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Flow Chemistry Highlights

A CHIMIA Column

Review of Recent Literature on Flow Chemistry. Selected Topic: **Purification**

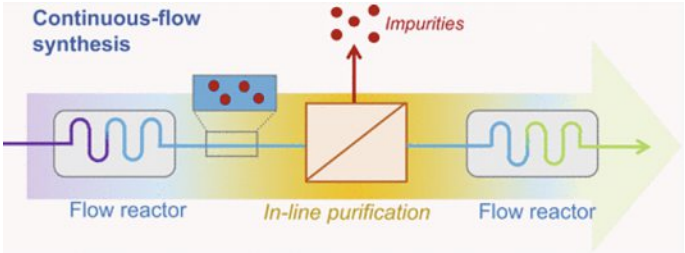
In-Line Purification: A Key Component to Facilitate Drug Synthesis and Process Development in Medicinal Chemistry

N. Weeranoppanant and A. Adamo* ACS Med. *Chem. Lett.* **2020**, *11*, 9-15, DOI: 10.1021/acsmedchemlett.9b00491

With the established capability of flow chemistry to run sequential chemical transformations, the off-line purification of intermediates in the sequence becomes a time-consuming operation, which is also unsuitable in the case of reactive or unstable compounds. In-line purification provides an elegant solution, and in this review four approaches are concisely outlined: use of scavenger resins; in-line distillation; nanofiltration & in-line extraction. Examples from each area are plentiful, and the latest developments are highlighted such as in-line evaporators capable of solvent-switching from high-boiling to low-boiling solvents; the use of polymers for organic solvent nanofiltration; as well as commercially available plug-and-play membrane separation devices which can also operate in a counter-current setup. Weaknesses of the approaches are also highlighted, and include trial-and-error scavenger resin selection; precipitation risks; gas-expansion upsetting flows; and the challenge of emulsions and solvents with low interfacial tensions. In-line purification is clearly in full development and can already support medicinal chemists in their integrated end-to-end syntheses.

***Author's comments**:*

''We have tried to provide an overview of current approaches to inline purification. Due to an ever growing demand for greater product quality and purity, we anticipated these technologies will keep on being developed and become available at different scales.''



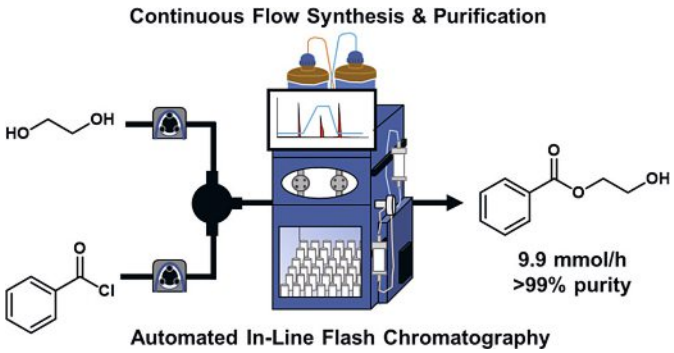
Expanding the Tool Kit of Automated Flow Synthesis: Development of In-line Flash Chromatography Purification

C. G. Thomson, C. Banks, M. Allen, G. Barker, C. R. Coxon, A.-L. Lee, and F. Vilela* *J. Org. Chem.* **2021**, *86*, 14079-14094, DOI: 10.1021/acs.joc.1c01151

Continuous flow systems are often regarded as easy to automate. While this may be true for the synthetic step, purification of the products is usually performed off-line. Thomson et al. present a solution to this issue by combining a commercial flash chromatography system with a flow reactor. Continuous operation is achieved by alternating between two chromatographic column systems: one collects the reaction mixture from the flow system while the other performs a chromatography run. Runs are synchronized by carefully matching the flow rates in the reactor and the duration of the chromatographic method. The authors demonstrated that re-equilibration of cartridges and storage in isopropanol when not in use are crucial to maintain good purification performance: a two-day experiment with a sequence of 100 runs showed excellent reproducibility. Four case studies showcase the utility of the setup: a proof-of-concept purification of 1:1 mixture of two components, a photochemical oxidation involving bi-phasic gas-liquid mixture, a heterogeneous photocatalytic oxidative coupling and finally an esterification with significant by-product formation. In all cases, products are isolated with 97–99% purity. In the final example, gram-scale productivity is reached. The paper finishes with useful recommendations on the system setup and operation.

***Author's comments**:*

"Automated synthesis and flow chemistry aim to expedite chemical discovery. Developing new 'tools' to facilitate fully automated synthesis systems is crucial for their success. Our system is significantly simplified from previous reports in literature and offers more flexibility, accessibility, and potential for further development."



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Would you like to propose a Flow Chemistry Highlight topic here?
Please contact Agnieszka Ladosz or Benjamin Martin, E-mail: agnieszka.ladosz@idorsia.com; benjamin.martin@novartis.com