

ENGINEERING FLOW CHEMISTRY

Klavs F. Jensen
Massachusetts Institute of Technology
Cambridge, MA 02139

Abstract

Flow chemistry” refers to the practice of organic chemistry in small continuous flow as opposed to the traditional batch chemistry approaches. The field has moved beyond single transformation to multistep synthesis with separation to produce active pharmaceutical ingredients (APIs). The presentation focuses on relevant reaction engineering challenges, specifically (1) automated screening and optimization of chemical reaction in microreactors and (2) integration of small-scale reactors and separators in on-demand continuous synthesis of APIs.

Keywords

Flow chemistry, automated optimization, on-demand multistep synthesis, surface tension driven separation.

Introduction

“Flow chemistry” is the term given by the organic chemistry community to organic synthesis in small continuous flow systems (tubes and microreactors) as opposed to the traditional batch chemistry approaches. In the past two decades, chemical synthesis in micro and mini systems has matured from simple demonstration examples to applications in pharmaceuticals and fine chemicals (Baxendale, 2013; Gutmann et al., 2015; Hessel et al., 2009; Jensen et al., 2014; Ley et al., 2015; Newman and Jensen, 2013; Wegner et al., 2012). Advantages of controlled mixing, enhanced heat and mass transfer, expanded reaction conditions, and ease of integration has driven this adoption of continuous flow techniques. Enhanced heat transfer allows safe operation of exothermic reactions with potential for run-away conditions. Moreover, continuous flow reduces accumulation of reactive or toxic intermediates and enables experimentation at conditions not easily accessed in batch, such as reactions at high pressure and temperatures.

The field has moved beyond single transformations to continuous multistep synthesis of active pharmaceutical ingredients (APIs) by incorporating in-line workup techniques (Baxendale et al., 2015; Heider et al., 2014). In the present contribution, the focus is on (1) automated screening and optimization of chemical reaction in microsystems and (2) integration of small-scale reactors and separators in on-demand continuous synthesis of APIs.

Automated Optimization and Screening

Integration of on-line measurements of reactant flows, reactor temperature, and outlet concentrations with feedback control systems has enabled automated optimization of reaction yields as well as determining kinetic information for subsequent scaling of the process. Measurements of reactants and products is typically the main analytical challenge. On-line Fourier transform infrared (FTIR) spectrometers based on attenuated total reflection (ATR) sampling are well suited for microreactor applications with microliter sample volumes (Carter et al., 2010; Moore and Jensen, 2012, 2014), but spectral overlap complicates the technique for complex organic reactions. For such cases, on-line high performance liquid chromatography (HPLC) sampling is the most general technique (McMullen and Jensen, 2010).

We have previously demonstrated the use of automated platforms to optimize reaction yields (Moore and Jensen, 2012) and to determine reaction kinetics (McMullen and Jensen, 2011; Moore and Jensen, 2014; Reizman and Jensen, 2012) by varying concentration and temperatures. However, in addition to those continuous variables, reactions have a large number of discrete variables (e.g., temperature, catalyst, ligands, and solvents). High-throughput technologies significantly enhance the speed of screening variables, but are often unable to account for temperature effects, reaction time, and reagent loading during the screen. In order to address

this challenge, we demonstrate the use of automated continuous/oscillating droplet flow microfluidic systems capable of simultaneously screening discrete variables (e.g., catalyst, ligands, solvents) in reactions while optimizing for continuous variables (temperature and reagent concentrations) (Reizman and Jensen, 2015).

A real-time design of experiments (DOE) based algorithm that applies feedback to the selection of discrete and continuous variables produces response surfaces and ultimately optimal conditions. The system is demonstrated for optimal selection of solvents and catalysts and well as library synthesis. Moreover, it is shown that oscillating droplet flow provides an effective separation of residence time and droplet speed enabling studies of reactions with large differences in reaction kinetics (Abolhasani et al., 2015).

On Demand Synthesis of APIs

The second topic concerns reaction engineering concepts for a plug-and-play, reconfigurable, refrigerator-sized manufacturing platform for on-demand synthesis of pharmaceuticals. This flexible system is capable of complex multi-step synthesis, in-line purification, post-synthesis work-up and formulation. The self-contained synthesis unit consists of clamshell reactors with an outer aluminum body for heat transfer and mechanical stability with inner coils of PFA (perfluoro alkoxy polymer), surface tension liquid-liquid driven extraction units, and multiline backpressure regulators to ensure flow distributions. Multistep synthesis occurs at elevated temperatures and pressures to enhance reaction rates, and the resulting residence times are a few minutes, in contrast to the multiple hour-long synthesis typically needed for batch. Typical production rates are grams/hour sufficient to produce thousands of doses per day of different APIs. Synthesis of common pharmaceuticals, including diphenhydramine, diazepam, lidocaine, and fluoxetine and is demonstrated.

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References

Abolhasani, M., Bruno, N.C., Jensen, K.F., (2015). Oscillatory three-phase flow reactor for studies of bi-phasic catalytic reactions. *Chemical Communications*, 51, 8916-8919.

Baxendale, I.R., (2013). The integration of flow reactors into synthetic organic chemistry. *Journal of Chemical Technology and Biotechnology*, 88, 519-552.

Baxendale, I.R., Braatz, R.D., Hodnett, B.K., Jensen, K.F., Johnson, M.D., Sharratt, P., Sherlock, J.P., Florence, A.J., (2015). Achieving Continuous Manufacturing:

Technologies and Approaches for Synthesis, Workup, and Isolation of Drug Substance May 20-21, 2014 Continuous Manufacturing Symposium. *Journal of Pharmaceutical Sciences*, 104, 781-791.

Carter, C.F., Lange, H., Ley, S.V., Baxendale, I.R., Wittkamp, B., Goode, J.G., Gaunt, N.L., (2010). ReactIR Flow Cell: A New Analytical Tool for Continuous Flow Chemical Processing. *Organic Process Research & Development*, 14, 393-404.

Gutmann, B., Cantillo, D., Kappe, C.O., (2015). Continuous-Flow Technology: A Tool for the Safe Manufacturing of Active Pharmaceutical Ingredients. *Angewandte Chemie-International Edition*, 54, 6688-6728.

Heider, P.L., Born, S.C., Basak, S., Benyahia, B., Lakerveld, R., Zhang, H.T., Hogan, R., Buchbinder, L., Wolfe, A., Mascia, S., Evans, J.M.B., Jamison, T.F., Jensen, K.F., (2014). Development of a Multi-Step Synthesis and Workup Sequence for an Integrated, Continuous Manufacturing Process of a Pharmaceutical. *Organic Process Research & Development*, 18, 402-409.

Hessel, V., Renken, A., Schouten, J.C., Yoshida, J., 2009. Handbook of Micro Process Technology (Volume 1 - 3), Handbook of Micro Process Technology. Wiley-VCH, Weinheim, Germany.

Jensen, K.F., Reizman, B.J., Newman, S.G., (2014). Tools for chemical synthesis in microsystems. *Lab on a Chip*, 14, 3206-3212.

Ley, S.V., Fitzpatrick, D.E., Myers, R.M., Battilocchio, C., Ingham, R.J., (2015). Machine-Assisted Organic Synthesis. *Angewandte Chemie-International Edition*, 54, 10122-10136.

McMullen, J.P., Jensen, K.F., (2010). Integrated Microreactors for Reaction Automation: New Approaches to Reaction Development. *Annual Review of Analytical Chemistry*, 3, 19-42.

McMullen, J.P., Jensen, K.F., (2011). Rapid Determination of Reaction Kinetics with an Automated Microfluidic System. *Organic Process Research & Development*, 15, 398-407.

Moore, J.S., Jensen, K.F., (2012). Automated Multitrajectory Method for Reaction Optimization in a Microfluidic System using Online IR Analysis. *Organic Process Research & Development*, 16, 1409-1415.

Moore, J.S., Jensen, K.F., (2014). "Batch" Kinetics in Flow: Online IR Analysis and Continuous Control. *Angewandte Chemie-International Edition*, 53, 470-473.

Newman, S.G., Jensen, K.F., (2013). The role of flow in green chemistry and engineering. *Green Chemistry*, 15, 1456-1472.

Reizman, B.J., Jensen, K.F., (2012). An Automated Continuous-Flow Platform for the Estimation of Multistep Reaction Kinetics. *Organic Process Research & Development*, 16, 1770-1782.

Reizman, B.J., Jensen, K.F., (2015). Simultaneous solvent screening and reaction optimization in microliter slugs. *Chemical Communications*, 51, 13290-13293.

Wegner, J., Ceylan, S., Kirschning, A., (2012). Flow Chemistry - A Key Enabling Technology for (Multistep) Organic Synthesis. *Advanced Synthesis & Catalysis*, 354, 17-57.