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Perspective

Reshaping Chemical Manufacturing Towards Green Process Intensification: Recent Findings and Perspectives

Giancarlo Cravotto

Department of Drug Science and Technology, University of Turin, Via P. Giuria 9, 10125 Turin, Italy; giancarlo.cravotto@unito.it; Tel.: +39-011-6707183

Abstract: The chemical industry faces major challenges despite recent progress in the transition to more environmentally friendly processes. Sustainable industrial chemistry relies on the optimization of protocols and downstream processes such as extraction, purification, and drying. Process intensification, which includes non-conventional techniques and continuous manufacturing, has emerged as a key strategy to improve efficiency and environmental impact. Technologies such as ultrasound, microwaves, mechanochemistry, and reactive extrusion offer improved performance but face scalability and proprietary barriers. Flow chemistry offers additional benefits, including smaller reactors, lower energy consumption (from 40 to 90%), and increased safety through continuous, automated reactions. However, implementing these methods requires overcoming engineering, economic, and regulatory hurdles. Biphasic catalysis and sonochemical activation in liquid–liquid systems are promising approaches for scalable reactions under mild conditions. The pharmaceutical industry, a major source of waste, has shown resistance due to high validation costs and complex regulations. Fortunately, international regulatory institutions have introduced programs to facilitate the introduction of advanced technologies. Future perspectives emphasize the integration of modular, intensified processes with digitalization and smart manufacturing. Collaborative, transdisciplinary research will be crucial for accelerating commercialization and addressing sustainability challenges in chemical production.

Keywords: process intensification; non-conventional technologies; smart manufacturing; hybrid techniques; cost competition; flow chemistry

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1. Introduction

Although significant progress has been achieved in recent decades, the transition to greener industrial processes remains a long-term endeavor [1]. The chemical industry plays a pivotal role in numerous value chains and serves as a key driver of innovation and new-product development. Many industrial sectors continue to suffer the inefficiencies of suboptimal energy, material, and solvent usage, as well as the limited application of advanced technologies beyond the laboratory scale [2]. This fact is particularly evident in pharmaceutical manufacturing, as Prof. Nickerson (Washington University in St. Louis) and Prof. Macher (Georgetown University) report in a study in which the performance of 42 production sites of 19 companies was analyzed. In summary, they found that in the United States, inefficient production in the pharmaceutical industry results in an annual loss of 50 billion dollars [3]. Enhancing the sustainability of industrial chemistry heavily depends on the optimization of downstream processes, such as extraction, purification, crystallization [4], drying [5], and wastewater treatment [6].

As the chemical industry navigates the dual pressures of sustainability demands and cost competition, next-generation technologies cannot rely on a "green premium" alone to succeed. While these solutions offer substantial benefits, such as reduced environmental impact, improved safety and market growth, the challenges of implementation and cost must be thoroughly addressed. Industrial leaders must balance upfront investments in time and financial resources with long-term advantages. Economically viable solutions must be practical, cost-effective and resource-efficient. Process intensification using non-conventional techniques and continuous-flow manufacturing has emerged as a transformative strategy in the pursuit of green chemistry [7]. These methodologies focus on optimizing reactions and streamlining processes, leading to safer, more efficient and environmentally friendly industrial practices. By minimizing waste generation, energy consumption and resource use, process intensification and flow chemistry are driving the shift towards more sustainable production [8]. The use of cutting-edge technologies enables the chemical industry to improve its production processes while complying with legal regulations. Batch reactors are advantageous for processes requiring flexibility, solid handling, or small production volumes while flow tubular reactors excel in process efficiency, safety, and scalability, especially for continuous high-throughput production.

The choice depends on the specific requirements of the chemical process, such as reaction type, production scale, and desired product consistency (Table 1).

Table 1. Features comparison between conventional batch reactors and modern flow-through plants.

Features	Industrial Batch Chemical Reactors	Industrial Flow Tubular Reactors
OPERATING MODE	Discontinuous	Continuous flow-through
SCALABILITY	Limited—inefficient heat/mass transfer in big reactors	Scalable by numbering-up—parallel reactors
START-UP AND SHUTDOWN	Long time for charging, heating, and cleaning	Quick start-up and shutdown with minimal material loss
REACTION CONTROL	Constant monitoring and adjusting at each step	Precise, real-time control of reaction conditions
RESIDENCE TIME AT OPERATIVE CONDITIONS	Broad distribution; mixing efficiency varies across the volume	Narrow distribution; predictable and uniform residence time
HEAT AND MASS TRANSFER	Slow in large volumes	High surface area-to-volume ratio and laminar flow allows rapid transfer
ENERGY EFFICIENCY	High energy consumption for heating/cooling and impeller	Low energy requirements
PRODUCTIVITY	Limited to batch size; reduced throughput for downtime cleaning	High throughput; continuous operation eliminates downtime
SAFETY	Requires extensive safety systems—risk of large-scale exothermic reactions	Intrinsically safer due to smaller reactor volumes
FOOTPRINT	Large equipment and considerable space	Compact; smaller reactors with modular design
PROCESS CONSISTENCY	Variability between batches due to changing conditions	Highly consistent product quality due to steady-state operation
COST	High operational and maintenance costs	High initial investment in advanced systems, lower operating costs
AUTOMATION	Limited; often requires manual intervention	Easy automation with real-time monitoring
MICROWAVES	Limited penetration depth	Efficient and safe irradiation
ULTRASOUND	Limited penetration depth	Efficient, high-power density

2. Scaling-Up of Non-Conventional Techniques

The gap between laboratory-scale advancements and industrial implementation remains substantial [9]. Despite the promising results achieved with both ultrasonic and hydrodynamic cavitation techniques, their industrial application is still limited. Current industrial use is mainly observed in food extraction, processing, and wastewater treatment [10]. If these techniques were evolved into continuous flow-through systems, their potential would be maximized, leading to a revolution in extraction protocols, which are traditionally performed in batch processes. The downstream impact of sonocrystallization and ultrasound-assisted filtration is also worthy of note [11]. However, the widespread adoption of these innovations is often restricted by patents and proprietary industrial know-how, which limit knowledge diffusion and broader commercialization. Despite their extensive use in the food industry, the application of microwaves and radio frequencies in chemical manufacturing remains limited. The process intensification that can be achieved using dielectric heating has been demonstrated in hundreds of chemical reactions but is particularly efficacious in heterogeneous catalysis due to its ability to provide volumetric and selective heating [12]. Several companies now offer custom-designed industrial flow-through reactors with advanced safety features and precise process monitoring, highlighting the growing potential of the wider industrial adoption of these technologies [13,14]. Mechanochemistry is another promising green technology in which the remarkable lab-scale results achieved using ball mills highlight the potential of solvent-free processes. However, scale-up entails the adaptation of protocols and conditions for larger systems. Beyond a few examples of semi-continuous mechanochemical processes in ball mills, the most promising continuous-flow approach involves the use of reactive extruders; single-screw, twin-screw, multi-screw extruders, and even sequential units can be explored to match specific synthetic targets and residence-time requirements [15]. The extensive expertise of polymer scientists in this field could serve as a valuable resource for other areas of synthetic chemistry that have yet to fully embrace the potential of reactive extrusion [16].

3. Benefits of Process Intensification

One of the primary advantages of process intensification is its ability to significantly reduce the physical and environmental footprint of chemical processes. Traditional batch processes often require large reactors, substantial energy input, and extended reaction times [17]. By contrast, process intensification involves designing compact, efficient reactors that enable optimized reaction conditions [18]. This approach reduces the volume of chemicals and solvents required, increases yields, and minimizes waste, in adherence to the core principles of green chemistry. Flow chemistry, a subset of process intensification, further enhances this concept by conducting reactions in a continuous flow of reactants. This allows precise control over reaction parameters, such as temperature, pressure, and residence time, leading to improved selectivity and efficiency. Additionally, continuous flow systems enhance safety by reducing the volumes of hazardous reagents to be handled and enabling real-time monitoring and automation. These features make flow chemistry an appealing option for industries in which safety, efficiency, and sustainability are critical. Process intensification and flow chemistry also support process integration, combining multiple reactions or unit operations into a single continuous process. These findings have proven particularly transformative for the pharmaceutical and fine-chemical sectors as they often require complex multi-step syntheses. By optimizing and integrating reactions, these methodologies can significantly reduce the time, resources, and environmental impact of drug development and production [19]. This not only accelerates the discovery of new drugs but also contributes to making the pharmaceutical industry more cost-effective and sustainable. This integration reduces the need for intermediate purification steps, lowering

energy consumption and operational complexity. By seamlessly combining reactions, these approaches improve resource efficiency and reduce waste generation.

4. Challenges in Implementation: Slurry Reactions and Processes in Biphasic Media

To minimize volume, energy consumption, and environmental impact, slurry reactions present a promising opportunity, particularly for converting residual biomass into platform chemicals [20]. The conventional strategy to address the limitations of slurry reactions involves optimizing process variables such as temperature, pressure, particle size of the feedstock, and mixing rate with an impeller and reagent concentrations. While these methods can be effective for processes utilizing high-grade materials or producing high-value products, they are often associated with significant environmental drawbacks, including high energy and raw material consumption, extensive residue generation, and the release of pollutants and greenhouse gases. For the treatment or valorization of low-grade or waste resources, such traditional approaches frequently become impractical at an industrial scale. This underscores the need to incorporate sustainable solutions enabling technologies to drive process intensification. Scientific efforts have focused on laboratory-scale experiments to develop and validate multiscale process intensification strategies, complemented by thermodynamic and computational modeling. Advanced characterization techniques have been employed to clarify reaction and transport mechanisms, facilitating the creation of effective macroscale process models.

Despite the numerous advantages, the implementation of process intensification and flow chemistry presents challenges. The design and engineering of continuous-flow systems, besides the lower energy consumption (from 40 to 90%) require a deep understanding of reaction kinetics and fluid dynamics. Additionally, scalability and cost-effectiveness for large-scale industrial applications remain active areas of research. Addressing these technical and economic barriers is essential to wider adoption. Liquid–liquid phase transfer catalysis is a multiphase catalysis technique that involves simultaneous reaction and extraction in a biphasic, typically aqueous-organic system [21] with several new pathways for stereoselective reactions [22]. A surface-active transfer catalyst, such as a tetrabutylammonium ion, facilitates the transfer of an inorganic anion from the aqueous to the organic phase, enabling key reactions that would otherwise not occur. A valid alternative is the sonochemical activation of reactions in biphasic systems or non-solvent media, such as on-water reactions [23]. This intensified system offers several advantages, including novel synthetic routes, high product purity and yield, operational simplicity, mild reaction conditions, and suitability for large-scale synthesis.

5. Barriers to Greener Technologies in the Pharmaceutical Industry

According to Sheldon's analyses (Professor of organic chemistry at Delft University of Technology—Green Chem. 2007, 9, 1273), the pharmaceutical industry is among the highest contributors to waste, generating 25 to 100 kg of waste per kilogram of final product, in particular for the large use of solvents [24]. Fine chemicals used as intermediates for pharmaceuticals, flavors, and fragrances are not far behind with a material consumption of 5–50 kg per kilogram of product. Discussions surrounding the economic, environmental, and quality advantages of continuous manufacturing for commercial drug production have taken center-stage in the pharmaceutical industry. Implementing continuous manufacturing during development offers enhanced quality assurance and improved scale-up efficiency. Nevertheless, companies often hesitate to adopt new technologies due to concerns about validation costs, staff retraining, and potential disruptions to production. Regulatory approval processes are time-consuming and require extensive documentation,

particularly for processes involving novel energy sources. Additionally, the practice of outsourcing drug production to third-party manufacturers, often under short-term contracts, discourages long-term investment in sustainable technologies. However, regulatory agencies such as the FDA and EMA are increasingly supportive of innovation [25]. The FDA's Emerging Technology Program (ETP) is designed to encourage the adoption of innovative pharmaceutical manufacturing technologies to improve product quality, enhance process efficiency, and increase supply chain robustness [26]. The program provides a platform for early engagement between the FDA and pharmaceutical companies to discuss novel manufacturing technologies and their regulatory implications. The main tasks are continuous manufacturing, advanced process monitoring and control, and the process analytical technology (PAT), all with the support of artificial intelligence and machine learning in production. In Europe, the EMA's Innovation Task Force (ITF) is a multidisciplinary group established by the European Medicines Agency to support the innovation in drug discovery and production development [27]. The main goal is to provide guidance and early engagement to facilitate the adoption of advanced technologies. A streamlined approval pathway for continuous-flow production has also been established, highlighting the regulatory shift toward greener manufacturing.

6. Process Scalability to Industrial Manufacturing

Scalability in chemical processes involves transitioning from laboratory-scale experiments to semi-industrial pilot reactors and then to large-scale manufacturing while maintaining efficiency, cost effectiveness, product quality, and safety [28]. The scalability of a chemical process depends on several critical factors and considerations based on chemical engineering simulation and calculations. Reaction kinetics and thermodynamic parameters must remain consistent across scales as well as mass and energy transfer. These balances need recalibration at industrial scales to prevent inefficiencies, such as reactant losses or energy waste. It is worth mentioning the importance of pilot-scale studies, which can bridge the gap between laboratory scale and industrial production and minimize the risks. Therefore, the scalability assumptions must first be validated on this scale, as must the fine-tuning of the operating parameters. The same applies to the use of non-conventional energy sources such as microwaves, radiofrequencies, ultrasound, and hydrodynamic cavitation, the correct setup of which must be optimized at this stage.

7. Conclusions and Perspectives

Process intensification using non-conventional energy sources in flow-through mode presents innovative approaches for sustainable and efficient chemical processes. By optimizing reactions, reducing waste and enhancing resource efficiency, these methodologies align with the principles of green chemistry and are transforming the chemical and pharmaceutical industries. The convergence of disciplines within these fields highlights the potential of innovation to address critical sustainability challenges. Only transdisciplinary research teams made up of chemists, chemical engineers, and experts in digitalization and artificial intelligence can accelerate technological innovation and commercialization. One promising strategy involves the scale-up of hybrid technologies that have been successfully applied on the laboratory scale, such as the combination of hydrodynamic cavitation and electrical discharge, where plasma generation can mineralize recalcitrant pollutants in water [29].

The future of chemical manufacturing is characterized by flexibility and smart processes, and conventional 20th century solutions are incapable of meeting modern demands. Modular and intensified processes, coupled with digitalization and additive manufacturing, will play crucial roles in developing next-generation, efficient, and sustainable production systems. While financial feasibility remains a key barrier, combining modularity with

intensification should enable the transition to adaptable production facilities without the increased costs typically associated with smaller equipment scales. Ultimately, there is no doubt about the valuable contribution of artificial intelligence and machine learning methods in this area [30].

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References

1. Mathiesen, B.V.; Magni Johannsen, R.; Kermeli, K.; Crijns-Graus, W.; Lund, H.; Skov, R.I. The green transition of industry—An introduction to IndustryPLAN. *Smart Energy* **2023**, *11*, 100111. [CrossRef]
2. Kumar, V.; Kumar, P.; Maity, S.K.; Agrawal, D.; Narisetty, V.; Jacob, S.; Kumar, G.; Bhatia, S.K.; Kumar, D.; Vivekanand, V. Recent advances in bio-based production of top platform chemical; succinic acid: An alternative to conventional chemistry. *Biotechnol. Biofuels* **2024**, *17*, 72. [CrossRef]
3. Available online: https://source.washu.edu/2006/10/pharmaceutical-industry-wastes-50-billion-a-year-due-to-inefficient-manufacturing/ (accessed on 8 January 2025).
4. Vaidya, S.N.; Agrawal, S.; Lambole, V.; Pimpale, A.; Telrandhe, U. Pharmaceutical manufacturing continuous crystallization procedures: A review. *Asian J. Pharm.* **2023**, *17*, 344–354.
5. Mehanna, M.M.; Abla, K.K. Recent advances in freeze-drying: Variables, cycle optimization, and innovative techniques. *Pharm. Devel. Technol.* **2022**, *27*, 904–923. [CrossRef] [PubMed]
6. Verdini, F.; Abramova, A.; Boffa, L.; Calcio Gaudino, E.; Cravotto, G. The unveiling of a dynamic duo: Hydrodynamic cavitation and cold plasma for the degradation of furosemide in wastewater. *Sci. Rep.* **2024**, *14*, 6805. [CrossRef] [PubMed]
7. Sagandira, C.R.; Nqeketo, S.; Mhlana, K.; Sonti, T.; Gaqa, S.; Watts, P. Towards 4th industrial revolution efficient and sustainable continuous flow manufacturing of active pharmaceutical ingredients. *React. Chem. Eng.* **2022**, *7*, 214–244. [CrossRef]
8. Cespi, D. Procedural life cycle inventory of chemical products at laboratory and pilot scale: A compendium. *Green Chem.* **2024**, *26*, 9554–9568. [CrossRef]
9. Sardon, H.; Mecerreyes, D.; Basterretxea, A.; Averous, L.; Jehanno, C. From Lab to Market: Current Strategies for the Production of Biobased Polyols. *ACS Sustain. Chem. Eng.* **2021**, *9*, 10664–10677. [CrossRef]
10. Hu, D.; Liu, S.; Zhang, G. Sonochemical treatment for removal of aqueous organic pollutants: Principles, overview and prospects. *Sep. Purif. Technol.* **2025**, *353 Pt A*, 128264. [CrossRef]
11. Xiang, L.; Fu, M.; Wang, T.; Wang, D.; Xv, H.; Miao, W.; Le, T.; Zhang, L.; Hu, J. Application and development of ultrasound in industrial crystallization. *Ultrason. Sonochem.* **2024**, *111*, 107062. [CrossRef] [PubMed]
12. Martina, K.; Cravotto, G.; Varma, R.S. Impact of Microwaves on organic synthesis and strategies toward semi-industrial applications. *J. Org. Chem.* **2021**, *86*, 13857–13872. [CrossRef] [PubMed]
13. Note: Among them: Sairem (France), Püschner GmbH (Germany), Mitsui & Co. Ltd. (Japan), Mitindustrial (Italy), etc.
14. Mooney, T.; Ilamanova, M.; Torok, B. Microwave-Assisted Flow Chemistry for Green Synthesis and Other Applications. *Curr. Microw. Chem.* **2022**, *9*, 65–69. [CrossRef]
15. Gomollón-Bel, F. Mechanochemists Want to Shake up Industrial Chemistry. *ACS Cent. Sci.* **2022**, *8*, 1474–1476. [CrossRef]
16. Bolt, R.R.A.; Leitch, J.A.; Jones, A.C.; Nicholson, W.I.; Browne, D.L. Continuous flow mechanochemistry: Reactive extrusion as an enabling technology in organic synthesis (Tutorial Review). *Chem. Soc. Rev.* **2022**, *51*, 4243–4260. [CrossRef] [PubMed]
17. Cole, T.; Ani, P.; Jasim, A.; Zeitoun, Z.; Smith, J. Process intensification in reverse flow reactors to boost various industrial applications: A review. *Chem. Eng. Process.* **2025**, *208*, 110097. [CrossRef]
18. 3rd International Electronic Conference on Processes—Green and Sustainable Process Engineering and Process Systems Engineering. Available online: https://www.mdpi.com/2673-4591/67/1 (accessed on 8 January 2025).
19. Lei, Z.; Ang, H.T.; Wu, J. Advanced In-Line Purification Technologies in Multistep Continuous Flow Pharmaceutical Synthesis. *Org. Proc. Res. Devel.* **2024**, *28*, 1355–1368. [CrossRef]
20. Santos, R.M.; Zhang, N.; Bakhshoodeh, R. Multiscale Process Intensification of Waste Valorization Reactions. *Acc. Chem. Res.* **2023**, *56*, 2606–2619. [CrossRef] [PubMed]
21. Bogaerts, A.; Centi, G.; Hessel, V.; Rebrov, E. Challenges in unconventional catalysis. *Catal. Today* **2023**, *420*, 114180. [CrossRef]
22. Albanese, D.; Penso, M. New Trends in Asymmetric Phase Transfer Catalysis. *Eur. J. Org. Chem.* **2023**, *26*, e202300224. [CrossRef]
23. Pagadala, R.; Kasi, V.; Shabalala, N.G.; Jonnalagadda, S.B. Ultrasound-assisted multicomponent synthesis of heterocycles in water—A review. *Arab. J. Chem.* **2022**, *15*, 103544. [CrossRef]
24. Aboagye, E.A.; Chea, J.D.; Yenkie, K.M. Systems level roadmap for solvent recovery and reuse in industries. *iScience* **2021**, *24*, 103114. [CrossRef] [PubMed]

25. Saurabh, S.; Shweta, N.; Nagarjun, R.; Rajeev, S.R.; Shashi, B.S.; Saurabh, S. Bridging the gap: Academia, industry and FDA convergence for nanomaterials. *Drug Dev. Ind. Pharm.* **2020**, *46*, 1735–1746. [CrossRef]
26. Available online: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-program-etp (accessed on 8 January 2025).
27. Available online: https://eic.ec.europa.eu/document/download/07d8682a-6a27-4148-a544-4e56c2adf53d_en?filename=2.%20F.Ehmann%20-%20ITF.pdf (accessed on 8 January 2025).
28. The pathway to process scale-up. *Nat. Chem. Eng.* **2024**, *1*, 387–388. [CrossRef]
29. Verdini, F.; Canova, E.; Solarino, R.; Calcio Gaudino, E.; Cravotto, G. Integrated physicochemical processes to tackle high-COD wastewater from pharmaceutical industry. *Environ. Pollut.* **2024**, *342*, 123041. [CrossRef] [PubMed]
30. Selvaraj, C.; Chandra, I.; Singh, S.K. Artificial intelligence and machine learning approaches for drug design: Challenges and opportunities for the pharmaceutical industries. *Mol. Divers.* **2022**, *26*, 1893–1913. [CrossRef] [PubMed]

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