a promising route for the production of highly pure active pharmaceutical substances (APIs) in modern pharmaceutical manufacturing.[177,178]

TRANSITION TO MODULAR AND CONTAINER-BASED CHEMICAL MANUFACTURING

The integration of continuous synthesis with inline purification and process analytics provides the technological foundation for the next level of pharmaceutical manufacturing: modular and containerized production. Once reaction, separation, purification, and monitoring functions can be implemented as interconnected continuous modules, the manufacturing system can be configured as a flexible process architecture rather than as a fixed sequence of conventional batch operations. This modular concept enables manufacturing capacity to be increased through parallelization and facilitates the deployment of compact production systems closer to the point of demand.

Short overview

In the past two decades, the chemical and pharmaceutical sectors have undergone a profound structural transformation that is characterized by a shift from large, centralized production facilities toward distributed, flexible, and low tonnage manufacturing systems. A central pillar of this transformation is the development of modular and container based "miniplants," which integrate the principles of process intensification, continuous flow chemistry, and digitalization of production (Figure S6).

The conventional life cycle of a chemical plant project comprises the following sequential stages: (1) Technology development; (2) Process and plant engineering; (3) Construction; (4) Commissioning; (5) Start-up of production.

When executed in the traditional linear fashion, this sequence may require up to ten years to complete.

In the modular paradigm, many of these stages are carried out in parallel: process development, module fabrication, and site preparation proceed concurrently. Consequently, the time required to bring a plant to operation can be reduced by a factor of two to three. This acceleration is especially critical for the pharmaceutical industry, where product life cycles often span less than ten years. For example, recent studies have demonstrated that replacing batch operations with continuous, modular production can increase the net present value (NPV) of a project by more than 30%.[179] Moreover, the reduction in construction time afforded by modularization contributes an additional ≈ 35% improvement in overall economic efficiency. These findings constitute a compelling argument for the industrialization of container based miniplants.

Container based miniplants are closely linked to the advancement of flow chemistry and microfluidic reactors. The continuous flow approach enables the seamless integration of synthesis, purification, and formulation into a single, uninterrupted technological chain. This integration underpins the "pharmaceuticals on demand" concept, whereby compact production units can be deployed at the point of consumption.[180] Furthermore, the transition to continuous manufacturing is regarded as a key element of "green chemistry," because it reduces energy consumption, minimizes waste generation, and lowers the risk of accidental releases.[181]

Concept of container based chemical production

Containerized plants consist of technological modules housed within standard shipping containers (typically 20- or 40-ft units) that incorporate a complete set of equipment required to carry out one or several stages of a chemical process (Figure S7).

A representative example of a readymade container platform is the Evotrainer system from Evonik Industries.[182] The deployment of an F3 container equipped with the primary utility system of the INVITE facility enabled a substantial reduction in process development time.[182,183] In general, the reactor suite provides robust scale up of laboratory results over extended operational periods without the risk of technological drif.

Contemporary investigations emphasize that modular installations are designed as standardized functional blocks comprising reactors, control systems, piping, pumps, and safety monitoring devices.

Key principles of the technology: (a) Standardization of equipment; (b) Scale up by addition of modules; (c) Transportability (containerized plants); (d) Digital integration and automation.

Modular installations permit rapid adaptation of production to new products and volumes, increasing flexibility and shortening the time required for plant start up and product launch.[186,187] Studies have shown that such systems are especially effective in niche and specialized chemical sectors (e.g., pharmaceuticals, biotechnology, specialty and low tonnage chemicals).[188] The modular approach can compress design timelines by several months and dramatically reduce capital expenditure, owing to the transferofalargeportionofassemblytothefactoryoftheequipmentsupplierandtothe standardization of processes. Moreover, "micro factories" can stimulate innovation by lowering the risk associated with the development of new technologies.[189]

A striking illustration is the development of a pilot scale synthesis of the rufinamide precursor. The cascade, multistep process operates essentially without organic solvents on a footprint of only 3 m^2, achieving a productivity of 47 g/h (> 400 kg/yr), which is seven fold higher than that obtained at laboratory scale.[184]

Because modular plants can be located closer to end markets and raw material sources, they diminish transportation costs and enhance the resilience of supply chains relative to large, centralized facilities.[186] These installations also handle smaller inventories of hazardous substances, feature compact equipment layouts, and lower the probability of accidents. Consequently, they achieve reductions in emissions, waste streams, and energy consumption.[190]

Containerized chemical plants demonstrate shorter payback periods and higher profitability than traditional technologies, especially for high value chemical products such as those used in the pharmaceutical industry, including darunavir (Johnson & Johnson), lumacaftor/ivacaftor/tezacaftor (Vertex), abemaciclib (Eli Lilly), and glasdegib (Pfizer).[48,185]

Concluding remarks

The analysis of recent scientific literature indicates that containerized and modular miniplants constitute one of the most promising paradigms for the future development of the chemical industry. The convergence of continuous

flow chemistry, process intensification, digitalization, and offsite construction creates a novel model of flexible, safe, and sustainable manufacturing. Numerous studies substantiate the economic, environmental, and technological advantages of modular installations, positioning them as a pivotal element of forthcoming distributed production networks. Accordingly, containerized and modular plants should not be viewed as a replacement for conventional large-scale facilities, but rather as complementary assets that together foster a resilient and adaptable industrial ecosystem.

CONCLUSIONS

The analysis of the recent literature demonstrates that continuous-flow chemistry and microfluidic technologies have progressed from promising laboratory concepts to one of the fundamental technological platforms of contemporary pharmaceutical industry. To date, approximately one hundred pharmaceutical compounds spanning diverse therapeutic classes have been reported in the literature as being synthesized under microfluidic conditions, underscoring the universality of flow chemistry for API production.

A particularly noteworthy observation is that the majority of modern processes already incorporate integrated PAT tools such as inline infrared (IR), nuclear magnetic resonance (NMR), ultraviolet (UV), Raman spectroscopy, high-performance liquid chromatography (HPLC), and refractometry. The combination of several analytical techniques within a single flow platform enables real-time quality control and markedly enhances process reproducibility. Further gains in efficiency are achieved through the integration of AI-driven optimization and self-optimizing reactors, thus laying the groundwork for autonomous chemical manufacturing. The next major breakthrough should be the development of autonomous, AI-driven, self-optimizing miniplants. Such fully closed-loop continuous production platforms should be capable of autonomous synthetic-route planning, real-time PAT-based feedback control, and self-healing parameter adjustment without human intervention.

Equally important is the development of continuous downstream-processing. It has been established that the incorporation of liquid–liquid extraction, membrane-based separations, scavenger systems, continuous chromatography, and microfluidic crystallization permits the construction of end-to-end platforms that minimize intermediate isolations and sharply reduce solvent consumption and energy demand. Membrane technologies and continuous crystallization are especially promising because they couple scalability with high selectivity, thereby decreasing intermediate handling, lowering solvent use, reducing the E-factor, and enabling the production of pharmaceutical substances in a fully continuous manner. A key objective for the next 5—10 years is therefore the creation of zero-waste, end-to-end continuous platforms integrating continuous reactions, inline organic-solvent nanofiltration (OSN) with solvent recycling rates above 95%, and continuous crystallization. Such integration could produce near-zero E-factors and support genuinely sustainable pharmaceutical manufacturing.

The economic implications of adopting flow chemistry are also significant. Contemporary studies indicate that transitioning from batch to continuous manufacturing can increase the net present value (NPV) of projects by more than 30% while simultaneously cutting operating expenses through reduced energy consumption, solvent usage, and waste generation. Capital expenditures are further decreased by employing modular and container-based production systems, which can shorten plant-commissioning times by a factor of two to three. Further progress will require standardized, plug-and-play containerized miniplants supported by universal international hardware and software standards. These systems could enable the rapid deployment of "pharmaceuticals-on-demand" manufacturing for personalized medicine and emergency responses to epidemics.

At the same time, the global market for flow chemistry and micro-reactor technologies is expanding rapidly. Current market analyses estimate the worldwide flow-chemistry market at over USD 2 billion, with a projected value exceeding USD 5 billion by 2033, representing a compound annual growth rate (CAGR) of approximately 11%. The microreactor segment is expected to grow even faster, driven by the expanding application of continuous synthesis in the pharmaceutical sector, advances in green chemistry, digitalization of production, and the implementation of AI-based control. Within this context, physics-informed AI digital twins represent another critical technological breakthrough. Hybrid machine-learning/kinetic digital twins could replace offline quality testing with instantaneous, regulatory-compliant Real-Time Release Testing, thereby accelerating batch release and strengthening real-time process control.

Nevertheless, large-scale deployment of continuous microfluidic technologies still faces several major challenges. Prominent among these are the absence of unified standards for equipment integration, limited chemical resistance of certain microreactor materials, difficulties associated with long-term operation, and the need to adapt existing regulatory frameworks to fully continuous manufacturing. An additional unresolved challenge is reactor clogging during the processing of high-solid-content streams. Addressing this limitation will require the design of clogging-free micro- and mesoreactors employing acoustic actuation, pulsatile flow, or active surfaces to handle highly concentrated solid suspensions and slurries without channel blockage. Moreover, the continued evolution of the field demands intensified interdisciplinary collaboration among chemists, engineers, automation specialists, data analysts, and AI experts.

Over the next 5—10 years, the industrial translation of continuous pharmaceutical manufacturing is likely to depend on five interconnected breakthroughs that directly reflect the four concepts introduced in this review. First, AI-assisted closed-loop systems should evolve from reaction optimization toward autonomous process operation and adaptive control. Second, physics-informed digital twins combining mechanistic models, PAT data, and machine learning could enable reliable prediction of process trajectories and support real-time release testing. Third, new reactor architectures capable of processing concentrated solids, slurries, and multiphase streams without persistent blockage will be required to extend microreactor technology to a broader range of pharmaceutical processes. Fourth, standardized modular and containerized production platforms could reduce the engineering and deployment time required for distributed manufacturing. Finally, the integration of continuous synthesis, purification, solvent recycling, crystallization, and formulation into end-to-end process trains could substantially reduce intermediate handling, solvent consumption, and waste generation. Together, these developments would transform continuous flow from an intensified reaction technology into an adaptive and distributed manufacturing architecture.

The engineering of comprehensive continuous manufacturing platforms for any dosage form constitutes a demanding technical problem. Yet, the number of peer reviewed publications that explicitly address this topic remains limited, revealing a clear lacuna in the scientific record. The development of fully integrated continuous systems for pharmaceutical synthesis, particularly for emerging drug-delivery modalities, offers pronounced technical and economic advantages and is anticipated to become a cornerstone of next generation pharmaceutical manufacturing.

In sum, the body of evidence presented herein confirms that continuous-flow chemistry, microfluidics, and digitized control platforms constitute the foundation of a new technological paradigm for pharmaceutical production. The convergence of flow chemistry, process intensification, AI-driven optimization, and modular manufacturing creates the conditions for highly efficient, sustainable, and intelligent chemical-pharmaceutical facilities of the next generation, capable of delivering a qualitatively distinct level of flexibility, safety, and environmental performance.

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Maxim S. Oshchepkov: Writing–original draft, Writing–review & editing, Visualization, Conceptualization; Konstantin A. Kochetkov: Investigation, Validation; Pavel A. Pavlov: Investigation, Visualization, Writing–review & editing; Mikhail Ilyin: Validation, Formal analysis; Alexander S. Oshchepkov: Writing–original draft, Project administration, Writing–review & editing. All authors contributed to and approved the final manuscript. All authors contributed to and approved the final manuscript.

DECLARATION OF INTERESTS

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ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.

SUPPLEMENTAL INFORMATION

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