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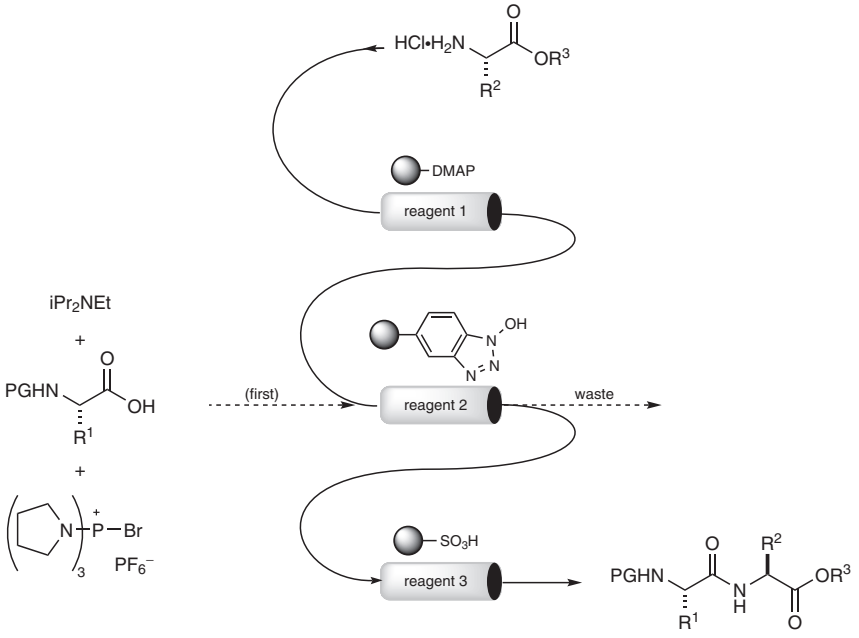
12 Pushing the Limits of Solid-Phase Peptide Synthesis with Continuous Flow

A. J. Mijalis, A. Steinauer, A. Schepartz, and B. L. Pentelute

Since its invention by Bruce Merrifield, solid-phase peptide synthesis has conventionally been performed in batch reactors. With systems created by Atherton, Dryland, and Sheppard in the 1980s, flow-chemistry techniques began to be applied to enhance solid-phase peptide synthesis, improving mixing and enabling time-resolved monitoring of Fmoc removal. Here, we review the history of flow-chemical techniques for solid-phase peptide synthesis, advances in solid supports that make flow chemistry on the solid phase feasible, the rationale behind using flow chemistry for amino acid activation, and other techniques for synthesizing peptides in flow, including the use of solid-supported coupling reagents and soluble macromolecular supports. Advantages of flow-chemistry techniques for both solid- and liquid-phase peptide synthesis include precise control of reagent heating and chiral integrity of incorporated amino acids, improvements in amino acid coupling times, and in-process detection of problematic peptide sequences.



Keywords: peptide synthesis · flow chemistry · amides · amino acids · activation · automation · solid phase

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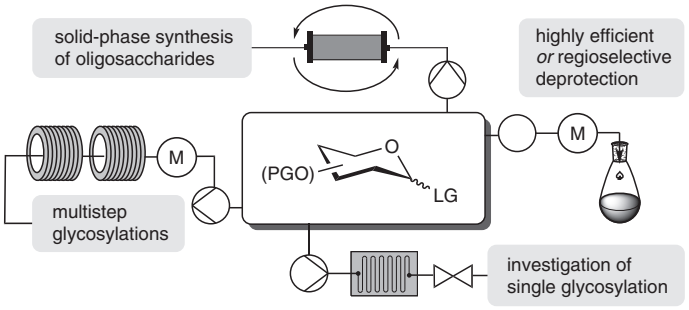
13 **The Controlled Synthesis of Carbohydrates**

S. Moon, K. Gilmore, and P. H. Seeberger

While the formation of the glycosidic bond is the key transformation in the synthesis of polysaccharides, a dominant class of biopolymer, the reaction is poorly understood and remains highly challenging to perform reliably and selectively in a laboratory setting. This is due to the numerous intermediates and competing mechanistic pathways present, all of which are extremely sensitive to the environmental conditions of the reaction. This sensitivity and irreproducibility is an excellent opportunity to take advantage of the inherent control over reaction conditions achievable in micro- and meso-flow reactors. In this chapter, the range of transformations performed under continuous-flow conditions related to the synthesis of carbohydrates, including glycosidic bond formation, functional-group manipulations, and multistep synthesis, are presented and discussed. The advantages gained in flow are highlighted and, where available, directly compared to the respective batch process.



Keywords: carbohydrates · flow chemistry · mixing · multistep · stereoselective · glycosylation · glycosidic bond · micromixer · microfluidic · monosaccharide · oligosaccharide · polysaccharide · automation · solid-phase synthesis

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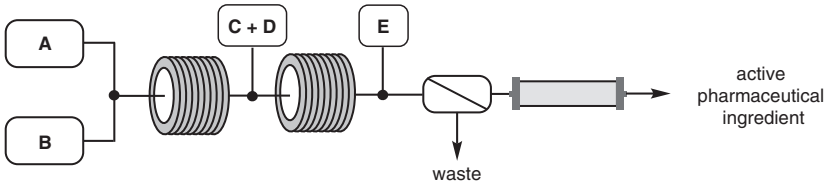
14 **Continuous-Flow Syntheses of Active Pharmaceutical Ingredients**

R. L. Beingessner, A. R. Longstreet, T. A. McTeague, L. P. Kelly, H. Seo, T. H. Tran, A. C. Wicker, and T. F. Jamison

This chapter describes synthetic strategies and technologies used to perform multistep flow syntheses of active pharmaceutical ingredients (APIs). The APIs or potential drug candidates highlighted are efavirenz, imatinib, (–)-oseltamivir, ibuprofen, rolipram, methylphenidate hydrochloride, and rufinamide.



Keywords: multistep processes · continuous-flow synthesis · essential medicines · polymer-supported catalysts · packed-bed reactors · copper tubing reactors · inline purification · biphasic synthesis · inline separation · semi-continuous · fully continuous

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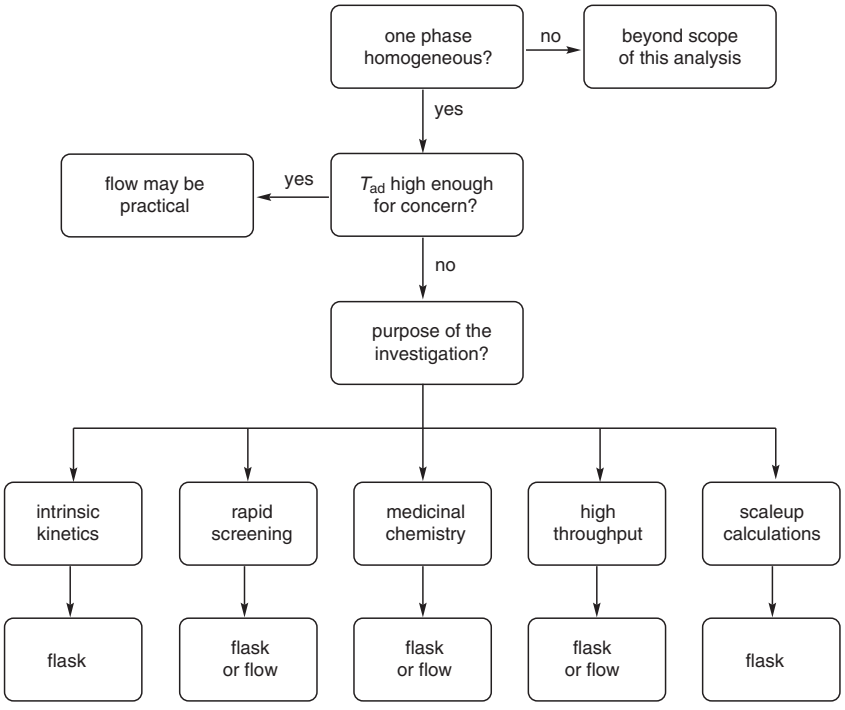
15.1 Flow Chemistry in the Pharmaceutical Industry: Part 1

A. G. O'Brien

The use of flow chemistry in the single- and multistep synthesis of active pharmaceutical ingredients has been well demonstrated. The pharmaceutical industry is now taking the next steps towards integration of flow chemistry into large-scale commercialized processes, which can effectively supply patient populations. This chapter details advances in this area, and outlines the data and knowledge required to select, develop, scale, and commercialize an efficient flow process.



Keywords: continuous-flow processes · pharmaceuticals · multistep processes · process selection · process development · scaleup · process optimization

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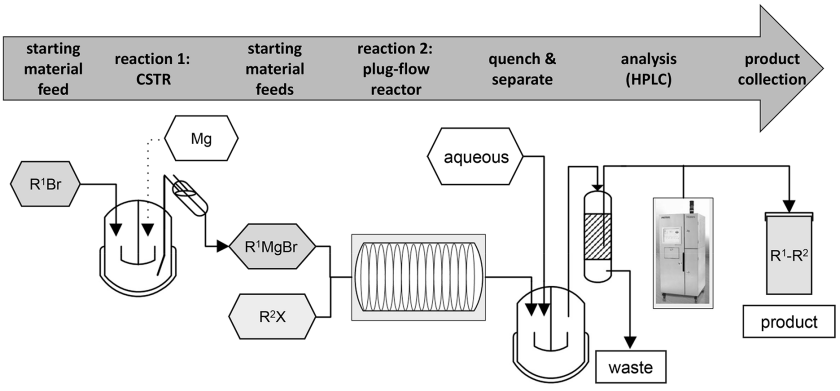
15.2 Flow Chemistry in the Pharmaceutical Industry: Part 2

S. A. May and M. S. Kerr

The development and application of continuous-flow drug-substance manufacturing at Eli Lilly is described. A series of examples are provided in which a continuous process was developed to solve problems associated with an existing batch process. The three distinct areas of focus are: facilitation of early phase delivery, hybrid batch/flow processes at manufacturing scale, and small-volume continuous manufacturing (linked multiunit operation processes at 10 kg/day throughput). An overview is provided of the types of reactors implemented in our program and the chemistries they enable. The use of online process analytical technology is also described for each of these systems. Special emphasis is placed on the examples pertaining to increased safety and improved product quality gained from flow processing.



Keywords: continuous processing · flow technologies · process analytical technology · plug-flow reactors · continuous stirred-tank reactors · intermittent stirred tanks · small-volume continuous manufacturing · process development · continuous crystallization

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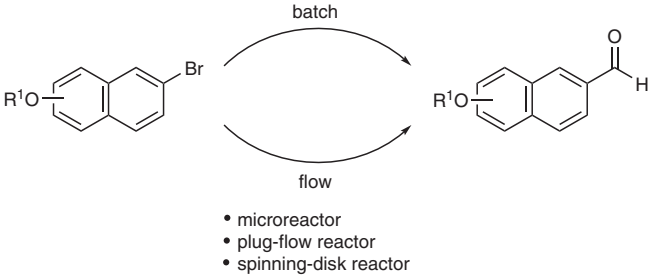
15.3 Flow Chemistry in the Pharmaceutical Industry: Part 3

S. M. Opalka, W. F. Kiesman, and D.-I. A. Kwok

When considering whether to develop a flow-chemistry approach to a particular synthetic route, the criteria of safety, quality, cost, sustainability, scalability, and speed are all considered. This chapter presents a case study of a single reaction, the formylation of an aryl bromide, being performed in a batch reactor, a microreactor, a plug-flow reactor, and a spinning-disk reactor. An assessment of the various technologies is made with respect to the abovementioned criteria.



Keywords: flow chemistry · scale-up · batch reactions · microreactors · plug-flow reactors · spinning-disk reactors · process development · optimization