Integrated Continuous-Flow Chemistry Enabled by Multistage Separations

by

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Abstract

Flow chemistry is becoming an accepted method of continuous synthesis with its considerable advantages over batch chemistry, such as smaller infrastructure, faster production, and safer operation for aggressive reactions or extreme conditions. However, to realize the full benefits of flow chemistry in multi-step reactions, continuous work-up techniques are needed. They will eliminate intermediate batch work-up steps that are often inefficient and time-consuming. This thesis describes the development of continuous liquid-liquid extraction and evaporation techniques along with their integration in multistep reaction sequences and purification on the mL/min scale.

Fully-integrated syntheses for active pharmaceutical ingredients (APIs), lidocaine and fluoxetine, were studied in detail. These two examples represent two different strategies for integrating multistep reactions. Sequential reactive steps in the lidocaine synthesis were designed to be compatible without any separation, while in-line purification, liquid-liquid extraction, was required for the fluoxetine synthesis. The key outcome of this work was the construction of a compact, reconfigurable system for manufacturing four different APIs, at throughput of hundreds to thousands dosages per day. The system represents a significant advance in continuous manufacturing by demonstrating feasibility of facility decentralization and on-demand production.

Another significant accomplishment of this thesis is the development of multistage liquid-liquid extraction using liquid-liquid membrane-based separators that enable highly efficient continuous extraction. While previous efforts have demonstrated a single stage or, at most, a few stages in crosscurrent configuration, the objective was to build a countercurrent extraction setup in the context of laboratory scale (i.e. mL/min). The setup was made possible with an integrated pressure control element, allowing non-precise interstage pumping to be employed. This setup was found effective for a wide range of industrially-relevant applications, from multicomponent solvent recovery to in-line removal of phase transfer catalysts.

The thesis provides opportunities for future directions. For example, improvement in unit operations, such as pumping, solid handling, evaporation, and process control, will be needed to reach the potential of flow synthesis. The countercurrent extraction setup can be automated for faster screening and optimization of extraction conditions as well as be applied to complex processes, such as reactive extraction and enantioseparation.

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Title: Warren K. Lewis Professor of Chemical Engineering
Professor of Materials Science and Engineering
This thesis is dedicated to my parents

Mr. Somphong and Mrs. Duangporn Weeranoppanant

for making all of my success possible
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Chapter 1. Introduction, motivation, and objectives

1.1 Introduction and motivations

1.1.1 Process intensification, microreaction technology and flow chemistry

Over the last few decades, manufacturing sectors have aimed to make a chemical production safer, greener, and more efficient. Such effort has revolved around a chemical engineering approach, process intensification [1]. While process intensification could refer to a wide range of scales such as reactive distillation on the macro scale [2, 3], a well-known example is microreaction engineering [4] in which a substantially smaller, micro-scale, device is utilized to create effects of significant thermal and concentration gradients. The result is a kinetically-enhanced reaction within a safe small setup which consumes less amount of reagents and generates less amount of waste. Numerous chemistries that gain benefit from this microfluidic paradigm have been demonstrated, ranging from the production of synthetic fuel and biofuel [5, 6] to ‘lab on a chip’ drug discovery [7] to the preparation of hazardous materials [8, 9].

Along with microreaction technology is the emerging field of flow chemistry – continuous flow applied to synthesis of fine chemical and pharmaceutical [10]. Flow chemistry promises to be a powerful tool with several advantages over batch chemistry. Sensitive reagents or intermediates are contained in a close system, making them less likely to decompose with exposure to oxygen and moisture in air [11]. Also, reactions in flow can be done at low volume. Aggressive and toxic materials can be handled more easily. The small length scale enhances mass as well as heat transfers, allowing chemists to explore a wider range of chemistry such as a highly exothermic reaction [12]. Moreover, traditionally, synthesis optimization is based on trial and error in a flask, a labor-intensive and expensive process due to large material consumption. Automated and monitoring systems can be integrated with flow synthesis to enable fast screening and optimizing of the reactive conditions [13-16]. The flow in a small channel is generally a laminar flow, its hydrodynamics of which can be reliably predicted and scaled to different throughputs. Lastly, recycle can be implemented to enhance mass efficiency of an overall process.

1.1.2 Continuous manufacturing of fine chemical and pharmaceuticals

With those benefits, researchers and industries have sought to expand flow chemistry’s applications. Most pharmaceutical companies, notably Novartis, have effects to transform the traditionally batch-wise, campaign-based operation into continuous manufacturing from preparation of active
pharmaceutical ingredients (API) to the final drug product. Continuous manufacturing addresses many present manufacturing challenges as discussed in the following three sections.

a) Efficiency and safety

As stated earlier, synthesis in flow can be conducted with smaller footprint for the same throughput as the batch operation. The short length scale not only improves mass and heat transfers but also facilitates reactions that require a short penetration depth to be effective, such as microwave reactions and photochemistry. The enhanced kinetics means a better yield with smaller amount of reagents, solvents, and wastes. Also the reduced footprint increases safety by allowing aggressive reactions to be handled in flow (e.g. oxidation, nitration, and reactions with carbon monoxide, cyanides, and phosgene) [17]. Because flow synthesis does not have headspace, evaporation and condensation can be avoided, and it is thus suitable for chemistry with low-boiling hazardous components, such as hydrazoic acid [18]. It has been reported that flow synthesis potentially benefits up to 30% of single-phase reactions and 60% of multiphase reactions [19-21]. For instance, Calabrese et al. showed a case study in which the time for hydrogenation can be reduced from an order of hours to minutes if changed from batch to flow [19].

b) Quality assurance

Batch operation is difficult to characterize due to its spatial and time-dependent variations in temperature, concentrations, and velocity profiles. On the other hand, the continuous process reduces problems into three dimensions because it is independent of time once it reaches a steady state. Reactions in flow with well-defined conditions lead to a greater level of consistency. A fast response of the continuous process to changes in process parameters result in a more robust process control [22]. Moreover, the current development in process analytical technology (PAT) can improve in-line monitoring to assure high-quality products.

c) Economic feasibility and supply chain

Pharmaceutical manufacturing is very expensive. The quantity required for stage 3 clinical trials is often as large as the quantity needed for an initial launch [23]; however, many products are abandoned for being insufficiently efficacious or unsafe for humans. Furthermore, the capital investment in building infrastructure for batch operation is estimated to be much higher than that for continuous production [24, 25]. Such high commercial risk makes it increasingly difficult to pursue batch manufacturing, which also incurs high operating cost. The highly efficient chemical process in flow brings about the reduction in reagent and solvent consumption and cost. Decentralized production is also possible owing to the small facility. Capability to produce drugs at local sites will enable the usage of local feedstock, shorten the
time for logistics, and eventually simplify the supply chain, especially for geographically different products [2].

In addition, the current markets for pharmaceuticals have been shifted away from blockbusters to more diversified drugs so as to respond to the new trend of personalized medicines and the specialized treatments. Owing to the high potency of new products, the production scale becomes an order of magnitude lower, from 100-1000 t.p.a. to 10-100 t.p.a., as shown in Figure 1 [26]. Manufacturing technology should allow quick change-overs and production for precise demands. The current production in batch has throughput scaling with the batch size, which often causes overproduction and high inventory cost. Sometimes, the excess products have to be discarded due to their short life or unsuccessful sales [25]. In a situation of product recalls (e.g. contaminated or out-of-spec products), a large amount of drugs from the same campaign must be returned, investigated, and destroyed.

![Production Scale Versus Potency](image)

Figure 1. Recent trend of moving towards lower production scale as a result of highly potent drugs [26]

Different unit operations can be fully integrated in flow such that fewer numbers of operators are needed. Overall, many case studies have shown that the operating and overall costs could be reduced by up to 40% if the production is conducted in flow [19, 24, 27].

From the industry perspectives, continuous manufacturing is chosen as a major priority to fulfill the concept of green engineering [28]. Flow syntheses of many active pharmaceutical ingredients have been studied such as Ibuprofen [29-31], Rufinamide [32], Diphenhydramine [33], and Alikasen [34, 35]. Recent survey indicates that 8 out of 9 big pharma companies have taken a continuous process to pilot or
even production scales [36]. However, a number of crucial elements, such as pumping and mixing, still need to be developed to ensure successful implementation, as shown in Figure 2 [25].

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Figure 2. Rating of crucial elements of implementation of flow processes by the American Chemical Society (ACS) Green Chemistry Institute (GCI) Pharmaceutical Roundtable [25].

1.1.3 In-line separation techniques

As shown in Figure 3, separations, usually contributing up to 75% of the total number of unit operations, play an important role in pharmaceutical synthesis [28].

![Figure 3](Image)

Figure 3. The frequency of different unit operations in current pharmaceutical production as surveyed by ACS GCI Pharmaceutical Roundtable [28].

However, the separations are normally performed in batch, and can be a bottleneck for flow synthesis. Although optimized conditions for each reactive step can be screened rapidly, the process still
demands laborious work for purification after reaction. In addition, work-up procedures can be major obstacles for scale-out to production scale. Multistep reactions often require extraction between steps, which are typically performed manually (e.g. with a separatory funnel) on laboratory scale. On larger scale, staged agitated batch vessels and centrifugal separators are often employed. The flows in most laboratory scale vessels are either laminar or transitional whereas industrial scale vessels are typically turbulent [37]. As a result, in terms of mixing, scaling from laboratory to production can be difficult.

In the past, several purification techniques under continuous flow have been proposed. Continuous crystallization has been developed. However, the method is difficult to implement, and it involves re-dissolution of the crystallized product. The use of scavenger resins in removal of trace metals and byproducts has been proved in flow chemistry applications [38-40]. However, this method requires frequent washing of solid-supported reagents, and it is limited to specific chemical species.

Chromatography is often used to purify compounds in the synthesis, typically for compounds that are thermally unstable and optically active. The classical preparative chromatography is linear and discrete rather than continuous [41], but the simulated moving bed chromatography (SMBC) has been developed to exploit the countercurrent flows of stationary and mobile phases to separate compounds in a continuous manner [6]. SMBC exists in both laboratory and industrial scales, widely used for separations of chiral molecules. Nevertheless, SMBC is only limited to binary mixtures and isocratic elution (i.e. the eluent composition remains the same over the course of operation). More importantly, SMBC’s investment cost is very high, making it economically infeasible in several processes.

Distillation is a common method of separating liquid mixtures, but its development at small scales remains challenging. In conventional distillation, gravitational force serves as a driving force for liquid flow. However, this requires sufficiently large dimensions of a distillation column for gravity to dominate interfacial forces (i.e., the Bond number, Bo $>> 1$). The small dimensions of laboratory flow chemistry systems mean that Bo$<1$, interfacial forces dominate. Another difficulty of microfluidic distillation arises from uncontrolled evaporation and flow instabilities [42]. A number of approaches have been developed to enable distillation in this regime. The use of a carrier gas for vapor transport has been employed. One of the early examples of carrier-gas distillation is the laminar evaporation by Wootton and deMello [43], in which the liquid is fed and mixed with a carrier gas stream. The mixture stream was maintained at high temperature (60 °C for DMF/acetonitrile separation), and then sent to the condensation section where the condensed liquid and gas was separated.

Hartman et al. engineered a microscale distillation operation with the use of inert gas that allows controlled boiling. Vapor-liquid segmented flows form, and are separated by membrane-based phase
separators. One equilibrium stage was achieved for 50% methanol-toluene mixture and 50% DCM-toluene mixture. The authors also extended the work to integrate this unit into multistep micro-chemical synthesis of the Heck reaction [44], as shown in Figure 4. The distillation serves as a means of solvent switch from dichloromethane to DMF (or Toluene), which is a polar aprotic solvent, suitable for the subsequent reaction step.

Figure 4. Left: distillation unit with gas-liquid membrane separator. Right: a single stage distillation integrated in multistage chemical synthesis

A capillarity-driven distillation uses materials such as fiberglass wick [45], woven stainless steel mesh [46] and metal foam [47] to guide a liquid flow and make contact with vapor. A similar approach, demonstrated by Lam et al. [48], incorporated micropillars in a serpentine channel in order to guide liquid flow, as shown in Figure 5. The system was tested with acetone/water mixture and methanol/toluene mixtures, and separation corresponding to 3 and 4 theoretical stages were achieved.

Figure 5. Left: capillarity-driven distillation unit. Right: distillation device with micropillars to guide liquid flow

Lastly, liquid-liquid extraction has been the most common method due to its high selectivity and large capacity with small energy consumption. It also offers a suitable way to purify heat-sensitive products. On the macro scale, the extraction mostly relies on density difference between phases.
Examples include mixer settlers, centrifugal contactor separators, and extraction-tray column. However, considering small scale, surface effect dominates over gravitational effect. The extent of gravity over surface tension can be implied by estimating the Bond number.

\[ B_o = \frac{\rho al^2}{\gamma} \]  

(Eq. 1)

where \( B_o \) is Bond number, \( \rho \) is density, \( a \) is acceleration (e.g. gravity), \( L \) is characteristic length scale, and \( \gamma \) is the surface tension.

On small scale (e.g. microscale, milliscale), \( B_o \ll 1 \), indicating that the surface phenomena becomes dominant. At this scale, the extraction occurs within two different types of flow patterns, stratified (side-by-side) and segmented flows, depending on its flow rate and solvent properties, such as viscosity and surface tension. Tokeshi et al. demonstrated the extraction of aqueous Co-2-nitroso-5-dimethylaminophenol to toluene, using a side-by-side microchannel [49], reduced the extraction time by 10-fold from the batch extraction using a separating funnel. The interface between phases can be even more stabilized using various approaches including half-channel surface functionalization and centerline structure. Although the side-by-side flow allows easy phase separation after extraction, the throughput is very limited (0.1 – 2 \( \mu \)L/min reported).

Segmented flow provides a larger interfacial area for mass transfer and higher system throughput, but it complicates phase separation. Kralj et al. [50] developed a liquid-liquid separator which incorporated a porous fluoropolymer membrane that selectively wets non-aqueous solvents. The authors subsequently demonstrated a practical example of multistage synthesis of carbamates that combined this device in the extraction step [51]. With the effect of capillary pressure inside membrane pores and applied pressures at the outlets, the aqueous and organic flow segments can be separated.
1.2 Thesis objectives

The primary objective of this thesis is to develop a full integration of multistep processes in flow. Examples of continuous pharmaceutical syntheses, at mL/min scale, will be presented. The result of this development is a compact, reconfigurable system for drug manufacturing that highlights several aforementioned advantages of continuous processes. Different approaches for telescoping multiple steps, such as use of compatible reactions or in-line separations, will be discussed.

In particular, the previous work on the membrane-based separation will be extended to a more complex setup. The aim for this part of the thesis is to establish a framework for multistage liquid-liquid extraction that leads to higher efficiency but reduced solvent consumption. The setup enables countercurrent extraction at laboratory scale. Different applications, ranging from solvent recovery to in-line purification of reaction streams, will be demonstrated to show the setup’s capability.
1.3 Thesis outlines

Chapter 2 provides an overview of the fully-integrated syntheses of the two drug molecules of interest, lidocaine and fluoxetine. Two major approaches for telescoping multistep reactions will be described along with the discussion of challenges and overall performance. The key process development steps will be provided in detail. In this chapter, another enabling tool for flow chemistry, a unit for in-line removal of volatile components, is presented.

Chapter 3 establishes a framework for the countercurrent liquid-liquid extraction setup. The design theory will be examined and validated. The setup performance is tested with standard systems. This chapter will also highlight some challenges as well as examine an operating window for this setup.

Chapter 4 presents applications of the countercurrent liquid-liquid extraction setup. The first example is a multicomponent solvent recovery system, which is usually difficult to optimize through simulation because physical properties become interdependent among different components. The second example is purification of phase transfer catalyst after alcohol oxidation in flow. The result is a high degree of separation with minimal solvent usage.

Chapter 5 summarizes the thesis results, offer opinions on various aspects of continuous manufacturing, and concludes the thesis with recommendations for future research.
Chapter 2. Integrated fully-continuous synthesis of pharmaceuticals

2.1 Introduction

Continuous manufacturing with synthesis in flow is becoming increasingly of interest to pharmaceutical industry over the last decade. There are several economic and technological drivers, such as shorter development time, lower cost, and more flexible facilities. Active pharmaceutical ingredients become more diverse in response to a current trend of personalized medicines, resulting in fewer blockbusters and more new competitive products. The flexibility of continuous production enables synthesis at low volume, making it feasible for making drugs with a small demand such as orphan drugs. Also, responses to a surge of demands such as epidemics and shortage crisis could be faster with decentralized facilities.

This chapter presents examples of continuous upstream syntheses of the active pharmaceutical ingredients. In particular, the production of fluoxetine highlights the full integration of multistep reactions and in-line purification with minimal amount of automated controls, simplifying the operation as well as providing the plug-and-play platform for the reconfigurable synthetic systems. A number of enabling devices, including a liquid-liquid separator, a sonicated reactor, and an in-line flash evaporator, were designed and incorporated into the syntheses.

2.2 On-demand, reconfigurable system for pharmaceutical production

Flow chemistry in a small channel opens up many opportunities for new synthetic routes since the fast heat dissipation implies that highly exothermic reactions can be handled safely and effectively. Multistep reactions can be connected to eliminate exposure to air (oxygen and moisture), providing a way to handle sensitive reagents and intermediates. Flow synthesis can easily be performed at elevated temperatures and pressures for enhanced kinetics. Those advantages generate interests in pharmaceutical and fine chemical industries to steer away from conventional batch processing and move towards continuous manufacturing.

Collaborations among three MIT research groups (Prof. Timothy Jamison, Prof. Klavs Jensen, and Prof. Allan Myerson research laboratories) allowed us to develop the first proof-of-concept system that is fully-integrated and reconfigurable for synthesizing and formulating four selected pharmaceuticals – namely lidocaine, diazepam, diphenhydramine, and fluoxetine – at a daily production rate of about one thousand dosages [52]. As shown in Figure 6, the developed refrigerator-sized Pharmacy of Demand (PoD) system had two main sections: upstream and downstream.
Figure 6. The refrigerator-sized PoD system showing (A) the upstream unit, (B) the downstream unit, (C) the reactor and liquid-liquid separator designs, and (D) the downstream processing units [52].

The upstream section synthesized the active pharmaceutical ingredients through integrated, continuous units for fluid delivery, metering, chemical reactions, separations, and online analysis. The downstream section conducted the final purification (e.g. crystallization, filtration) and liquid formulation. Several units in the PoD system were not commercially available, requiring us to develop those units in-house. The upstream section was arranged in sequential modules such that the system could be reconfigured for different productions, as depicted in Figure 7.
In the PoD system, three out of four syntheses consist of multiple reactive steps. There are two major approaches for integrating multiple reactions into one continuous flow. In the first approach, sequential reactive steps are completely compatible, eliminating necessity for any additional in-line purifications or solvent switch. This strategy is demonstrated through two examples: the syntheses of lidocaine and diazepam - both have very similar synthetic routes. The following discussion will be about the synthesis of lidocaine to exemplify the first approach of telescoping multistep reactions. Detailed description is provided in Appendix A.

In the synthesis of lidocaine, a stream of neat chloroacetyl chloride \((L2)\) was first mixed in a T junction with \(N\)-methyl-2-pyrrolidinone (NMP), and then in another T junction with a stream of 2,6-
xylyidine in NMP (L1). Here, the chloroacetyl chloride was not prepared off-line in NMP due to its time-dependent decomposition in NMP. The mixed stream flowed into a 10 mL reactor that was heated to a 120 °C, which was equivalent to a residence time of 18.4 min. The reaction stream was then combined in a T-junction with a stream containing 1) aqueous KOH solution and 2) diethylamine in a 1:1 solution of MeOH and ID water. Here in the amination step, the intermediate 2-chloro-N-(2,6-dimethylphenyl) acetamide was reacted with diethylamine to form crude lidocaine in a 30 mL reactor at 130 °C (equivalent to 17.1 min). The crude lidocaine could be subsequently processed downstream for further purifications such as (off-line or on-line) extraction and crystallization.

(A)

(B)

Figure 8. (A) The two-reaction synthetic route for lidocaine free base, (B) The flow chart shows the continuously streamlined reactors, separators, and downstream processes for producing lidocaine

In this example, the byproduct from the amidation step, HCl, was quenched by the aqueous KOH solution. Also, NMP was completely compatible for the amination step and miscible with water. No solvent switch or in-line extraction was required for this two-step flow sequence, which yielded 90% yield after an extraction with hexane and NaCl solution.

While the lidocaine example represents an excellent proof of concept of the telescoping strategy, finding compatible reactions becomes increasingly difficult with an increasing number of reactions. In that case, it becomes necessary to integrate multistep reactions using in-line purifications or solvent switches. Without the constraints of telescoping compatibility, each reactive step can be studied and optimized independently, providing advantages of flexibility and efficiency over the first approach. This approach is also more industrially relevant because small-molecule productions are mostly conducted with multiple reactions. An example of fluoxetine synthesis is demonstrated.
2.3 Design of integrated fully-continuous synthesis of pharmaceutical: Fluoxetine

2.3.1 Current state of fluoxetine synthesis

Fluoxetine hydrochloride, commercially known as Prozac®, is marketed as racemic drug for treating depression, eating disorders and obsessive-compulsive disorder (OCD). The original synthesis was developed by Molly Schmiegel at Eli Lilly in 1982 [53], consisting of 6 steps with acetophenone as a starting material. As shown in Figure 9, this batch synthesis requires slow additions of reagents such as diborane in the second step and sulfuryl chloride (SO₂Cl₂) in the third step, solvent switch using evaporation and time-consuming refluxes.

![Figure 9. The original synthetic scheme of fluoxetine developed by Eli Lilly Co. (adapted from [54]).](image)

With the growing interest in flow chemistry, a methodology for preparing fluoxetine with multiple flow processing steps was also developed by Ahmed-Omer and Sanderson [55], as shown in Figure 10. The synthetic route was adapted from the one developed for conventional flask preparation [56]. It consisted of three-step reactions, starting with a starting ketone molecule, 3-chloropropiophenone. The ketone group was first reduced to the secondary alcohol with borane (BH₃) in THF solution and continuously quenched with water. The reaction mixture was collected and processed with manual extraction and flash chromatography before feeding back to the flow system for the subsequent step. This step involved the biphasic (aqueous-toluene) iodination and amination of the alcohol with manual extraction and flash chromatography in between. After being purified using off-line “catch-and-release” method, the amino alcohol was mixed with p-chlorobenzotrifluoride and standard Mitsunobu reagents, tributylphosphine (PBU₃) and diethyl-diisopropyl-azo-dicarboxylate (DIAD), for an arylation via nucleophilic substitution into fluoxetine.
Figure 10. The fluoxetine synthesis in flow developed by Ahmed-Omer and Sanderson [55] involves three reactions and manual workups in between. A [ ] symbol indicates an off-line step.

The work proved feasibility of the flow-based system for synthesizing drug molecules, even in the presence of multiple steps. However, in order to take full advantages of the flow, the process needed to be continuously integrated. Manual work-ups between reactive steps are conducted off-line, and often time-consuming and laborious. Moreover, methods such as flash chromatography are difficult to scale-up and need to be replaced by in-line purification methods. The following section presents our example of the fully-integrated synthesis.

2.3.2 Process overview

We adapted the synthetic route developed by Ahmed-Omer and Sanderson, as highlighted in the previous section. As depicted in Figure 11. The process consisted of three reactive steps: ketone reduction, amination, and aromatic substitution. All the units in this synthesis were fully-integrated and pressurized at 250 psi. First, the starting material, 3-chloropropiophenone, was combined with the solution of 1 M DIBAL in toluene. Instead of BH₃, di-isobutyl aluminum hydride (DIBAL) was chosen as a reducing agent. BH₃ was thermally instable, and required cooling upon reagent delivery. The first reaction happened in a 5 mL reactor, equivalent to 10 min of residence time, at room temperature. The reaction stream was then quenched with aqueous 4 M HCl solution, resulting in the generation of aluminum salts. To prevent accumulative precipitation and clogging, an ultrasonic transducer was in-house built onto the reactor to enhance the dissolution of the aluminum salts. The following separation of biphasic stream was carried out in-line with membrane-based liquid-liquid separators. To completely remove excess DIBAL, an additional stage of extraction with another injection of 4 M HCl solution was used.
The intermediate alcohol in toluene was then mixed with the aqueous methylamine solution, forming again biphasic reaction. At 135 °C, the high conversion (93%) of the amination was achieved after a nominal residence time of 10 mins, even in the absence of iodination. The enhanced reactivity was likely due to the elevated temperature and pressure and the high mass transfer in the slug flow regime. Only minor gas bubbles of the amine were observed probably as a result of occasional overshooting of reactor heating. The amino alcohol was then extracted with the co-injections of THF and 20 wt% sodium chloride solution. The aqueous phase was removed again using the membrane-based separator while the organic phase was then sent to a drying column loaded with molecular sieves (MS, 4Å) to remove any residual water, which could cause precipitation in the subsequent reactor. The preheated amino alcohol in toluene was treated with 4-fluorobenzotri fluoride in DMSO and potassium tert-butoxide (0.25 M)/18-crown-6 (0.05 M) in DMSO. The reaction was completed within a residence time of 2.6 min at 140 °C. DI water was immediately injected at the outlet of the reactor to avoid any precipitation and clogging. The crude fluoxetine stream was finally depressurized and extracted with TBME using gravity-operated liquid-liquid separator, giving the overall yield of 43%.

![Reaction Scheme](image)

**Figure 11.** (A) Our synthetic route features three reactions of fluoxetine. Telescoped in-line workups are not shown in the scheme. (B) The flow chart shows streamlined reactors, separators, column, and preheating for the fluoxetine synthesis at 250 psi.

### 2.3.3 Process development and strategies

The earliest stage of process development here involved the optimization of the three reactions independently in μL/min scale with off-line purification. The reaction was carried out in the perfluoroalkoxy alkane (PFA) tubing with 0.03” ID and 1/16” OD, and heated in a temperature-controlled oil bath. This stage provided information about the optimal temperature, residence time, and
stoichiometry of reactants for each individual reaction. The next stage involved the scale-up and telescoping of the three reactions into one continuous flow. The flow rates of reagent streams and reactor sizes were scaled proportionally to achieve the target production of approximately 1000 dosages/day.

Unlike the synthesis of lidocaine, the three reactions of the fluoxetine synthesis were not compatible to one another, and they could not be directly linked. First, the byproducts, Al(OH)₃ and AlCl₃, and excess HCl needed to be removed before the amination because they could protonate MeNH₂ and in turn reduced the reactivity of the amination. Second, the amination occurs in a biphasic mode, but the following arylation did not tolerate water, so it was critical to remove the aqueous phase after the amination. In-line liquid-liquid extraction with membrane-based separators served as a means to integrate the three reactive steps. A two-stage crosscurrent extraction with aq. HCl solution was used to ensure complete removal of the Al(OH)₃. The amino alcohol intermediate after the amination was partitioned in favor of the aqueous phase. Different extraction solvents and ratios were tested. The co-injection of 20% NaCl solution and tetrahydrofuran (THF) resulted in the highest extraction yield. NaCl makes THF water-immiscible, and at the same time, THF carried the amino alcohol intermediate with it into the organic phase. THF was also a facilitating solvent for the subsequent aromatic substitution because THF was fairly polar, and it could lower the transition state energy.

Table 1. Screening of conditions for the extraction of the amino alcohol intermediate

<table>
<thead>
<tr>
<th>AQ extraction solvent</th>
<th>OR extraction solvent</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>33%</td>
</tr>
<tr>
<td>2 mL/min, 20% NaCl solution</td>
<td>None</td>
<td>44%</td>
</tr>
<tr>
<td>2 mL/min, 20% NaCl solution</td>
<td>0.5 mL/min, Toluene</td>
<td>56%</td>
</tr>
<tr>
<td>2 mL/min, 20% NaCl solution</td>
<td>0.5 mL/min, THF</td>
<td>91%</td>
</tr>
</tbody>
</table>

The last reaction was the most challenging due to its sensitivity to moisture. The potassium hydroxide (KOH) salt formed when potassium tert-butoxide (KO'Bu) reacts with water, potentially causing clogging. However, the solubility of the potassium salt in the organic solvent (i.e. mixture of toluene and THF) was higher with increasing temperature. Therefore, the reaction stream was preheated, but significant solid accumulation of the potassium salt still occurred with implications for the reactor design. Initially, the reactor size after scale-up for this reaction was 30 mL, equivalent to 10 min in residence time. The 30 mL reactor was made of the PFA tubing with 3/8” ID and 1/2” OD, contained in an aluminum shell. Due to its large inner diameter, the mixing was not efficient without an additional mechanism. Therefore, a static mixer of 4” in length was inserted at the entrance of the reactor. However,
the accumulation of solid salt happened easily inside the static mixer (Figure 12), prompting us to re-configure the reactor. Instead, smaller tubing (1/16” ID, 1/8” OD) was used to eliminate the need for static mixers, and found to provide an effective mass transfer such that only 10 mL volume (residence time of 2.6 min) was sufficient for the reaction to go to completion.

Figure 12. Solid salt accumulation inside the static mixer at the entrance of 30 mL reactor

Solid formation remained a problem for the last reaction. From multiple runs of experiment, we identified the mixing point between the reaction and reagent streams to be the most probable location of clogging. First, despite preheating of the reaction stream to 100 °C, the cross-mixer was at room temperature (ca. 18-22 °C). Second, the swept volume of the cross-mixer was only 22.8 µL with 0.05” thru hole. To solve the problem, the cross-mixer was re-configured into a tube-in-tube injection, in which the reaction stream was first combined with the stream of fluorobenzotrifluoride in DMSO. The mixed stream then flowed into the PFA tubing of 1/16” ID and 1/8” OD. The stream of KO’BU/18-crown-6 in DMSO was injected via the smaller tubing made of stainless steel with 0.024” ID and 0.03” OD. The inner tubing created a stream going immediately into the heating section of the reactor (Figure 13). The outlet of the reactor was re-configured similarly so that the reaction stream met with the water stream before the T-mixer. The added water dissolved any flowing solid potassium salt.
To further minimize KOH salt formation, a cartridge containing 0.4-nm molecular sieves was also incorporated before the preheating. The reaction stream contained water content of about 12,000 ppm. However, experimental results indicated that the moisture content needed to be less than 1500 ppm to avoid excessive salt formation. Different methods of residual water removal were tested. Molecular sieves proved more effective in drying the process fluid than anhydrous MgSO₄.

Table 2. Different methods for drying a reaction stream before the arylation

<table>
<thead>
<tr>
<th>Method of drying amino alcohol intermediate</th>
<th>Moisture content</th>
<th>Clogging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off-line drying with micro-sieve powder</td>
<td>100 – 500 ppm</td>
<td>No</td>
</tr>
<tr>
<td>Off-line drying with anhydrous MgSO₄</td>
<td>5000 ppm</td>
<td>Yes</td>
</tr>
<tr>
<td>In-line drying with fresh drying columns after 4 hours</td>
<td>450 ppm</td>
<td>No</td>
</tr>
</tbody>
</table>

Also, the flow sequence had to be kept under high pressure, 250 psi, to maintain process fluids in the liquid-phase reaction at the elevated temperatures needed for fast reactions. Operating the membrane-based separators at 250 psi was challenging. The original design of the separator was in polycarbonate or soft polymer such as polyethylene. To increase the mechanical tolerance of the device, the separator was redesigned to have an aluminum shell [57]. Furthermore, the integrated pressure control worked with the pressure difference on the outlets (P_retentate outlet - P_permeate outlet) between +5 and -30 psi. (The detailed description of the integrated pressure control is described in the next chapter.) When the retentate outlet pressure is much higher than the permeate outlet pressure, the diaphragm was kept inflated and integrated pressure control no longer regulated the membrane operation. Consequently, the back-pressure regulators on the aqueous outlets (retentate) from all the separators were set to be 235 psi. Setting the pressure on the organic outlet (permeate) to be lower than 250 psi prevented instability on the aqueous outlets from interrupting the membrane separation.
2.3.4 Results and discussions

The synthesis was continuously operated for more than 4 hours, including the time to steady state of 1.5 hours. The final organic stream containing crude fluoxetine a mixture of toluene, THF and DMSO was collected in a holding tank for further downstream processing. Different procedures for final extraction were screened for a compromise between a high yield and relative simplicity of the downstream precipitation. Initially, the crude fluoxetine was purified with an addition of water and ethyl acetate, which provided an overall yield of 37%. However, the precipitation of fluoxetine free base in ethyl acetate was very difficult. Ethyl acetate carried relatively high amount of DMSO and water which prevented the fluoxetine-HCl salt from precipitation. Other potential solvents included hexane, toluene, and ethers (see Table 3). The extraction with hexane and aqueous NaCl solution instead of pure DI water resulted in the highest overall yield of 53%. However, the precipitate from such condition appeared to be oily and amorphous. Therefore, either TBME/water or TBME/5% NaCl aqueous solution was chosen as a final condition, producing suitably white powder form of precipitate with a reasonable overall yield of 43%.

Table 3. Summary of screening conditions for the final extraction (both solvents are run at 4 mL/min)

<table>
<thead>
<tr>
<th>Aqueous solvent</th>
<th>Organic solvent</th>
<th>% Overall yield</th>
<th>Quality of precipitate</th>
</tr>
</thead>
<tbody>
<tr>
<td>DI water</td>
<td>Toluene</td>
<td>19%</td>
<td>N/A</td>
</tr>
<tr>
<td>DI water</td>
<td>Ethyl acetate</td>
<td>33%</td>
<td>N/A</td>
</tr>
<tr>
<td>5% NaCl solution</td>
<td>Hexane</td>
<td>53%</td>
<td>Oily, amorphous</td>
</tr>
<tr>
<td>10% NaCl solution</td>
<td>Hexane</td>
<td>52%</td>
<td>Oily, amorphous</td>
</tr>
<tr>
<td>DI water or 5% NaCl solution</td>
<td>TBME</td>
<td>43%</td>
<td>White powder</td>
</tr>
</tbody>
</table>

2.3.5 Evaluation of the overall process

The yield of the upstream synthesis is 43%, equivalent to 88% for each step considering 3 reactive and 4 in-line extraction steps. The E-factor for the upstream synthesis is 166, which is similar to the number reported for most pharmaceutical processes [58, 59]. The E-factor calculation here accounts for all the reagents and solvents except water. Solvents from the final extraction and last reaction are the major contributors to waste generation, with about 68% of the total waste from the two steps. This agrees with case studies by pharmaceutical companies, including the ones from GSK that estimated more than 80% of total chemical mass in pharmaceutical manufacturing to be solvents [60]. As shown in Figure 14, the reagents for the last reaction are much diluted to avoid excessive precipitation, so the high solvent consumption (i.e. DMSO) in turn results in high amount of waste. On the other hand, the first two
reactions, ketone reduction and amination, have high mass efficiency, in agreement with the concept of process intensification.

![Pie chart showing waste generation contributions in fluoxetine synthesis](image)

Figure 14. Contributions to the waste generation in the upstream synthesis of fluoxetine

The green aspect of this process could be improved by conducting the last reaction in a cascade of stirred tank reactors (CSTRs) capable of handling solids so that higher concentrations of reagents can be used. Moreover, TBME from the final extraction could be recycled by in-line evaporation.

### 2.4 In-line removal of volatile components

In-line evaporation or removal of volatile components could be a useful addition to flow chemistry. For instance, a reaction stream can be pre-concentrated for better overall reaction rates by solvent evaporation. Occasionally, there is a need for solvent switch between two or more miscible solvents. In-line evaporation can be applied to switch from low to high boiling-point solvents [61]. Also, as discussed in the previous section, solvent recycle will greatly improve the sustainable aspect of flow chemistry. Industrially, it is common to use distillation columns to separate out solvents, especially in the bulk and commodity chemical manufacturing. In contrast, for flow synthesis, solvent recycle or reuse is rare due to possible cross-contamination as well as lack of proper devices. Thus, a tool that can evaporate solvent in-line would be valuable for this application.

As covered in chapter 1, there have been several studies of small-scale evaporation including falling film technique [46, 47] and vacuum membrane distillation [62]. However, both techniques usually require careful monitoring, making them less suitable for interconnecting with multistep reactions in flow. Inert gas-assisted evaporation presented by Hartman et al. [44] is a promising method owing to its small filling volume, high efficiency, and stable gas-liquid interface. Their work demonstrated that one vapor-liquid equilibrium stage was achieved, enabling the switch from to dichloromethane to dimethyl
formamide. This section of the thesis will focus on adaptation of the gas-assisted evaporation approach for in-line solvent evaporation and removal of volatile components. The former example studies use of flash evaporation to form a vapor-liquid slug flow, instantly followed by membrane-based separation. The latter example involves use of inert gas stripping to take out volatile byproducts.

2.4.1 In-line flash evaporation of solvent

The method presented in this section is similar to the approach by Hartman et al. [61], except that no inert gas is added to the system. Instead, flash evaporation, generation of partial vapor when a saturated liquid stream undergoes an instant reduction in pressure eliminates the use of a gas tank. As shown in Figure 15, the in-line flash evaporator comprises three sections: 1) heating, 2) depressurization, and 3) vapor-liquid separation. The design combined three different tools developed in-house. The integration ensured heating-temperature uniformity. The heating section featured a square channel with 3 mL in volume and inserting holes for cartridge heaters. The superheated liquid was then passed into a dome-loaded type back pressure regulator that depressurized and flashed the liquid into vapor and residual liquid. The two phases were instantaneously separated by the membrane-based separator. All the parts were made of aluminum for high heat transfer. Although better chemically compatible materials such as Hastelloy® could be used, aluminum was chosen for the first prototype due to its low cost and acceptable chemical resistance. Two types of materials, fiberglass wool and a sand bath, were used for thermal insulation surrounding the whole device.

![Figure 15. The design of in-line flash evaporator that entirely integrates (a) back-pressure regulator for depressurization, (b) heating section, (c) membrane-based separator](image)

Since the properties of membrane and polymer film changed considerably with elevated temperatures, their performances were characterized over a wide range of temperatures. The pressure differential created by a PFA film with 0.002 mm in thickness was measured at temperatures between 25 and 70 °C. As expected, the polymer film became more elastic at higher temperature. The pressure differential \( P_{\text{dia}} \) decreased from 25 kPa to 4 kPa at 25 and 70 °C, respectively. This decrease in diaphragm pressure \( P_{\text{dia}} \) was a concern since \( P_{\text{dia}} \) must be lower than a capillary pressure \( P_{\text{cap}} \). Otherwise, the vapor could breakthrough into the liquid permeate phase. Likewise, we needed to examine
how the capillary pressure changed over temperatures. Saffarini et al. showed that microstructure of the PTFE microporous membrane was temperature-dependent [63]. In their finding, a liquid entry pressure, similar in the context to $P_{\text{cap}}$, decreased by 55% with increasing temperature from 25 and 70 °C. Surface tensions of organic solvent-air typically range from 16 to 63 dynes/cm [64]. Using these data, the capillary pressures at the range of temperatures could be estimated. $P_{\text{dia}}$ was obtained experimentally with a Pall™ Zeflour PTFE membrane supported by a PTFE layer with 1.0 μm in nominal pore diameter and 165 μm in nominal thickness. As shown in Figure 16, although both $P_{\text{dia}}$ and $P_{\text{cap}}$ decreased with rising temperatures, $P_{\text{dia}}$ was always about an order of magnitude lower than $P_{\text{cap}}$. Due to such big difference between $P_{\text{dia}}$ and $P_{\text{cap}}$, the breakthrough of vapor into permeate liquid side was unlikely.

On the other bound, the permeation pressure ($P_{\text{per}}$) can be estimated using Hagen – Poiseuille equation along with nominal geometry of the membrane and physical properties of residual liquid. To prevent the residual liquid from being retained, $P_{\text{dia}}$ has to be greater than $P_{\text{per}}$. At higher temperature, liquid viscosity tends to decrease, and the pore size tends to be expanded [63]. Both phenomena reduce $P_{\text{per}}$, a lower bound for the operating window of $P_{\text{dia}}$. At room temperature, organic solvents have a viscosity between 0.2 and 4.0 cP [65]. For the 1.0 μm membrane with a total area of $4.4 \times 10^{-5}$ m$^2$, $P_{\text{per}}$ at room temperature is estimated to be between 0.1 and 4.2 kPa for flow rates between 1 and 5 mL/min. From Figure 16, $P_{\text{dia}}$ can be as low as 4.3 kPa at 90 °C. For higher flow rate operation, a few design parameters (e.g. larger membrane area, larger pore size) can be adjusted to ensure $P_{\text{dia}} > P_{\text{per}}$ for complete phase separation.
Figure 16. Left: $P_{\text{dia}}$ decreases with increasing temperature, Right: $P_{\text{dia}}$ (●) and $P_{\text{cap}}$ bound (solid line) are plotted together against temperatures. Note that $P_{\text{cap}}$ is estimated using $\sigma = 16$ dynes/cm and 55% decrease with an increase in temperature from 25 to 70 °C.

The prototype of the in-line evaporator had a total area of $4.4 \times 10^{-3}$ m$^2$, which was suitable for a liquid flow rate up to 5 mL/min. It was first evaluated by its capability to partially evaporate a pure solvent, as shown in Figure 17. Small error bars indicated its reproducibility within a run, but different runs could produce different percent evaporation due to inconsistent setup of the thermal insulation. The extent of evaporation strongly depended on solvent’s boiling point and supersaturation temperature, but had a weak correlation with heat of vaporization and evaporation rate provided by German National Standard [66].
Figure 17. Left: Logarithm-scale percent evaporation for different solvents at 2.5 mL/min, $6.89 \times 10^2$ kPa, and varied supersaturation temperatures. Right: Percent evaporation correlates well with normal boiling points.

The in-line evaporator was then applied to a flow synthesis of neostigmine. The synthesis consisted of two main reactions: nucleophilic substitution and methylation. The following discussion focuses on the incorporation of the in-line evaporation into the flow sequence rather than the synthetic route and overall process development. As shown in Figure 18, after the first reaction, the 3-(dimethylamino) phenyl dimethylcarbamate is extracted first with co-injections of the aqueous $\mathrm{K}_3\mathrm{PO}_4$ solution and toluene, then with DI water. The organic stream containing the carbamate intermediate needs to be pre-concentrated as well as dried to remove residual water as the methylation is water-sensitive.
Figure 18. The synthetic route and process flow chart for the synthesis of neostigmine with the use of in-line evaporator to pre-concentrate a reaction stream.

The evaporator was set to 413 kPa and 110 °C, which resulted in ca. 30% evaporation of solvent. This is equivalent to 1.43-times pre-concentration, yielding the carbamate concentration of 0.05 M that is sent to the methylation. As shown in Figure 19, the samples collected after the evaporator show that the residual liquid became more concentrated with visibly darker color, as shown in Figure 19. The condensed vapor phase was colorless, mainly comprising toluene and residual water.

Figure 19. The left vial was the sample collected before the evaporator, the middle and right vials were the concentrated liquid sample and condensed vapor sample after the evaporator.

The example proves the device’s feasibility for pre-concentrating a stream to a subsequent reaction. However, there are a number of potential improvements. First, despite its excellent heating properties, aluminum has weak resistances to acid and basic salts. Corrosion was observed after a long period of use. It should be replaced with a more chemically compatible material such as Hastelloy®. Second, thermal insulation is critical for this device. Better insulation material and assembly should be considered for a future prototype. Moreover, different types of membranes with better stability at high temperatures, such as a glass microfiber membrane, should be considered.
2.4.2 Removal of volatile component with gas stripping technique

Volatile components sometimes can be separated without thermal input. For instance, gas-stripping method works on the basis of mass transfer. An addition of gas creates a gas-liquid interface that allows volatile components to cross favorably from liquid to vapor phases. Industrially, stripping has been widely used in tray or packed bed columns, and can be done with either cocurrent or countercurrent flows [67]. In laboratory, on the other hand, removal of volatile components is usually performed off-line with sparging or rotary evaporation. Another simple setup for continuous separation of volatile component is use of gas-permeable polymer tubing. For example, Teflon AF-2400 is an amorphous fluoropolymer that allows permeation of gas but not liquid [68], and its use as a degasser for gas-liquid stream has been demonstrated [69]. Nevertheless, Teflon AF-2400 has some limitations. Permeability through Teflon AF-2400 is molecular size-limited. The polymer is expensive and fragile, only suitable for specialized applications. Membrane-based separator emerges as a promising alternative since vapor-liquid separation is based on wetting properties. Mass transfer of components between the two phases occurs until it reaches vapor-liquid equilibrium before the separation.

This part of thesis presents an example of multistage gas stripping using membrane separators to remove volatile components continuously in a streamline. A case study involves an enantiomeric resolution using enzymatic-racemization focused approach. As shown in Figure 20, the first reaction is enantioselective enzymatic transesterification of a chiral alcohol molecule, and the other unreacted enantiomer will then go through racemization using Ru-immobilized catalyst. However, the byproduct of the first reaction is acetaldehyde, which can react with one of the alcohol enantiomers to form acetophenone, an undesired side product. A recycle can be implemented to obtain high enantioselectivity, but in-line removal of acetaldehyde is required to prevent accumulation of the side product, which in turn can reduce the overall yield greatly.
Since acetaldehyde is very volatile (b.p. 20.2 °C), it vaporizes readily without any heating. To enhance the extent of vaporization, an inert gas was added to strip out the acetaldehyde from the reaction liquid stream. Different scenarios were studied using FlowIR for in-line detection of acetaldehyde. The results indicated that more than 90% acetaldehyde removal could be achieved with 4 stages of gas strippers (Figure 21). Note that a higher ratio of gas to liquid streams also enhanced the amount of acetaldehyde removal.

Figure 21. Different scenarios for in-line gas-stripping to remove acetaldehyde
2.5 Conclusion

This chapter highlights different tools, which can be implemented to integrate multistep reactions into one continuous flow. This eliminates the need for any laborious and time-consuming workup conventionally performed in a batch. Some sequential reactions can be telescoped directly without any purification or solvent switch step in between as demonstrated in the synthesis of lidocaine. On the other hand, for other syntheses, in-line extractions are required to remove excess reagents or impurities that are incompatible with a subsequent reactive step, as shown in the synthesis of fluoxetine. At the end of the chapter, methods for in-line removal of volatile components were introduced along with case studies on pre-concentration of a reaction stream and separation of volatile byproducts.
Chapter 3. Design of multistage countercurrent liquid-liquid extraction (M-CCE) platform

3.1 Introduction

The previous chapter has introduced the in-line liquid-liquid extraction to separate out excess reagents and impurities. However, the extraction was performed with, at most, two stages in crosscurrent configuration in which solvent was not used efficiently. This chapter will provide a framework on assembling membrane-based separators into a more complex multistage configuration, countercurrent. This configuration was designed to work with non-precise interstage pumping.

3.2 Current development of liquid-liquid extraction

Liquid-liquid extraction (LLE) plays an important role in multistep chemical processing as it has advantages of minimal energy consumption and suitable method for purification of thermally sensitive compounds and separation of azeotropic mixtures. The LLE process is considered as efficient when it has high mass transfer and complete separation of two immiscible phases. Traditional mixer-settlers, columns, and centrifugal extractors are widely used, but they have disadvantages of large hold-up volumes (i.e. infeasible for laboratory scale), low efficiency, long settling times for droplet coalescence, and excessive maintenance for high-speed machine [67].

The mass transfer can be enhanced by generating a large contacting surface between the two immiscible phases. Agitation, packed bed, and spraying are among common methods for achieving a high surface-to-volume (S/V) ratio, up to 32-450 m²/m³ [70]. Recently, contacting flow in small channels has emerged as an alternative. The S/V ratio in slug flow regime can be as high as 830-3200 m²/m³ [70, 71]. Plus, the internal circulation inside the slug improves the mass transfer between phases [72]. This type of contacting is dominated by interfacial forces so alternative methods to the gravity have to be used to separate the two phases after contacting [73]. Krajl et al. utilized a PTFE membrane with a pore size of 0.1-1 µm for aqueous-organic separation taking advantage of the preferential wetting of membrane by the organic phase [50]. In order to drive the organic phase through the membrane, a pressure difference across the membrane must be maintained but also be less than the capillary pressure. Adamo et al. developed the integrated pressure regulator to meet the operational criteria [57].
Multistage extraction is often required to achieve high extraction efficiency, particularly for those systems with low partition coefficients or low selectivity. Industrially, mixer-settlers and columns have been used to obtain a high number of theoretical stages [74], but the designs for mL/min throughput are rare due to complex moving parts. Most works in the mL/min scale are demonstrated with a single stage or simple crosscurrent cascading [75, 76]. Only a few works describe countercurrent flow, which yields the highest extraction efficiency among all types of multistage cascading [67]. Holbach et al. showed two-stage configuration that combined effects of gravity, capillary, and surface forces for the phase separation, but the setup required highly precise pumping to maintain pressure balance [70]. Flooding remains a main challenge for miniaturization of columns [77] while small centrifugal extractor suffer from large holdup volume (e.g. 1.9 L/min as the smallest available by CINC [78]) and inefficiencies caused by emulsification.

### 3.3 Design theory

As shown in Figure 22, we refer to \( P_1 \) and \( P_2 \) as the liquid pressure on the retentate and permeate sides of the membrane, respectively. The pressure difference across the membrane (\( \Delta P_{\text{mem}} \)) is equal to \( P_1 - P_2 \).

![Figure 22. Schematic showing the cross section of a membrane separator with integrated pressure control element.](image)

Previous studies indicate that successful separation depends on \( \Delta P_{\text{mem}} \) [57]. \( \Delta P_{\text{mem}} \) must be below a capillary pressure (\( P_{\text{cap}} \)); otherwise, breakthrough of the retentate phase (i.e. the aqueous phase if a hydrophobic membrane is used) will occur. In addition, \( \Delta P_{\text{mem}} \) has to be above the minimum pressure to cause all the permeate phase to flow through the membrane (\( P_{\text{per}} \)) so as to prevent partial retention of the permeate phase. These two limits can be rewritten as

\[
P_{\text{cap}} > \Delta P_{\text{mem}} > P_{\text{per}}
\]

(Eq. 2)
\( P_{\text{cap}} \) can be calculated using the Young-Laplace equation:

\[
P_{\text{cap}} = \frac{2\gamma_{1,2}\cos(\theta)}{r}
\]  

(Eq. 3)

where \( \theta \) is the contact angle between the liquid-liquid interface and the membrane pore wall, \( \gamma_{1,2} \) is the interfacial tension between the two liquids, and \( r \) is the radius of curvature of the interface, which can be assumed to be equal to the radius of membrane pores. Assuming a cylindrical shape of the membrane pore, \( P_{\text{per}} \) can be calculated:

\[
P_{\text{per}} = \frac{8\mu_2Q_2L}{nA\pi R^4}
\]  

(Eq. 4)

where \( \mu_2 \) and \( Q_2 \) are viscosity and flow rate of the permeate liquid, respectively. \( L, n, R, \) and \( A \) are thickness, membrane pore number density, membrane pore radius, and membrane area, respectively.

In the past, proper \( \Delta P_{\text{mem}} \) was obtained through balancing the flow resistances of the two outlets independently [79]. Our previous work incorporated a pressure control element, which was made of an elastic diaphragm that sealed against and provided an additional force \( (P_{\text{dia}}) \) on the retentate flow path. Therefore, \( P_1 = P_2 + P_{\text{dia}} \), and the inequality becomes

\[
P_{\text{cap}} > P_{\text{dia}} > P_{\text{per}}
\]  

(Eq. 5)

The phase separation could thereby be isolated from the downstream pressure disturbance. This device allowed us to set up a three-stage countercurrent extraction setup, using two HPLC pumps for interstage pumping [57] as shown in Figure 23. Using a graphical method, an extraction efficiency of nearly 100% was achieved for the toluene-acetone-water example.
Figure 23. Experimental McCabe-Thiele plots for extractions with three physical stages. Left: extraction of acetone from water into toluene. Right: extraction of acetone from toluene into water. The dotted and dashed lines represent equilibrium curves and operating lines, respectively [57].

Despite its high efficiency, this setup posed many challenges. First, the in-line HPLC pumps were not self-priming. Gas bubbles or droplets of other liquid could cause loss of priming and eventually failure of pumping. Also, the pump chambers were required to be initially filled with liquid. Thus, an operator needed to prime the pumps off-line before connecting them to a network of separators. Second, the number of pumps required for n stages was at least n+1, making the setup costly and impractical. In order to find an alternative pumping method, three possible scenarios of pumping actions were investigated, as depicted in Figure 24.
Figure 24. Different scenarios of suction flow rates. (a) Experimental setup. (b) \( Q_p > Q_1 \). (c) \( Q_p = Q_1 \). (d) \( Q_p < Q_1 \).

Under normal condition, \( P_1 \) will be automatically tuned to \( P_2 + P_{dia} \). This also happens when the retentate flow rate \( (Q_1) \) matches perfectly with the downstream suction rate \( (Q_p) \), as shown in Figure 24 (c). When \( Q_p > Q_1 \), the separation still works because \( P_2 \) is sufficient to force the diaphragm to close the retentate flow path and provide a tuning pressure for \( P_1 \), as in Figure 24 (b). On the other hand, when \( Q_p < Q_1 \), the pump becomes a partial blockage for the retentate outlet. \( P' \) will build up enough to hold the diaphragm valve to always open, meaning no proper pressure tuning and incomplete separation, as depicted in Figure 24 (d). To summarize, it is possible to implement interstage pumping even with non-precise pumps as long as we set \( Q_p \geq Q_1 \).

Multi-head peristatic pumps were chosen for the countercurrent extraction application to limit the number of pumps used. The small amounts of slippage associated with the peristaltic pumping mechanism would provide the flexibility to handle the volume changes of the fluid streams as solute is moved from process stream to extraction fluid. In a peristaltic pump soft tubing is compressed, and the corresponding tube volume occluded, by a roller against the wall of the housing. The tubing diameter and the roller’s revolution speed determine the flow rate, and the number of rollers determines the amount of fluid being dispensed for each pulse. Although its pulsatile and non-precise natures make it unsuited for many specialized applications, it has advantages of being self-priming and inexpensive. It can be operated at a wide range of flow rates and accommodates multiple channels, commercially available up to 24 channels per pump.
3.4 Experimental section

3.4.1 Setup and startup procedure

The membrane separator was modified from the original design in polycarbonate [57]. To ensure chemical compatibility, the wetted structure was machined in ultra-high molecular-weight polyethylene (UHMWPE), which was compatible to most organic solvents. The outer shell was made of aluminum for enhanced mechanical properties. The filters used were Pall Zeflour™ 0.5 μm PTFE membrane and Sterlitech 0.1 μm PTFE laminated membrane. The 0.1 μm pore diameter was more suitable for low interfacial tension system because it provided higher $P_c$. The diaphragm was made of PFA film with 50 and 127 μm in thickness. To validate our assumptions, the separator was tested with different suction flow conditions: higher, equal, and lower than the actual retentate flow rate. The pressure differential as well as the separation performance was measured.

The pump used for the interstage pumping was a Masterflex L/S 8-channel, 3-roller peristaltic pump (Cole-Parmer, USA) that accepted up to 8 cartridges for synchronous flow. The cartridge could be snapped in and out for quick and simple tubing changes. The peristaltic tubing used were Gore™ Style 500, Gore™ Style 100, Norprene™ A-60-G tubings with L/S 14 size. They were used in different tests due to their different nature of chemical resistances.

Figure 25 shows arrangement of extraction stages. All tubings were PFA with 1/8” OD and 1/16” ID (McMaster-Carr, USA). The two phases were mixed in a T-mixer. For slug flow in a milli-scale channel, the mass transfer coefficient is generally between 0.2-1.7 s⁻¹ [80, 81]. Therefore, an inlet tubing to each separator was made long enough to allow more than 10 seconds in residence time in order to ensure equilibrium mass transfer. A stage number was counted from a low pressure to a high pressure. A retentate outlet of stage $i$ flowed to stage $i + 1$ through the peristaltic pumping. A permeate outlet of stage $i$ flowed to stage $i - 1$ driven by the pressure drop. As for a start-up procedure, only the membrane-wetting solvent (i.e. organic solvent) was first flowed through the setup, generally from Nth stage to 1st stage. If the permeate flow path of the separator was not filled with liquid, the diaphragm PFA film might inflate excessively in the presence of the retentate liquid, resulting in possible damage to the film. Once all the separators were filled with organic solvent, then the pump for the non-wetting liquid (i.e. water) and the peristaltic pump could be both started at the same time.
Figure 25. (A) The scheme for 4-stage countercurrent extraction, (B) The image of the setup for 11-stage countercurrent extraction, with total footprint dimensions of 1.0 m x 0.6 m x 0.2 m, including the feed and interstage pumps.
3.4.2 Standard test systems

Two ternary systems were selected for testing the extraction efficiency of the setup (Table 4). The first system is the extraction of acetone between toluene and water. It is a standardized system recommended by the European Federation of Chemical Engineers (EFCE) with a moderate interfacial tension [82]. The other system is the extraction of acetic acid between water and ethyl acetate to demonstrate the setup’s capability for low interfacial tension system. The testing conditions are given in Table 4. The extraction efficient was determined for each system at number of stages \( N \) = 1, 3, 5, and 7.

<table>
<thead>
<tr>
<th></th>
<th>Toluene-acetone-water</th>
<th>Ethyl acetate-acetic acid-water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feed at stage 1</td>
<td>0.50 mass fraction of acetone in water, 2.0 mL/min</td>
<td>0.05 mass fraction of acetic acid in water, 0.5 mL/min</td>
</tr>
<tr>
<td>Feed at stage N</td>
<td>Toluene</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>Peristaltic pump rate</td>
<td>2.5 mL/min</td>
<td>0.7 mL/min</td>
</tr>
<tr>
<td>Characterization</td>
<td>Gas chromatography-FID</td>
<td>Titration</td>
</tr>
</tbody>
</table>

3.5 Results and discussions

3.5.1 Verification of assumptions

In order to verify our assumptions claimed in Section 3.3 Design theory, we examined separation performance at varying \( Q_p \). The experiment was conducted with a pair of water and organic solvent that were mutually completely immiscible, at the rate of \( Q_{\text{water}} \) and \( Q_{\text{organic}} \) mL/min, respectively. Therefore, when separation is complete, \( Q_1 = Q_{\text{water}} \) and \( Q_2 = Q_{\text{organic}} \). When the breakthrough of water into the permeate phase occurs, \( Q_1 < Q_{\text{water}} \) and \( Q_2 > Q_{\text{organic}} \), and vice versa for when partial amount of organic solvent gets retained with the aqueous phase. The separation performance was represented by the normalized permeate flow rate, which was equal to the \( Q_2/Q_{\text{organic}} \) ratio. The normalized permeate flow rate was 1 for complete separation. The normalized permeate flow rate was plotted against the normalized suction rate (i.e. \( Q_p/Q_1 \))

As shown in Figure 26, the normalized permeate flow rate was greater than 1 when the normalized suction rate was below 1. This indicates that the breakthrough of the water into the permeate phase happened when \( Q_p < Q_1 \). This breakthrough problem was a result of partial blockage on the retentate side, which in turn forced the diaphragm valve to always open. The extent of partial blockage
became more prominent and generated pressure buildup of $P$ when the normalized suction rate decreased.

On the other hand, complete separation was observed (i.e. the normalized permeate flow rate is 1) when the normalized suction rate was greater than 1. It is worth noting that when the normalized suction rate was greater 1, the suction led to degassing (i.e. negative $P$), and entrained gas bubbles were observed on the retentate outlet, but the separation remained complete. This observation was in line with our assumption that when $Q_p = Q_1$ or $Q_p > Q_1$, the retentate phase could fully flow out of the separator. Without the pressure buildup, the diaphragm could close the retentate flow path and thereby control $\Delta P_{\text{mem}}$.

![Graph](image)

Figure 26. Experimental results verified the assumptions that complete separation can be achieved when $Q_p > Q_1$.

3.5.2 Extraction efficiency of standard test systems

The M-CCE setup was evaluated in terms of extraction efficiency with the two test systems: water-acetone-toluene and water-acetic acid-ethyl acetate. Both are standardized systems for testing conventional extraction equipment. They can be handled accurately by thermodynamic models because their interaction parameters are well-defined in literatures [83, 84]. Therefore, we could use simulation results to compare directly to the results from our M-CCE setup.

Upon conducting extraction of these two test systems, incomplete separation was not at all observed. Furthermore, Figure 27 shows that the results from our M-CCE setup agree closely with the
simulation results that assumed 100% extraction efficiency; this agreement indicates that mass-transfer equilibrium was reached in the M-CCE setup, regardless of number of stages.

![Bar chart](image1.png)  
**Figure 27.** High efficiency was achieved for the two examples demonstrated, regardless of number of stages. Left: Extraction of acetone from water to toluene. Right: Extraction of acetic acid from water to ethyl acetate.

In addition, the same simulation could generate the flow profile across stages. Figure 28 shows the simulation results for the two test systems when \( N = 7 \). The flow rates could vary significantly from one stage to another due to the interphase transfer of the key components. The variation of the flow rates was more prominent in the toluene-acetone-water system because of large fraction of transferred species, i.e. acetone. The flow variation was handled robustly with the M-CCE setup as complete separation was observed in all stages. If HPLC pumps were used, flow rates leaving each stage would need to be determined accurately; otherwise, it might cause cavitation and mechanical failures. In the M-CCE, peristaltic pumps provided some slippage and flexibility for varying flow rates.
Figure 28. Simulation results show variation in flow rates across stages for the two examples demonstrated at $N = 7$. Left: Extraction of acetone from water to toluene, Right: Extraction of acetic acid from water to ethyl acetate

3.5.3 Operating window for $P_{dia}$

The diaphragm pressure control element must provide $P_{dia}$ that falls between $P_{cap}$ and $P_{per}$ so as to ensure complete phase separation. In this section, we determine the desired value of $P_{dia}$ in the context of aqueous-organic liquid-liquid extraction at 1-10 mL/min throughput. Then, we will examine how process parameters affect $P_{dia}$.

As highlighted previously, the upper and lower bounds of $P_{dia}$ are $P_{cap}$ and $P_{per}$. The value of $P_{cap}$ can be roughly estimated if interfacial tensions and pore size of membrane are known. Table 5 shows that the typical interfacial tension of water-organic system has a wide range, from 2 to 53 mN/m. The interfacial tension of 10 mN/m was taken as a benchmark in our calculation of $P_{cap}$ for two reasons. First, alkanes, aromatics, ethers, and esters are more common in chemical industry [85]. Ketones and alcohols with short carbon chains ($C_1$-$C_4$) are miscible with water and not suitable for extraction. Second, the interfacial tension is strongly correlated with solute concentration. With the total solute mass fraction of 0.2, the interfacial tension tends to be around 10 mN/m [86]. The calculated values of $P_{cap}$ for different membranes are shown in Figure 29.
Table 5. Typical interfacial tensions between water and organic solvents at 25°C (excerpt from [87])

<table>
<thead>
<tr>
<th>Types of organic solvents</th>
<th>Interfacial tension (mN/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkanes (C_5-C_{12})</td>
<td>45-53</td>
</tr>
<tr>
<td>Halogenated alkanes (C_1-C_{4})</td>
<td>30-40</td>
</tr>
<tr>
<td>Aromatics (single ring)</td>
<td>30-40</td>
</tr>
<tr>
<td>Ethers (C_{4}-C_{6})</td>
<td>10-30</td>
</tr>
<tr>
<td>Esters (C_{4}-C_{6})</td>
<td>10-20</td>
</tr>
<tr>
<td>Ketones (C_{4}-C_{6})</td>
<td>5-15</td>
</tr>
<tr>
<td>Organic acids (C_{5}-C_{12})</td>
<td>3-15</td>
</tr>
<tr>
<td>Aniline</td>
<td>6-7</td>
</tr>
<tr>
<td>Alcohols (C_{4}-C_{6})</td>
<td>2-8</td>
</tr>
</tbody>
</table>

Similarly, the lower bound, $P_{\text{per}}$, can be determined if the flow rate and viscosity of the permeate phase as well as the geometries of the membrane are known. Most of these parameters, except the pore number density, can be obtained from the membrane’s manufacturer. The pore number density was experimentally measured by flowing only membrane-wetting phase to a membrane. The flow resistances of the two sides of the membrane were manually adjusted to vary $\Delta P_{\text{mem}}$. Different values of $\Delta P_{\text{mem}}$ result in different fractions of solvent permeating into the membrane, and these two parameters can be used to calculate the pore number density. The pore number densities and $P_{\text{per}}$ for different membranes are reported in Table 6. $P_{\text{per}}$ is calculated with a viscosity of 1.0 mPa.s.
Table 6. Experimentally measured pore number densities for selected membranes

<table>
<thead>
<tr>
<th>Material (active/support layer)</th>
<th>Nominal Pore size (µm)</th>
<th>Nominal Thickness (µm)</th>
<th>Measured pore number density (pores/m²)</th>
<th>Permeation pressure (psi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTFE/PP (Advantec®)</td>
<td>0.1</td>
<td>130</td>
<td>2.39E+15</td>
<td>1.18</td>
</tr>
<tr>
<td>PTFE/PP (TF-200)</td>
<td>0.2</td>
<td>139</td>
<td>3.59E+14</td>
<td>0.76</td>
</tr>
<tr>
<td>PTFE/PTFE (Zeflour®)</td>
<td>0.5</td>
<td>178</td>
<td>2.18E+13</td>
<td>0.41</td>
</tr>
<tr>
<td>PTFE/PTFE ((Zeflour®)</td>
<td>1.0</td>
<td>165</td>
<td>4.51E+12</td>
<td>0.12</td>
</tr>
</tbody>
</table>

1 PTFE = Polytetrafluoroethylene and PP = Polypropylene
2 The permeation pressure was estimated using the Hagen–Poiseuille equation with viscosity = 1.0 mPa.s and flow rate = 5 mL/min.

\[ P_{\text{cap}} \text{ and } P_{\text{per}} \] for different membranes are plotted in Figure 29. The membrane with a smaller pore size tends to have a larger operating window. According to the operating windows of the microfiltration membranes tested, the desired value of \( P_{\text{dia}} \) is between 2 and 4 psi. The PFA film with thickness of 50-200 µm was found to effectively provide \( P_{\text{dia}} \) in this range. Note that in some cases the operating window for \( P_{\text{dia}} \) could behave very different from these values, depending on the properties of membrane and liquids.

![Figure 29](image)

Figure 29. The nominal operating window for different membranes. The upper and lower bounds correspond to \( P_{\text{cap}} \) and \( P_{\text{per}} \), respectively, calculated with \( \mu_2 = 1.0 \text{ mPa.s, } Q_2 = 5 \text{ mL/min, } \gamma_{1,2} = 10 \text{ mN/m,} \) and nominal values for membrane thickness and pore size.

For complete analysis, tests were performed to study how process parameters affect \( P_{\text{dia}} \). Using a monolithic silicon pressure sensor with < 5 ms response time, \( P_{\text{dia}} \) was measured. As shown in Figure 30, \( P_{\text{dia}} \) was found to be dependent of the flow rate and flow ratio of the two phases. These dependences are well correlated, and an empirically linear regression can be derived:
\[ P_{\text{dia}} = \alpha + \beta_1 Q_1 Q_2 + \beta_2 \ln(Q_1/Q_2) \]  
(Eq. 6)

Where \( \alpha, \beta_1, \beta_2 \) are fitting parameters, and they depend on the elastic properties of the diaphragm material. For example, a thinner film tends to have a smaller \( \alpha \). To provide an idea of how large \( P_{\text{dia}} \) varies, the values of \( \alpha, \beta_1, \beta_2 \) were empirically determined for a new PFA film with 50 \( \mu \)m in thickness to be 3.20 psi, 0.04 psi.min/mL, and 0.29. \( P_{\text{dia}} \) can vary from 2.5 to 4.3 psi for the range of flow rates from 1 to 10 mL/min and the range of \( Q_1/Q_2 \) ratio from 0.1 to 10.

Figure 30. Experimental results showed the dependence of \( P_{\text{dia}} \) on flow conditions. Left: keeping \( Q_1/Q_2 \) constant at 1, \( P_{\text{dia}} \) linearly correlates with the total flow rate. Right: keeping the total flow rate constant at 10 mL/min, \( P_{\text{dia}} \) linearly correlates with the natural log of \( Q_1/Q_2 \). The diaphragm material is PFA with 0.002" in thickness.

Furthermore, \( P_{\text{dia}} \) could fluctuate as a result of pulsation from the peristaltic pumping. The measured \( P_{\text{dia}} \) on each separator in the 11-stage extraction setup indicated that the deviation could be as large as 40% of the mean value for \( P_{\text{dia}} \). There are a number of ways to dampen the pulse. For example, the pulse dampener, generally made of a vessel containing compressible gas or air, can be installed. Multiple rollers or two peristaltic lines with offset occlusion can also provide a smoother flow. Alternatively, the use of soft tubings after a discharge point can alleviate the pulsation.

3.6 Conclusion

This chapter presents a framework on how to set up and operate the multistage countercurrent liquid-liquid extraction using membrane-based separators. The integrated pressure control element enables the separation with non-precise pumping. As long as the pump withdraws liquid on retentate side faster than its actual flow rate, the separation should be completed. This setup has a small filling volume, suitable for laboratory-scale experiment or process development. High efficiency was demonstrated through the two examples, toluene-acetone-water and ethyl acetate-acetic acid-water. The setup was
capable of handling different conditions (e.g. flow rates) and physical properties (e.g. viscosity) across stages. A number of applications were performed with this setup and discussed in the next chapter.
Chapter 4. Case studies of the M-CCE platform

4.1 Introduction

There are four major configurations for liquid-liquid extractions: 1-stage, cocurrent, crosscurrent and countercurrent. By assuming equilibrium and working around mass balances, one can derive the following expressions for the fraction of transferred species remaining in a raffinate phase, as shown in Table 7 [67].

Table 7. Schemes and expressions for a fraction of a component \( i \) in a raffinate phase for different configurations of liquid-liquid extraction.

<table>
<thead>
<tr>
<th>Single stage</th>
<th>Cocurrent</th>
<th>Crosscurrent</th>
<th>Countercurrent</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \frac{1}{1 + E_i} )</td>
<td>( \frac{1}{1 + E_i} )</td>
<td>( \frac{1}{1 + E_i / N} )</td>
<td>( \frac{1}{1 + E_i / N} )</td>
</tr>
</tbody>
</table>

Where \( E_i \) is an extraction factor \( E_i = K_i \frac{S}{F} \); \( K_i \) is a partition coefficient \( K_i = \frac{C_{\text{species}}}{C_{\text{organic}}} \); \( S \) and \( F \) are volumetric flow rates for solvent and feed, respectively.

When the expression is small, the transferred species is mostly removed from the raffinate phase, indicating an effective extraction. The countercurrent configuration yields the best result. Often, multiple stages of extraction are required to achieve target yield and purity. Table 8 shows an extent of extraction for components with different \( K_i \) if a solvent-to-feed ratio of 1:1 is used. For systems with \( K_i < 10 \), multiple stages are required to achieve more than 91% yield.

<table>
<thead>
<tr>
<th>( K_i )</th>
<th>1</th>
<th>5</th>
<th>10</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>% extraction with 1 stage</td>
<td>50%</td>
<td>83%</td>
<td>91%</td>
<td>99%</td>
</tr>
</tbody>
</table>

Similarly, a system containing two components or more with similar partition coefficients will not obtain effective separation with only a single stage as they tend to partition preferentially into the same phase. In conclusion, there are two main cases in which multiple stages of extraction will be needed: (1) ternary systems with \( 0.1 < K_i < 10 \), (2) multicomponent systems with a low separation factor \( S_{AB} \).
which is defined as $S_{A/B} = K_A / K_B$. This chapter presents two main case studies that gain benefits from the M-CCE setup: multicomponent solvent recovery and purification of phase-transfer catalyst.

### 4.2 Multicomponent solvent recovery

The first case study concerns multicomponent liquid-liquid extraction. Traditionally, development and optimization of this process begins with thermodynamic simulations or semi-empirical methods to obtain a preliminary design. Then, the design is tested on a pilot-scale plant. However, as a number of components increase, the simulations become unreliable because values of $K_i$ are interdependent among components in the system. Therefore, many common analytical expressions, such as UNIFAC, UNIQUAC, Wilson, and Non-random two-liquid (NRTL) models, are incapable of predicting the multicomponent thermodynamic behavior. Alternatively, equilibrium data for multicomponent systems can be generated empirically. Batch simulation of multistage countercurrent has been demonstrated [88], but this method becomes extremely tedious with an increasing number of stages. Furthermore, as discussed in Chapter 3, multistage extraction equipment for laboratory scale is rare. The multistage liquid-liquid extraction setup developed in this thesis can be a solution to the problem of multicomponent process development.

#### 4.2.1 Experimental section

A multicomponent solvent recovery system, an industrially relevant example, was chosen. The primary objective was to separate tetrahydrofuran (THF) and ethyl acetate from the other components comprising methanol, ethanol, isopropanol (IPA), and tert-butanol. Specifically, the separation aimed at removing more than 98% of methanol, 90% of ethanol, and 75% of isopropanol while maximizing recovery of THF and ethyl acetate. The compositions of the feed stream are listed in Table 9. Decane and water were found to be effective extraction solvents. THF and ethyl acetate have $K_i$ below 1, suggesting that they will be favorably transferred into the organic phase. On the other hand, all the alcohol species will be largely in the aqueous phase.

Table 9. The compositions in the feed stream and the partition coefficients ($K_i$), measured with the feed: water: decane ratio of 1:1:1.

<table>
<thead>
<tr>
<th></th>
<th>THF</th>
<th>Ethyl acetate</th>
<th>Methanol</th>
<th>Ethanol</th>
<th>IPA</th>
<th>Tert-butanol</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass fraction</td>
<td>0.384</td>
<td>0.339</td>
<td>0.085</td>
<td>0.005</td>
<td>0.045</td>
<td>0.045</td>
<td>0.096</td>
</tr>
<tr>
<td>$K_i$</td>
<td>0.5</td>
<td>0.2</td>
<td>19.7</td>
<td>5.6</td>
<td>2.6</td>
<td>1.6</td>
<td></td>
</tr>
</tbody>
</table>

As shown in Table 9, it is possible to separate methanol effectively with a single stage owing to its high $K_i$. Nonetheless, the other components require multiple stages of extraction to obtain high degree of...
separation. Many design variables, such as a solvent-to-feed ratio, a number of stages, a feed stage location, and temperature, can be adjusted to optimize the process. Rather than complete optimization studies, the following discussion will focus on improving the degree of extraction by varying a number of stages to prove the feasibility of this setup. The system was tested for \( N = 1, 3, 5, 7, \) and \( 9 \). The feed, decane, and water entered at middle stage (i.e. \( \left( N+1 \right)/2 \), \( 1^{st} \) stage, and \( N^{th} \) stage, respectively. Their flow rates were set at 2, 3, and 4 mL/min, respectively. The two outlets were collected at different time points and characterized with headspace gas chromatography (HS-GC).

4.2.2 Results and discussions

This example of THF and ethyl acetate recovery was challenging in two main aspects. First, the main six components had a wide range of polarity, causing a mixture to have a low interfacial tension (Table 10), i.e. low \( P_{\text{cap}} \), and thus a small operating window for the membrane separation.

Table 10. The surface and interfacial tensions from literature and measurements with a pendant drop analyzer.

<table>
<thead>
<tr>
<th>Solvent system</th>
<th>Tension(mN/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water-decane</td>
<td>53.2\textsuperscript{a}</td>
</tr>
<tr>
<td>Feed-decane</td>
<td>5.9\textsuperscript{b}</td>
</tr>
<tr>
<td>Feed-decane-water</td>
<td>3.9\textsuperscript{b}</td>
</tr>
<tr>
<td>Feed-water</td>
<td>23.0\textsuperscript{c}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The referenced interfacial tension at the liquid-liquid interface at 22 °C [89].
\textsuperscript{b}The measured interfacial tension at the liquid-liquid interface at 18 °C.
\textsuperscript{c}The measured surface tension at the air-liquid interface at 18 °C.

Second, flow properties such as flow rates, viscosity and interfacial tension, could vary greatly between stages. The flow profiles for multicomponent systems, as stated earlier, were difficult to predict with the simulation packages. Therefore, the setup’s robustness and capability for handling those variations can be investigated.

The mass transfer equilibrium was verified by comparing the results from M-CCE setup \((N=1)\) with a shake-flask experiment. The shake-flask experiment used long mixing and settling times (>24 hours in total) in a separatory funnel for complete transfer of components; therefore, it served as benchmark for equilibrium. The results from M-CCE and shake-flask experiment closely agreed, as shown in Figure 31. Therefore, it was reasonable to conclude that each physical stage of M-CCE yielded an equilibrium stage. The other thermodynamic models including NRTL, UNIQUAC and UNIFAC, on the other hand, failed to predict the results for some key components, as highlighted with asterisks in the figure.
For the M-CCE setup, the interstage pump must be set to be higher than the maximum flow rate of the retentate phase possible. In this example, the maximum retentate flow rate was the sum of the water and feed flow rates, assuming that all the feed components got transferred to the aqueous phase. For all the experiments, the M-CCE was operated for 1-2 hours. Minor degassing was observed, but it did not affect the phase separation.

To meet the design specifications, the M-CCE setup was used to simulate results at varying process variables, one of which was a number of stages. Figure 32 showed the results when the flow rates of water, feed, and decane were set to be 4.00, 1.77, and 2.19 g/min, respectively. The experiments were all performed at 20 °C. The separation degree increased with a number of stages. With 9 stages, more than 95% of all four alcohols were removed from the desired organic outlet. At the same time, the recovery of THF and ethyl acetate was increasing with a number of stages. The target specifications stated in experimental section were achieved. Note that further optimizing the process, e.g. temperatures and solvent-to-feed ratios, is possible but beyond the scope of this study. In conclusion, the M-CCE setup was proved to be useful for multicomponent systems, particularly when the equilibrium data from multistage extraction is needed.
Figure 32. Left: Percent recovery of alcohols in the organic outlet, Right: Percent recovery of THF and ethyl acetate in the organic outlet. (conditions: \( N = 1, 3, 5, 7, \) and \( 9 \). The feed, decane and water streams enter the setup at the middle, the \( N^{th} \), and the \( 1^{st} \) stages, with flow rates of \( 1.77, 2.19, \) and \( 4.00 \), respectively.)

4.3 **Purification of phase-transfer catalyst after alcohol oxidation in flow**

The second case study concerns purification of products from continuous synthesis of alcohol oxidation. Oxidation of alcohols into aldehydes and ketones is a valuable chemical transformation in industry \([90, 91]\). Recently, new oxidation pathways have been developed to utilize less toxic and inexpensive oxidants, such as oxygen and hydrogen peroxide (\( \text{H}_2\text{O}_2 \)) \([92]\). The work described in this section involves the use of \( \text{H}_2\text{O}_2 \) along with a homogeneous catalyst and phase transfer catalyst (PTC) to improve efficiency and selectivity. Specifically, transition metal substituted sandwich-type polyoxometalates (POMs) was used as a catalyst and tetrabutylammonium hydrogen sulfate (97\%) (TBAHS) was used as a PTC. The reaction was performed in bi-phasic mode and developed for different scales.

The bi-phasic stream after the synthesis contained both products and impurities including the catalyst and PTC. While the POMs catalyst was readily removed with the aqueous portion from the reactor, the PTC required an additional step. Several methods of separation of PTC from the reaction matrix, including column chromatography, extraction, distillation, adsorption to an insoluble support, have been studied \([93, 94]\). Extraction is the most common for the separation of water-soluble PTC owing to its high efficiency, easy setup, less heating-intensive operation (which may cause PTC decomposition), and simple downstream processing for recovery and recycle \([95, 96]\).

In this section, the multistage setup was applied to the purification of PTC. The countercurrent was proved to the most efficient with the smallest amount of solvents required.
4.3.1 Experimental section and analytical method

This part of thesis focuses on purification steps. Details about the synthesis can be found in Appendix E. There were two post-reactor steps for purification of the product from POMs and PTC: a) aqueous portion removal and b) PTC extraction (Figure 33). For the aqueous portion removal step, the biphasic reaction stream was first separated using the membrane-based separator with a Pall Zeflour\textsuperscript{TM} 0.5 μm hydrophobic PTFE membrane. The wetted structure of the separator was made of ultra-high molecular-weight polyethylene (UHMW), which provided excellent chemical compatibility, and embedded in an aluminum shell for enhanced mechanical support. The current design of the separator accommodates the total flow rate between 1-20 mL/min. A scaled-up version of the separator was also designed (Figure 33).

![Figure 33. A block diagram of the three main steps for the fully-continuous oxidation of alcohols (dotted line: biphasic stream, solid line: single-phase stream)](image)

Next, for the PTC extraction, the separated organic stream was mixed with extraction solvents, toluene and Milli-Q water. Different operational conditions (e.g., solvent-to-feed ratio) and cascading configurations for the liquid-liquid extraction were studied (Table 11). Each extraction stage required the sufficient length of tubing before the phase separation in the membrane-based separator to allow complete mass transfer of the solute (PTC). Batch extraction using rigorous mixing and long setting time served as a benchmark for equilibrium extraction. All the experiments were carried out at room temperature (20 °C). The purification of benzaldehyde, the product of benzyl alcohol oxidation, was selected as a case study for these extraction experiments. Both organic and aqueous outgoing streams were collected after 3-5 residence times, and analyzed using LC-MS.
Table 11. Various conditions and configurations for the PTC extraction experiment for LFR and AFR system

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Low-flow reactor (LFR) experiment</th>
<th>Advanced-flow reactor (AFR) experiment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(F_T^1)</td>
<td>(F_w^1)</td>
</tr>
<tr>
<td>Low-1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Low-2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Low-3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Low-4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Adv-1</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Adv-2</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Adv-3</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

\(^1\)\(F_T\) and \(F_w\): volumetric flow rates of toluene and water, respectively, in mL/min.
\(^2\)S/F: Solvent-to-feed ratio is defined as the sum of water and toluene volumetric flow rates divided by the flow rate of the organic stream from the previous step.
\(^3\)Number of extraction stages
\(^4\)Batch refers to the gravity-based extraction (i.e. shake-flask) whereas the continuous extraction refers the use of segmented flow inside the small-diameter tubing, followed by the membrane-based separation.

4.3.2 Continuous separation of biphasic reaction stream

Traditionally, the phase separation of a biphasic reaction mixture is performed using gravity. However, for the current system, the density difference between the organic and aqueous phases that come out of the reactor is very small, i.e. the densities of the organic and aqueous phases at 15 °C are about 1.05 and 0.99 g/cm\(^3\), respectively. This property results in slow droplet coalescence and time-consuming phase separation using gravity, as observed by performing batch extraction experiments (Figure 34).
To resolve this issue, we employed the liquid-liquid extraction in laminar slug flow, followed by microporous membrane-based phase separation. This method allowed the mass transfer of the key components between the two immiscible phases to happen without any droplet breakup and coalescence. The two phases were subsequently separated based on their wettability natures instead of density.

The oxidation of benzyl alcohol into benzaldehyde using the synthesized catalyst was selected as a case study to demonstrate the continuous workup. After the completed alcohol oxidation in Corning® LFR and AFR, the biphasic reaction stream was flowed in PFA tubing for residence times of 52.5 and 15 seconds for the LFR and AFR systems, respectively. These allowed sufficient times for interphase equilibrium. Then, the membrane-based separator was used to remove the aqueous phase from the flow system. At this stage of separation, significant amount of catalyst was removed with the aqueous phase. However, major amount of PTC still remains in the benzaldehyde phase. The PTC concentration in the benzaldehyde phase varies between 3.4 and 3.6 mg/mL for both LFR and AFR systems.

4.3.3 High extraction of PTC with multistage cascading

Use of toluene and water as extraction solvents were found to be effective in extracting out PTC from the benzaldehyde. In a shake-flask test, one proportion of the benzaldehyde phase was combined with two proportions of toluene and one proportion of water. This choice of a solvent ratio was driven by a compromise between maximized removal of PTC and minimized amount of solvent consumption. Upon this ratio, 77% of PTC was removed after very long mixing and settling by gravity (> 20 hrs) at 20 °C. Assuming the two phases at equilibrium, this result provided a benchmark that can be used not only to assess continuous setups but also to determine a distribution coefficient of PTC in organic and aqueous phases, $K_{PTC}$. 
A material balance for PTC was set up to approximate $K_{PTC}$. Three ideal assumptions were made to simplify the equation, particularly when it was extended to different types of cascades later in this section.

- A value distribution coefficient for the PTC, $K_{PTC}$, was constant.
- Feed was completely miscible with toluene but immiscible with water.
- Extraction generated mutually insoluble organic raffinate and aqueous extract phases.

The last two assumptions implied that the flow rates of raffinate and extract phases are $F_r + F$ and $F_w$, respectively. The material balance of PTC around a single stage of extraction is as follows:

$$C_{PTC}^{ben} \cdot F + 0 \cdot F_r + 0 \cdot F_w = C_{PTC}^{raf} \cdot (F + F_r) + C_{PTC}^{ext} \cdot F_w$$  \hspace{1cm} \text{(Eq. 7)}

The concentrations and flow rates have units of mg/mL and mL/min. Rearrangement of Eqn.7 gives

$$\frac{C_{PTC}^{raf}}{C_{PTC}^{org}} = \frac{1}{1 + E}$$  \hspace{1cm} \text{(Eq. 8)}

Which represents that the fraction of PTC that is not extracted out with the aqueous phase. Note that $C_{PTC}^{org}$ is the concentration of PTC in the organic phase entering the extraction step, given by

$$C_{PTC}^{org} = \frac{C_{PTC}^{ben}}{1 + \frac{F_r}{F}}$$  \hspace{1cm} \text{(Eq. 9)}

$E$ is the extraction factor, given by

$$E = K_{PTC} \cdot \left( \frac{F_w}{F + F_r} \right)$$  \hspace{1cm} \text{(Eq. 10)}

$$K_{PTC} = \frac{C_{PTC}^{ext}}{C_{PTC}^{raf}}$$  \hspace{1cm} \text{(Eq. 11)}

Similar expressions can be derived for crosscurrent and countercurrent cascades as summarized in Table 12.
Table 12. Expressions of the PTC remaining in the raffinate phase and the extraction factor (E)

<table>
<thead>
<tr>
<th>Configurations</th>
<th>Expression for $\frac{C_{PTC}^{up}}{C_{PTC}^{org}}$</th>
<th>Expression for $E$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single stage</td>
<td>$\frac{1}{1+E}$</td>
<td>$E = K_{PTC} \cdot \frac{F_w}{(F + F_T)}$</td>
</tr>
<tr>
<td>N-stage crosscurrent(^a)</td>
<td>$\frac{1}{(1+E)^N}$</td>
<td>$E = K_{PTC} \cdot \frac{F_w}{F \cdot N + F_T}$</td>
</tr>
<tr>
<td>N-stage countercurrent</td>
<td>$\frac{1}{\sum_{n=0}^{N} E^n}$</td>
<td>$E = K_{PTC} \cdot \frac{F_w}{F + F_T}$</td>
</tr>
</tbody>
</table>

\( ^a \) The expression based on an assumption that the water and toluene flow rates, $F_w$ and $F_T$, are divided into equal portions that are sent to each stage.

With 77% removal of PTC, $K_{PTC}$ was calculated to be 10.04 using equations 8-11. This value was used to determine the fraction of PTC removed with different types of configurations and number of stages. As shown in Figure 35, more than 92% removal of PTC was achieved by simply adding another stage of extraction. The plot also indicated that the countercurrent cascade always performed more efficiently than the crosscurrent cascade, i.e. a higher degree of extraction for a given amount of solvent and number of stages.

![Figure 35. Percent extraction of PTC when calculated with the toluene to water to feed ratio of 2:1:1](image)

4.3.4 Continuous extraction of PTC and scale-up

The analysis above prompted an implementation of membrane-based separators into the multistage countercurrent cascade. For the LFR system, each stage accommodated a residence time of 15 seconds for mixing. According to Table 13, this length of time was sufficient for the mass transfer to
reach equilibrium, as indicated by close agreement between the benchmark (Low-1) and the single-stage continuous extraction (Low-2) results.

The membrane-based separators were assembled into the 3-stage countercurrent cascading. As for clarification, the mixing in each stage happened in cocurrent slug flow, but the arrangement of multiple stages was countercurrent such that the overall aqueous and organic phases flowed in the opposite directions. The aqueous phase was delivered from stage \( i \) to \( i+1 \) by peristaltic pumping while the organic phase flowed from stage \( i \) to \( i-1 \) by the pressure drop of the system. From Table 13, the 3-stage countercurrent cascading (Low-4) resulted in 92% extraction of PTC, with only 0.3 wt% PTC in the final stream of benzaldehyde. As shown previously, the countercurrent cascade is, theoretically, more efficient than the crosscurrent cascade. Experimentally, the 2-stage crosscurrent cascade (Low-3) required twice of extraction solvents as much as the 3-stage countercurrent cascade (Low-4) in order to achieve the same degree of purification, i.e. 92% extraction of PTC.

Table 13. Results of the PTC extraction experiments at different conditions for LFR system

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Conditions</th>
<th>% PTC extraction</th>
<th>PTC wt.% in the product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-1</td>
<td>Batch (shake-flask)</td>
<td>77</td>
<td>0.86</td>
</tr>
<tr>
<td>Low-2</td>
<td>Continuous single stage</td>
<td>75</td>
<td>0.94</td>
</tr>
<tr>
<td>Low-3</td>
<td>Continuous 2 stage crosscurrent</td>
<td>92</td>
<td>0.3</td>
</tr>
<tr>
<td>Low-4</td>
<td>Continuous 3 stage countercurrent</td>
<td>92</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Similarly, the PTC extraction was scaled up to the throughput of the AFR system. The membrane-based separator was modified in terms of the membrane area and the sizing of integrated pressure control element. It had the filling volume of 40 mL. This new design was tested to be capable of maintaining consistent pressure drop across the membrane (ca. 2-4 psi) for complete separation over hours.

These separators were assembled into the 3-stage countercurrent extraction, similar to the setup in the LFR system; each stage had the PFA tubing for the completed mass transfer before the separator. We used the tubing with the same diameter as the LFR system (1/8” O.D. and 1/16” I.D.) but with a shorter length, i.e. shorter mixing time. At this scale, the short residence time (15 seconds) was sufficient for the mass transfer completion due to enhanced mixing in high flow velocity. This was verified by similar percent extractions obtained from the shake-flask test (Adv-1) and the continuous single-stage extraction (Adv-2), as shown in Table 14. The 3-stage countercurrent cascade (Adv-3) gave about 89% extraction of PTC. This was similar to the result from the LFR system (92% in Low-4), demonstrating the scale-up capability of our process.
Table 14. Results of the PTC extraction experiment at different conditions for the AFR system.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Condition</th>
<th>% PTC extraction</th>
<th>PTC wt.% in the product</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Batch</td>
<td>63</td>
<td>1.4</td>
</tr>
<tr>
<td>A2</td>
<td>Continuous single stage</td>
<td>67</td>
<td>1.2</td>
</tr>
<tr>
<td>A3</td>
<td>Continuous 3 stage countercurrent</td>
<td>89</td>
<td>0.4</td>
</tr>
</tbody>
</table>
Chapter 5. Conclusions and outlook

5.1 Summary of key thesis contributions

This thesis has revolved around the design of fully-continuous flow synthesis at mL/min scale using a number of the enabling tools. Telescoping of multistep reactions was accomplished by two approaches. The first approach was to link directly reactive steps that are compatible to one another. As an example, the lidocaine synthesis comprising two sequential reactions, amidation and amination, was demonstrated. The byproduct from the amidation could be quenched and then directly delivered to the second step. Also, NMP, the solvent from the amidation, was compatible with the amination. Therefore, no solvent switch or in-line separation is required. An overall yield of 90% after the final extraction with hexane and NaCl solution was obtained. The other approach involves use of in-line separation to deal with sequential reactions that are not compatible to one another. The example of fluoxetine synthesis was provided to prove feasibility of this approach. The conventional fluoxetine syntheses, either in batch or flow, contain time-consuming work-up steps such as evaporative solvent switch, reflux, and flash chromatography. In this thesis, the fully-integrated fluoxetine production was demonstrated. The flow sequence consists of three reactions and three in-line extractions, performed at elevated temperatures and pressures for better kinetics. All the steps were optimized to achieve high yield as well as high degree of robustness, particularly in the presence of solid formation. In the end, an overall yield of 43% upon isolation was obtained.

Furthermore, this thesis presents a number of enabling tools that can be integrated into flow chemistry. First, in-line evaporator is designed to partially evaporate a solvent. In this design, flash evaporation, the generation of partial vapor when a saturated liquid stream undergoes an instant reduction in pressure, was utilized. The device consists of three elements: heater, de-pressurizer, and membrane-based separator. Its applications include in-line pre-concentration. An example of neostigmine synthesis was highlighted to assess the evaporator’s performance. The evaporator enabled pre-concentration of the organic stream containing a carbamate intermediate compound at a factor of 1.43 before the last reaction.

Another enabling tool presented in this thesis is multistep separation based on a membrane-based separator. A pressure differential across a membrane is regulated by an integrated pressure control element, enabling complete phase separation without any additional units of pressure regulators. In other words, the separation is decoupled from downstream operations. For that reason, multiple separators can be simply constructed into a countercurrent liquid-liquid extraction setup. The flexibility in downstream pressure manipulation allows use of non-precise pumps, such as peristaltic pumps. The setup has the
advantages of small footprint, low filling volume and flexible operation. Standard systems were tested to evaluate the extraction performance. An extraction efficiency of nearly 100% was achieved, regardless of a number of stages. The high efficiency was probably a result of intensified mass transfer inside a slug flow.

The setup was extended to other applications. Two main case studies were presented in this thesis. The first study investigated a multicomponent liquid-liquid system. A solvent recovery of THF and ethyl acetate from a mixture with alcohols was selected as a model system. Due to the setup’s high efficiency, equilibrium data could be generated. The setup facilitates process optimization for a multicomponent system, which is difficult to predict from existing thermodynamic models. Another case study concerns purification of products after flow synthesis. Removal of a phase transfer catalyst after continuous alcohol oxidation was chosen as a model system. The multistage setup was shown to provide efficient separation with minimal amount of solvents required. In summary, the multistage setup can be extended to other versatile applications thanks to its small volume, high efficiency, and robust operation.

5.2 Outlook and opportunities for future research

Flow chemistry has further potentials that will allow chemists to explore new synthetic routes at conditions, which are difficult to be performed in batch. It can also be employed to facilitate continuous manufacturing which has the advantages of greater safety, better kinetics and quality controls, and smaller footprint over the traditional batch production. This thesis covers several examples of pharmaceutical syntheses in flow and thus proves feasibility of full integration of multistep reactions.

Nonetheless, in order to expand this concept to a wider range of applications, a number of process elements need to be developed and improved. For instance, current pumping methods are not robust. For high pressure applications, high performance liquid chromatography (HPLC) pumps are commonly used. Several internal parts, such as check valves, seals and o-rings, are expensive yet prone to damage and incompatible with most organic solvents. Peristaltic and diaphragm pumps are used for low pressure applications. Again, they have the problems of chemical compatibility (e.g. tubing material) and short lifetimes. A pulseless, high-rotation milliGAT® pump is an interesting alternative – it has no check valves, and it is self-priming. Some modifications in the current design can be carried out to accommodate corrosive reagents and high-pressure operations. Apart from the pumping issue, solid formation is another major challenge for flow chemistry. Throughout many processes discussed in this thesis, solid clogging was avoided by means of sonication, heating and dilution. However, each strategy was not investigated thoroughly enough. For instance, an optimal frequency of the ultrasonic transducer
for preventing solid agglomeration was not determined. Comprehensive studies on solid formation (i.e. nucleation and growth) and aggregation will afford insights into solid handling as well as reactor designs.

One major advantage of flow synthesis is potential for reagent and solvent recycle. However, cross-contamination gives a primary cause for concern. In-line monitoring, such as pH meters, IR, and UV/Vis units, should be incorporated to ensure quality of the recycle stream. In-line separations, including extraction and evaporation discussed in this thesis, can be developed further to facilitate recycle.

Furthermore, the multistage liquid-liquid extraction setup designed in this thesis can be improved. The peristaltic pump in the setup can be changed to other pumping types (e.g. centrifugal pump) for higher pressure or better chemical tolerances. Mixing can be enhanced further to reduce a total residence time in the system. Automated system can be built upon the setup to screen and optimize extraction process variables. Ideally, the setup can be constructed into a compact box, which researchers can perform full development and optimization for extraction processes in a rapid manner.
References


Appendix A. Process descriptions for the fully-integrated syntheses for lidocaine and fluoxetine.

This appendix provides detailed process descriptions for the upstream syntheses of the two drugs, lidocaine and fluoxetine, which were performed in the PoD system. The synthesis protocols are given in Section A.1 and A.2. Details about separator, reactor, and back-pressure regulator designs can be found in Section A.3. List of reagents and solvents for Figure 7 is given in Section A.4.

A.1 Protocol for lidocaine synthesis

A stream of neat chloroacetyl chloride (L3) (1.15 equivalents, flow rate 2.7 mL/h) was combined with N-methyl-2-pyrrolidinone (NMP) (L4) (0.15 mL/min) in a T-mixer. Then, the stream was injected with a stream of 1.43 M solution of 2,6-xylidine in NMP (L2) (1.0 equivalents, 0.35 mL/min). The fluid was delivered into a 10 mL reactor (a residence time of 18.4 min) that was heated at 120 °C. Then, a stream of KOH (1.2 equivalents) and diethylaniline (3.0 equivalents) in a 1:1 solution of MeOH and DI water (1.15 mL/min) (L5) was introduced and the mixture was maintained in Reactor II at 130 °C for 17.7 min. HPLC analysis revealed complete conversion (99%) of 2,6-xylidine (L2) to the crude lidocaine. The resulting stream (flow rate 1.65 mg/mL, 0.15 M of crude fluoxetine) was depressurized through a back pressure regulator set at 1.7 MPa. The final liquid-liquid extraction was performed with concomitant injection of hexane (3 mL/min) (L6) and a saturated solution of NaCl and NH₄Cl (2 mL/min) (L7). The extraction was completed by flowing the mixture through a short packed-bed column of 0.1 mm glass beads and separating the organic and aqueous phases via a gravity-operated liquid-liquid separator. Steady state was reached after 60 minutes and lidocaine was obtained in 90% yield as a solution in hexane.
A.2 Protocol for fluoxetine synthesis

The fluoxetine synthesis started with a mixing between a 3 M solution of 3-Chloropropiophenone in toluene (F2) at a flow rate of 0.12 mL/min and a 1 M solution of DIBAL in toluene (F3) at a flow rate of 0.36 mL/min in a T-mixer. The reactive stream then went into a 5 mL spiral reactor (a residence of 10 mins) that was maintained at room temperature. After that, an aqueous solution of 4 M HCl (F4) was injected at a flow rate 1 mL/min in order to quench the reaction. The material was passed into a reactor with an ultrasonic transducer to ensure fast dissolution of the aluminum salts. The organic and aqueous phase was separated in-line by a membrane liquid-liquid separator. A successive injection of 4 M HCl (F5) and membrane separation was implemented to completely remove excess DIBAL. A 91% yield post-separation was obtained. At this point, the continuing stream contained 0.75 M of the intermediate alcohol (F13) in toluene. This stream was then directed to a 10 mL spiral reactor for a biphasic amination reaction with a 40% wt aqueous methylamine solution (F6, flow rate 0.5 mL/min). The conversion of the starting alcohol reached 93% after a residence time of 10 minutes at 135 °C (89% yield). The crude amino alcohol F14 was then efficiently extracted (90% after in-line separation) by concomitant injection of THF (0.5 mL/min) and an aqueous solution of 20 wt% sodium chloride (flow rate 2 mL/min). After the organic phase was separated, it was passed through a cartridge loaded with molecular sieves (MS, 4Å) to remove the residual DI water. The amino alcohol F14 was then preheated and treated with consecutive streams of 4-fluorobenzotrifluoride in DMSO (0.24 M) at a flow rate of 1.7 mL/min and potassium tert-butoxide (0.25 M)/18-crown-6 (0.05 M) in DMSO at a flow rate of 1.29 mL/min. After a residence time of 2.6 min, a stream of DI water (F11, 4 mL/min) was injected to avoid precipitation of the KF salt and clogging of the back pressure regulator. An injection of tert-butyl methyl ether (F12, 4 mL/min) followed by a gravity-operated liquid-liquid separation, provided the crude fluoxetine as a solution in hexane (43% overall yield).

3-chloro-1-phenylpropan-1-ol (F13)
3-(methylamino)-1-phenylpropan-1-ol (F14)
A.3 Design details for reactors and separators

Membrane-based separators. The membrane-based separators used in all the syntheses mentioned in Sections 2.2 On-demand, reconfigurable system for pharmaceutical production and 2.3 Design of integrated fully-continuous synthesis of pharmaceutical: Fluoxetinewere modified from the original design [57]. As shown in Figure 36, the redesigned separators were now machined with perfluorinated polymers for wetted internal parts and aluminum of a non-wetted shell. The shell was to prevent perfluorinated components from deforming under a high pressure. The membrane and diaphragm of the integrated pressure controller were PTFE and PFA, respectively. FEP coated o-rings were used to provide a leak proof.

![Figure 36. Internal structure of a membrane separator, showing perfluorinated wetted parts and an aluminum shell [52].](image)

Back pressure regulators (BPRs). The syntheses mentioned in Sections 2.2 On-demand, reconfigurable system for pharmaceutical production and 2.3 Design of integrated fully-continuous synthesis of pharmaceutical: Fluoxetinewere pressurized with BPRs constructed in-house. The BPRs were dome loaded-type in which a diaphragm with a compressed gas loading exerted force onto a liquid flow path. Similar to the separators, the wetted bodies were made of perfluorinated materials and contained within an aluminum shell. A multiple-inlet BPR was designed with a similar concept to provide the exact same pressure set point for several reactor lines. It was employed for the aqueous outlet lines in the fluoxetine synthesis.

Reactors. All the reactors in Sections 2.2 On-demand, reconfigurable system for pharmaceutical production and 2.3 Design of integrated fully-continuous synthesis of pharmaceutical: Fluoxetinewere tabular-flow reactors as shown in Figure 6-C. Unless noted otherwise, the reactors were made of PFA
tubing with 1/16” ID and 1/8” OD that was embedded in aluminum shells. Different reactor volumes could be made with defined lengths of the tubing. The center hole of the aluminum shell was made for inserting heater cartridges along with a thermocouple. The temperature control was installed.
A.4 List of reagents and solvents for Figure 7.

<table>
<thead>
<tr>
<th>Stream</th>
<th>Target API</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>diphenhydramine HCl</td>
</tr>
<tr>
<td>L1</td>
<td>lidocaine HCl</td>
</tr>
<tr>
<td>D1</td>
<td>diazepam</td>
</tr>
<tr>
<td>F1</td>
<td>fluoxetine HCl</td>
</tr>
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</table>

### Production of diphenhydramine hydrochloride (1)

<table>
<thead>
<tr>
<th>Stream</th>
<th>Reagents/Solvents</th>
</tr>
</thead>
<tbody>
<tr>
<td>B2</td>
<td>2-dimethylaminoethanol</td>
</tr>
<tr>
<td>B3</td>
<td>chlorodiphenylmethane</td>
</tr>
<tr>
<td>B4</td>
<td>NaOH aqueous solution (3M)</td>
</tr>
<tr>
<td>B5</td>
<td>hexanes</td>
</tr>
<tr>
<td>B6</td>
<td>water</td>
</tr>
<tr>
<td>B7</td>
<td>HCl/ Et₂O</td>
</tr>
</tbody>
</table>

### Production of lidocaine hydrochloride (2)

<table>
<thead>
<tr>
<th>Stream</th>
<th>Reagents/Solvents</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2</td>
<td>2,6-xylidine (1.43 M in NMP)</td>
</tr>
<tr>
<td>L3</td>
<td>chloroacetyl chloride</td>
</tr>
<tr>
<td>L4</td>
<td>N-methyl-2-pyrrolidone (NMP)</td>
</tr>
<tr>
<td>L5</td>
<td>Et₂NH (3.0 eq.), KOH (1.2 eq.) in MeOH/H₂O</td>
</tr>
<tr>
<td>L6</td>
<td>hexanes</td>
</tr>
<tr>
<td>L7</td>
<td>sat. NaCl/ NH₄Cl</td>
</tr>
<tr>
<td>L8</td>
<td>HCl/ Et₂O</td>
</tr>
</tbody>
</table>

### Production of diazepam (3)

<table>
<thead>
<tr>
<th>Stream</th>
<th>Reagents/Solvents</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2</td>
<td>5-chloro-2-(methylamino)benzophenone (1M in NMP)</td>
</tr>
<tr>
<td>D3</td>
<td>chloroacetyl bromide</td>
</tr>
<tr>
<td>D4</td>
<td>N-methyl-2-pyrrolidone (NMP)</td>
</tr>
<tr>
<td>D5</td>
<td>ammonia solution (3.5 M in MeOH:H₂O, 9:1 mixture)</td>
</tr>
<tr>
<td>D6</td>
<td>20% NaCl aqueous solution</td>
</tr>
<tr>
<td>D7</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>D8</td>
<td>HCl aqueous solution (4M)</td>
</tr>
<tr>
<td>D9</td>
<td>NH₃/H₂O</td>
</tr>
<tr>
<td>Stream</td>
<td>Reagents/Solvents</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>F2</td>
<td>3-chloropropiophenone in toluene</td>
</tr>
<tr>
<td>F3</td>
<td>DIBAL in toluene</td>
</tr>
<tr>
<td>F4</td>
<td>4 M HCl</td>
</tr>
<tr>
<td>F5</td>
<td>4 M HCl</td>
</tr>
<tr>
<td>F6</td>
<td>MeNH₂ aqueous solution</td>
</tr>
<tr>
<td>F7</td>
<td>NaCl solution</td>
</tr>
<tr>
<td>F8</td>
<td>THF</td>
</tr>
<tr>
<td>F9</td>
<td>4-fluorobenzotrifluoride in anhydrous DMSO</td>
</tr>
<tr>
<td>F10</td>
<td>KOtBu and 18-crown-6 in DMSO</td>
</tr>
<tr>
<td>F11</td>
<td>water</td>
</tr>
<tr>
<td>F12</td>
<td>TBME</td>
</tr>
<tr>
<td>F13</td>
<td>HCl/Et₂O</td>
</tr>
</tbody>
</table>
Appendix B. Detailed process description of enantiomeric resolution of racemic alcohol compounds

The dynamic resolution of racemic alcohol compounds was mentioned in Section 2.4.2 Removal of volatile component with gas stripping technique. This appendix provides more details on the process as well as the gas stripping setup.

*Reactor loading and feed preparation.* Unless noted otherwise, all the reagents and solvents were purchased from Sigma-Aldrich. Reactor I was loaded with 1 g of lipase powder after swelling with toluene. The racemization catalyst used was Ruthenium on silica particles (0.12 – 0.32 mol %), and the amount of catalyst loading into Reactor II was about 3.6 g. The residence times of the enzyme and racemization reactors were about 25 and 35 minutes, respectively. Only the racemization reactor was heated (100 °C). The setup scheme was shown in Figure 37. The alcohol feed was prepared by adding 1 mL of 1-phenylethanol in 30 mL reactor. The solution was sparged under argon for 30 minutes before adding 1 mL of vinyl acetate. For a recycle ratio of 10 and a total flow rate of 50 µL/min, the feed was delivered by a Harvard Apparatus syringe pump at a flow rate of 4.55 µL/min, and the recycle was carried out by a milliGAT® pump at a flow rate of 45.45 µL/min. The reaction was performed for 12 hours before the first sample collection. The samples were analyzed with HPLC.
Gas stripping setup. The 4-stage gas stripping setup consisted of four membrane separators. The design of the membrane separators was identical to the one described in Appendix A.3 Design details for reactors and separators. Argon was introduced from a tank into the system by peristaltic pumping. This created slug-flow conditions in which the gas phase took out the volatile component, acetaldehyde. Inside the membrane separator, the gas phase was retained while the liquid permeated through the membrane.
Appendix C. Multistage extraction characterization

1. ASPEN Plus simulation for Toluene-acetone-water

Thermodynamic model: UNIQUAC, liquid-phase activity coefficient, \( T = 298 \, \text{K} \)
Interaction parameters: \( a_{ij} = a_{ji} = d_{ij} = e_{ij} = f_{ij} = 0 \) for any pair of species
\( c_{ij} = 0 \)

<table>
<thead>
<tr>
<th>i</th>
<th>j</th>
<th>( b_{ij} ) (K)</th>
<th>( b_{ji} ) (K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Toluene</td>
<td>-350.21</td>
<td>-950.6</td>
</tr>
<tr>
<td>Water</td>
<td>Acetone</td>
<td>74.348</td>
<td>-336.17</td>
</tr>
<tr>
<td>Toluene</td>
<td>Acetone</td>
<td>-269.35</td>
<td>141.79</td>
</tr>
</tbody>
</table>

These parameters are given in ASPEN as LLE-LIT (from literature LLE correlation data)
Other specifications: Extraction column with temperature profile (isothermal at 298K)
The 1-stage simulation was run with a decanter model.

2. ASPEN Plus simulation for Ethyl acetate-acetic acid-water

Thermodynamic model: NRTL, liquid-phase activity coefficient, \( T = 298 \, \text{K} \)
Interaction parameters: \( a_{ij} = a_{ji} = d_{ij} = e_{ij} = f_{ij} = 0 \) for any pair of species
\( c_{ij} = 0.2 \)

<table>
<thead>
<tr>
<th>i</th>
<th>j</th>
<th>( b_{ij} ) (K)</th>
<th>( b_{ji} ) (K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Acetic acid</td>
<td>-79.001</td>
<td>-153.38</td>
</tr>
<tr>
<td>Water</td>
<td>Ethyl acetate</td>
<td>1287.5</td>
<td>150.63</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>Ethyl acetate</td>
<td>-758.51</td>
<td>960.85</td>
</tr>
</tbody>
</table>

These parameters were obtained from Colombo and Battilana, 1999 [83].
Other specifications: Extraction column with temperature profile (isothermal at 298K)
Appendix D. Headspace gas chromatography method for characterizing the multicomponent case study

Inlet condition:
The heater was operated at 250 °C. The inlet flow was set to be 66 mL/min with 29.303 psi pressure. The septum purge flow was 3 mL/min. The split mode was used with the ratio of 20:1, 60 mL/min.

Column condition:
The column used was J&W 122-1334, 30m x 250um x 1.4um, operating at 260 °C.
In: Front SS Inlet He
Out: Front Detector FID
Control mode: Flow, 3 mL/min, 16 min

Oven condition:
Equilibration time, 0.5 min
Maximum oven temperature 260 degC

<table>
<thead>
<tr>
<th>Rate, degC/min</th>
<th>Value, degC</th>
<th>Hold time, min</th>
<th>Run time, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>70</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>220</td>
<td>0</td>
<td>16</td>
</tr>
</tbody>
</table>

Detector condition:
FID, front; Heater, 300 degC
H₂ flow: 35 mL/min
Air flow: 350 mL/min
Makeup flow (He): 20 mL/min

Headspace unit condition:
The headspace unit used was Agilent G1888 Headspace sampler. The temperatures of the oven, loop and transfer line are 100, 110, and 115 °C, respectively. The vial was allowed to equilibrate within 8 minutes, with the times for pressurization, loop fill, loop equilibration, and injection to be 0.08, 0.50, 0.05, and 0.50 minutes, respectively. The GC cycle was 17.5 minutes.
Appendix E. Detailed synthetic descriptions for homogeneous-catalyzed alcohol oxidation

_Preparation of feed solution and reaction conditions_. Unless noted otherwise, all the catalysts, reagents and solvents were purchased from Sigma-Aldrich. The catalyst used was zinc-substituted sandwich-type polyoxotungstate (Na_{12}[WZn_{3}(ZnW_{9}O_{34})_{2}]), synthesized by a similar approach to the literature [97]. This catalyst showed comparable result to the commercial sodium tungstate dihydrate. The 35 wt% hydrogen peroxide solution was used as an oxidant, and the phase transfer catalyst was tetrabutylammonium hydrogen sulfate (97%) (TBAHS). The alcohol substrate was benzyl alcohol. The feed solutions were prepared by combining ~1.66 g of the substrate with 185 mg of the catalyst and 1.63 g of the hydrogen peroxide solution. The molar PTC-to-catalyst ratio was 6. The feed was delivered to the Corning low-flow reactor (LFR) system at a total flow rate of 1.15 mL/min. The system consisted of nine plates, each one of which is 0.45 mL, resulting the total residence time of 5 min. The product reaction stream continued into the membrane-based separation units, which removed the aqueous phase and further extracted the organic phase with toluene and water to remove remaining PTC. The reaction samples were collected after 3-5 residence times and the organic and aqueous phases were analyzed using GC-FID or HPLC. The synthesis and separation were also scaled-up using the Corning advanced-flow reactor (AFR). The total system volume was 100 mL, and the feed flow rate was adjusted to 20 mL/min.