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

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ABSTRACT: In-line purification is an important tool for flow chemistry. It enables effective handling of unstable intermediates and integration of multiple synthetic steps. The integrated flow synthesis is useful for drug synthesis and process development in medicinal chemistry. In this article, we overview current states of in-line purification methods. In particular, we focus on four common methods: scavenger column, distillation, nanofiltration, and extraction. Examples of their applications are provided.

KEYWORDS: Flow chemistry, flow synthesis, in-line purification, continuous separation; drug synthesis

In the early decades of drug discovery, medicinal chemistry relied on in vivo testing of a limited set of potential therapeutic molecules. However, after the 1980s, drug discovery has been accelerated by many technologies such as high-throughput in vitro screening and receptor-based pharmacology.¹ At the same time, characterization methods have been greatly developed, allowing for extensive studies of synthetic routes. Consequently, such advances in pharmacological testing and characterization have resulted in the rapid growth of new pharmaceutical entities.

In response to the increasingly large compound libraries, engineering work has progressed in order to enable efficient drug synthesis and process development. Traditionally, molecules are synthesized in batch. However, the batchwise approach can be time-consuming and inefficient. A number of reactions suffer from slow mass transfer, which in turn results in limited apparent kinetics.² Some highly exothermic reactions are difficult to operate in batch due to slow heat dissipation from a batch reaction unit.³ Moreover, a batch process also has several logistical disruptions such as material transfers between reaction units. This aspect renders a batch process unsuitable for high-throughput screening as well as synthesis that involves unstable or air-sensitive intermediates.^{4–6}

Flow chemistry has emerged as an approach that addresses the above-mentioned challenges. This technique is closely related to the concept of microreaction in which a particular transformation occurs as it flows through a micron-sized channel. In particular, flow chemistry refers to the methodology in which reactions are performed in tube reactors rather than fabricated microreactors.⁷ Flow chemistry and micro-reaction offer many similar benefits, including increased mass and heat transfer, which in turn allows for a more efficient

process, smaller reaction unit size, and greater safety. In some cases, reactions are more efficient in flow than batch such as multiphase reactive systems.⁸ Flow system also means that chemicals are handled and synthesized continuously, eliminating challenges caused by the disconnected nature of batchwise operations.

As a result, both flow chemistry and microfluidics continue to expand in applications in chemical synthesis. In the past, microreactors have been used to study reaction mechanisms and obtain kinetic information.^{9,10} Furthermore, with its efficient process, flow chemistry is useful for generations of a large set of compounds, particularly in serial parallel solution-based organic syntheses as well as combinatorial chemistry.¹¹ In the flow systems, process parameters such as reaction time and temperature can be precisely regulated. Therefore, drug candidates with specific bioactivity-focused structures can be produced via assembly of building blocks and known chemical reactions. Alternatively, flow synthesis can be integrated with computational target prediction to facilitate medicinal chemists in producing drug candidates.¹² Recently, researchers at MIT have developed a flow synthesis platform that uses software to identify possible synthetic routes for a target molecule and control a robotic arm to assemble units (e.g., reactors).¹³

Aside from automated drug synthesis, process development can also benefit from a flow chemistry approach. During the process development phase, engineers aim to obtain optimal operating conditions for synthesizing a target drug. Many works have reported the use of automated microfluidic systems

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for optimizing reaction conditions.^{14–18} Process variables, either continuous (e.g., temperature, concentration) or discrete variables (e.g., solvent and catalyst types), can be adjusted in an adaptive response to inline or online analytical results such as a LC/MS, a FTIR monitoring, and a UV–vis spectrometer. A similar concept for automated synthesis optimization and data acquisition was applied for continuous-flow reactors.¹⁹

Furthermore, a flow approach is beneficial to multistep synthesis. Drug molecules are complex and need to be transformed stepwise from simple precursors. Therefore, the synthesis of most drug compounds contains multiple steps of reactions. A flow system allows unstable intermediate to be transferred rapidly to a subsequent step. General examples of multistep organic synthesis in flow have been comprehensively overviewed.²⁰ Steps are often arranged sequentially although some of them can be carried out in parallel in order to produce different intermediates. In our perspective, multistep synthesis in flow can be developed by three approaches, as shown in Figure 1.

Figure 1. Schemes show different approaches for operating multistep synthesis in flow: (1) telescoping, (2) integration with off-line purification, (3) integration with in-line purification.

The first approach is to telescope multiple reactions or adjust reaction conditions such that all the steps are compatible. Solvents, excess reagents, products, and side products need to be considered. Examples include the syntheses of Ibuprofen,²¹ CCR8 ligands,²² Rolipram,²³ and Lidocaine.²⁴ This approach is simple to implement since it does not require any purification. However, telescoping multistep synthesis becomes more difficult as the number of steps increases. The second approach handles the intermediate purification off-line. Therefore, multistep synthesis via this approach is not fully continuous. Off-line purification methods include batch extraction, rotary evaporation, and chromatography. Off-line purification has major disadvantages of being time-consuming and unsuitable for highly reactive or unstable intermediates. In the third approach, all the purification steps are done in-line and continuously. In-line purification can separate impurities out from the main stream or remove excess reagents that may not be compatible with the subsequent reactive step. In this innovation article, we will overview the state-of-the-art techniques for in-line purification, particularly for applications in flow chemistry. There are four common methods that will be discussed, namely scavenger column, distillation, nanofiltration, and extraction.

To begin with, use of scavenger resins has been of great interest to many synthetic chemists because of its simplicity to separate desired and undesired compounds. Often, impurities will experience either an electrostatic or covalent interaction

with the resins, so that they can be isolated from the solution.²⁵ In batch, filtration can be employed to separate the resin-bound impurities from the product in the solution.²⁶ In flow, the resins are packed in a column; hence, the products remain in the reaction stream. Over the past decades, many examples of scavenger resins have been demonstrated in flow chemistry.²⁷ For example, the immobilized benzyl amine resins were used to remove isocyanide and acid chlorides, which were in excess during the preparation of oxazole derivatives.²⁸ The authors also showed that the immobilized phosphene resins could scavenge residual azide, which was a starting material in the process.²⁹ In another example, Omnifit glass tubes were used to pack scavenger materials for the multistep synthesis of triazoles and incorporated into the commercial flow-synthesis platform, Vaportec R2+/R4,³⁰ as shown in Figure 2. In the

Figure 2. (a) Scheme of the triazoles synthesis with scavenger resins to remove impurities. (b) Vaportec R2+/R4 with scavengers in glass columns. Adapted with permission from ref 30. Copyright 2009 Wiley-VCH.

system, the resins, Quadrature-benzylamine (QP-BZA) and Quadrature-thiourea (QP-TU), removed excess aldehyde and any leached copper. The base Amberlyst A-21, immobilized on polymer resins, was employed to catch unreacted carboxylic acid during the racemic resolution of flurbiprofen.³¹

Second, distillation is another method that has been used in flow chemistry. One of the early developments is vacuum membrane distillation on a microfluidic chip.³² In such a unit, a membrane layer is sandwiched between two channels, and serves as liquid-vapor contact. Methanol–water separation was achieved in the unit. Similarly, the microfluidic distillation from Klavs F. Jensen's group was demonstrated for solvent switch from dichloromethane to *N,N*-dimethylformamide between sequential reactive steps³³ (Figure 3a). Moreover, continuous reactive distillation could also be performed using a simple glassware setup with a Hickman still head.³⁴ The head had two ports, top and side. The intermediate was continuously withdrawn by a pump through the side port and sent to the subsequent reaction directly (Figure 3b). A closely related device is an in-line evaporator for concentrating or switching solvent during the flow process. The in-line evaporator was

Figure 3. (a) Microfluidic distillation for in-line solvent switch. Adapted with permission from ref 33. Copyright 2010 Wiley-VCH. (b) Hickman still head setup for continuous reactive distillation. Reproduced from ref 34 with permission from The Royal Society of Chemistry. (c) Prototype glass column for solvent switch. Adapted from ref 35 with permission from The Royal Society of Chemistry.

prototyped by Steven Ley's group using a glass column and metal fittings³⁵ (Figure 3c). The prototype was successfully implemented for solvent switch from toluene to methanol in a telescoped flow synthesis.

Third, nanofiltration is a promising in-line purification that is based on molecule sizes. In the past, nanofiltration has been applied to facilitate solvent switch,^{36,37} recovery of catalysts and solvent,^{38,39} as well as removal of impurities.⁴⁰ Recently, it has been found useful for the development of continuous synthesis, thanks to the progress in membrane materials and properties such as organic solvent nanofiltration (OSN). Gursel et al. (2015) overviewed several examples that employed OSN for recovery of homogeneous catalysts in continuous-flow process⁴¹. As an example, sustainability of the continuous-flow Michael addition process was improved by operating the in situ OSN to recover and recycle solvent and excess reagent.⁴² As a relatively young area, OSN has begun to be used in pharmaceutical synthesis. For instance, as shown in Figure 4a, a flow-through reactor/separator assembly was built

Figure 4. (a) Continuous-flow reactor/separator cell assembly for performing Heck coupling reactions and separating Pd catalysts. Adapted with permission from ref 43. Copyright 2013 American Chemical Society. (b) Nanofiltration module for separating metathesis catalysts. Reprinted with permission from ref 45. Copyright 2014 Wiley-VCH.

with the polymeric OSN membrane to separate the Pd catalyst from the Heck coupling reactions.⁴³ Similarly, the same research group also implemented two stages of OSN to separate a desired API, Roxithromycin, from a potential genotoxic impurity, 4-dimethylaminopyridine (DMAP).⁴⁴ Their design achieved a purity of 99% or greater. The use of Puramem 280, a commercial membrane for OSN (Figure 4 b), was reported for its function to separate and recycle metathesis catalysts in the flow setup.⁴⁵ Their work has proved that the flow system could separate the catalyst at 99.0–99.8%

rejection, which was similar in performance to the large-scale batch filtration.

Lastly, liquid extraction is a method to separate desired solutes from impurities, based on their different solubilities in liquids. As it involves liquid, this method can be made continuous. For applications in medicinal chemistry, extraction has been integrated with synthesis for two main applications: final and intermediate purifications. For the former application, continuous extraction is installed at the end of a flow synthesis to purify the final compound before using or sending to further downstream processing or formulation.^{46–49} On the other hand, the intermediate extraction is in between reactive steps in order to remove any impurities, including byproducts and excess reagents, from the desired intermediate.^{24,50–52} Researchers at MIT integrated in-line extraction with three reactive steps under pressure of 1.7 MPa in order to synthesize fluoxetine²⁴ as shown in Figure 5.

In the past decade, different designs of continuous extractors have been reported. The common designs are based on either a gravity or capillary force. The gravity-based extractor is similar to a conventional mixer-settler, but with a smaller volume. As shown in Figure 6a, a prototype high-efficiency extraction device (HEED) has been developed.⁵³ The device passed liquid streams to sparge-like adapters in order to generate thin streams into the glass column, where the light and heavy phases settled down as top and bottom layers, respectively. In some cases, a level detector is needed to maintain the position of the interface between the two layers such that the streams can be continuously pumped in and out. An electrical impedance probe could be used to control the phase separation between organic and aqueous phases,⁵⁴ as shown in Figure 6b. Another example monitored a position of a floating ball using a camera and a feedback control system.⁵⁵ This type of camera-based systems has been implemented for in-line extraction in many reactions including hydrazone formations^{55,56} and iodination.⁵⁷

Alternatively, the extractor can take advantage of surface forces. In 2007, a membrane-based microfluidic extraction device was developed by Krajl et al.⁵⁸ The main part of the device is a polytetrafluoroethylene (PTFE) membrane that selectively wets only nonaqueous phase and enables the separation between the aqueous and organic streams after their mixing in the tube. Pressure drop across the membrane must be balanced to ensure complete separation.⁵⁹ Microfluidic extraction was integrated with a microreactor to perform a multistep continuous-flow microchemical synthesis.⁶⁰ Related

Figure 5. Integrated multistep synthesis of fluoxetine with in-line membrane separations. From ref 24. Reprinted with permission from AAAS.

Figure 6. (a) High-efficiency extraction device in a glass column. Adapted with permission from ref 53. Copyright 2016 American Chemical Society. (b) Use of electrical impedance probe to monitor the phase separation in a glass tube. Adapted by permission from Springer, Journal of Flow Chemistry, Sprecher, H.; Payán, M. N. P.; Weber, M.; Yilmaz, G.; Wille, G., Copyright 2012. (c) Flow setup with a camera-based separator for hydrozone formations. Adapted from 55 with permission from The Royal Society of Chemistry.

approaches have been reported using different geometries of the separator, including a porous capillary^{61–63} and a slit shape.⁶⁴ To eliminate the need for manual control of the pressure drop across the membrane, Adamo et al. (2013) integrated a self-tuning pressure regulator to Krajčí's design. The regulator relies on a similar concept as a valve that can close or open a fluid channel. This allows the device to build up the pressure drop just enough to force only a wetting phase through the membrane⁶⁵ (Figure 7a). The device has now

been marketed by Zaiput Flow Technologies (Figure 7b). As a simple plug-and-play device, this membrane separator has been useful in continuous drug synthesis.^{24,46,66–68} Apart from drug production, it has also found many applications such as flow chemistry,^{69,70} separation of radioisotopes,⁷¹ and gas–liquid separation.⁷² The membrane separator has also been configured as multistage countercurrent extraction to improve the extraction efficiency,^{73–75} as shown in Figure 7c. Similarly, the setup has now been commercialized by Zaiput Flow Technologies, as shown in Figure 7d. Besides the membrane separator, some other examples of the multistage extraction setups have been reported.^{76,77}

In conclusion, this article provides an overview of current technologies for in-line purification that can be incorporated in continuous-flow synthesis. We discussed four techniques: scavenger resins, distillation, nanofiltration, and extraction. They are potential tools for drug synthesis. They can be implemented for diverse applications including removal of impurities, separation of volatile components/solvents, isolation, and recycling of catalysts. However, each of these techniques has its own challenges. For the scavenger resins, the resins need to be carefully chosen in order to have a high selectivity toward binding only impurities, and not a product. Moreover, the resins may be saturated after some time, so the flow synthesis needs to be stopped in order to replace the column. For in-line distillation/evaporation, the precipitation of the residue materials on the evaporator wall has been reported.³⁵ Gas expansion can cause an unsteady flow, making it difficult to implement in between reactors that require a steady flow. Likewise, there are a number of challenges with nanofiltration such as chemical incompatibility of the membranes, membrane fouling, insufficient rejection of solutes, and limited lifetime of the membranes.⁷⁸ Lastly, liquid extraction may also have limitations in some cases such as systems with an emulsion layer and those with a very low interfacial tension. It is sometimes challenging to choose an optimal solvent that has a high selectivity toward key solutes as well as a compatibility with all species in the stream.

As for future prospects, we expect that there will be developments of the devices that enable diverse applications at once. Ideally, a unit could be inserted into any synthetic route without the need for time-consuming customization or optimization. These types of ideal units can be used also in automated systems for drug-compound generations or process development. Higher selectivities can be achieved via improve-

Figure 7. (a) Prototyped membrane separator with self-tuning pressure control. Reprinted with permission from ref 65. Copyright 2013 American Chemical Society. (b) Membrane separators as commercialized by Zaiput Flow Technologies. Copyright Andrea Adamo. Used with permission. (c) Continuous-flow multistage extraction setup. Reprinted with permission from ref 73. Copyright 2017 American Chemical Society. (d) Multistage setup on market by Zaiput Flow Technologies. Copyright Andrea Adamo. Used with permission.

ments in chemical and engineering aspects. For example, different resins should be developed to enhance selectivity; alternatively, units can be arranged in multistage fashion to increase a level of separation.

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