The chemical plant of tomorrow and the future : process-design intensification at different production scales

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The Chemical Plant of Tomorrow and the Future

Process-Design Intensification at Different Production Scales

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Technische Universiteit Eindhoven,
op gezag van de rector magnificus prof.dr.ir. F.P.T. Baaijens,
voor een commissie aangewezen door het College voor Promoties,
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door

Iris Vural Gürsel

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voorzitter:	prof.dr.ir. J.C. Schouten
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In process intensification,
the journey is the reward.
Prof. Dr. Frerich J. Keil

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Iris Vural Gürsel
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Summary

Chemical Plant of Tomorrow and the Future – Process-Design Intensification at Different Production Scales

Vision: Europe's chemical industry is under pressure to find sustainable and cost-efficient solutions to improve its competitiveness in Europe and worldwide, The European Union with its public-private partnerships in the FP7 and SPIRE/H'2020 programs has started top-down to bring to reality the vision of the "Factory of the Future/Future Chemical Manufacturing" which considers development of compact, modular plants with embedded process intensified equipment. A major driver came from the existing modularization assembly technology. Additionally, a step change improvement can be realized with process intensification. Micro process technology is one of the key enablers and it is implemented within the modular plants. Meanwhile, several of such compact plants are in pilot operation and one is even used for production in industry. Aim of this research is to complement such step-changes in chemical production by a bottom-up approach and look for chances of intensification of plants.

Moreover, a holistic and systemic approach should be governed which gives focus to the chemical process as a whole, which does allow quantum leaps through unifying contradictions to a new window of opportunity (as the TRIZ method does for systematic development of innovative patent ideas). With a new field of process-design intensification under Novel Process Windows this can be achieved. It heads for integrated and simplified smart-scale flow process design. It is beyond the existing transport intensification field that considerably improves mass and heat transfer and increasingly explored chemical intensification field that uses highly intensified, unusual and typically harsh process conditions to boost micro-processing. Process-design intensification can make use of transport and chemical intensification when transferring these to full-process level and thus making the impact holistic. The use of these three intensification fields of flow processing together with the use of modular plants can enable reduction in number of apparatus in the plant, a reduction in apparatus size, and a higher predictability in the scale-out of the apparatus. All these have potential for (much) decreased overall development time. This is discussed in Chapter 2 with generic impact analysis.

One possibility to bring step-change improvement in chemical production such as pharmaceutical production is to enable switch from batch to all flow synthesis. It was seen that further development of flow separation units is required to achieve multi-step synthesis in flow. The coupling of microseparation units with microreactors is not rare anymore, but still far from being commonly applied. In this regard, Chapter 3 describes the development

of a flow liquid-liquid extraction unit that enables metal separation in flow and its coupling with a metal catalyzed flow reactor.

Connected Reaction and Metal Separation in Flow – Drop-in process integration at lab scale (Ch 3): Increasing usage of metal catalyzed reactions calls for efficient removal of metal traces from the product. Especially for pharmaceutical substances this purification is vital to meet stringent requirements. Therefore, a continuous metal separation unit was developed and optimized which enables liquid-liquid extraction based on slug flow using chelating agents and phase separation with a porous fluoropolymer membrane. It was coupled to the copper-catalyzed azide-alkyne cycloaddition reaction studied in one-pot eliminating the need to isolate and handle potentially explosive azide. The triazole product was attained in flow with yield of up to 92% and the level of purity requirement of 15 ppm was met in one stage of extraction.

The vision is to achieve such multi-step synthesis in flow on pilot scale. This calls for scale-up of separation units. This study is rare in micro flow literature and community and thus conducted here as explained in Chapter 4 for a liquid –liquid extraction unit.

Scale-up of Flow Extraction Utilizing Coiled Flow Inverter – Drop-in process integration at pilot scale (Ch 4): A milli-scale flow extraction setup was developed using coiled flow inverter (CFI, 3.2 mm ID, 210 cm length) and a phase separator. Two separator concepts were investigated: membrane-based and wettability-based. The performance of the setup was tested for two model systems that differ in terms of interfacial tension. For the first system flow rate up to 7.2 l/h was achieved. It is important to point out that slug flow regime that is limited to microfluidic systems was maintained even at such pilot scale (58 m^3/y). This is the highest flow rate reported in literature for slug flow and also for phase separation using capillary force for immediate separation of phases. For both systems extraction efficiency close to thermodynamic equilibrium was attained. Compared to a straight tube, using CFI showed 20 % higher performance at high flow rates due to intensified secondary flow and inversions.

Another possibility to bring step change improvement in chemical production is the use of modular plants. They are seen as key to faster market introduction of a new product (50% idea) by shortening time-to-market resulting in higher cash flows. In Chapter 5, detailed cost calculations are done to quantify the benefits of modular plants and their synergy with micro process technology.

Compact Modular Plants for Fine Chemistry – Modular process integration at pilot scale (Ch 5): The economic benefits of modular plants and their combination with process intensified smart-scaled equipment was studied at the example of the EcoTrainer of Evonik Industries. A detailed cash-flow analysis was carried out for the fine chemical of 2,4-dihydroxy benzoic acid at 200 t/y capacity. It revealed that the new modular plant technology has a faster payback and a higher earning as compared to conventional technology; in particular when serving high-priced markets and the combination with micro process technology is advantageous.

Modular compact plants can also enable decentralized production, this is studied in Chapter 6 with biofuel production taken here as application case. It involves an initial techno-economic analysis to analyze the feasibility of a novel process for biofuel production.

Decentralized Biofuel Production – Modular process integration at commercial scale (Ch 6): Biomass being widely distributed and its composition differing from location and season, requires biofuel production to be done locally in small-scale. Decentralized production in modular compact plants was taken to benefit from flexibility, scalability and standardization enabling savings in engineering and construction expenditure. Process integration and intensification was achieved by coupling of reforming of biogas and bio oil in a microchannel plate heat exchanger. Complex separation steps were eliminated by production via methanol. Cost calculations showed that these benefits can outweigh the higher investment cost of decentralized plants. The calculation of cost of production of gasoline revealed that this biofuel production process can be economically competitive with petroleum-based and Fischer-Tropsh process.

Finally, a step change improvement can be realized by bringing direct chemistries on a full-process level. Direct chemistries have the potential to reduce the cascades of separation units. The demonstration example taken here is the direct adipic acid synthesis which is an important intermediate for the nylon industry. Chapter 7 describes the investigation of the process simplification potential of this direct route by cost, energy and environmental analysis. It also includes comparison with the commercial two-step route to benchmark the flow process against conventional technology.

Bulk Chemistry Process Simplification – End-to-end process integration at commercial scale (Ch 7): The direct adipic acid synthesis route is through the oxidation of cyclohexene with hydrogen peroxide. It offers an innovative alternative to the commercial route that has two-steps. The use of microreactor was considered to safely handle hydrogen peroxide and to fasten reaction rate. To propose the flow diagram and conditions for this direct route, the reaction characteristics were considered together with the downstream equipment of the two-step commercial route. Process simulation was done and a comparison with two-step commercial route revealed profound simplification due to requirement of much less process units. This resulted in total purchase cost of equipment to be halved although a more advanced flow reactor was used. Through simplification or elimination of energy intensive separation units, energy requirement was reduced significantly. Life cycle assessment showed that for a number of impact categories the direct process is greener; yet there are also categories for which the conventional route is more environmentally sustainable.

In Chapter 8 an energy efficient process is searched with the application of heat integration for the novel direct micro-flow route of adipic acid synthesis introduced in the previous chapter. Also, the importance of heat exchanger selection is highlighted with information regarding compact (including microchannel-based) heat exchangers.

Bulk Chemistry Heat Integration – End-to-end process integration at commercial scale (Ch 8): To design an energy efficient heat exchanger network for this direct route pinch analysis was employed. Aspen Energy Analyzer was used to design the improved heat exchanger network. Compared with the initial heat exchanger network where energy requirements are supplied with utility streams, the improved heat exchanger network designed enabled up to 70 % saving in utility cost which enabled to pay back the extra capital cost requirement in less than one year. Further, it was shown that with the use of compact heat exchangers, due to their higher heat transfer coefficient, reduced space requirement and increased safety compared to shell and tube heat exchangers, it is possible to achieve operating cost as well as capital cost reduction which can add to the benefits achieved by heat integration

Overall, this research provides insight at different production scales what chemical plant of tomorrow and the future can look like. The main conclusions of this thesis are summarized and recommendations are provided in Chapter 9.

CHAPTER 1

Introduction

1.1. Novel Process Windows

The chemical industry is under pressure due to strong competition with emerging markets (especially in the Near East and Asia), increasing product requirements demanded by the customer and increasing environmental and social legislations.[1–3] Therefore, there is a strong demand for sustainable and cost-efficient solutions. Often this cannot be solved anymore by process optimization since many processes are performed almost always at utmost efficiency. Entirely rethinking of the chemical process and its process development is required.[4,5] A step change improvement can be achieved by use of new apparatus and new approaches in processes. That is found in an entire new way of conceptual thinking in chemistry and chemical engineering, which manifests in process intensification,[6–11] green chemistry and green engineering[12–16]. Process intensification presents a set of radically innovative principles in process and equipment design, which can bring significant benefits in terms of process and chain efficiency, capital and operating expenses, quality, wastes, process safety, and more as defined by the European Roadmap for Process Intensification.[5] Green chemistry and green engineering approaches bring sustainable solutions in a different way. Green chemistry promotes new chemical synthesis strategies through use of renewable and other 'green' (air as oxidant, visible light for energy) resources, gives emphasis on safety, and reduction of waste by yield and selectivity improvements. Green engineering deals with the design of novel equipment, new production methods, or new operating modes. [17]

Novel Process Windows (NPW) can serve as new technological concept to all three strategic approaches (Figure 1.1).[17–22] It considers the use of high temperature, high pressure, high concentration (solvent-free), new chemical transformations, explosive conditions and process simplification and integration to boost synthetic chemistry on both the laboratory and production scale.[22] These could hardly be exploited so far since it would be beyond the capability of conventional equipment. NPW relate to creating new kinds of intensification as follows with three kinds of process intensification fields. Those are transport, chemical and process-design intensification. Latter two constitute NPW. Chemical intensification is an essential part of green chemistry whereas process-design intensification is a strong pillar for green engineering with the NPW combining both for sustainable chemical process development.

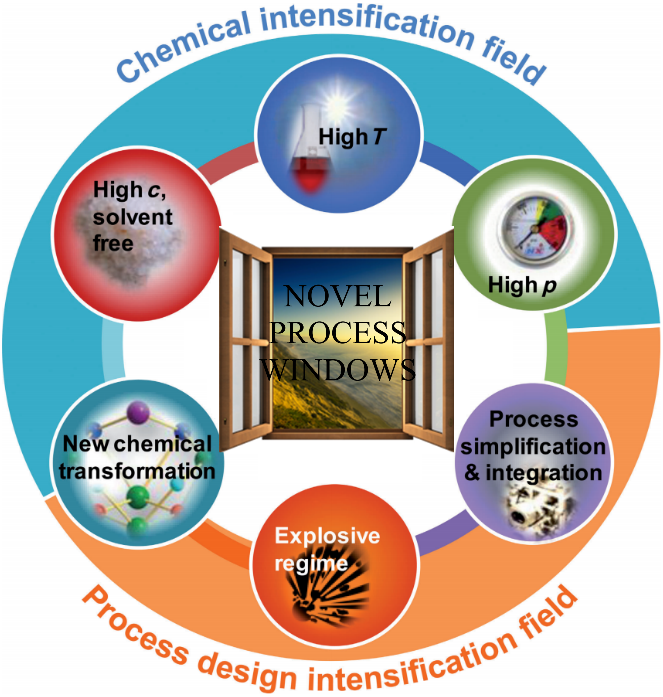

Figure 1.1. Schematic representation of Novel Process Windows (adapted from Hessel et al.[22])

The American Chemical Society Green Chemistry Institute (ACS GCI) Pharmaceutical Round Table is a multi-industrial platform with the companies Boehringer, Pfizer, Eli Lilly, Glaxo-SmithKline, DSM, Johnson & Johnson, AstraZeneca, and Merck (US).[22] They developed a list of ten key green engineering research areas: 1)continuous processing, 2) bioprocesses, 3)separation and reaction technology, 4)solvent selection, 5)process intensification, 6)life-cycle analysis, 7)integration of chemistry and engineering, 8)scale-up, 9)process energy intensity, and 10)mass and energy integration.[23] Micro process technology is a major force in the switch of processes from batch to flow and thus is given the top 1 priority. The study of microreactors falls as well under the key areas of 3 and 5. Key areas 2 and 4 refer to chemical intensification and 6 to 10 refer to process-design intensification.

Micro process technology allows processing far from state of the art. It enables to reach conditions which are not accessible, or which are at least unscalable with conventional equipment.[17] Microreactors are not the only modern devices to achieve process intensification. Other notable examples are spinning-disk, membrane and microwave /ultrasound/plasma reactors and reactive separation, hybrid separation units.[8–11,24–28] Nevertheless, microreactors are considered to be the most potent and typical example.[22] Therefore the concept of NPW is considered with micro process technology here.

The transport intensification field is given by the miniaturization of flow dimensions which considerably improves mass and heat transfer.[29,30] The reduction or elimination of mass transfer hindrance increases (effective) reaction rates; the ability to heat up and cool down fast keeps residence times as short as chemically needed and thus improves productivity; the latter is also given by the ability to operate even highly exothermic reactions with large heat release due to superior cooling (impacting selectivity as well by lowering side reactions).[19,31,32] All of this allows to reach high space-time yields and gives thus rise to compact reactors and plants.[33,34] In addition, transport intensification and the use of short residence times, almost at the kinetic limit (intrinsic kinetics), allow to lower the share of parallel and follow-up reactions, respectively, enhancing selectivity.[35] Furthermore the small level of hold-up in microreactors reduces the damage potential of toxic or explosive reagents. The improved safety in microreactors may even be the door-opener to further scale-up development otherwise prohibited.[36] The impact of efficient mixing and heat transfer, short residence time accompanied by the improved safety within microchannels has already been demonstrated by numerous successful research groups.[37–49] After enabling this development from a batch protocol into a continuous flow setup in the laboratory, scale-up to achieve commercial production was also studied.[50–57]

The chemical intensification field refers to using highly intensified and typically harsh process conditions to exploit faster kinetics.[21,22] Massive increases in temperatures, pressures and/or concentration can speed up reactions by orders of magnitude and reaction times shrink from hours to minutes and even to seconds.[19] Meanwhile there are numerous examples for the high temperature flow processing (most often conducted in the superheated regime) also in combination with high pressure.[58–65] The mechanical stability of microstructured devices allows one to run processes in a high pressure regime in safety.[20] Apart from facilitating superheated conditions, high pressure affects the reaction through the influence on the reaction equilibrium and rate constants and reaction medium via the effect on its physical properties.[66–70] There are also some examples for the concentration effect.[71–75] Solvent-less and -free operations profit from increased concentration of the reactants and the reduced solvent load reduces waste and simplifies/eliminates of process steps for the removal of solvents. In addition, the use of alternative solvents (ionic liquids, supercritical fluids, fluorous fluids) allow to tailor the reaction environment in terms of diffusivity, separation capability and dissolution power.[76–79] Besides speeding up of chemistry, a new chemical transformation based on reduced or combined elemental steps is also considered as chemical intensification (also as this has large chance to change the process design, see below). This includes direct syntheses[80–82] and multi-step syntheses in "one-flow" (in analogy to "one-pot")[83–85]. Speeding-up chemistry is a means to make chemistries happen which are otherwise to slow. Changing chemistry is finally the key to sustainability, for efficient use of materials and reduction of waste.

The process-design intensification field is a third means and is based on process simplification and integration. While these are common engineering principles also for conventional processes, simplification in flow can reach much further, due to the power of the chemical intensification mentioned above. Similarly, process integration can come to new horizon in flow, as the miniaturization can lead to entire new level of compactness, in the way microelectronics have impressively demonstrated.

Yet, there is a (current) drawback about this which can hamper implementation. Flow processes with micro- or other smart-scale reactors are different in design than conventional reactor systems. Micro flow process design is currently not covered and supported through the existing education / training and through its plant- and process design software such as Aspen for the following reasons[86,87] :

- No standard modules exist – the (by orders-of-magnitude) intensified components often do not match to each other and to existing process units and control structure.
- As a result of the aforementioned, no additive (plug & play-type) design from units into a process-chain exists – rather design is interactive: each flow unit development has again the potential of changing the whole plant design.
- Flow process design is reaction dominant, whereas today's plants are utility- and separation dominated – with totally different cost, energy and process control structure.
- Integration of process units has to be considered as a new step in between the process unit and plant level in process development into production.

In view of the last statement, in a more advanced, but not so distant step, due to the compactness of the basic elements within the units and high speed of processing, integrated reactors will partly replace consecutive arrangement of otherwise separated units – which is process integration. Already today heating and reaction or exothermic and endothermic reactions are combined in microreactors.[88–90] This is already largely given for the field of fuel processing utilizing microreactors comprising energy and mass flow integration.[91] In fine chemistry, this is not so prominent so far. A logical step is to combine separation and reaction, and actually that has been started with the use of membranes.[92–95] Another eminent integration issue is to incorporate functionalities such as process control and analysis which can enable optimum operation of the system.[96,97]

In continuation of the latter, as discussed above new chemical transformations have large chance to change the process design. A direct (one-step) synthesis can largely eliminate separation equipment needed for otherwise consecutively done reactions – which is process simplification.[86,87,98] If not eliminated, there is a chance for replacing separation units by simpler and more inexpensive units. Other chances for process simplification are provided by elimination of heating/cooling units through achieving room temperature processing at same productivity, purification units due to a decrease in the levels of by-product to traces through increased selectivity and recycle loops through higher reaction yields.[18,99]

1.2. Flow Separation and Coupling with Flow Reaction

1.2.1. Flow separation units

The majority of microchemical synthesis applications were so far restricted to one or few reaction steps with the separation done offline.[33,44,46] Therefore, further development of microseparation units is needed. From about 2011 onwards, there is an increasing number of developed microseparation devices for chemical purposes.[100] Still most of these devices have been characterized as stand-alone tools, i.e. without connection to a flow reaction device. These devices were mainly liquid-liquid extraction units. Recently, several distillation [101–104], absorption [105–107] and chromatography [108–110] units were also described.

Since the early investigations in micro process technology, microextraction has received a considerable amount of attention. With miniaturization, a high surface area to volume ratio leads to enhanced mixing efficiency and mass transfer between the two phases.[35] Several microextraction devices are found differing according to how immiscible phases contact each other. With the use of different mixing elements and process conditions (e.g. velocity of the phases, velocity ratio of the phases, physical properties of the phases) different flow patterns are observed.[111] Generally four flow patterns can be observed in microcapillaries, i.e. the parallel flow, the slug flow, the droplet flow, and the dispersed flow (Figure 1.2).

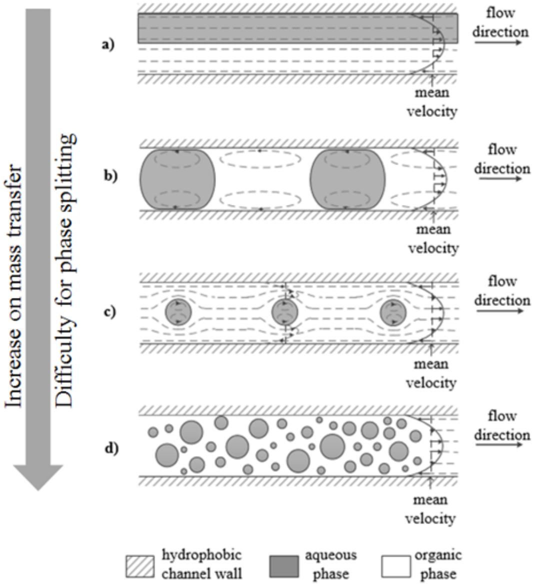

Figure 1.2. Liquid-liquid flow patterns in microchannels (adapted from Holbach and Kockmann[112]); a) parallel flow; b) slug flow; c) droplet flow; d) dispersed flow.

The flow pattern used has a large effect on the mixing and separation performance.[113] Slug flow was shown to have better mass transfer compared to parallel flow.[114] This is due to slug flow providing convection through internal circulations as well as interfacial diffusion between two adjacent slugs.[111] Mass transfer in dispersed flow was seen to be the most effective due to larger interfacial area.[115] Several micromixer types have been evaluated for this purpose such as interdigital[116–118] and split-and-recombine[119,120] type micromixers. They can achieve even higher specific interfaces than slug flow does by virtue of the small droplets. However, the phase separation performance should be taken into consideration when evaluating the whole extraction process. Emulsions are often very stable and long time may be required for the coalescence of produced droplets.[115] On the other hand, phase separation of slug flow can be much easily achieved in short times. Therefore, slug flow has found wide practical use in flow applications.

There has been extensive research on slug flow especially within studies of identifying liquid-liquid two-phase flow regimes. The mass transfer performance using different types of microchannels for various non-reacting and reacting systems were investigated and pressure drop measurements were made.[121–128] Slug flow was also applied for liquid-liquid extraction applications.[111,114,115,129–131] In some of these applications phase separation was also achieved in flow. Some studies were focused on the development of phase separation units for separating the aqueous and organic phases of the slug flow.[132–135] Effective liquid-liquid slug flow separation was achieved with PTFE membrane or microdevice that selectively lets the organic phase pass through.[129,132,133,135] Also, it was achieved with wettability-based separation units with branched hydrophobic and hydrophilic outlets.[111,125,134] Review of most prominent literature on slug flow is given in Table 1.1 with information besides others the maximum flow rate achieved with slug flow regime. So far, slug flow has only been realized on a laboratory scale. Highest flow rate of 4.8 L/h was presented by Cervera-Padrell et al.[135] for the application of phase separation of toluene and water. This research enables operation up to 7.2 L/h in slug flow regime as explained in detail in Chapter 4.

Table 1.1. Review of studies on liquid-liquid slug flow reported in literature

Reference	Microchannel	Maximum Flow Rate	System	Separation	Application
Dessimoz et al. (2008) [121]	T d_H = 400 µm glass chip	12 ml/h	Hexane-trichloroacetic acid-water+NaOH	-	Flow regime, mass transfer
Burns and Ramshaw (2001) [122]	Cross d_H = 380 µm glass chip	18 ml/h	Kerosene-acetic acid-water+NaOH	-	Mass transfer
Dummann et al. (2003) [123]	Y d_t = 0.5-1 mm capillary tube	36 ml/h	Aromatic-nitration acid	-	Reaction

Sarkar et al. (2012) [124]	Cross d_H = 272 µm serpentine channel glass chip	72 ml/h	Water-succinic acid-n-butanol	-	Flow regime
Ghaini et al. (2010) [125]	Y d_t = 0.5-1 mm capillary tube	160 ml/h	N-butyl formate-water+NaOH	Wettability based separator	Mass transfer
Kashid et al. (2011) [126]	T-square: d_H = 400 µm T-trapezoidal: d_H = 400 µm Y-rectangular: d_H = 269 µm Concentric: d_t = 1600 µm Caterpillar: d_H = 150 µm	T-square: 180 ml/h T-trap.: 180 ml/h Y-rect.: 120 ml/h Concentric: 300 ml/h Caterpillar: 420 ml/h	Water-acetone-toluene	-	Flow regime, mass transfer
Cherlo et al. (2010) [127]	T d_H= 0.54,1mm	200 ml/h	Kerosene-water	-	Flow regime
Kashid and Agar (2007) [128]	Y d_t =0.25 - 1mm capillary tube	200 ml/h	Water-cyclohexane	-	Flow regime, pressure drop analysis
- - -	- - -	- - -	- - -	- - -	- - -
Kralj et al. (2007) [129]	d_H = 255 µm serpentine channel silicon chip	3 ml/h	DMF-DCM-water DMF-DEE-water	PTFE membrane	Extraction
Fries et al. (2008) [114]	T d_H = 225 µm PDMS chip	18 ml/h	Toluene-water-vanillin	Capillary force based separator	Extraction
Castell et al. (2008) [132]	T d_H = 654 µm PTFE chip	24 ml/h	Chloroform-water	PTFE device	Phase separation
Jovanovic et al. (2012) [130]	Y d_t = 0.25 mm capillary tube	36 ml/h	Toluene-2-butanol-water	-	Flow regime, mass transfer, extraction
Okubo et al. (2008) [115]	T d_t = 0.5–1 mm capillary tube	300 ml/h	Dodecane-phenol-water	-	Extraction

Kashid et al. (2007) [111]	Y $d_t = 0.5–1$ mm capillary tube	120 ml/h	Kerosene-acetic acid-water Water-iodine-kerosene Water-succinic acid-n-butanol	Wettability based separator	Extraction
Adamo et al. (2013) [133]	T $d_t = 1.6$ mm capillary tube	960 ml/h	Hexane-water Ethyl acetate-water	PTFE membrane	Phase separation
Kashid et al. (2010) [131]	6 parallel Y $d_t = 0.5$ mm capillary tube	1200 ml/h	Water-cyclohexane Kerosene-acetic acid-water	-	Flow regime, mass transfer, extraction
Gaakeer et al. (2012) [134]	Y $d_t = 1.5$ mm capillary tube	3000 ml/h	Water-n-heptane	Wettability based separator	Phase separation
Cervera-Padrell et al. (2012) [135]	T $d_t = 1.6$ mm capillary tube	2400 ml/h (THF-water) 4800 ml/h (toluene-water)	THF-water Toluene-water	PTFE membrane	Phase separation
Present work	Cross $d_t = 3.2$ mm capillary tube Coiled flow inverter	3000 ml/h (butyl acetate-water-acetone) 7200 ml/h (toluene-water-acetone)	Butyl acetate-water-acetone Toluene-water-acetone	PTFE membrane / Wettability based separator	Extraction

1.2.2. Coiled flow inverter

Liquid-liquid extraction consists typically of two process steps, namely mixing and phase separation. Effective phase separation can be achieved, for example, with PTFE membrane or wettability based separator units as discussed above. Mixing and contacting of the two liquid phases, as outlined in Section 1.2.1., has been achieved typically inside a straight capillary tube (or just slightly bended for reasons of compactness). Using the latter deliberately and tightly, however, enhanced mixing performance can be achieved with curved channels that enable generation of vortices.[136] Because of the action of centrifugal force that acts perpendicular to the flow direction of the fluid, a secondary flow develops in curved channels that is called Dean vortices.[137] Dean vortices enhance the radial mixing in case of single-phase flow and thus narrower residence time distribution compared to straight capillaries can be achieved.[138,139]

Mixing can be further enhanced by complete flow inversions by inducing 90° bends at equal intervals along the length of the tube.[139] Coiled flow inverter (CFI) is based on this principle. The direction of the centrifugal forces inducing the formation of secondary flow profile in helically coiled tube is changed with the 90° bends. Therefore, the secondary flow profile is developed after the 90° bend in a different plane that is perpendicular to the previous plane (see Figure 1.3). As a result, the radial mixing can be further enhanced in CFI. Hence, a narrow residence time distribution close to an ideal plug flow reactor can be achieved even at laminar flow regimes.[140,141]

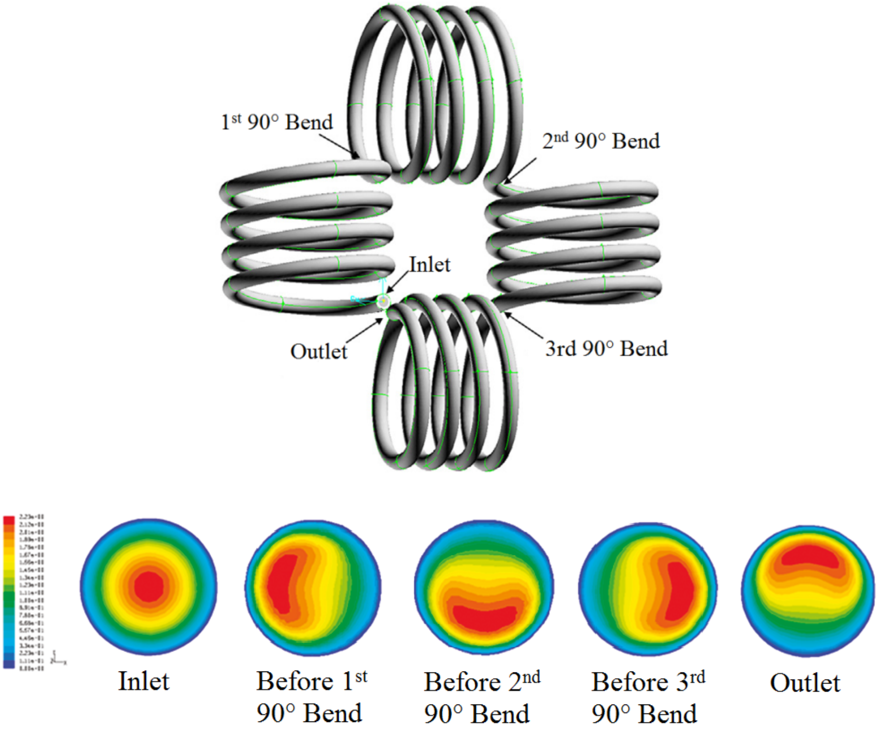

Figure 1.3. CFI structure and cross-sectional velocity contours (adapted from Singh et al.[142] and Mandal et al.[143])

1.2.3. Multi-step flow synthesis

The fine chemical synthesis typically involves multiple reactions and intermediate separations. To achieve such synthesis in continuous flow several strategies have been used. One strategy was telescoping reaction sequences in which one molecule automatically converts to the next alike a domino cascade .[144–146] In many cases however this is not feasible, e.g., due to impurities formed affecting the following reactions. A second strategy involves the use of multi-step flow synthesis with individual reactors connected in a row with the flow separation in between the reaction steps achieved by solid supported reagents packed into columns in flow. They allow scavenging of unreacted reagents enabling the product to be collected at the outlet without requirement of further purification. Different types of such columns can be connected in series allowing multiple reactions to take place.[147–153] However, the necessity to periodically replace the cartridges interrupts the continuous flow process. Also, they are not found suitable for applications at large scale.[154]

The final strategy is to implement micro flow separation units together with microreactors to allow purification in continuous flow. This coupling of different microfluidic unit operations in continuous flow has great potential for waste and energy minimization. It is also very beneficial for reactions involving generation of hazardous intermediate products. However, as discussed above although a great progress has been made to develop the required flow separation units still more research is required especially to achieve operation at high throughput. A very few commercial microextraction devices are now available, e.g. the flow liquid-liquid extraction FLLEX module from Syrris, UK[155] and liquid-liquid separators from Zaiput Flow Technologies[156]. The coupling of microseparation units with microreactors is not rare anymore, but still far from being commonly applied. So far, there are only few demonstrations [42,157–159].

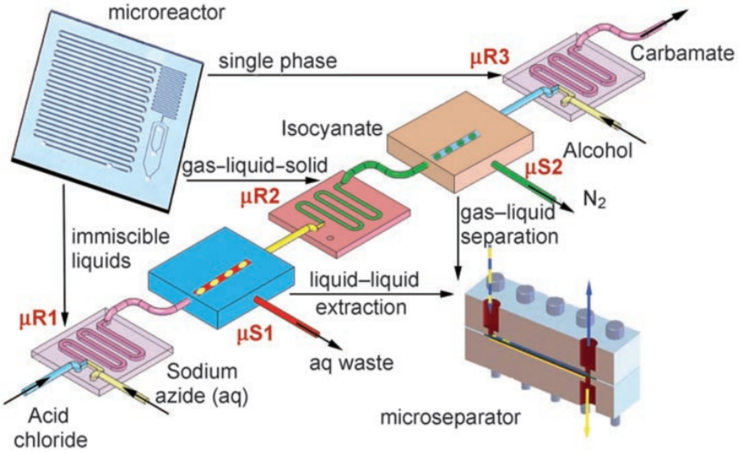

Figure 1.4. Schematic of the microfluidic setup for the multistep synthesis of carbamates[157]

A good example to illustrate the sequence of functions in a practical multi-step flow system is provided by a microfluidic reactor network with two reactors and a microfluidic extraction unit in between was realized for the synthesis of biaryls starting from substituted phenols.[159] Impurities generated in the first reaction are poisonous for the catalyst system of the second reaction. The intermediate separation step enabled the extraction of the impurities with aqueous solvent and the aqueous phase was separated and removed from the system with phase separation. In another example, a continuous-flow, multistep microchemical synthesis of carbamates starting from aqueous azide and organic acid chloride by using the Curtius rearrangement reaction was described (See Figure 1.4).[157] It involved three reaction steps and two separation steps. The first separator enabled separation of organic and aqueous phases after the first reactor. The second separator was used to remove the nitrogen gas generated in the second reactor from the liquid stream. As a final example, a multistep Heck synthesis was achieved with two reaction steps and two separation steps in between.[158] The intermediate was removed by microfluidic extraction after first reaction. Next, solvent switch was enabled by a microfluidic distillation.

1.3. Process Intensification at Plant Level

1.3.1. Modular, compact plants

Modular plants were seen as main enablers to reduce development time as discussed at the 48th Tutzing-Symposium with the “Die 50%-Idee – Vom Produkt zur Produktionsanlage in der halben Zeit” (translated: The 50% idea – from product to production facility in half the time).[160,161] This shortening of the time-to-market can help increase Net Present Value of an investment and reduce investment risks (see Figure 1.5). This engineering concept of modularization is increasingly discussed in literature for chemical production.[162–167]

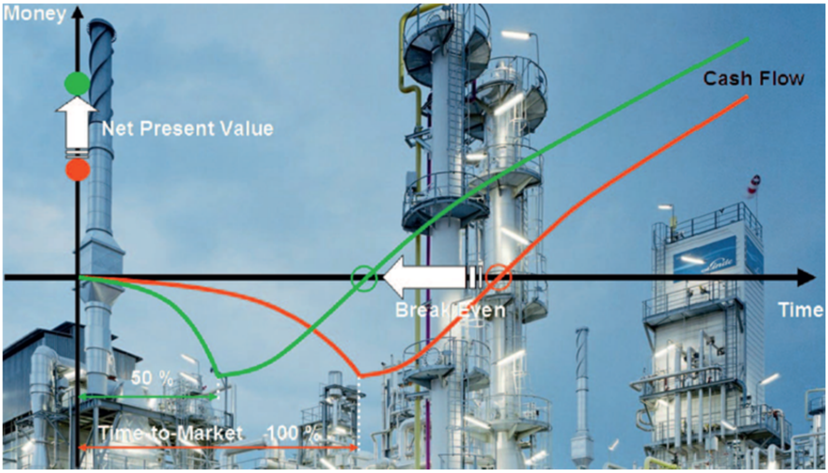

Figure 1.5. 50%-Idea - from product to production facility in half the time[168]

Modularization is already established in equipment and instrument manufacturing industries such as electronics (TV, computer), automotive and the airline industry.[169,170] However, modularization is, so far, rarely applied to the production of chemicals.[171]

Demonstration projects hereto were undertaken in European Union's FP7 Call for Process Intensification.[172] Such theoretical and experimental first steps are in line with the holistic ambition and vision of the "Factory of the Future" and "Flexible Future Production Strategies", i.e., to combine micro process technology with modular plants.[173] This full-chain ambition of European funding policy is expressed as the realization of "new, intensified process and plant concepts for speeding up market penetration, for enhancing the product life-cycle and improving sustainable production".[173] Five large-scale projects on Future Factories with many of the major industrial players are: F^3 Factory, COPIRIDE, POLYCAT, PILLS, and SYNFLOW.[174–178] These projects target basically all the different chemical industries, including bulk-chemical, fine-chemical and pharmaceutical manufacturing, as well as applications in polymerization, cosmetics, and renewable resources. These five Future Factory EU projects supplement each other in focusing on different aspects of the whole value added chain – starting from new tailored catalyst development over new reactors towards new types of processing and finally approaching the plant and systemic process evaluation level. This is esteemed to give the first building blocks for the sustainable chemical production platforms of the future. ACHEMA 2012 has put modular plants 1st in the list of top five trends in the process industry.[179]

These plants are not yet built fully modularly but are built as so called skid mounted units. The advantages to such manufacturing concept have already been demonstrated for the construction of pilot plants (such as the ones built by company Zeton B.V.). Within the F^3 Factory project seven industrial case studies are demonstrated. The developed process equipment containers and respective process equipment assemblies are integrated with the backbone infrastructure services at INVITE facility (see Figure 1.6). This backbone facility supplies utilities like electricity, heat, cooling water and service gases.

Figure 1.6. Bayer's Process Equipment Container Unit installed at INVITE (from F^3 Factory newsletter[174])

Among the most developed Future Factory approaches which has approach commercial level is a compact container-platform plant concept of Evonik Industries, the Evotrainer (meanwhile renamed as the EcoTrainer), which is designed as multifunctional and all-purpose plant platform[180–182] (see Figure 1.7). The concept orients particularly on the manufacture of specialty products with tonnage which are at present typically made as campaign products in conventional multi-product plants. It provides a mobile chemical development platform which can be upgraded to a production plant of a capacity of 200 metric tons per year.[180]

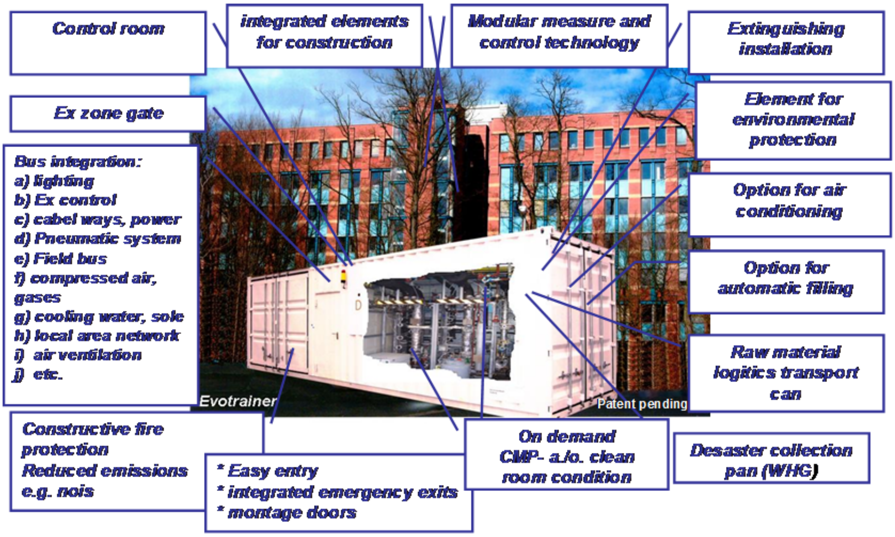

Figure 1.7. The Evotrainer: a modern, compact, low-investment plant platform (Courtesy of Evonik Industries, meanwhile renamed as the EcoTrainer)

The EcoTrainer provides a modern, compact and highly efficient process- and plant concept covering the whole manufacturing chain to the chemical product in one system – including reactant, product, by-product supply and storage, reaction and purification.[182] This EcoTrainer concept links research with process development, production and plant engineering. It is ideally suited for apparatus for process intensification – in particular milli- and micro process technological apparatus.[182]

The EcoTrainer is divided into several cabinets for logistics, reaction/purification and instrumentation, and control.[181] Its infrastructure supplies the raw materials, product and by-product logistics and the utility requirements Every EcoTrainer is tailored to the reaction that will take place with the processing equipment being adapted to the specific chemical process.[180] It can house a complete chemical plant or just a single module, such as a reactor or a processing step. It has high flexibility concerning diverse chemical syntheses and correspondingly diverse products.

1.3.2. End-to-end process integration

In literature and community related to microreactors and other intensified smart-scaled equipment, it was common to focus on the design of one equipment and testing its processing – the drop-in (retrofit) concept. However, with process-design intensification we focus our attention towards the complete chemical process, therefore it is regarded as end-to-end process integration. It considers the comprehensive evaluation of new, novel production routes or processing approaches in an early development stage. It involves cost, energy and environmental analysis based on process simulation. Since it is concerned with the whole system and considers the interdependence of its parts it is holistic in approach.

Such research is becoming more and more important as evidenced by the increasing number of holistic process papers in all chemical engineering literature (see Figure 1.8). The term holistic covers comprehensive, full-chain, multiparameter (criteria), system-engineering analysis or similar complexity-driven analysis. A paper from the DOW company entitled Holistic Route Selection is in accordance to this vision.[183]

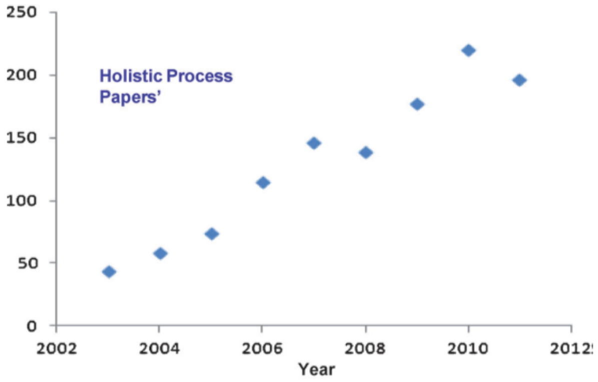

Figure 1.8. The number of holistic papers published[22]

Ex-ante analysis has already been done to aid in process development by enabling comparison between chemical synthesis routes, different process conditions, raw material alternatives, etc. for the flow reaction under consideration. Life cycle assessment (LCA)[184] is a common method employed to evaluate the environmental impact and it is mostly used with cost assessment tools. Such evaluation approaches are helpful to provide an early-bird view, the viability of the intensified units with NPW conditions in terms cost efficiency and sustainability. Several examples of this analysis are found in the literature for the use of high temperature and pressure conditions and the use of alternative solvents such as ionic liquids and supercritical carbon dioxide.[17,29,64,185]

The process-design intensification through flow processing is new in literature and this research gives first introduction to it. It has been started to be investigated for the first time by the author on one reaction example of direct adipic acid synthesis. Apart from the reactor all the downstream processing units is considered in the evaluation. This is exactly where innovation through the new flow process design has to set in. There is another PhD project of the ERC Advanced Grant Novel Process Windows (Hessel) supporting it (by Minjing Shang) with microreactor development to achieve this direct synthesis in flow.[82,186] This research gave light to further end-to-end studies including European Union large scale projects BIOGO and MAPSYN.[187,188] Accordingly, now new two PhD projects are dedicated to such comprehensive analysis under these projects in Hessel's group.

1.4. Scope and Outline of the Thesis

Process intensification spans to all scales existing in a chemical process, from molecular to meso- and macroscale. Molecular scale considers the molecules such as molecular collisions and molecular diffusion. Maximization of the effectiveness of intra- and intermolecular events is given as a primary principle for process intensification as it can change the inherent kinetics of chemical reactions. It is the least documented scale so far in literature. Still there are numerous examples showing the effect of intensification on this scale as highlighted by Stankiewicz.[9] At the macroscale, process units such as reactors are considered for process intensification which is highly researched and the examples are ever increasing. As mentioned before microreactors are considered to be the most potent and typical example for process intensification, as outlined by Hessel. Such reaction-oriented research in flow chemistry is also studied by other research groups as given in Section 1.1. On a process level, this resembles the drop-in concept with the microreactor replacing a conventional reactor.

In this research focus is given more on the process side. There are mainly three parts of integrated drop-in, modular and end-to-end process integration (Figure 1.9). The first is called 'Integrated Drop-in' and it refers to coupling of microreactor with microseparator in flow. As described in Section 1.2.3 such multi-step synthesis in flow has very few demonstrations. Therefore, it is taken in this research and studied in **Chapter 3**. It describes connecting metal catalyzed microreaction and metal separation enabled with microextraction unit in flow to achieve the product separated from the catalyst. The vision is to achieve multi-step synthesis in flow on pilot scale. The scale-up of microreaction units has been demonstrated. However, there is very limited research on microseparation units and the study of their scale-up is very rare. Thus it is conducted here in **Chapter 4** for a flow extraction unit utilizing coiled flow inverter and a phase separator.

The second part of research considers the use of the new compact, modular container technology and it is referred to as 'Modular' process integration. There are known benefits of such modular production platform such as saving in the design and construction time and expenditure. An analysis was lacking in the literature to quantify these benefits in terms of impact on costs. Therefore, in **Chapter 5** a detailed discounted cash flow analysis is done to estimate how these advantages of modular plants are reflected in the Net Present Value. Furthermore, the combined benefits of process intensification enabled by smart-scaled process-intensified reaction equipment and of modular compact plants was analyzed with six scenarios for a fine chemical production. The modular plants are also beneficial because of their flexibility and scalability. Therefore, they are ideally suited for decentralized production. This is evaluated with application case of decentralized biofuel production in **Chapter 6**. It involves an initial techno-economic analysis to analyze the feasibility of a novel process for biofuel production.

The third part of research is on comprehensive assessment of the flow process as a whole. It provides an 'End-to-end' vision of intensified process design. It is performed for the reaction example of direct adipic acid synthesis. A step change improvement can be realized by bringing such direct chemistries on a full-process level. The process simplification potential of the direct adipic acid synthesis route is investigated in **Chapter 7** by cost, energy and environmental analysis. In **Chapter 8** an energy efficient process is searched with the application of heat integration for the novel direct micro-flow route of adipic acid synthesis introduced in the previous chapter.

The use of the three intensification fields introduced in Section 1.1 together with the use of modular plants can enable reduction in number of apparatus, reduction in apparatus size, and higher predictability in the scale-out of the apparatus. All these have potential for (much) decreased overall development time which is discussed in **Chapter 2**.

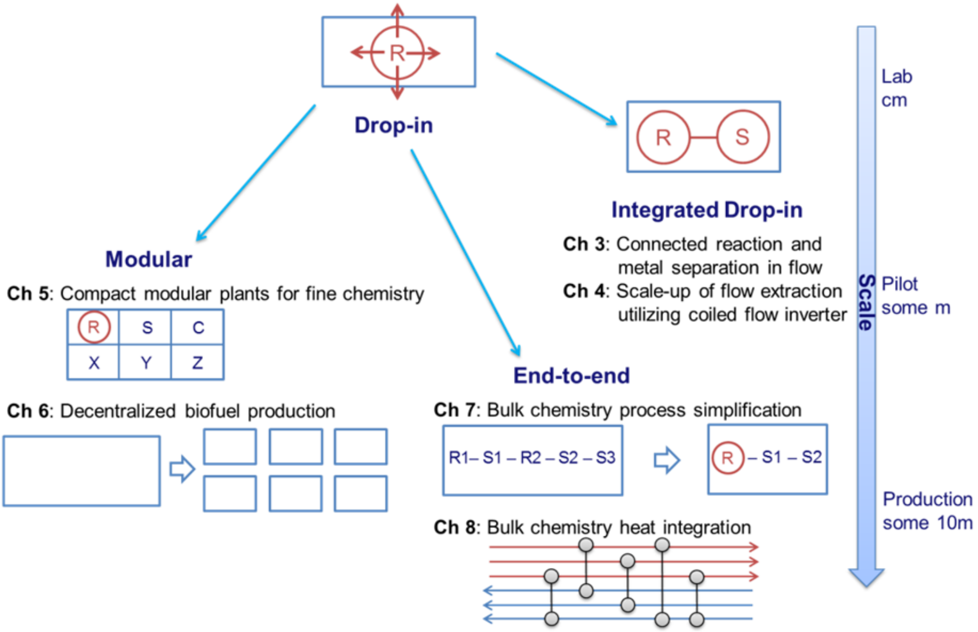

Figure 1.9. A schematic representation of the chapters in the thesis

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CHAPTER 2

Potential of Intensification through Flow Processing and Use of Modular Plants to Reduce Development Time

This chapter is based on :

Hessel, V., Vural Gursel, I., Wang, Qi, Noël, T. & Lang, J. (2012). Potential analysis of smart flow processing and micro process technology for fastening process development - Use of chemistry and process design as intensification fields. Chemical Engineering & Technology, 35(7), 1184-1204.

Hessel, V., Vural Gursel, I., Wang, Q., Noël, T. & Lang, J. (2012). Potenzialanalyse von Milli- und Mikroprozesstechniken für die Verkürzung von Prozessentwicklungszeiten : Chemie und Prozessdesign als Intensivierungsfelder. Chemie Ingenieur Technik, 84(5), 660-684.

Abstract:

Flow processes with microstructured reactors allow paradigm changes in process development and thus can enable a faster development to the final production plant. So far, this was mainly achieved via transport intensification – improved mixing and heat transfer which increase productivity and possibly improve selectivity. A newer idea is chemical intensification through deliberate use of harsh chemistries at unusual (high) pressure, temperature, concentration, and reaction environment which again increases productivity. A very new idea is the process design intensification – reaction-intensified flow processes need less separation expenditure and the small unit size together with the high degree in functionality gives large potential for system integration. The modular nature of the small flow units allow an easy implementation to modern modular plant environments (Future Factories) which enables to perform all the testing cycles (lab, pilot, production) in one plant environment. The final result can be a reduced number of apparatus in the plant, a reduced apparatus size, and a higher predictability in the scale-out of the apparatus. All these have potential for (much) decreased overall development time.

2.1. Introduction

The pull from the market and the push from technology have initiated a race, in which the lead time of bringing innovation into plant commissioning and final product has become a crucial role. Therefore a dedicated team of professionals from university and industry discussed at the 48th Tutzing-Symposium “Die 50%-Idee – Vom Produkt zur Produktionsanlage in der halben Zeit” (translated: The 50% idea – from product to production facility in half the time).[1,2]

Chemical process development is divided into different phases. It starts in the laboratory exploring the chemical synthesis where a suited chemical protocol is established; sometimes and especially in pharmacy using fast, automated screening methods. The process concept is further developed and validated using modeling techniques and lab and pilot plant operation.[3,4] Process design is then elaborated through basic engineering and detailed engineering studies when design data for each component is determined. Having purchased the components, the construction and commissioning of the production plant is initiated. Since in traditional engineering the phases need to be done in sequence, with each phase needing the input from the former phase, the only option to reduce the time is to reduce the time of one or more phases – here standardization through pre-manufactured modules assembled into a modular and highly functional plant environment is a major innovation approach.

Micro process technology has initiated a rethinking of processes from batch to flow and even has entered the stage of commercial valorization, as e.g. demonstrated by giving continuous processing Top-1 priority in the 10 Green Engineering prime measures stated by the multi-industrial ACS GCI Pharmaceutical Roundtable.[5] Still, microstructured reactors are a new technology for chemical production. Experience is just based on some reports about companies which approached or entered production with such flow reactors in the last years; the total number of reports being estimated to be around 50 or so in the year 2011.[6–10] Some deeper insight in cost details was mainly given in industrial presentations and as well in a few papers both from industry and academia.[11–14] Quite detailed sustainability view has been given from the life-cycle assessment and cost analyses.[15–18] However, the reduction of development time – ‘time-to-market’ – albeit also often mentioned as motivation for flow process development, has so far seldom investigated in depth or even quantified. This lack in knowledge is mainly due to the fact that development time cannot be modeled. And also different from the other investigations, no experimental data are available which can be used as input for further analysis. There is the need to consider the full-chain process (with all or most components utilizing micro process technology). This is at present quite complicated, since such kind of processes do simply not exist. In almost all currently known cases only the reactor within the total process chain (with all its reaction and separation units) was changed to microreactor. This is sufficient to judge on costs, sustainability, and safety; but the full potential in speeding up process development can just vaguely be seen at this time.

Despite these deficiencies in data availability/modeling, we approached as first group the eminent topic of speeding up process development in a qualitative theoretical impact analysis as follows.

What is precisely clear at this point of time is which key steps are at hand to speed up the reaction and finally process development, starting from intensification of the chemistry itself up to using complete compact plant architectures.[19–21] Thus, this chapter aims at showing in a generic ('impact-wise') manner the respective chances of a flow process chemistry development under the frame of a holistic plant development. The generic keys considered follow the analysis of intensification given in chapter 1. The first is based on utilizing - much more than in the past and now in deliberate manner - the so-called chemical and process-design intensification fields in addition to the well-known transport intensification field of microstructured reactors.[21] The second tries to connect the flow developments with the just recently undertaken developments on intensified and modular plants, and here most notably those using container environments. Microreactors are not the only modern devices to achieve process intensification however they are considered to be the most potent one. This is why this reactor tool is considered in this study.

The effect of the intensification measures and use of modular plants will be given and, wherever possible, will be quantified. This will give the industrial expert an idea on the reduction in process development, although this cannot be straightforwardly quantified. However, additional development tasks for flow processes such as the exploration of new reaction pathways and of new, harsh process conditions may shoot down advantages gained by faster development through these key technologies. Some of these tasks are related to technology ripeness, and accordingly the technologies considered were classified as ready-for-use and near-future-use. Increased process development time may also be given by the less characterized performance of large-scale microstructured reactors and of microseparators even at the laboratory stage. While it is thus pretty clear that the step-change potential in process intensification can result in a significant reduction in development time, this is so far alone a theoretical potential. The full release of this into a practical potential suffers from the above mentioned unknowns; being pretty normal for a young technology.

2.2. Effect of Intensification Fields and Modular Plants

Following the arguments given in the introduction about that an overall judgment on the speed-up of process development through micro process technology and flow chemistry is quite difficult, it is here aimed to give answers at a level reduced in complexity, i.e. on the apparatus level; assuming that such effects are at least beneficial, additive, and at best synergetic on the higher process level. The distribution into individual impacts allows further in the last section of this chapter to make a scenario-wise analysis which approaches in intensification ensure already today a good practice in fastened process development, which are better used in near future, and which do not save time in process development at all (but might give superior costing and sustainability).

The impact of the three intensifications fields can be:

- Reduced size of apparatus
- Reduced number of apparatus
- Ease of scalability of the apparatus

All of these three measures certainly and inevitably should lead to a (much) decreased overall development time.

2.2.1. Effect of the transport intensification (1st) field

Transport intensification can make possible reduction in reactor volume and number when switching from batch to flow processing. This is due to improved mass and heat transfer through the miniaturization of flow dimensions. Microreactors enable high surface to volume ratios, short diffusion paths and well defined flow profile.[22] Process parameters can be controlled easily.[19] Therefore, reaction rates are increased, residence times are decreased and side reactions are suppressed.[21] This results in increased yield and selectivity. This also allows high space-time yields to be reached enabling compact apparatus.[19] Reaction times can be shortened from hours to seconds with the use of much smaller reactor volumes.[23] Even for large-scale applications, the volumes of the reactors do not exceed a few liters, whereas the industrial stirred vessels used are a factor of 1000 larger. Also, with the high yield provided a single microreactor can replace series of batch reactors .

Transport intensification can also enable reduction in the number of apparatus to be used and investigated in process development. This can be achieved through the elimination of heating/cooling units through achieving room temperature processing at same productivity, purification units due to a decrease in the levels of by-product to traces through increased selectivity and recycle loops through higher reaction yields.[19]

Furthermore, the small level of holdup in microreactors reduces the damage potential of toxic or explosive reagents. Also, fast and highly exothermic reactions can be handled safely preventing hot spots.[24] The improved safety in microreactors is essential for further development when moving from laboratory to production scale of formerly prohibited reactions in batch processing.

Less clear is the potential of a batch-to-flow exchange of more than one apparatus, particularly concerning separation units, up to a process scheme composed of flow units only. While after about 15 years development there is at hand a palette of process components in microreaction technology (reactors, mixers and heat exchangers.), the development of robust and preparative flow separation components is still largely missing. Actually, this is not due to missing flow concepts and components for separation. A number of microfluidic separation concepts were developed, but most often in the frame of lab-chip's analytical and biochemical developments. Since these devices were developed for a completely different flow range than usual for chemical applications, it is rather difficult to couple these to microreactors. From about 2011 onwards, there is a slowly, but steadily increasing number of developed microseparation devices which are developed dedicatedly for chemical purposes. Initially, these devices were mainly liquid-liquid extraction units.[25] Recently, several micro distillation-/rectification, absorption and chromatography units were also described.[26] Still most of these devices have been characterized as stand-alone tools, i.e. without connection to a flow reaction device. So far there are only few demonstrations of coupling of microseparation units with microreactors.[27–29]

For the reasons given above, Lonza in 2008 preferred the step-wise integration of flow reactors rather than of reactors to separators (see Figure 2.1).[30] Yet, as mentioned this is pharma's preferred drop-in strategy and the mission of this thesis is to go beyond. Lonza has now, also an adapted view to fully integrated flow processes with microreactors and other units in flow.[31]

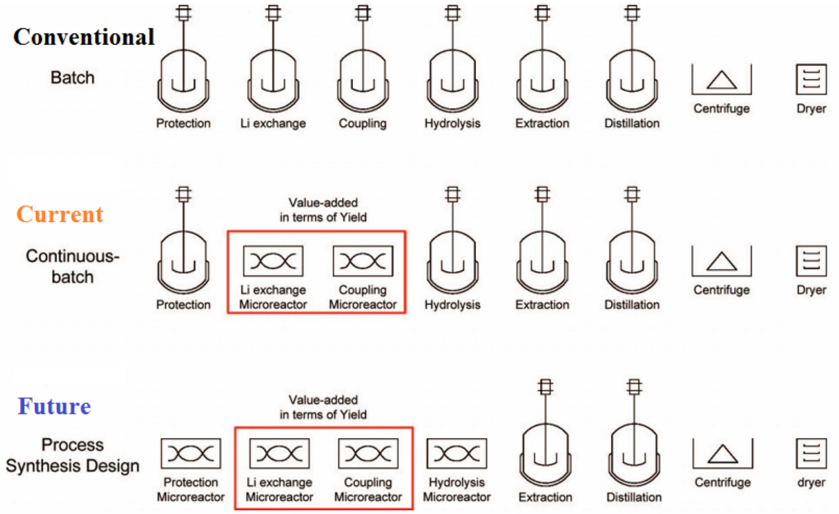

Figure 2.1. Lonza prediction of future development of micro process engineering for commercial pharmaceutical production in 2008

2.2.2. Effect of the chemical intensification (2nd) field

Enhancing chemistry is named chemical intensification and this is one of the two fundamental pillars of the new process chemistry approach termed Novel Process Windows (NPW).[15,19–22] Chemical intensification stands for the use of highly intensified, unusual, and typically harsh process conditions to boost microprocess technology. Chemical intensification follows the constitutional elements of every reaction protocol, that is, to define the optimal reaction path/synthetic strategy; to determine the required reagents; and to boost the reactivity by virtue of temperature, pressure, and concentration changes. It has resulted for many reactions speed-up by a factor of 100 or even 1000. This necessarily will facilitate for given productivity replacing several large volume batch reactors with a microreactor enabling both reduction in reactor volume and number. It also suggests that for the required higher productivity the need of numbering-up can be reduced significantly. By using intensification approached it has been demonstrated by companies, most notably Lonza, that one (or a few) microreactor is sufficient to achieve industrial fine chemical production.[32–35]This significantly reduces the work required in scale-up.

High temperature and pressure flow processing is a widely applicable approach as initiated by the group of Kappe.[36–38] In laboratory equipment, for example, glass flask, autoclaves, etc. the reaction temperature is mostly maintained by using, for example, a water bath, oil bath, electrical heating, liquid nitrogen and dry ice mixtures in various alcohols. Microstructured reactors now offer improved heat transfer capabilities and therewith better temperature control during the chemical process. Also they allow fast heating-up and cooling-down steps. Therefore microreactors are ideally fit to exploit high temperatures to speed up the reaction rate. The reaction times are reduced from typically (many) hours to minutes and sometimes even to seconds.

When reaction temperatures above the boiling point of a solvent used (superheated processing) are targeted, it is necessary to increase the system pressure to avoid boiling and to keep the reaction mixture in a liquid state. The mechanical stability of microstructured devices allows one to run processes in a high pressure regime in safety. Usually pressurization is assured by either HPLC or high pressure syringe pumps and a back pressure regulator after the microreactor. Both laboratory and technical batch processing is typically limited by this condition as autoclave operation is complex, requires larger volumes, and needs longer reaction times when compared to microreactors. There are numerous examples available demonstrating such transformation and the associated massive speed up in reactivity under superheated conditions in microreactors.[36–43]

Apart from facilitating superheated conditions, high pressure affects the reaction through the influence on the reaction equilibrium and rate constants and reaction medium via the effect on its physical properties. In case where occupied volume by the product after the reaction is lower than given for the two separate reactants, the overall volume change is negative and application of high pressure will have an acceleration effect. This has been demonstrated for cycloaddition and Claisen rearrangement reactions.[37] Increased viscosity of the liquid at high pressure was also found to accelerate chemical processes.[44] Due to increase in solubility of gases with the with the increase in pressure, gas-liquid reactions can be performed with high concentrations of dissolved gases increasing reaction rates.[45,46]

The use of solvents in chemical synthesis is in most cases necessary to dissolve reactants and to adjust the reaction volumes to the standard processing space of common glass flasks. Solvents have to be removed later (stripping), which is energy intensive. Solvents cannot be recycled in all cases so the generated waste may be enormous and deteriorates the eco-efficiency of the process. Large volume of solvents also slow down reactions by creating larger diffusion paths and reducing molecular collision.[19] Depending on the reaction mechanism, an increase in concentration (reduction of solvent) can speed up reactions. A solvent-free operation might even result in a volume reduction which is so extreme that the remaining reaction volume is too small to be produced efficiently with batch technology. Smart-scaled flow apparatus are for this limitation an enabling solution.[47–49]

In addition, the tailoring of the solvent conditions by a much wider use of temperature and pressure (affecting solubility, viscosity, dielectric constant, etc.) can enhance reactivity and selectivity of such species. This can be even strengthened when using alternative solvents, such as ionic liquids or supercritical fluids which can speed-up reactions be orders of magnitude.[36,50–52] Their low energy requirement, low toxicity and flammability and easy recovery make them considered as green.[53] Ability to have superheated processing with microreactors enable switch from harmful to green solvents that were not possible to be used at higher temperatures with batch technology.[37]

2.2.3. Effect of the process-design intensification (3rd) field

The second NPW pillar is termed process-design intensification and is based on process simplification and integration. Transport and chemical intensification can have an impact on the whole process (holistic). These new possibilities can lead to a radical rethinking of the whole process design. The most evident effect on a full process level is that due to the intensified operation the higher yield and selectivity achieved with lower solvent loads can lead to reduction in separation requirements and equipment sizes. Simplification of the process can also be achieved with the ability to turn former catalytic reaction into non-catalytic. Due to intensified operation with microstructured reactors catalyst use could be omitted simplifying process.[54,55]

In a more advanced, but not so distant step, due to the compactness of the basic elements within the units and high speed of processing, integrated reactors will partly replace consecutive arrangement of otherwise separated units. Already today heating and reaction or exothermic and endothermic reactions are combined in microreactors.[56–58] This is already largely given for the field of fuel processing utilizing microreactors comprising energy and mass flow integration.[59] In fine chemistry, this is not so prominent so far. A logical step is to combine separation and reaction, and actually that has been started with the use of membranes.[60–63] Another eminent integration issue is to incorporate functionalities such as process control and analysis which can enable optimum operation of the system.[64,65] Equipment number and size reduction has a direct impact on the plant footprint, this makes scale-up much simplified reducing process development time. A comprehensive analysis of current possibilities in flow process integration is given in both references.[21,66]

On top of that, a step change may be realized via exploring new reaction designs (pathways). A one-step synthesis can largely simplify process via elimination of separation equipment needed for otherwise consecutively done reactions. If not eliminated, there is a chance for replacing separation units by simpler and less expensive units. This leads to significant reduction in separation equipment and size. This can change the ‘plant footprint’ from being separation-dominated (as given by the numbers and sizes of respective equipment) to reaction-dominated. Engineering, procurement, and construction phases can be performed significantly faster with much less number of equipment required. Consequently, it can have a major impact on process development time, however the time spent on development of completely new chemistry needs to be considered as well.

The combination of process steps can have a time dimension, when fast, simultaneous operation of several steps occurs within one process (such as multiple reactant dosing) or when several reactions are combined in one process through the flow-chemistry adaptation of a multistep one-pot synthesis.[67] It may also have a spatial dimension through the integration of function and system, i.e., combined reaction and separation or combined reaction and heat exchange.

2.2.4. Effect of the compact, modular plants

The vision is to have transfer from batch to flow chemistry, favorably by use of micro-process technology, intensify the operation with the use of NPW and to develop modular, compact, fast-responsive and flexible production facilities which the intensified equipment will be embedded.

There are two benefits of such modularization. By premanufacturing of standardized base units and assembling them in a lego-type manner, fabrication/assembly time is shortened and costs are saved. Thus, this reduces the development time to production. A second benefit arises when in one tailored plant environment, all the development stages, lab, pilot and production, can be conducted.[68] This gives a compact joint concept for utility, process control and safety. Several recent funding top themes approach these two issues this such as the *Factory of the Future* which is the central objective within EU’s *Flexible Future*

Production Strategies.[69,70] The full-chain ambition is the realization of ''new, intensified process and plant concepts for speeding up market penetration, for enhancing the product life-cycle and improving sustainable production''.[70] Among other large-scale EU projects, especially the projects CoPIRIDE[71,72] and F^3 Factory[73–75] were intended to develop modular production units for the chemical industry and to develop new intensified continuous processes utilizing new/enhanced reactor technologies such as microreactors for integration in these plants. Within F^3 Factory project, several Process Equipment Containers were successfully installed and integrated with the backbone infrastructure services in the INVITE facility by the industrial project partners including Evonik, BASF and Bayer.[76–78] Within CoPIRIDE project, modular container unit was demonstrated with the EcoTrainer developed by Evonik Industries.[68,72] EcoTrainer is designed as an all-purpose plant platform. It includes in one unit, reactant, product, by-product supply and storage, reaction and purification.[79] The design of the container meets fire prevention standards. Emergency exits are provided, and there is a containment basin in compliance with water management regulations.[79] This allows the realization of highly efficient solutions for warranty on-the-job and environmental safety standards, for process control, cross compliance, and maintenance. Due to the entire modular plant concept comprising all utilities – far beyond the reaction & processor parts – it covers the whole development cycle.

The modular plants are seen as main enablers to cut in half the time it takes to get through the development process from the product idea to the final production process (50% idea).[1,2] With its standardized infrastructure, utility and process control it supports also the standardization of modules. It is efficient in terms of construction and mounting. Main advantage is a short assembly time and drastic cost reduction in terms of planning and construction. The continuous processing with smaller apparatus leads to a decrease in plant footprint. It also allows fast plant start-up and shut-down. For many of the arguments given above, the innovation cycle can be shortened. But besides these technical arguments, modular plants provide also financial flexibility and in this way speed-up of management procedures and decisions needed in the process development. The lower risk in development allows to lower interest rates to finance plant installation and to intensify cash flow at specific higher plant investment.[68] This results in an earlier return-on-investment and a larger flexibility to react to changes in volatile markets.

2.3. Case Scenarios with Stepwise Intensification

2.3.1. Fine chemistry

In the following, the main case scenarios relevant for flow process development are considered which can be derived from the process intensification fields given above. Their relative time-scales are judged by an impact analysis based on expert opinions taken from the latter. This leads to a prognosis of shortenings, all done as a theoretical intrinsic potential of the enabling technologies, ignoring specific effects of different reactions and their bottlenecks. For separation, a near-future scenario was considered rather than the present state of the art due to the analysis presented above regarding the development of flow separators. This is seen to better reflect the intrinsic technology status.

Analysis - of such generic nature and being superficial to specific data of individual processes - naturally cannot be taken at all to forecast real time-scale, i.e. how many years such process development might take. What it can provide, however, is to give recommendation for priority in using enabling technologies, as far as speed-up of process development is considered; see Figure 2.2. It can give an idea where substantial and where just mediocre savings in process time are expected. It can oppose benefits in costs and sustainability to those of process development time.

2.3.1.1 Predictions based on theoretical impact analysis

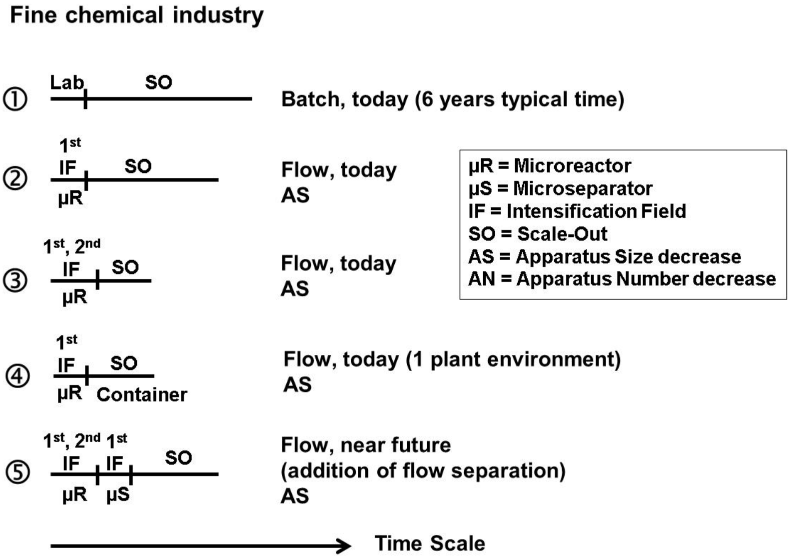

Figure 2.2. Generic impact analysis of intensification fields on the process development time in fine chemistry. The different cases and their total and partial time-scales are meant to present trends, rather than a concrete time scale.

The current case to be considered for a flow process is with only reactor being changed from batch to flow, while all other equipment remains as batch. This flow scheme is now widely used in fine chemistry, has been taken over by industry and transferred even to production.

Case (1) Batch processing needs a certain development time in laboratory and all other steps (pilot, production) then consume a longer amount of time; here summarized as scale-out. As typical time 6 years was assumed.

Case (2) Microreactors, being commercially available, allow in this way for many applications “automatically” transport intensification (mixing, heating/cooling, safety) (1st field). While certainly for other applications, such as multiphase systems, more elaborate process development is needed. Transport intensification can save process development time mainly for reasons of apparatus size decrease. As discussed above it can also enable reduction in the number of apparatus and can make possible scale-up of formerly prohibited reactions due to improved safety in microreactors. Higher predictability in the scale-out of the apparatus is achieved with microreactors since the performance achieved at lab scale can be maintained at higher scale resulting in decrease in the scale-out time.

Case (2) essentially has been studied in literature and there was no need for this thesis to reinvestigate.

Case (3) Quite straightforward, although more elaborate is to gain chemical intensification (2nd field). Therefore the development in lab can be longer but it can save even more process development time in scale-out. As explained above chemical intensification can speed-up reactions tremendously leading to significant reduction of apparatus size. Since they suffice to handle higher productivity, some scale-out steps can be eliminated as well. In this manner, it is not unrealistic to expect development times of 3 years under good conditions.

Case (3) essentially has been studied and realized in the ERC Grant framing this thesis. See works of Shang, Shahbazali, Borukhova, Stouten and and more.[80–84]

Case (4) The use of one plant environment during all development stages such as provided by container plants will reduce the scale-out time. In conventional plant approach the development starts in lab to test the feasibility and the reaction conditions. Large production campaigns can only be performed in another production environment with larger units in shift-work organization. With the modular container plants all development stages can be completed in one environment resulting in simplification of scale-out. Container plants can save time also by standardization of modules enabling saving in planning and construction time and expenditure. This enables a faster time-to-market.

Case (4) essentially has been studied in this thesis; see chapter 5.

Case (5) In near future, flow separation units might sometimes be added leading to a full (integrated) flow process. For some applications, a separator-specific intensification (1st field) might be beneficial also for the overall process. This adds development time. This effect will probably not be reduced much in the next decade or so. Thus, at least for the time being, longer development times need to be considered. Still, such undertaking is highly valuable, as it will lead to cost improvements and better sustainability.

Case (5) essentially has been studied in this thesis; see chapter 3.

When really integrating reaction and separation, the additional separation intensification automatically sets in place and the additional efforts are a must, leading to the same conclusions as given above of longer development time. The development of new reaction designs leading to new process designs (3rd field) has large potential, but also needs much additional chemistry and catalyst development. Thus, although this takes large promises in the direction of saving costs and providing a more sustainable chemistry; it is not so suited for time reduction in process development for fine-chemical production.

2.3.1.2 Companies' strategies for fine-chemical process development in flow

Lonza, Visp/Switzerland has given most insight in a chemical company's approach and success in process development for continuous flow production. Lonza has designed and tested a series of microstructured devices in continuous-flow plants, and performed lab studies of pharmaceutical reactions with successful transfer to commercial production. Summing up all reports from Lonza, at least 10 reactions were transferred to production based on year 2011 analysis, but probably now in 2015 there are more.[32–35,85,86]

Lonza's microstructrured reactors are designed for scale-out and, due to smart increase in dimensions, the favorable single channel approach might be used throughout the whole process development avoiding parallelization from lab development to pilot-scale production. Four microreactor classes were described of increasing channel sizes, with glass as material for laboratory and steel for piloting and production.[32]

DSM in Austria and NicOx, based in France, developed a pilot-scale process based on numbering-up multiple parallel microreactors to make an arthritis drug. The drug, naproxcinod, is the nitroxybutyl-substituted form of naproxen, the well-known nonsteroidal anti-inflammatory drug. This compound containing a nitro group is difficult to make, since nitration reactions are strongly exothermic. Together with Corning, Inc. a microreactor system was designed that combines three process steps - the nitration reaction, neutralization, and workup. Dr. Hartmann from DSM quoted the achieved decrease in process development time: "Along with the safety and processing advantages, NicOx appreciated how quickly large amounts of material could be made available … the development efforts and investment are much less."[7] The pilot-scale process of DSM with a throughput of hundreds of kilograms was achieved after about six months work. The whole time from feasibility studies to large-scale production took only about 18 months.[7]

2.3.2. Bulk chemistry

2.3.2.1 Predictions based on theoretical impact analysis

For bulk-chemical processes, the impact and time demands are different from the conclusions given for fine chemistry; see Figure 2.3. Process design with all its chances for mass- and energy integration is here the key. Thus, the idea for developing a flow process in bulk chemical industry must be to forecast process simplification based on the opportunities provided by microreaction technology. So, the first step is to chemically establish a new reaction route which allows to simplify process design. Subsequently, the next step is to intensify this new (direct) process utilizing microreactors with the 2nd chemical intensification field. Finally, a full-flow process needs incorporation of microseparators and there might be additional momentum through the 1st transport intensification field. The key to process time reduction here is to achieve process simplification in the first step which reduces the number of equipment that needs to be developed (finally at large scale) in flow. Similar to Figure 2.2, this can be made in stepwise fashion as follows.

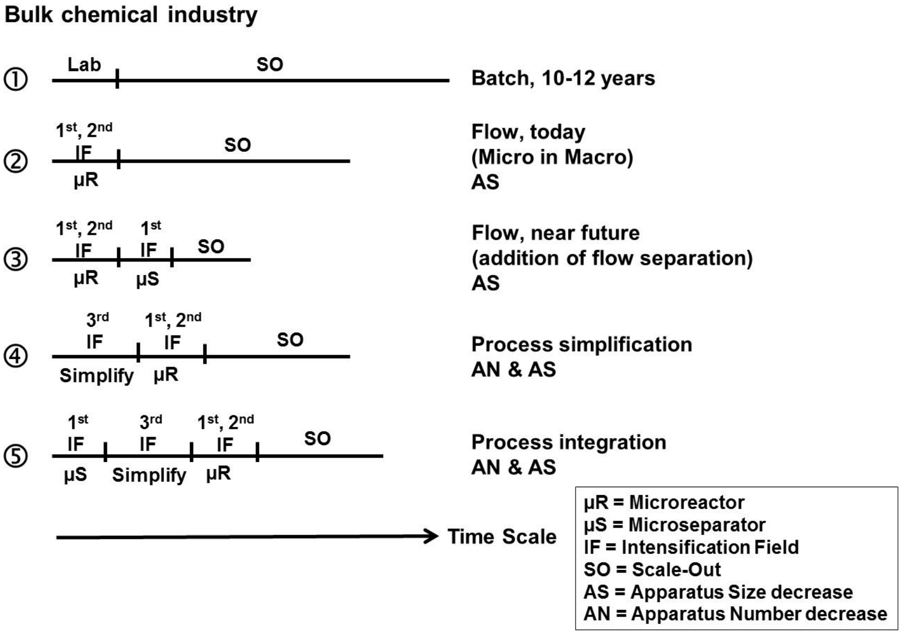

Figure 2.3. Generic impact analysis of intensification fields on the process development time in bulk chemistry. The different cases and their total and partial time-scales are meant to present trends, rather than a concrete time scale.

Case (1) Development times in bulk chemistry, based on batch and other conventional (including classical continuous) processing, are much longer than for fine chemistry. As typical time 10-12 years was assumed. This is not so much due to development time in laboratory, but caused by the more complex scale-out (pilot, production) requiring long times for planning, engineering and construction.

Case (2) Microreactors for bulk chemistry are commercially not available, yet even their prototyping has hardly been demonstrated, although some challenging developments were undergone in this direction. Thus, different from fine chemistry, transport intensification (mixing, heating/cooling, safety, 1st field) cannot "automatically" be utilized now. It rather requires further development, especially for heat integration and catalyst immobilization. Rather than using "pure" microtechnology, the solution probably is given by mesoscaled or flat-plate reactors with catalysts as foams or fixed-beds, providing continuous processing. This has compromises to transport intensification to allow productivity high enough for the large scales. It is still expected that with such solutions at hand the scale-out can be reduced due to the replication or representativeness of the process units from lab to production. Especially with the implementation of chemical intensification (2nd field) further benefits in ease of scalability can be achieved with significant reduction in apparatus size.

Case (2) has not been studied and realized in this thesis. Yet, we tackle with predicting operation and costs of such unknown large-scale microstructured reactors; see chapter 7.

Case (3) Since separation units comprise the majority of the process units in bulk chemistry, the addition of flow separation units with their changes for replication and ease of scalability should have an additional, actually stronger impact on decreasing scale-out time as compared for flow transfer of only the reaction unit. Therefore, although development of flow separators constitutes an additional development time, in overall the development time can be reduced.

Case (3) has not been studied and realized in this thesis. Yet, our separation concept as described in chapter 4 is valid for fine-chemical capacities.

Case (4) In near future, the development of new reaction routes might allow to propose simplification of the process-design which is the process-design intensification field (3rd field). This adds a development time for the new reaction design. However due to apparatus size as well as number decrease plant footprint is much reduced. Therefore, savings are expected as scale-out is much simpler and in sum this may lead to a shorter overall development time.

Case (4) has been studied in this thesis; for the first time in literature. See chapter 7.

Case (5) In future, process integration of flow reaction and separation can be achieved under the process-design intensification field (3rd field). This adds a development time for the new integrated reaction-separation design. The scale-out of such solutions, however, may not be possible just by strict replication and this will add development times so that the overall benefit in time savings is considered to be minor.

Case (5) has not been studied and realized in this thesis. It is a very new concept and recently being investigated in literature with membranes. [60–63]

As a net result, the longer development times in bulk chemistry offer larger possibilities for savings than given in fine chemistry; on the other side, the state of the art in development of respective (micro-/milli-/meso-) structured flow reactors is much lower as for fine-chemical flow reactors and this adds additional development challenges and times. Thus, opportunities and challenges largely come to balance and savings in development time are predicted to be similar as for fine chemistry. However, cases (4) and (5) make also evident that when releasing the true flow potential for bulk chemistry – which is process simplification and integration – the main argument is probably not saving in development time, but is savings in costs and gains in sustainability (which is not shown in this article).

In the examples that use microstructured equipment for applications at a scale of the upper limit of fine chemistry and bridging to bulk chemistry, they were inserted into the existing large scale plant (retrofit). They were motivated by safety, heat-transfer limitations and requirement of throughput increase.[87]

2.4. Conclusion

After having seen almost two decades of flow-related developments of micromixers, microreactors, micro heat exchangers, and recently microseparators, the time is ripe for the next round of the implementation of microreactor and flow techniques. This is devoted towards bringing all of the above-mentioned devices to industrial productivity and embedding them in a modern Future Factory type plant environment with an overarching process and plant approach.

Intensified flow processing and micro process technology can make process development somewhat simpler and save development time. One main reason is the higher predictability in the scale-out of the apparatus achieved with microreactors since the performance achieved at lab scale can be maintained at higher scale resulting in decrease in the scale-out time. This allows also to develop modular reactor and separator concepts which fit well to modular plant concepts (such as containers), developed also currently. With the modular container plants all development stages can be completed in one environment resulting in simplification of scale-out. Container plants can save time also by standardization of modules enabling saving in planning and construction time and expenditure.

Another main reason is that microstructured reactors and similar flow and process intensified equipment (milli/meso) enable transport and chemical intensification, e.g. open the door to harsher process chemistries. This allows to safely process high throughput in smaller equipment. A final main reason, but much less exploited so far as compared to the other two mentioned, is the chance for radical changes in process design when using a flow intensified plant called process-design intensification. The focus is here much on the reaction part and this can largely reduce the number and size of separation equipment. Such process simplification is at best not only achieved by the higher selectivity of flow reactions, but by an additional radical change in reaction design, e.g. by newly developed direct syntheses or multi-step cascaded reactions in one flow. Such far-fetching development adds development time, with chance for pay back due to reduced plant footprint. Process integration, reaction with separation, may reduce somewhat the impact on time savings in process development, but undoubtedly offers large chances for cost saving and sustainability.

Finally, with the present microreactor and flow technology, it seems that time savings in process development are likely for fine-chemical applications up to the border of bulk-chemical processes; but that for true bulk-chemical applications, the cost and sustainability arguments are the main motivation for present investigations here.

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CHAPTER 3

Connected Reaction and Metal Separation in Flow – Drop-In Process Integration at Lab Scale

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This chapter is based on :

Vural Gursel, I., Noël, T., Wang, Q. & Hessel, V. (2015). Separation/recycling methods of homogeneous transition metal catalysts in continuous flow. Green Chemistry, 17, 2012-2026.
Vural Gursel, I., Aldiansyah, F., Wang, Q., Noël, T. & Hessel, V. (2015). Continuous metal scavenging and coupling to one-pot copper-catalyzed azide-alkyne cycloaddition click reaction in flow. Chemical Engineering Journal, 270, 468-475.

Abstract:

Increasing usage of catalytic chemistry calls for efficient removal of metal traces. This chapter describes the development and optimization of a scavenger-based extraction in flow to remove metal catalysts. It enables liquid–liquid extraction with slug flow and phase separation with a porous fluoropolymer membrane. The use of this unit for copper scavenging of various copper sources from organic solvent was studied. The effects of scavenger type (EDTA, DTPA, EDDS), concentration and pH were also investigated. Such analysis allowed to achieve extraction performance as high as 99% at pH of the scavenger solution adjusted to 9.4 and molar ratio of scavenger to copper of 10. Process integration is achieved by coupling this unit downstream to a flow reaction using homogeneous metal-based catalysis, i.e. presenting a continuous uninterrupted metal scavenging unit. The copper-catalyzed azide-alkyne cycloaddition click reaction is studied in one-pot eliminating the need to isolate and handle potentially explosive azide. The triazole product is attained in flow with high yield of up to 92% with 30 min residence time. The level of purity requirement for pharmaceuticals is met in one stage of extraction.

3.1. Introduction

Process intensification through micro-process technology allows to reach processing far from state of the art through entirely new and innovative equipment and means of processing in continuous flow mode [1–3]. In the past, it was based mainly on transport intensification that improves mixing and heat exchange [4,5]. More recently, chemical intensification is increasingly explored which uses highly intensified, unusual and typically harsh process conditions to boost micro-processing (high temperature, high pressure, high concentration, safety) [6–11]. The last two mentioned means are an essential part of Green Chemistry. Beyond, as third momentum, process-design intensification heads for simplified and integrated flow process design (Green Engineering) [12]. The latter two intensification fields constitute 'Novel Process Windows', a term coined by Hessel in the past and further developed by our group [1,13–15].

In the microreactor literature and community it is common to focus largely to one equipment (designed and tested) and its processing. However, with process-design intensification we focus our attention toward the chemical process as a whole, thereby rendering a true holistic picture [16,17]. The majority of microchemical synthesis applications were so far restricted to one or few reaction steps with the separation done offline [18–20]. Microreactors are highly developed at scales up to industrial production [21,22]. However, further development of microseparation units is needed. From about 2011 onwards, there is an increasing number of developed microseparation devices [23]. Still most of these devices have been characterized as stand-alone tools, i.e. without connection to a flow reaction device. The coupling of microseparation units with microreactors is not rare anymore, but still far from being commonly applied. So far, there are only few demonstrations [24–27]. To be able to achieve multi-step synthesis in flow and make the flow process chain complete, further development of microseparators is required.

Since the early investigations in micro process technology, microextraction has received a considerable amount of attention. Microextraction involves mixing and contacting of the organic and aqueous phases and consequently achieving the phase separation. Extraction based on liquid-liquid slug flow in microchannels facilitates convective mass-transfer between the phases [28]. Due to internal circulation flow, high mixing performance is achieved [4]. After extraction the two phases can be easily separated. Effective liquid-liquid separation can be achieved using membranes [29,30]. Separation of the two phases can also be performed with branched hydrophobic and hydrophilic outlets [31,32].

For extraction of copper and a wide range of metals, chelating agent solutions are effective [33]. These scavenging agents extract metal by forming a metal-chelate complex which can further be removed from the solution [34]. It enables high extraction efficiency of the metal and is fast, compatible with many solvents and causes no loss of product. It was used effectively for extraction from spent catalyst [34–36] and also waste waters [37,38]. Most used scavenging agents include ethylene diamine tetraacetic acid, EDTA and diethylene triamine pentaacetic acid, DTPA [39]. Due to their high complexation strength they are effective scavenging agents but are resistant to degradation [36]. Biodegradable [*S,S*]-ethylene diamine disuccinic acid ([*S,S*]-EDDS) has been proposed as an alternative scavenging agent and it has also been found to have high extraction efficiency [35,36,40].

The copper-catalyzed azide-alkyne cycloadditon (CuAAC) was taken as the reaction of industrial relevance. It is established as one of the most important examples of click chemistry [41–43]. The resulting 1,2,3 triazoles find use in variety of applications from drug discovery and development to material science and chemical biology [41,42,44–47]. Several approaches to perform CuAAC in continuous flow processing have been reported [9,48–50]. This is motivated by improved mass and heat transfer as well as the safety aspects, azide being unstable, and scalability of flow processing opposed to conventional batch procedures. Microwave irradiation was also tested and major reduction in reaction time was observed [48,51,52]. Another advance in this field is generation of the required azides in situ [50–53]. This one-pot methodology eliminates the need to synthesize azide separately in continuous flow [54]. All these examples used heterogeneous catalysis. Although heterogeneous catalysis has advantage of being recyclable, the copper species leach into the solution [48,49]. Scavenger resins in cartridges has been used to remove these copper species from the solution. One example is QuadrapureTM TU that has been successfully used for CuAAC reactions [48,49]. However, the need to periodically replace these cartridges interrupts the continuous process.

A microseparation unit has been developed to achieve continuous uninterrupted extraction of metal catalyst in flow. It involves liquid-liquid extraction based on slug flow with the use of chelating agent and phase separation using porous fluoropolymer membrane. The coupling of CuAAC reaction with continuous copper extraction was achieved in flow in previous studies [9]. However, three stages were required to reduce the copper content of triazole product below the limit for APIs of 15 ppm [55]. Since this is not optimal, more extensive analysis of microseparation unit was needed. This is carried out and presented in this chapter. In this study, first the performance of the microseparation unit is benchmarked using EFCE-recommended extraction systems. Also its performance is compared with a similar flow extraction unit described in literature. Then the copper extraction experiments are performed that enable continuous uninterrupted separation of copper species in solution. To achieve the optimum extraction performance, the use of different types of copper catalysts and metal scavengers (EDTA, DTPA and EDDS) are investigated together with variation of metal scavenger concentration and pH. Based on this analysis and optimization of parameters, the copper scavenging unit is coupled to the CuAAC click reaction using homogeneous copper catalyst with the aim to get the triazole product at high yield and purity in one stage of separation.

3.2. Homogeneous Metal Catalyst Separation/Recycle in Flow

Homogeneous catalysis is of great interest for its high activity and selectivity. However, their separation from the product remains a challenge. Transition metals and especially platinum group metals are used extensively. They are expensive and there are strict regulations on the permitted levels of these metals in pharmaceutical products.[55] Moreover, we are running short of these metals. Therefore, their effective separation and recycle is of great importance. In industry, classical methods of homogeneous catalyst separation involve thermal or other costly processes. The most common method of distillation requires high energy and also can result in irreversible deactivation of the catalyst system.[56] This has stimulated researchers to look for entirely new processes as more gentle, low energy alternatives to separate /recycle homogeneous catalysts in continuous flow. These include heterogenization, scavenging, use of biphasic conditions and organic solvent nanofiltration. There are numerous successful demonstrations on laboratory scale and recently also on an industrial scale. The advantages and disadvantages of them are summarized in Table 3.1.

Table 3.1. Summary of the advantages and disadvantages of the separation/recycling methods of homogeneous metal catalysts in continuous flow

Separation methods	Advantages	Disadvantages
Heterogenization	○ Catalyst is immobilized on supports enabling easy reuse	○ Lower catalytic activity ○ Significant problem of leaching in the case of the homogeneous mechanism ○ Catalyst deactivation due to deposition of impurities
Scavenging	○ High efficiency	○ Need for replacement of scavenging columns after saturation
	○ No loss of product ○ Especially advantageous for trace amounts of metals	○ Use of scavenging columns not suitable at larger scales
Use of biphasic conditions	○ The phase containing the catalyst can be separated and recycled easily	○ The chemistry needs to be compatible with the biphasic reaction conditions
	○ Applicability at the industrial scale	○ Systems with fluorous solvents, ionic liquids and supercritical fluids have high initial cost
Organic solvent nanofiltration	○ Low energy separation ○ Catalyst retained enabling easy reuse	○ Catalysts need to be molecular weight enlarged to achieve high retention performance
	○ Applicability at the industrial scale	○ Concentration polarization can occur for dead-end filtration

A schematic representation of these methods is given in Figure 3.1. There are two ways of heterogenization of homogeneous catalyst. First is by immobilizing homogeneous catalysts on solid support. The drawback is the significant leaching and degradation of the catalyst during its use and recycle leading to loss of metal.[57] Because of the high catalyst cost this has an economic impact and this is the reason this method has no application at a large scale. However, there are successful examples, and commercialization in future can be possible.[58–61] Second is recently studied immobilization of homogeneous catalyst in a stationary liquid phase. In this system, the catalyst is dissolved in a thin film of liquid which is supported within the pores of silica. Ionic liquids have been used for this purpose.[62–64] With the successful examples of the supported ionic liquid systems, there is potential for their further application, especially since only a small amount of ionic liquid is required.

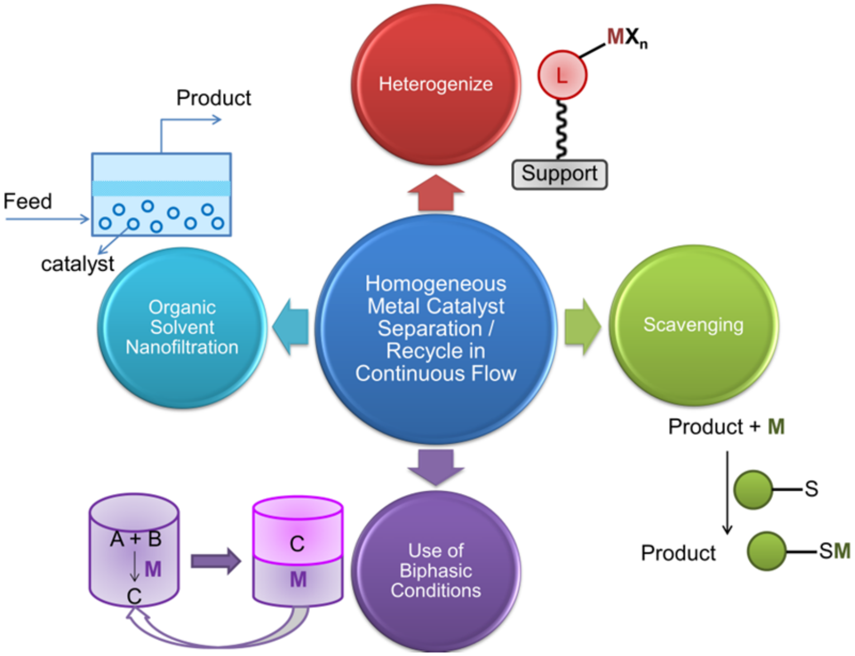


Figure 3.1. Overview of separation/recycling methods of homogeneous metal catalysts in continuous flow

Homogeneous catalyst separation can also be achieved by scavenging which is typically done utilizing solid-supported scavenging resins packed into columns [65,66]. The scavenging agents extract metal by forming a metal-chelate complex which can further be removed from the solution [34]. They are very efficient in capturing very low amounts of metals in metals which is attractive for pharmaceutical production on a small scale [67,68]. However, they need to be replaced when saturated interrupting the continuous process. As a kind of extension and as a solution to this problem, scavenging agents in solution has been investigated in this chapter which holds promise to be applied at a large scale.

Another method is the use of liquid–liquid biphasic conditions. This is achieved with one phase selectively dissolving the catalyst while the other dissolving the product. After separation of the phases, the phase containing the catalyst can be easily recycled to the reactor. There are several commercial applications of aqueous-organic and organic-organic biphasic conditions for large scale production showing economic and environmental benefits.[69–71] Biphasic systems can also be created with fluorous solvents, ionic liquids and supercritical carbon dioxide which have a number of successful applications on a lab-scale due to their unique properties[72,73] being utilized for facile catalyst separation.[74–79] They have not found commercial application so far, most likely due to the high cost of the chemicals or the equipment required. But with efficient processes, they can be recycled almost totally with a long lifetime.[69] Then their initial selling price becomes less significant. With the number of successful examples of their application increasing, it can be expected that their advantages will be exploited in industry especially in fine chemical production.

Finally, there is a relatively new method of organic solvent nanofiltration (OSN). It has been studied in flow for a large range of reactions to retain the homogeneous catalyst in the reactor.[80–82] Also catalysts have been molecular weight enlarged with dendrimers,[83,84] polymers[85] and polyhedral oligomeric silsesquioxanes[86,87] to achieve better retention with OSN. There are numerous examples of their application in lab. Currently there are also few examples of its application by industry.[56,88–91] The economic potential is seen to be very promising.[92] With the ongoing development, more and better performing commercial membranes are becoming available. Their industrial applications are thus expected to increase in the near future.

3.3. Experimental

3.3.1. Experimental setup of microseparation unit

For testing the performance of the microseparation unit for liquid-liquid extraction experiments are performed with one 5 mL syringe loaded with feed containing solute and another 5 mL syringe loaded with extraction solvent. For copper scavenging experiments a 5 mL syringe is loaded with mixture of copper catalyst and organic solvent, another 5 mL syringe is loaded with aqueous EDTA solution. Equipment configuration is shown in Figure 3.2. Plastic syringes from DB are used. The two syringes are mounted to Chemyx Fusion 200 Touch Syringe Pump. All the tubing used in this setup is of PFA capillary tubing (1/16" OD x 500 μm ID). T-mixer used for mixing of the two coming streams from syringe pump is made of PEEK with 500 μm ID purchased from IDEX Health and Science. Fluidic connections are made with ¼-28 flat bottomed flangeless fittings (IDEX Health and

Science). Contacting of the phases takes place on capillary tubing of 100 cm length. Two phases are then separated with flow liquid liquid extraction (FLLEX) module by Syrris Ltd., UK and are subsequently collected in vials and analyzed. Syrris FLLEX module contains a porous PTFE membrane (0.22 µm pore size) placed inside a separator chip. The membrane is hydrophobic and selectively allows organic stream to pass through. To ensure good separation the pressure across the membrane is controlled via two back pressure regulators. To achieve pressure difference along the separator it is connected to an air or nitrogen source of 4 bar. The back pressure is set to 2 bar. Then the cross membrane pressure is adjusted to achieve good separation of the phases.

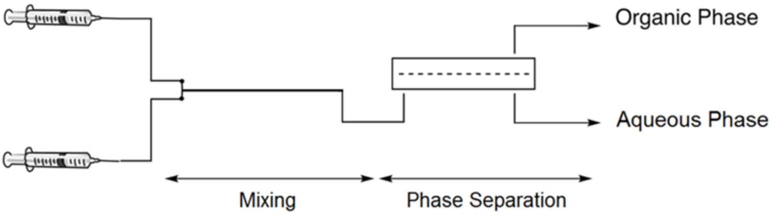


Figure 3.2. Experimental setup of microseparation unit used for liquid-liquid extraction and copper scavenging experiments

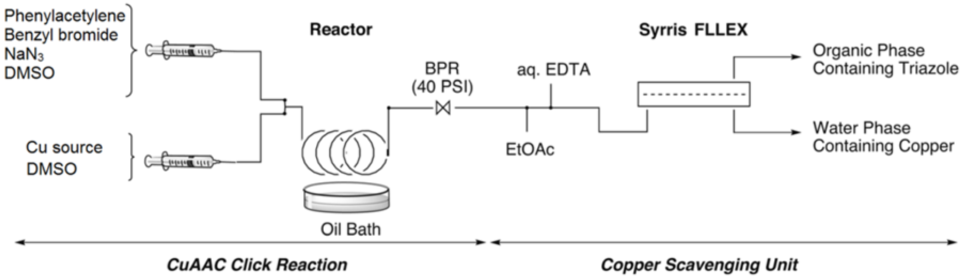


Figure 3.3. Experimental setup of one-pot CuAAC click microreactor coupled with copper scavenging unit in flow

3.3.2. Experimental setup of one-pot CuAAC click reaction and inline copper scavenging in flow

Equipment configuration of one-pot CuAAC click reaction coupled to copper scavenging is shown in Figure 3.3. Chemyx Fusion 200 Touch Syringe Pump is used to deliver reagents from BD plastic syringes to the reactor. A 3 mL syringe with phenylacetylene, benzylbromide, sodium azide (NaN_3) and DMSO is mounted to the syringe pump. Another 3 mL syringe containing the copper catalyst and DMSO is also mounted to the syringe pump. All tubing used in this setup is made of PFA capillary tubing (1/16" OD x 500 µm ID). T-mixer used to mix the reagents is made of PEEK with 500 µm ID purchased from IDEX Health and Science. Fluidic connections are made with ¼-28 flat bottomed flangeless fittings (IDEX Health and Science). Reactor has a volume of 400 µL made of PFA capillary tubing (200 cm length, 1/16" OD x 500 µm ID). It is submerged in an oil bath with temperature controlled via thermocouple (IKA ETS-D5) and maintained with a heating plate (IKA RCT Basic). Backpressure regulator of 40 psi (IDEX Health and Science) is used. Upon exiting the reactor, solution is quenched with ethyl acetate (EtOAc) and EDTA which are loaded into two separate 5 mL BD plastic syringes delivered by another Chemyx Fusion 200 Touch Syringe Pump. With a PEEK cross mixer (IDEX Health and Science) these two streams are brought together with the reaction outlet mixture. They flow along PFA capillary tubing (100 cm length, 1/16" OD x 500 µm ID) and then are delivered to Syrris FLLEX module. The organic and aqueous phases are separated and subsequently collected in vials and analyzed.

3.4. Results and Discussion

3.4.1. Performance characterization of the flow liquid-liquid extraction unit

Three two-phase model systems are used to evaluate the extraction efficiency of the flow liquid-liquid extraction unit (Table 3.2). The first one constitutes the extraction of dimethylformamide (DMF) from dichloromethane (DCM) into water. A second system is extraction of acetone from water into toluene. Third system is extraction of succinic acid from water into *n*-butanol. The latter two model systems are recommended standard systems of the European Federation of Chemical Engineering (EFCE). They were applied in the past successfully by us to characterize flow extraction of dispersed flows (emulsions) made by micromixers.[93] They differ considerably in their interfacial tension where water (acetone) / toluene system has a high value and water (succinic acid) / *n*-butanol system has a low value as seen in Table 3.2.

For the system of water (succinic acid) / *n*-butanol the phase separator failed to achieve complete separation of the phases for all the cross membrane pressure variation (50-300 mbar) made. Due to very low interfacial tension of this system, an emulsion readily forms and it is difficult to break.

Table 3.2. Model systems used to evaluate performance of the liquid-liquid extraction unit

Model System	Feed		Solvent	Interfacial Tension (mNm^{-1})
1	DMF	in DCM	Water	39.1
2	Acetone	in Water	Toluene	33.0
3	Succinic acid	in Water	*n*-Butanol	1.7

3.4.1.1. Model system of DMF-DCM-water

For the model system of DMF-DCM-water, experiments are performed with three different DMF content in DCM of 9.2 mol.%, 11.5 mol.% and 13.7 mol.% and the resulting concentration of DMF in the extract stream is measured. Values from our experiments match closely with experimental results achieved with a similar flow extraction unit exhibiting slug flow in literature[29] as seen in Figure 3.4. With their silicon microfabricated device packaged with the membrane, flow rates of aqueous and organic phases of 25 μL min^{-1} each were achieved.[29] With this device flow rates of aqueous and organic phases of 500 μL min^{-1} each is achieved.

For a system with a constant partition coefficient, the extraction yield is constant. By performing a mass balance, this DMF extraction yield is calculated as 60 %. The partition coefficient which is the ratio of mol.% of DMF in extract to mol.% of DMF in feed is nearly constant as evidenced by good fit of experimental points to straight line. The partition coefficient which is the slope of this line is found as 0.15. These values agree well with equilibrium data obtained from shake-flask experiments and literature.[29] Thus, a single equilibrium extraction stage is achieved.

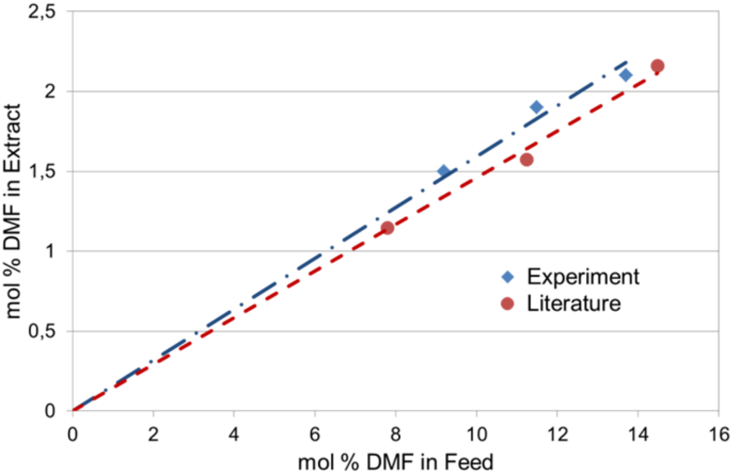


Figure 3.4. Extraction of DMF from DCM into water, performance comparison of our work and literature

3.4.1.2. Model system of acetone-water-toluene

For the EFCE recommended standard system of acetone-water-toluene, a satisfactory partition coefficient up to 0.5 is achieved, yet still below the thermodynamic partition coefficient of 0.8. This is expected as the flow rate of the setup is limited to 60 mL h^{-1} due to maximum flow rate limit of the phase separator. At flow rates above 800 mL h^{-1}, conditions close to thermodynamic equilibrium were reached for this model system in previous experiments utilizing micromixers.[93] Yet otherwise, a perfect phase separation is consistently achieved for this system indicating good performance of the membrane.

Feed and solvent are fed at equal rate and alternate slugs are visualized. Slug lengths are seen to get larger by decreasing the flow rate (Figure 3.5). This observation agrees with the work of Dessimoz et al. for the toluene water system studied with a T-mixer.[94]

According to the performance characterization with the three model systems, flow liquid-liquid extraction unit is seen to have good, applicable performance apart from the systems that have low interfacial tension.

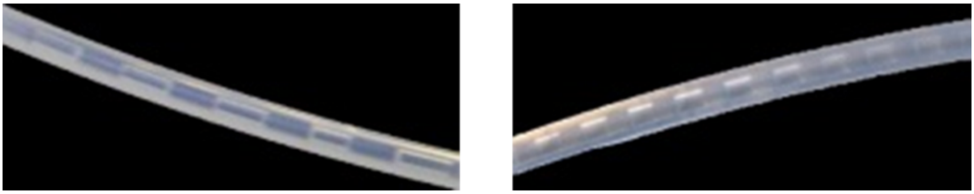


Figure 3.5. Flow pattern of acetone-water-toluene system for 9 mL h^{-1} (left) and 30 mL h^{-1} (right)

3.4.2. Continuous copper scavenging using flow liquid-liquid extraction unit

With this confirmation of the good performance of the liquid-liquid extraction unit, copper scavenging experiments were performed. The use of different types of copper catalysts and metal scavengers were investigated together with variation of metal scavenger concentration and pH.

3.4.2.1. Copper scavenging performance for different types of copper catalysts

Copper scavenging of various copper sources ($CuBr(PPh_3)_3$, $[Cu(phen)(PPh_3)_2]NO_3$, CuI, $CuSO_4$, $Cu(OAc)_2$) from organic solvent was studied. The copper extraction performance achieved with the unit for the various copper sources tested is presented in Table 3.3. Toluene is selected as solvent and it is fed at the same flow rate with the aqueous EDTA. However, CuI, $CuSO_4$ and $Cu(OA_C)_2$ are not miscible in toluene so a mixture of DMF and toluene is used. In all cases slug flow is observed. Experimental results show excellent performance of copper extraction at EDTA concentration of 0.016 M and pH of 9.4 and extraction performance as high as 99% is achieved. Catalyst source of $CuBr(PPh_3)_3$ is used as basis to study the effects of other parameters. In aqueous solution Cu^{II} is the more stable oxidation state. Cu^{I} ions in solution can be oxidized into Cu^{II} form. The Cu^{II} form is the only species which complexes with EDTA in aqueous solution. The copper-EDTA complex formed is very stable with a high stability constant of log K 18.8, making this process practically irreversible.[95]

Table 3.3. Copper scavenging performance for different types of copper sources

Copper Source	Solvent	Copper Content (ppm)			Extraction (%)
		Feed	Aq. outlet	Org. outlet	
$CuBr(PPh_3)_3$	Toluene	123	120	3	98
$[Cu(phen)(PPh_3)_2]NO_3$	Toluene	123	122	1	99
CuI	DMF/Toluene	123	121	2	98
$CuSO_4$	DMF/Toluene	162	136	26	84
$Cu(OAc)_2$	DMF/Toluene	183	160	23	88

3.4.2.2. Copper scavenging performance with variation of scavenger type and concentration

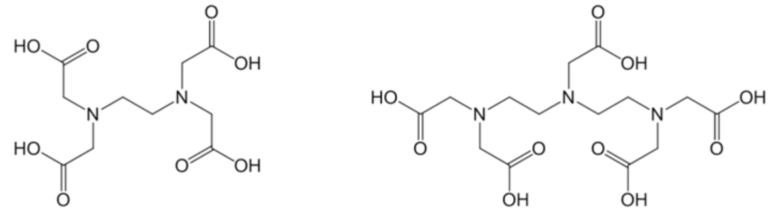
For the experiment with $CuBr(PPh_3)_3$ in toluene given in Table 3.3, the molar ratio of scavenger to copper is 10 using 0.016 M EDTA. The effect of changing the scavenger concentration is also investigated (Table 3.4). For EDTA concentration of 0.0016 M, which corresponds to an equimolar scavenger and copper concentration, the copper extraction performance of 91% is achieved. The residual copper content in the organic phase is still below API limit indicating that lower amounts of scavenger are sufficient to achieve required performance.

Additionally, the use of other metal scavengers, such as DTPA and [*S,S*]-EDDS, is studied for both scavenger concentrations for extraction of $CuBr(PPh_3)_3$ in toluene. These results are also presented in Table 3.4. DTPA shows slightly higher extraction performance than EDTA at 0.0016 M concentration. This can be explained by its molecular structure (Figure 3.6). EDTA has six coordination sites (four acid and two amine) available to bind the metal whereas DTPA has eight sites (five acid and three amine). This behavior is also observed by others.[39] [*S,S*]-EDDS, a structural isomer of EDTA, shows lower performance. This is because it forms relatively weak complexes with metal.[36] But this property enables it to be easily biodegradable making it attractive to be used.

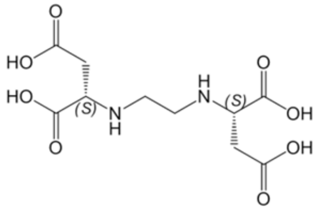
For studying the effects of other parameters the concentration is set to 0.016 M and scavenger type of EDTA is used. At this concentration, EDTA and DTPA have similar extraction performance. EDTA is the most widely used scavenger in literature therefore it is selected as basis for analysis of other effects.

Table 3.4. Copper scavenging performance for different types of copper sources

Metal Scavenger	Concentration (M)	Copper Content (ppm)			Extraction (%)
		Feed	Aq. outlet	Org. outlet	
EDTA	0.0160	123	120	3	98
DTPA	0.0160	142	139	3	98
[*S,S*]-EDDS	0.0160	118	114	4	97
EDTA	0.0016	126	115	11	91
DTPA	0.0016	124	118	6	95
[*S,S*]-EDDS	0.0016	118	81	37	70



Ethylene diamine tetraacetic acid (EDTA) Diethylene triamine pentaacetic acid (DTPA)



[*S,S*]-ethylene diamine disuccinic acid ([*S,S*]-EDDS)

Figure 3.6. Molecular structure of EDTA (left), DTPA (middle) and [*S,S*]-EDDS (right)

3.4.2.3. Copper scavenging performance with variation of scavenger solution pH

The acidity of the scavenger solution also affects the extraction performance. Therefore, the effect of pH of scavenger solution is studied in the range 6-11 for the extraction of $CuBr(PPh_3)_3$ in toluene using 0.016 M EDTA. As seen in Figure 3.7, extraction performance increases with the increase in pH up to pH of about 10 and after that it shows a decrease. Therefore, the optimum pH range is seen to be between 8.5 and 9.5. For studying effects other than pH an optimum value of pH is set as 9.4. It is explained in literature that the increase in pH changes the protonation stage providing availability of metal binding sites.[35]

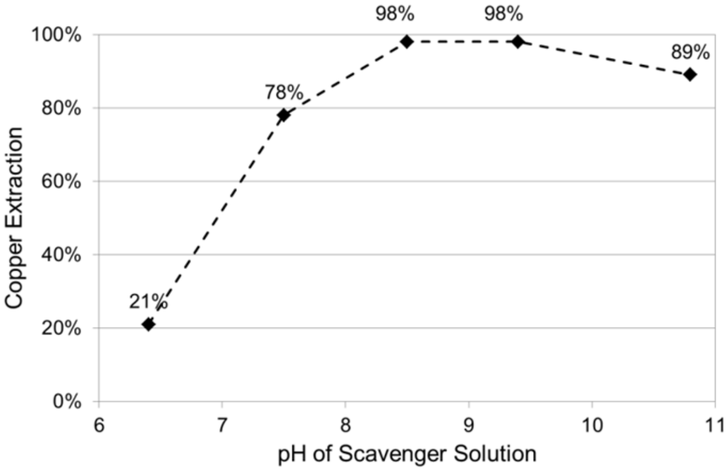


Figure 3.7. Copper scavenging performance with variation of scavenger solution pH

3.4.2.4. Recovery and reuse of chelating agent EDTA

Recovery and recycling of EDTA is attractive in terms of cost saving. It is also beneficial regarding environmental concern of EDTA being not easily degradable. EDTA recovery is performed by acidification of the aqueous outlet from phase separation using sulfuric acid. Lowering the pH breaks the metal-chelate complex and EDTA is recovered in the form of precipitate. About 87 % of EDTA is recovered by filtration. To investigate its reusability it is redissolved to identical concentration with fresh EDTA experiments. Its copper content is analyzed and seen to be less than 1 ppm indicating it can be recovered mostly free from metal. Significant extracting performance is observed with the recycled EDTA of 92 % (Table 3.5). Overall, recovered EDTA still has high extraction efficiency.

Further recycle was not performed but in literature extraction efficiency of recovered EDTA was investigated up to four recycles. It was seen that extraction efficiency decreased after each recycle. After the fourth recycle, approximately 20 % less extraction efficiency than fresh EDTA was observed and consequently no further recycling was carried out.[35] Overall, recycled EDTA was still effective and showed that EDTA can be used effectively up to four cycles.[34]

Table 3.5. Copper scavenging performance comparison between fresh and recycled EDTA

Metal Scavenger	Concentration (M)	Copper Content (ppm)			Extraction (%)
		Feed	Aq. outlet	Org. outlet	
Fresh EDTA	0.0160	123	120	3	98
Recycled EDTA	0.0160	134	127	11	92

3.4.3. One-pot CuAAC click reaction and inline metal scavenging in flow

After demonstrating the high performance of the continuous copper scavenging unit, reaction experiments were started. The copper-catalyzed cycloaddition of benzylazide and phenylacetylene is studied. However, instead of producing benzylazide separately and then reacting it with phenylacetylene a one-pot methodology is adapted.[51] Accordingly, benzylazide is formed in situ from benzylbromide and sodium azide and is directly reacted with phenylacetylene with the reaction scheme given in Figure 3.8. In this way isolation and handling of instable azide is eliminated and the process is simplified. It makes the process also safer by enabling consumption of the azide as soon as it forms. The catalyst of [Cu(Phen)(PPh$_3$)$_2$]NO$_3$ is selected based on previous work showing this catalyst to give the highest performance.[9] A tubular PFA microreactor of 400 µl volume is used. For reaction temperature of 170 °C, pressure of 40 psi and catalyst loading of 5 mol.%, a good yield of 66 % is obtained in 10 minutes. By increasing the reaction/residence time, the triazole yield is improved up to 92 % in 30 minutes. After achieving good performance with the microreactor we set to explore the efficiency of our copper scavenging unit by connecting it after the reactor with the setup seen in Figure 3.3. The reactor outlet is mixed with 0.016 M EDTA and ethyl acetate that is used for quenching. Scavenging takes place along the tube and then the mixture is passed through the FLLEX module. Complete separation of organic and aqueous phases is achieved. The copper content in the organic phase is analyzed and found to be lower than API limit of 15 ppm for three residence time variations studied as given in Table 3.6.

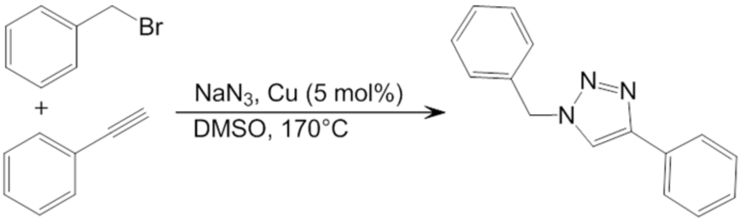


Figure 3.8. One-pot copper-catalyzed azide alkyne cycloaddition

Table 3.6. Triazole yield and copper scavenging performance with variation of residence time

Residence time (min)	Triazole yield (%)	Copper Content (ppm)			Extraction (%)
		Feed	Aq. outlet	Org. outlet	
10	66	577	574	3	99
20	84	547	533	14	97
30	92	547	538	9	98

3.5. Conclusion

In order to develop a complete chemical processes on a micro-scale or related somewhat higher continuous scale (milli, meso), the joint development of reaction as well as separation techniques in microfluidic or other smart-scaled flow devices is required. It is seen that to achieve this further especially the development of microseparation units and respective effective flow protocols is needed. We decided to start our investigations on microseparation and its connection with the copper-catalyzed azide-alkyne cycloadditon (CuAAC) reaction. A continuous uninterrupted metal scavenging unit is developed based on liquid-liquid extraction using slug flow. The phase separation is achieved with a porous PTFE membrane. The unit is tested with model extraction systems and found to give good, applicable performance apart from the system with low interfacial tension. With such confirmation, copper scavenging experiments were performed. The use of different types of copper catalysts and metal scavengers were investigated together with variation of metal scavenger concentration and pH. For scavenger to copper molar ratio of 10, the scavengers EDTA, DTPA and EDDS all showed high performance of about 98 %. For molar ratio of 1, DTPA showed slightly better performance than EDTA whereas EDDS showed lower performance as explained by their molecular structure. With the lower EDTA concentration, the residual copper content in organic is found still below API limit indicating less amount of scavenger is sufficient to achieve required performance. For studying the effects of other parameters the molar ratio of 10 and scavenger type of EDTA is used. The scavenger was seen to have high performance for extracting various copper sources with up to 99 % extraction efficiency. Strong effect of pH of scavenger solution on extraction performance was seen. The optimum pH range for copper extraction with EDTA was found to be between 8.5 and 9.5. Recovery of EDTA was also performed. The recycled EDTA successfully extracted 92 % of copper, only 6 % lower than fresh EDTA. Finally, the copper scavenging unit was coupled to one-pot CuAAC click reaction and yield of 92 % was obtained with 30 minutes residence time using 5% mol loading of $[Cu(Phen)(PPh_3)_2]NO_3$ as homogeneous catalyst. Residual copper was efficiently removed in flow and the level of purity required for pharmaceuticals (APIs) was met in one stage of separation.

In conclusion, a microextraction unit has been developed for metal catalyst scavenging, widely applicable for modern organic synthesis. Coupling it to chemical reaction in flow enables high yield and low metal content of the desired product. This opens doors to exploit process-design intensification at a multi-step synthesis with vision to achieve synthesis on a pilot scale.

3.6. Appendix

3.6.1. General chemicals information

Chemicals were purchased in their highest purity available from Sigma Aldrich. Scavenging solutions from ethylene diamine tetraacetic acid (EDTA) and diethylene triamine pentaacetic acid (DTPA) were prepared by mixing with demineralized water (purified with a Millipore Elix UV-5 machine) and careful addition of ammonium hydroxide (NH4OH) 5 M drop by drop until the solids disappear and the desired pH is achieved. [*S,S*]-ethylene diamine disuccinic acid ([*S,S*]-EDDS) was purchased as solution (35% water), it is diluted to desired concentration and NH4OH is added to get the desired pH.

3.6.2. General analytical information

Analysis for performance characterization experiments are done using GC-FID on a Varian 430-GC with a flame ionization detector using a CP-Sil 8 CB column (length 60 m, diameter 0.25 mm, film thickness 0.1 μm), with helium as the carrier gas. External calibration is performed by making solutions of varying concentrations 0, 2, 4, 6, 8, and 10 wt.% of solute in organic phase. Sample from organic outlet is taken and analyzed for amount of solute.

Analysis for copper scavenging experiment is performed using Inductively Coupled Plasma – Optical Emission Spectroscopy (ICP-OES) from Sysmex SpectroBlue. 1 mL sample of aqueous outlet (containing EDTA–copper complex) is diluted to 100 mL using oven dried volumetric flask, sample is then analyzed using ICPOES with prior calibration. Calibration is performed by making a calibration curve from 0 to 10 ppm of copper. Calibration samples were prepared using 1000 mg L^{-1} TraceCERT standard solution available from Sigma–Aldrich.

Analysis for one-pot CuAAC click reaction to determine yield of triazole is done using ^1H NMR. Nuclear magnetic resonance spectra were recorded on a Varian Mercury 400 instrument. All ^1H NMR are reported in δ units, parts per million (ppm), and were measured relative to the signal of tetramethylsilane (0 ppm) in deuterated solvent ($CDCl_3$). Prior to NMR analysis, high purity toluene is added as internal standard for quantification of yield. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

3.6.3. Typical experimental procedure for performance characterization of the flow liquid-liquid extraction unit

Experimental procedure for model system of dimethylformamide (DMF) - dichloromethane (DCM) - water for feed of 10 wt. % (11.5 mol.%) DMF in DCM is described. One 5 mL syringe is loaded with a solution of 10 wt. % DMF in DCM. Another 5 mL syringe is loaded with demineralized water which is the solvent for this system. A single syringe pump is used to deliver the chemicals in two syringes at flow rate of $30\ \mathrm{mL\ h^{-1}}$ making total flow in the unit $60\ \mathrm{mL\ h^{-1}}$. They are mixed with a T-mixer and flow along 100 cm capillary tubing where partitioning takes place. The phases form alternate slugs along the tube and they are separated passing through the Syrris FLLEX module. Cross membrane pressure is adjusted to 250 mbar to achieve good separation of the phases. The organic stream is collected from the top and aqueous stream from the bottom of the module into vials. Analysis of the organic phase is performed using GC-FID to determine the amount of solute. The amount of solute in aqueous stream is then determined with mass balance and subsequently partitioning coefficient is calculated. The experiment is conducted at room temperature.

3.6.4. Typical experimental procedure for continuous copper scavenging using flow liquid-liquid extraction unit

Experimental procedure of extraction of copper using $CuBr(PPh_3)_3$ as copper source in toluene using 0.016 M EDTA with 9.4 pH is described. In a volumetric flask EDTA (116.8 mg) is added with 25 mL demineralized water. Solution pH is adjusted adding drop by drop 5 M NH_4OH (about 10 drops) until pH of 9.4 enabling EDTA to be fully dissolved. One 5 mL syringe is loaded with this 0.016 M EDTA aqueous solution. Another 5 mL syringe is loaded with $CuBr(PPh_3)_3$ (7.8 mg) dissolved in 5 mL toluene (123 ppm Cu). A single syringe pump is used to deliver the chemicals in two syringes at flow rate of $30\ \mathrm{mL\ h^{-1}}$ making total flow in the unit $60\ \mathrm{mL\ h^{-1}}$. They are mixed with a T-mixer and flow along capillary tubing of 100 cm where chelation between EDTA and copper takes place. The phases form alternate slugs along the tube and they are separated passing through the Syrris FLLEX module with the cross membrane pressure adjusted to 250 mbar. The aqueous phase collected from the bottom contains the copper source removed from the organic phase and organic phase collected from the top is mostly free from copper. The aqueous phase is analyzed using ICP-OES to determine the copper amount scavenged. The experiment is conducted at room temperature.

3.6.5. Typical experimental procedure for recovery of EDTA

To the sample from aqueous outlet of the copper scavenging experiment, sulfuric acid 5M is added drop by drop until pH of 2 is attained resulting in a slurry which is monitored with a pH meter. Slurry is then filtered using oven dried Whatman filter paper with known dry weight. After filtering, filter paper with the captured solids is dried in 70 °C oven for 120 minutes and subsequently weighed to determine percentage recovery. The solid is then redissolved and analyzed using ICP-OES to determine the copper content of the recovered EDTA. This recovered EDTA is then reused in copper scavenging experiments by preparing a solution of 0.016 M.

3.6.6. Typical experimental procedure for one-pot CuAAC click reaction and inline copper scavenging in flow

An oven dried volumetric flask is charged with sodium azide (39 mg, 0.6 mmol dissolved in DMSO), phenylacetylene (0.45 mmol), benzylbromide (0.45 mmol). It is flushed with argon and DMSO is added to make the solution volume 3 mL and is loaded in a syringe. Another 3 mL syringe is loaded with $[Cu(phen)(PPh_3)_2]NO_3$ (5% mol, 18.6 mg, 0.0225 mmol) dissolved in DMSO. A single syringe pump is used to deliver the chemicals in two syringes. Flow rate is adjusted for each residence time variation (1.2 mL h^{-1} each for 10 minutes residence time). They are mixed with a T-mixer and then flowed through the reactor with a volume of 400 μL. The reactor is submerged in an oil bath temperature adjusted to 170 °C. A backpressure regulator of 40 psi (2.76 bar) is used. Upon exiting the reactor the reactor stream is quenched with ethyl acetate and 0.016 M EDTA loaded into two separate 5 mL syringes. These two streams are delivered by an additional syringe pump with a flow rate adjusted to 7.2 mL h^{-1} for 10 minutes residence time experiment. With a cross mixer these two streams are brought together with the reaction outlet mixture. They flow along PFA capillary tubing of 100 cm length where chelation between EDTA and copper takes place. Finally passing through the Syrris FLLEX module organic and aqueous phases are separated. The aqueous phase sample is analyzed using ICP-OES to determine the copper amount scavenged. The organic phase sample is washed with demineralized water and extracted with diethylether four times (4 × 2 mL). The organic layers after each extraction are collected. The combined organic is dried over $MgSO_4$ and filtered. Then the solvent is removed under vacuum to yield triazole as solid. Deuterated solvent of $CDCl_3$ and toluene as internal standard (0.5 mmol) is then added and ^1H NMR analysis is done to determine the yield. 1-benzyl-4-phenyl-1H-1,2,3-triazole: ^1H NMR (400MHz, $CDCl_3$): δ = 5.57 (s, 2H), 7.25 – 7.44 (m, 8H), 7.66 (s, 1H), 7.73-7.85 (m, 2H) ppm.

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CHAPTER 4

Scale-up of Flow Extraction Utilizing Coiled Flow Inverter – Drop-In Process Integration at Pilot Scale

This chapter is based on :

Vural Gursel, I., Kurt, S.K., Aalders, J., Wang, Q., Noël, T., Nigam, K.D.P., Kockmann, N. & Hessel, V. (2015) Utilization of milli-scale coiled flow inverter in combination with phase separator for continuous flow liquid-liquid extraction processes. Chemical Engineering Journal, 283, 855-868.
Kurt, S.K., Vural Gursel, I., Hessel, V., Nigam, K.D.P. & Kockmann, N. (2015) Liquid-liquid extraction system with microstructured coiled flow inverter and other capillary setups for single-stage extraction applications. Chemical Engineering Journal, 284, 764-777.

Abstract:

Process-design intensification situated under the umbrella of Novel Process Windows heads for process integration with the coupling of flow devices and here most development is needed for flow separators. The vision is to achieve multi-step synthesis in flow on pilot scale. This calls for scale-up of separation units. This study is rare in micro flow literature and community and thus conducted here. The coiled flow inverter (CFI) was considered as the right tool to work at higher flow rates. We report hereby for the first time, to best of our knowledge, the use of the CFI for immiscible liquid-liquid mixing and its application for liquid-liquid extraction. A milli-scale CFI with tube internal diameter of 3.2 mm and tube length of 210 cm was used where partitioning takes place in slug flow. Phase separation was achieved with PTFE membrane flow separator or slit shaped flow separator composed of glass and Teflon rectangular capillaries. The microextraction unit was tested for European Federation of Chemical Engineering recommended model extraction systems of toluene-water-acetone and n-butyl acetate-water-acetone. The effects of variation of total flow rate at equal volume fraction as well as variation of aqueous volume fraction at

constant total flow rate on extraction performance were investigated. High extraction efficiency close to thermodynamic equilibrium was achieved for both systems. The CFI setup was also compared with straight tube and CFI showed about 20 % higher extraction performance with the increase in flow rate. In straight tube, parallel flow developed at higher flow rates whereas the CFI kept operating in the slug flow regime. Membrane separator could be used up to 20 ml/min, however pure organic phase was attained throughout. With slit shaped separator, for the butyl acetate-water-acetone system, 20 % breakthrough at both outlets occurred at a flow rate of 32 ml/min. For the model system of toluene-water-acetone flow rate up to 120 ml/min (7.2 l/h) was achieved at same breakthrough level indicating the influence of interfacial tension on the operating window of separator. It is important to point out that slug flow regime that is limited to microfluidic systems was maintained even at such pilot scale (58 m^3/y). It was seen that higher flow rate is achieved in this study than the ones reported for slug flow in literature.

4.1. Introduction

The new and innovative equipment available with micro-process technology opens up new opportunities of processing that are far from conventional practices [1–4]. This new concept was called Novel Process Windows [5–7]. It has two fundamental pillars that are chemical intensification and process-design intensification. Chemical intensification makes use of highly intensified, unusual and typically harsh process conditions to boost micro-processing [8–17]. Process-design intensification is based on process simplification and integration [18–20]. It takes into consideration the chemical process as a whole, therefore is holistic in approach [21–23]. The majority of research in micro-process technology was focused on the development of process units to be utilized in reaction, mixing and heat exchange [24–29]. Application of these units on large scale has also been studied [30–35]. However, the development of flow separation units is still largely limited. They are highly desired and required to enable downstream unit operations in flow. Therefore, to realize a whole production process in flow, further development of flow separators is asked for that can be coupled to other processing units. This coupling is not rare anymore, but far from being commonly applied [36–40]. Furthermore, for pilot-scale application, flow separation units that can handle high throughput are required. This was rarely studied [41], thus development of a flow separation unit on a moderately large scale is conducted here.

There is an increasing number of flow separators developed dedicatedly for chemical purposes [42]. Liquid-liquid extraction has gained the most interest [43] but recently several distillation [44–47], absorption [48–50] and chromatography [51–53] units were also described. Liquid-liquid extraction is very important for chemical industry and it especially finds wide application in pharmaceutical production [41]. Additionally, high surface-to-volume ratios in microchannels is especially advantageous for effective liquid-liquid contacting [43]. Liquid-liquid extraction has two parts of mixing and phase separation. At micro- and milliscales surface tension dominates over gravitational and inertial forces [41]. Thus, surface tension is used as the driving force for separation [54].

With the use of different mixing elements and process conditions different flow patterns are observed [55]. The flow pattern used has a large effect on the mixing and separation performance [43]. Slug flow was shown to have better mass transfer compared to parallel flow [56]. This is due to slug flow providing convection through internal circulations as well as interfacial diffusion between two adjacent slugs [55]. Mass transfer in dispersed flow was seen to be the most effective due to larger interfacial area [57]. However, the phase separation performance should be taken into consideration when evaluating the whole extraction process. Emulsions are very stable and long time is required for the coalescence of produced droplets [57]. On the other hand, phase separation of slug flow can be much easily achieved in short times. Effective liquid-liquid slug flow separation was achieved with PTFE membrane or microdevice that selectively lets the organic phase pass through [41,54,58,59]. Also, it was achieved with wettability-based separation units with branched hydrophobic and hydrophilic outlets [55,60,61]. Therefore, slug flow can be regarded as suited best for practical use in flow applications. So far, slug flow has only been realized on a laboratory scale. Highest flow rate of 4.8 L/h was presented by Cervera-Padrell et al.[41] for the application of phase separation of toluene and water.

Liquid-liquid extraction based on slug flow was achieved in previous studies with a setup including a T-mixer, straight tube where partitioning takes place and a PTFE membrane phase separator [39]. Maximum flow rate attainable was 1 ml/min. Its coupling to the copper-catalyzed azide-alkyne cycloaddition (click chemistry) reaction was achieved in flow. The vision now is to achieve such multi-step synthesis in flow on pilot scale. This calls for scale-up of flow separation unit and this is carried out here. So far, no application examples of extraction using microeffects in higher-throughput are reported. For performing the mixing, the coiled flow inverter (CFI) introduced by Saxena and Nigam[62] was selected to enable efficient mixing at higher flow rates. For performing the phase separation two different units were tested. The first is a PTFE membrane separator developed by IMM which is the Institut fuer Mikrotechnik Mainz GmbH (meanwhile renamed as Fraunhofer-ICT Mainz) and the second is a slit shaped flow separator composed of glass and Teflon rectangular capillaries developed by Gaakeer et al.[60] Extracting efficiency of the setup was tested for the European Federation of Chemical Engineering (EFCE) recommended model extraction systems of toluene-water-acetone and n-butyl acetate-water-acetone [63]. Flow pattern was characterized using high-speed photographic system. Effects of variation of flow rate and aqueous phase fraction on extraction efficiency were investigated. The extraction efficiency of the setup was compared with a straight tube setup. Lastly, the performances of the two separators were evaluated.

4.2. Coiled Flow Inverter

Numerous mixing strategies have been proposed to enhance mixing performance in microfluidic systems. Curved channels offer a simple design that enable generation of vortices.[64] Formation of vortices remarkably contribute to convective mixing and, thus, the axial dispersion can be decreased.[65–68] Because of the action of centrifugal force that acts perpendicular to the flow direction of the fluid, a secondary flow develops in curved channels.[69] The magnitude of this effect is characterized by the dimensionless Dean number.[70] At higher Dean numbers higher mixing performance is attained.[71] Dean vortices enhance the radial mixing in case of single-phase flow and thus narrower residence time distribution compared to straight capillaries can be achieved.[62,72]

Mixing is further enhanced by arranging the curved channels in a way that chaotic advection is created. It was achieved by complete flow inversions by inducing 90° bends at equal intervals along the length of the tube.[62] Coiled flow inverter (CFI) is based on this principle. The direction of the centrifugal forces inducing the formation of secondary flow profile in helically coiled tube is changed with the 90°-bends. Therefore, the secondary flow profile is developed after the 90° bend in a different plane that is perpendicular to the previous plane (Figure 4.1). As a result, the radial mixing can be further enhanced in CFI in comparison to helically coiled tube. Hence, a narrow RTD close to an ideal plug flow reactor can be achieved even at laminar flow regimes.[73,74]

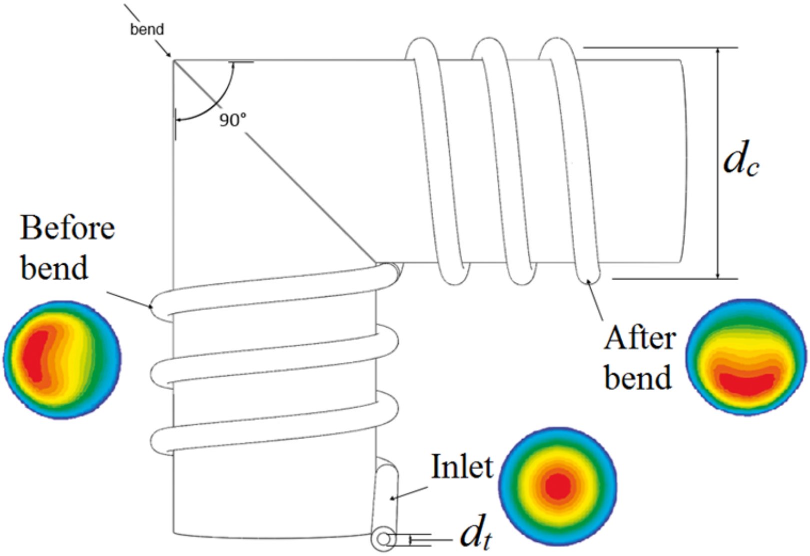

Figure 4.1. CFI structure and cross-sectional velocity contours and streamlines at the inlet, before and after 90° bend, where d_t is the inner tube diameter and d_c is the coil diameter (adapted from Kurt et al.[75]).

CFI was shown to be very effective as a heat exchanger [76–80] and as an inline mixer of two miscible liquids [81,82] Furthermore, it was used for chemical reaction [83] and to study fluid flow in two-phase gas-liquid systems [84–87]. CFI was tested already for pilot plant scale with tube internal diameter of 10 mm allowing for a liquid flow rate up to 2000 l/h [77].

These studies show that the high mixing efficiency of CFI for single phase and two phase gas-liquid systems is very well understood. The use of CFI for immiscible liquid-liquid mixing is open for research. The study of two-phase flow characteristic of CFI for the application of liquid-liquid extraction is to be discussed below with a milli-scale CFI for pilot scale. It has also been investigated in micro-scale with CFI of 1 mm inner diameter[75]. The complete system was able to be operated with slug flow pattern for total volumetric flow rates and volumetric flow ratios (aq/org) in the range of 1-8 ml/min and 0.5-2.0, respectively. Extraction efficiency results revealed that the microstructured coiled flow inverter provides better extraction efficiency up to 20 % compared to straight capillaries at constant contact times. For a constant length of tube, increasing slug flow velocities slightly increased the extraction efficiency of CFI due to increase in the intensity of Dean vortices. The results show that the Dean vortices inside the helically coiled tubular devices offers enhanced mixing than the internal circulations that occur in straight capillaries in case of slug flow pattern. Volumetric liquid-liquid mass transfer coefficient values were found 1.5 to 2 folds greater compared to straight capillaries. Therefore the microstructured CFI was found very promising for extraction purposes and CFIs are also compact in design which is a further advantage compared to straight capillaries.

4.3. Experimental

4.3.1. Model systems used

Liquid-liquid extraction of two systems were considered: acetone from its aqueous solution into toluene (toluene-water-acetone) and acetone from its aqueous solution into butyl acetate (butyl acetate-water-acetone). These are two of the standard test systems investigated by European Federation of Chemical Engineering (EFCE) [63]. They differ in terms of interfacial tension. In both systems 10 wt. % of acetone in water was used as aqueous feed. The interfacial tension of the systems at this acetone concentration was calculated with the correlation given in the EFCE book [63]. The models systems are given in Table 4.1.

Table 4.1. Model systems used

Model systems	Interfacial tension [mN/m]
1) Toluene / Water + Acetone (10 wt.%)	17,8
2) n-Butyl Acetate / Water + Acetone (10 wt.%)	8,6

4.3.2. Experimental setup

The experimental setup used is shown in Figure 4.2. For the visualization of the flow methylene blue was added to the aqueous phase. Aqueous feed was loaded into two plastic syringes and these two syringes were mounted to one Chemyx Fusion 200 Touch syringe pump. Organic feed was loaded into one plastic syringe and it was mounted on to another Chemyx Fusion 200 Touch syringe pump. The syringes were connected to 1/8" OD, 1.55 mm ID PFA capillary tubing. The liquids were introduced to Swagelok stainless steel 1/8" tube OD union cross mixing element. The aqueous streams enter from the sides and organic stream enters from the middle as shown in Figure 4.2. CFI made with PFA tube (1/4" OD, 3.2 mm ID), which is explained in detail in the next paragraph, was attached downstream of the union cross. At the end of this mixing and contacting stage, a phase separator was connected. The separated phases from the two outlets of the phase separator were collected in sampling bottles. Experiments were carried out in room temperature.

The CFI was made by coiling 1/4" OD PFA tube with tube internal diameter (d_t) of 3.2 mm around a 1" OD stainless steel cylindrical bar that is welded to make a square shape. This results in coil diameter (shown as d_c in Figure 4.1) of 32 mm. This is the distance from center to center of the tube so it is found as the sum of cylindrical bar diameter and tube outside diameter.

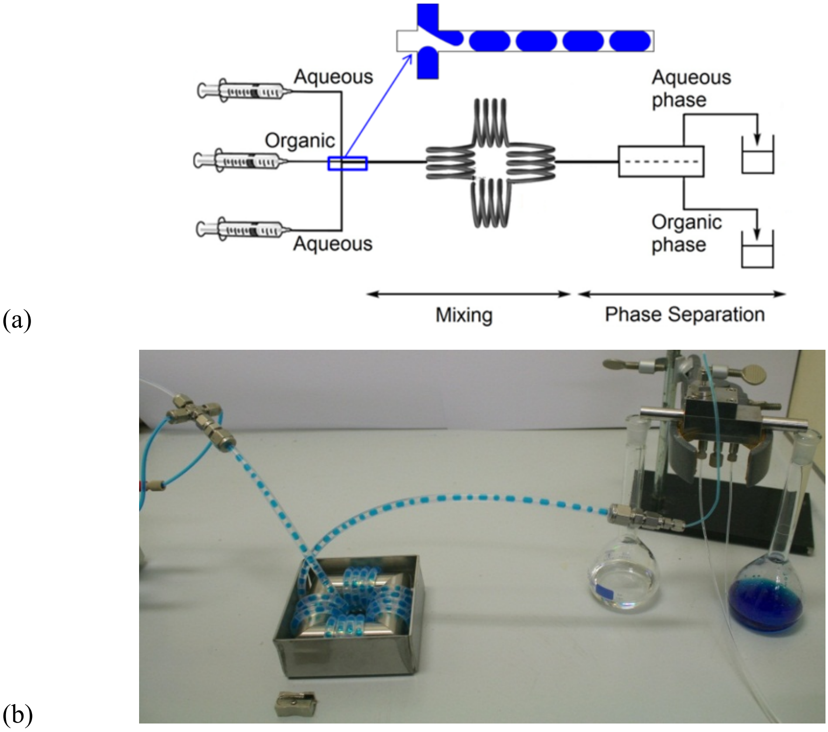

Figure 4.2. (a) Schematic diagram and (b) Photograph of experimental setup

The corresponding curvature ratio ($\lambda = {}^{d_c}/_{d_t}$) is then equal to 10. With the square shape, 90° bends are introduced and it enables the direction of the centrifugal forces to change 3 times resulting in more efficient mixing. There is equal tube length before and after the bends. Including the straight tube parts at the inlet and outlet of CFI, the mixing contacting part has a total tube length of 210 cm.

4.3.3. Flow separation devices

For performing the phase separation two different units were tested. The first is a PTFE membrane separator developed by IMM which is the Institut fuer Mikrotechnik Mainz GmbH (meanwhile renamed as Fraunhofer-ICT Mainz) and the second is a slit shaped flow separator composed of glass and Teflon rectangular capillaries developed by Gaakeer et al. [60]. The pictures of the separators are provided in Figure 4.3.

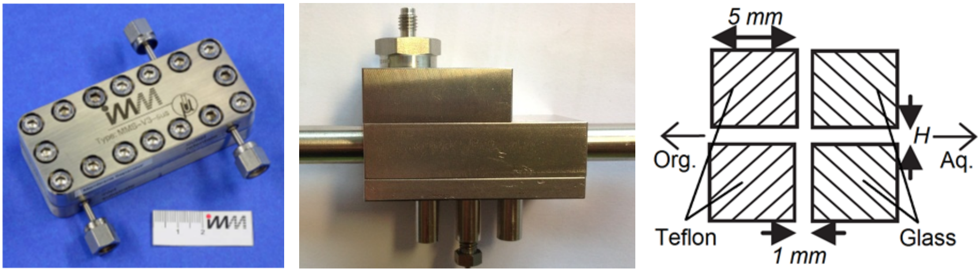

Figure 4.3. Flow separation devices, left: membrane separator, middle: slit shaped separator and right: inside view of the bars within slit shaped separator

The IMM membrane separator is composed of microstructured plates with the membrane sandwiched in between. Each of the two plates have 10 channels and channels have dimensions of length x width x depth = 38 mm x 500 µm x 280 µm. The membrane used is Pall Zefluor 0.5 µm pore PTFE membrane. It was cut to 44 mm x 14 mm from a 47 mm round disk. The membrane allows permeation of the organic phase while aqueous phase is retained. The device is sealed with allen screws. 1/4" OD PFA tube coming from the CFI was directly connected to the separator inlet. The outlet tubes used were each 30 cm PFA tubes of 1/16" OD, 500 µm ID. The setup with the membrane separator is given in Figure 4.4.

The slit shaped separator consists of a slit between two glass bars and a slit between two Teflon bars assembled in stainless steel housing. Stainless steel spacers are used to set the desired slit height. In this study slit height (H as shown in Figure 4.3, right) of 0.4 mm was used. Separation is achieved based on the preferential wetting properties of the liquids on solid material. Organic phase has affinity toward the hydrophobic Teflon capillary whereas aqueous phase has affinity to flow through the hydrophilic glass capillary. Details about this device can be found in Gaakeer et al.[88] From the CFI the tube was reduced to 1/16" OD, 500 µm ID as it enters the slit shaped separator. The side outlets of the separator are open to atmosphere. To drain the separator two PFA tubes of 1/16" OD, 500 µm ID were connected at the bottom outlets but there was no flow at these outlets during operation of the experiments. The setup with the slit shaped separator is shown in Figure 4.2 b.

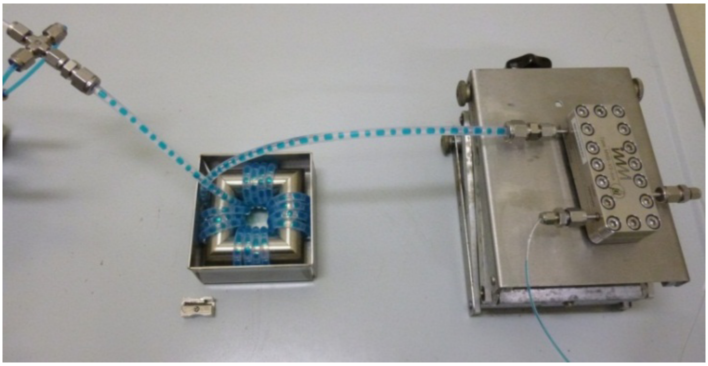

Figure 4.4. Photograph of the experimental setup with the membrane separator

4.4. Results and Discussion

4.4.1. Liquid – liquid two-phase flow patterns in CFI

To study the two-phase liquid-liquid patterns a frame of 10 ml/min organic flow rate by 10 ml/min aqueous flow rate was chosen. This is the same frame used in the papers by Kashid et al.[89,90] In other studies of flow regime, the flow rates used were lower. The aqueous and organic phases were fed at all combinations of 2, 4, 6, 8, 10 ml/min of each phase. Snapshots for each condition were taken. Not to make the figure overcrowded, pictures of all conditions are not shown but a selection of them is provided. These are seen in Figure 4.5 for the toluene-water system. For the butyl acetate-water almost identical pictures were obtained. On all pictures a bar showing the diameter of the tube is placed on one slug to give an indication of size. The experiments show that the water is the dispersed phase and forms convex shaped slugs while the organic is the continuous phase and has a concave shape. Slug flow regime is defined with the slug lengths longer than the diameter of the channel.[91] This was observed almost in all points of the map. Only at very low aqueous to organic ratios of 2 to 8 and 2 to 10 the slug sizes are slightly smaller than the diameter. These points can be regarded to be in drop flow regime.[91] For all the experiments no coalescence or break-up of the slugs were observed.

It was observed that with this system the total flow rate doesn’t have much influence on the slug size. This was also observed by Jovanovic et al.[92] However, in some studies it was seen that the slug lengths decrease with the increase in flow rate.[91,93] This was explained to occur due to rapid penetration of one phase into other segregating the stream into more slugs. The reason why this was not observed by us could be because of the larger tube diameter used in this study, this effect could be seen at much higher flow rates.

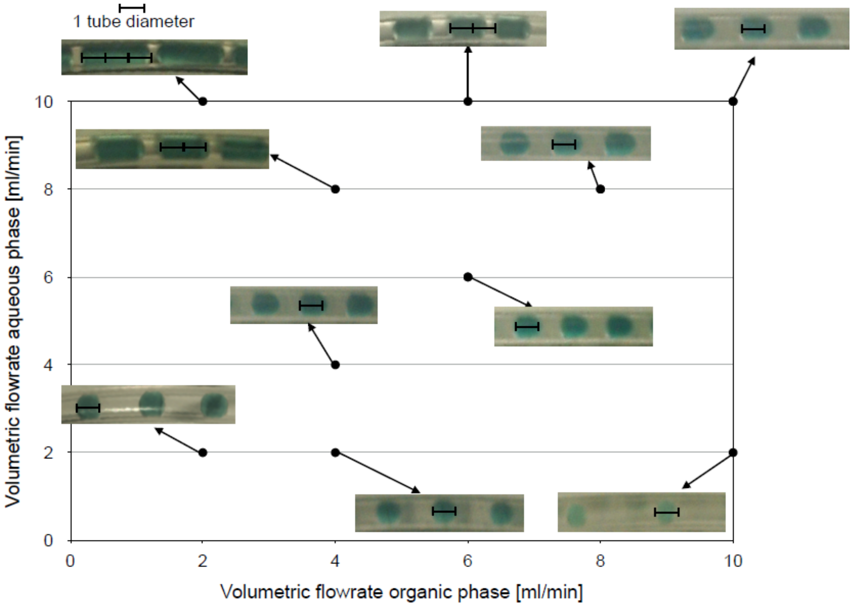

Figure 4.5. Flow pattern map of toluene-water system

The slug size was observed to be highly dependent on the ratio of the aqueous and organic flow rates. It was seen that the aqueous slug length decreases as the organic flow rate increases at constant aqueous flow rate. This is to be expected since with the decrease in relative flow rate of the aqueous phase its volume fraction in the channel would decrease. Similarly it was observed that the aqueous slug length increases as the aqueous flow rate increases at constant organic flow rate.

Kashid and Agar[91] observed that by using larger diameter capillaries the area in the flow map where uniform slug flow is observed expanded. When 0.5 mm ID tube was used the maximum flow rate for both liquids was 1.2 ml/min. This was increased to 1.7 ml/min each when 0.75 mm and 1 mm ID tubes were used. This was the flow rate limit in their study. Observing slug flow regime in a wider flow rate range using 3.2 mm ID tube in present study is in accordance with their finding.

In their more recent study, Kashid et al.[90] investigated using six parallel capillaries as scale-up of their previous system. They observed that the slug flow regime expanded six fold enabling it to be achieved at a flow rate of 10 ml/min for both liquids. They concluded that this scale-up enabled the flow pattern can be preserved while total throughput is increased. In this present study, it is also observed that slug flow regime can be preserved while higher flow rates are achieved. Several authors studied mapping of the flow regimes in terms of dimensionless numbers to define quantitatively the influence of different forces. Dessimoz et al.[93] made flow transition maps based on mean Capillary (Ca) and Reynolds (Re) numbers. Zhao et al.[94] proposed to the Weber (We) number for the mapping of the flow patterns to express whether interfacial tension or inertia is the dominant force.

Several authors plotted their maps as We_{org} vs. We_{aq}.[92,94,95] For the maximum flow rates used in Figure 4.5 of 10 ml/min of each phase the calculation of these dimensionless numbers were made for toluene-water (T-W) and butyl acetate-water (B-W) systems. This is given in Table 4.2. Please note that acetone was not used in flow pattern investigation experiments and therefore is not included also in these calculations. For interfacial tension 34 and 14 mN/m are used for toluene-water and butyl acetate-water, respectively.

Table 4.2. Reynolds, Capillary and Weber numbers of the organic and aqueous phases for the two systems

System	Q_{org}, ml/min	Q_{aq}, ml/min	Re_{org}	Re_{aq}	Ca_{org}	Ca_{aq}	We_{org}	We_{aq}
T-W	10	10	103	75	3.4×10^{-4}	5.5×10^{-4}	3.5×10^{-2}	4.1×10^{-2}
B-W	10	10	85	75	1.0×10^{-3}	1.3×10^{-3}	8.9×10^{-2}	1.0×10^{-1}

Dessimoz et al.[93] calculated the average value of the two phases for the dimensionless numbers Ca and Re. They plotted Ca_{mean} vs. Re_{mean} and identified a transition line between parallel and slug flow regime. The equation of this curve can be calculated from the figure and it shows that to be in slug flow regime the ratio of Ca_{mean} to Re_{mean} should be below about 8.3×10^{-5}. Making this calculation using Table 4.2 it is seen that the ratio is much below this value confirming the slug flow regime observed in our studies. It was also calculated for the different composition of aqueous and organic phases. It was seen that the ratio is higher when the aqueous to organic ratio is higher and also higher for the butyl acetate-water system. However, for all the conditions the ratio of Ca_{mean} to Re_{mean} was much below this threshold value.

Jovanovic et al.[92] observed slug flow at Ca values below 10^{-2}. The Ca values calculated for our system are below this value as well. The Weber number values for both phases being below 1 indicate that interfacial tension dominates compared to inertial forces producing slugs. It is explained that the interfacial tension tends to reduce the interfacial area, while inertia and viscous forces act to extent and drag the interface downstream.[94] Surface stresses resist break-up and keeps the aqueous phase in a slug structure.

4.4.2. Extraction performance with variation of aqueous phase volume fraction at fixed total flow rate

The aqueous volume fraction is the aqueous flow rate divided by the total flow rate. Extraction performances of the two systems were investigated with variation of aqueous phase volume fraction from 0.1 to 0.9, while keeping the total flow rate constant. For toluene-water-acetone system given in Figure 4.6 total flow rate was kept at 20 ml/min. And for butyl acetate-water-acetone system given in Figure 4.7 total flow rate was kept at 10 ml/min.

It was observed that for toluene-water-acetone system (Fig. 4.6), the extraction efficiency decreases with the increase in the aqueous volume fraction. This is because by increasing the aqueous volume fraction the amount of toluene that can extract acetone from water decreases.

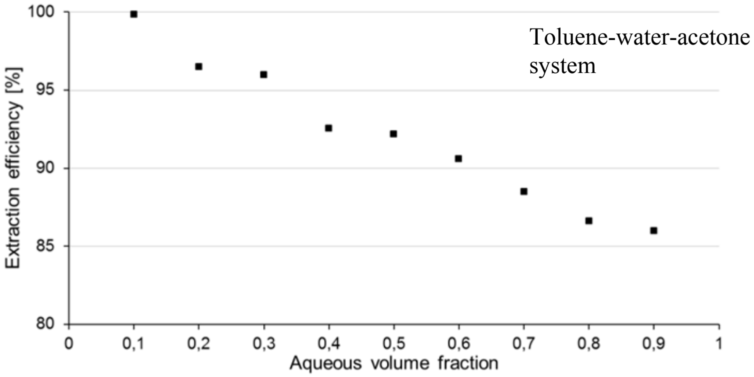

Figure 4.6. Extraction efficiency as a function of the aqueous volume fraction for the toluene-water-acetone system, total flow rate: 20ml/min

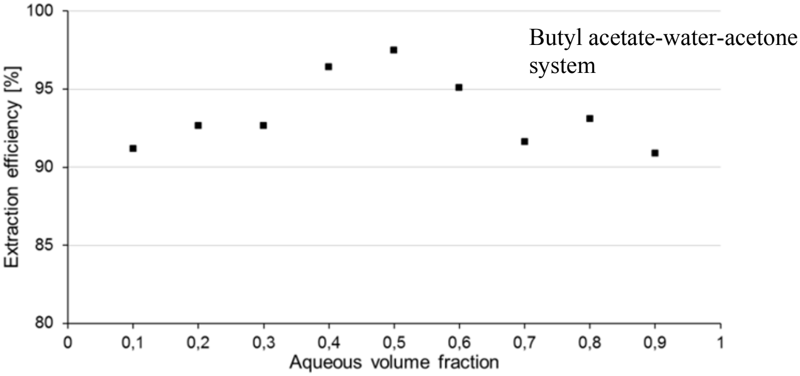

Figure 4.7. Extraction efficiency as a function of the aqueous volume fraction for the butyl acetate-water-acetone system, total flow rate: 10ml/min

For butyl acetate-water-acetone system (Fig. 4.7), it was observed that the aqueous volume fraction has less influence with the extraction efficiency staying at 94 % ± 3. It is observed that the extraction efficiency has a maximum. This is because mass transfer is influenced by internal circulation flow in both water and butyl acetate slugs. With the increase in aqueous volume fraction, the length of water slugs increases therefore mass transfer in these slugs decreases. However, the length of butyl acetate slugs decreases enabling enhanced mass transfer. Due to these opposing effects a maximum is seen. This was also observed by Okubo et al.[57]

4.4.3. Extraction efficiency with variation of flow rate and comparison of CFI with straight tube

The extraction efficiency was studied as a function of the total flow rate with aqueous volume fraction kept at 0.5 so equal flow rate of aqueous and organic streams were fed. In order to evaluate the extraction efficiency achieved using CFI, its performance was compared with a simple straight tube. Experiments were performed by replacing only the CFI part with a straight tube of same diameter and length. The results are presented in Figure 4.8 and 4.9 for toluene-water-acetone system and butyl acetate-water-acetone system, respectively.

For the toluene-water-acetone system, study was done up to a maximum of 120 ml/min (7.2 l/h) which was the maximum limit of the pump. It can be seen from Figure 4.8 for both systems extraction efficiency increases with increase in flow rate up to about 30 ml/min. This is because the intensity of internal circulations within the slugs increases enabling better mass transfer. The difference in extraction efficiency between CFI and straight tube is about 8 % at this part. After that, for the straight tube the extraction efficiency starts to drop. This is due to the decrease in the contact time. For straight tube this effect overshadows the convection through internal circulations. This was also observed by others.[55,90] The difference in extraction efficiency between CFI and straight tube than expands to about 20 %.

As mentioned earlier, secondary flow is generated due to centrifugal forces inside coiled tubes. Dean number is a measure of the magnitude of the secondary flow. It represents the balance between inertial, centrifugal and viscous forces. By rearrangement it is calculated as:

$$De = Re\sqrt{\frac{1}{\lambda}} \tag{4.1}$$

where λ is the curvature ratio described previously and is 10 for this system. CFI exploits this effective utilization of secondary forces to enhance mixing. It also employs multiple flow inversions that create chaotic advection leading to higher radial mixing. The better performance of the CFI results from this. It was observed that even at much higher flow rates high extraction efficiency was maintained. This is because with the increase in flow rate, Reynolds number increases and thus also Dean number increases intensifying secondary flow (Table 4.3 and 4.4).

For the butyl acetate-water-acetone system shown in Figure 4.9, study was done up to 50 ml/min (3 l/h) which was the limit for the flow separator due to lower interfacial tension of this system. Similar observation is made with the previous system.

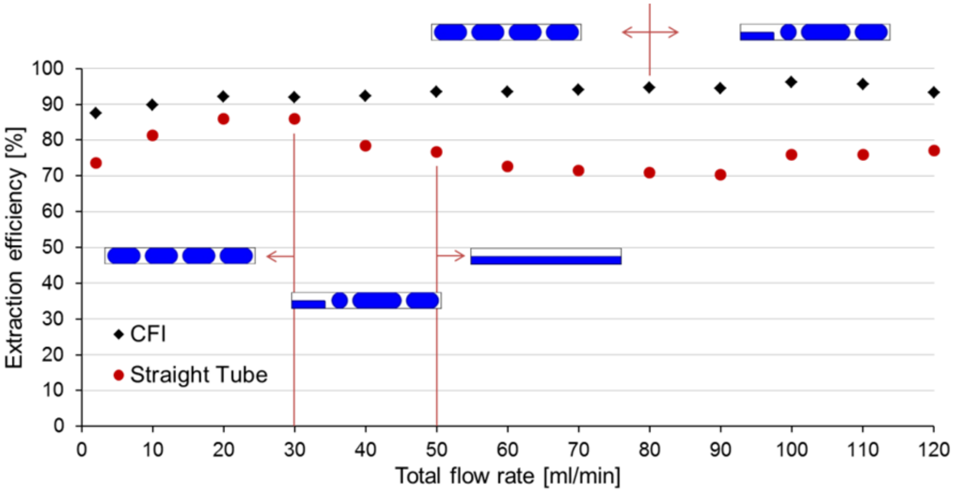

Figure 4.8. Extraction efficiency as a function of the total flow rate comparing CFI with straight tube for the toluene-water-acetone system with schematically drawn flow patterns

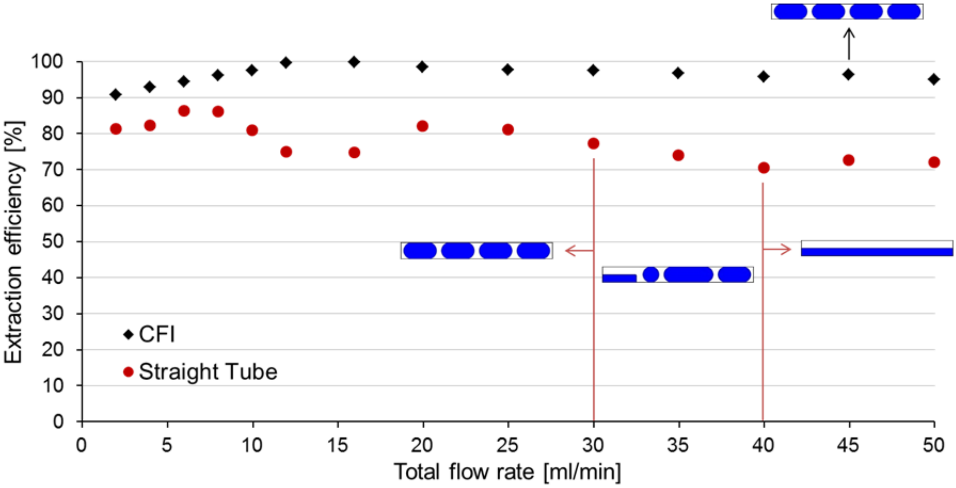

Figure 4.9. Extraction efficiency as a function of the total flow rate comparing CFI with straight tube for the butyl acetate-water-acetone system with schematically drawn flow patterns

For the straight tube systems, the extraction efficiency increases up to about 8 ml/min as seen in Figure 4.9 where the difference with the CFI is on average about 10%. After that its extraction efficiency drops due to decrease in contact time and the difference with CFI increases to about 21% in average. For the CFI, high extraction performance was sustained due to Dean vortices and especially with flow inversions that create chaotic advection.

It was observed for both systems that the extraction efficiency of CFI dropped slightly with the increase in flow rate further signifying a small influence of the decrease in contact time. From Figure 4.8 and 4.9 this drop is not very visible due to the scale of the graphs. Therefore more close up figures are provided in Figures 4.10 and 4.11.

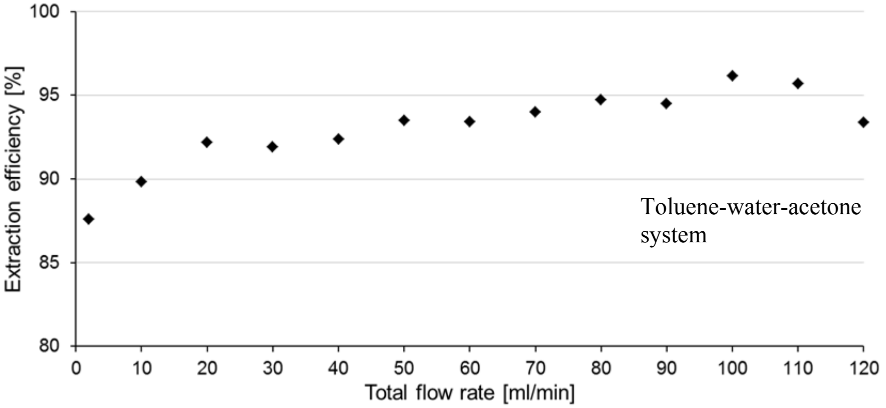

Figure 4.10. Extraction efficiency as a function of the total flow rate for the toluene-water-acetone system

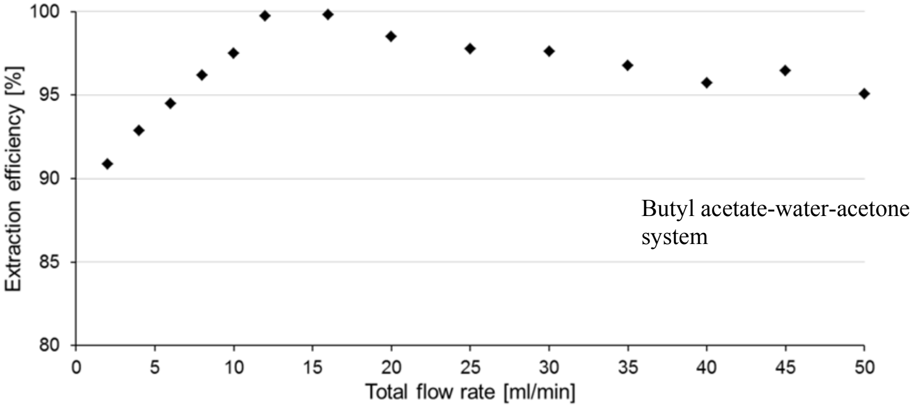

Figure 4.11. Extraction efficiency as a function of the total flow rate for the butyl acetate-water-acetone system

For the toluene-water-acetone system, the extraction efficiency increases steadily up to 96 % at 100 ml/min and then it slightly drops to 93 % at 120 ml/min which was the flow rate limit of the pumps. For the butyl acetate-water-acetone system, the extraction efficiency increases and reaches 100 % and then slightly drops and plateaus at about 96 %.

While carrying out experiments it was observed that although CFI operated in slug flow regime, with the increase in flow rate parallel flow occurred in the straight tube. This change in the flow regime is also shown schematically in Figures 4.8 and 4.9. This is due to viscous and inertia forces having more influence with the increase in the flow rate. To see this, dimensionless numbers are calculated for the two systems considering equilibrium distribution of acetone for determining the physical properties of the aqueous and organic phases. Reynolds (Re), Capillary (Ca) and Weber (We) numbers of the organic and aqueous phases are given in Table 4.3 for toluene-water-acetone system and Table 4.4 for butyl acetate-water-acetone system at the selected flow rates in the range studied for the systems.

Also to show the difference between the CFI and straight tube, and the change with the flow rate Dean (De) number is calculated using Eq. 4.1 and presented in the Tables 4.3 and 4.4. For that, a two phase Reynolds (Re) is calculated which is also given in tables using mixture properties for density and viscosity and considering total flow rate of the system for velocity.

Capillary number shows the ratio of viscous force to interfacial tension force and it is directly proportional to velocity. With the increase in the flow rate and therefore velocity, viscous forces increases and produces parallel flow since they extend and drag the interface downstream. Weber number gives the ratio of inertia force to interfacial tension and it is proportional to square of velocity. Therefore, with the increase in flow rate it increases rapidly and inertia forces become more prominent causing the change in the flow regime to parallel flow in straight tube. This was also observed by others working with straight capillaries.[89,92–94]

Table 4.3. Two-phase Reynolds and Dean numbers together with Reynolds, Capillary and Weber number of the organic and aqueous phases for toluene-water-acetone system

Q_{tot}, ml/min	Re_{TP}	De_{TP}	Re_{org}	Re_{aq}	Ca_{org}	Ca_{aq}	We_{org}	We_{aq}
10	79	25	53	32	3.2×10^{-4}	6.1×10^{-4}	1.7×10^{-2}	2.0×10^{-2}
30	237	75	160	97	9.6×10^{-4}	1.8×10^{-3}	1.5×10^{-1}	1.8×10^{-1}
60	474	150	320	194	1.9×10^{-3}	3.6×10^{-3}	6.1×10^{-1}	7.0×10^{-1}
120	948	300	639	387	3.8×10^{-3}	7.3×10^{-3}	2.4	2.8

Table 4.4. Two-phase Reynolds and Dean numbers together with Reynolds, Capillary and Weber number of the organic and aqueous phases for butyl acetate-water-acetone system

Q_{tot}, ml/min	Re_{TP}	De_{TP}	Re_{org}	Re_{aq}	Ca_{org}	Ca_{aq}	We_{org}	We_{aq}
10	73	23	45	32	8.1×10^{-4}	1.3×10^{-3}	3.6×10^{-2}	4.1×10^{-2}
30	220	70	134	95	2.4×10^{-3}	3.9×10^{-3}	3.2×10^{-1}	3.7×10^{-1}
50	366	116	224	158	4.0×10^{-3}	6.5×10^{-3}	0.9	1.0

For the toluene-water-acetone system, Weber numbers for both phases get above 1 around 80 ml/min. Indeed after around this flow rate we observed that the slug flow became somewhat irregular showing still slugs but not of equal length as depicted in Figure 4.8. However, overall the CFI system continued operation in slug flow regime in the same conditions where the straight tube changed to parallel flow at higher flow rates. This difference is most likely due to the fact that there are secondary flow effect and flow inversions in CFI whereas in straight tube these are not present. In straight tube systems it was seen that slug flow lends itself to stable parallel flow at higher flow rates [94]. In CFI, with the increase in flow rate Dean number increases (Tables 4.3 and 4.4) enabling increase in angular velocity and intensification of vortices. We believe that centrifugal forces and angular velocity present in CFI acts to overcome the downstream dragging effect of stream wise viscous and inertia forces enabling to keep the slug structure.

4.4.4. Performance of flow separators

It is important to achieve separation of the phases immediately following extraction and contacting of the phases. Gravity based separation was employed commonly to achieve this separation. However, this separation is generally slow and adds to the contacting time and affects the extraction performance. Therefore, it is necessary to adapt a separation method that enables immediate separation of the phases. At micro- and milliscale surface tension dominates over gravitational forces. Thus, capillary forces can be used effectively as the driving force for separation of immiscible liquids. There are generally two methods used for this: wettability based separation and membrane based separation. In this study, we use example units of both types.

The wettability based separator of slit shaped flow separator developed by Gaakeer et al.[60] has Teflon and glass bars with rectangular channels. The hydraulic pressure drop at each side of the separator can be calculated using Hagen-Poiseuille equation for pressure drop:

$$\Delta P_h = \frac{12\mu L Q}{W H^3} \tag{4.2}$$

where μ is the viscosity, Q is the volumetric flow rate of the phase through that outlet, L, W and H are length, width and height of the slit which are 5 mm, 10 mm and 0.4 mm respectively. Viscosities of both phases are calculated based on the distribution at thermodynamic equilibrium of acetone at equal flow rate of the organic and aqueous feeds.

To enable proper operation of the separator, capillary pressure ΔP_c must be higher than the pressure difference across the interface. The ΔP_c for the slit shaped separator can be predicted using the Young-Laplace equation:

$$\Delta P_c = \gamma \left(\frac{2}{H} + \frac{2}{W} \right) \tag{4.3}$$

Where γ is the interfacial tension. Gaakeer et al.[60] indicated that the capillary pressure must be at least twice the hydraulic pressure in the opposite slit to prevent breakthrough. Hydraulic pressure in the Teflon slit, hydraulic pressure in the glass slit and capillary pressure with respect to flow rate is given in Figure 4.12 together with half of capillary pressure as an indicative threshold for breakthrough for the two systems studied.

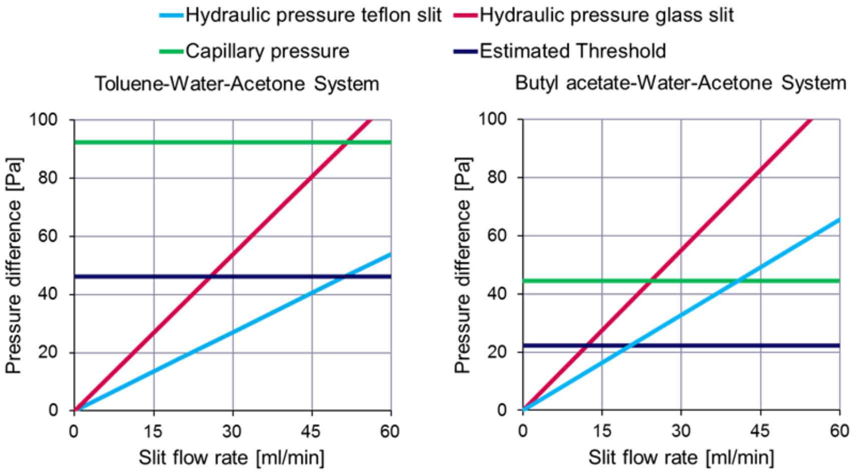

Figure 4.12. Hydraulic and capillary pressure with respect to flow rate for slit shaped separator with slit height of 0.4 mm

When the hydraulic pressure of water in the glass slit exceeds the capillary pressure threshold it is expected to observe water breakthrough at the Teflon slit. In a similar way, when the hydraulic pressure of organic in the Teflon slit exceeds the capillary pressure threshold it is expected to observe organic breakthrough at the glass slit. It can be expected from Figure 4.12 that water breakthrough at the Teflon slit will occur at a lower flow rate than organic breakthrough at the glass slit. Also, it can be seen that for the lower interfacial tension system of butyl acetate-water-acetone the breakthrough at both sides occur at a lower flow rate that the other system. For this reason good separation performance can be maintained at much lower flow rates that the toluene-water-acetone system.

The membrane based separator was developed by IMM and it houses a PTFE membrane with a pore size of 0.5 µm and dimensions of 44 mm x 14 mm. For membrane based separators to function properly there are two conditions. First is to prevent the aqueous phase to cross the membrane and exit with the permeate phase which is the organic phase. For this, the pressure difference across the membrane should be less than the capillary pressure, ΔP_c. This breakthrough pressure can be estimated with Young-Laplace equation where membrane pores are taken to be an array of cylinders:

$$\Delta P_c = \frac{2\gamma}{R} cos\theta \tag{4.4}$$

The second condition is that the pressure drop at the retentate (aqueous) side of the membrane should be above the sum of pressure drop at the permeate (organic) side of the membrane and the pressure difference across membrane for the desired flow rate (ΔP_m) which can be approximated using Hagen-Poiseuille equation as:

$$\Delta P_m = \frac{8\mu LQ}{n\pi R^4} \tag{4.5}$$

where μ is the viscosity of organic phase, L is the membrane thickness, Q is the flow rate of organic phase, n is the number of pores and R is the pore size. This is the pressure difference required to enable all the organic phase to flow through the membrane.

4.4.4.1. Toluene-water-acetone system

From Figure 4.12, it can be expected that, for the toluene-water-acetone system, the hydraulic pressure of water in the glass slit will exceed the capillary pressure threshold for a flow rate of about 26 ml/min. After this flow rate it is expected to observe water breakthrough at the Teflon slit. The same can be expected for the toluene to breakthrough at the glass slit above about 50 ml/min.

As can be seen from Figure 4.13 left side, the breakthrough of water at the Teflon outlet is observed from about 25 ml/min as expected. For the limit of this study of 120 ml/min it reaches about 20 % breakthrough. The breakthrough of toluene at the glass slit is observed from 32 ml/min but stays below 5 % up to 50 ml/min. Above 50 ml/min it increases up to 20 % at 120 ml/min.

When the membrane separator was used (Figure 4.13, right), it was observed that some of the organic phase was retained in the aqueous phase. This resulted in about 30 % of organic phase to be lost at the aqueous side. This can be because some of the organic phase is entrained in the aqueous phase. It can also be because no differential pressure was applied there was not enough pressure difference to force all the organic to pass through the membrane. The operation was limited to flow rate of 20 ml/min because pumps failed to pump the liquids forward above this flow rate. This could also be because no pressure difference mechanism was applied. Cervera-Padrell et al.[41] employed back pressure regulator in the aqueous outlet to generate high fluidic resistance but below the capillary pressure to achieve perfect separation. Castell et al.[59] created pressure difference between the two outlets by connecting the aqueous outlet to a sealed vessel where its outlet pressure is modulated. In this study, initial attempts were made to improve the operation by generating pressure difference by changing the length and diameter of the outlet tubes at each side and by using back pressure regulators. But the presence of many factors studied in this chapter: different systems with different interfacial tension, different flow rates and different aqueous volume fractions, it was found cumbersome to employ a different element to create the required pressure difference for each condition. Development of a separator with an integrated pressure controller like the device of Adamo et al.[58] that can handle the high flow rate required in this study could be the solution to this problem. However, this was found outside the scope for this study. Nevertheless, with the membrane separator at permeate side always pure organic phase was attained (Figure 4.13, right bottom) meaning the PTFE membrane did its job successfully to only let the organic phase to pass through. This shows that capillary pressure is not exceeded since breakthrough of the aqueous phase is not taking place at the flow range studied. If it is required to have pure organic phase, than membrane has similar performance with the slit separator which has pure organic phase until 26 ml/min but there is significant loss of some organic phase at the aqueous side which could be overcome using an integrated pressure control system.

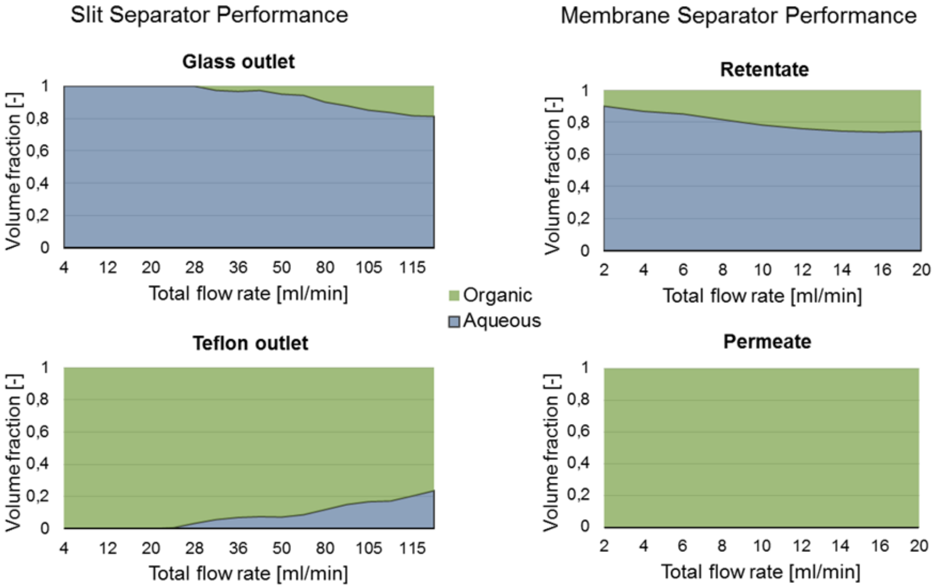

Figure 4.13. Separator performance as a function of total flow rate for the toluene-water-acetone system – volume fraction of organic phase and aqueous phase in two outlets, left slit shaped separator: top glass outlet and bottom Teflon outlet, right membrane separator: top retentate outlet and bottom permeate outlet

The variation of aqueous volume fraction on the separation performance was also investigated. The result for the toluene-water-acetone system is given in Figure 4.14. When the slit shaped separator was used (Fig. 4.14, left), by increasing the aqueous flow rate hydraulic pressure in the glass slit increases. Accordingly at aqueous volume fractions above 0.6, water breakthrough in the Teflon slit was observed. This is also due to the fact that while the aqueous flow rate increases, organic flow rate decreases. When there is significant difference in the flow rates the inertial flow forces overcome the wetting forces and the high flow rate liquid of aqueous exits from the low flow rate liquid of organic's side. This was also observed by Kashid et al.[55] When membrane separator was used (Fig. 4.14, right), no breakthrough of the aqueous phase through the membrane occurred. However, at low aqueous volume fraction when the organic flow rate is much higher than the aqueous flow rate, it is observed that there is high amount of organic at the retentate side. This is because of the low amount of fluidic resistance at the aqueous side at the low flow rate; the organic phase with high flow rate can also exit from this side. With the increase in the aqueous volume fraction this is seen to decrease. If pure organic phase is required at high aqueous volume fractions membrane separator could be preferred.

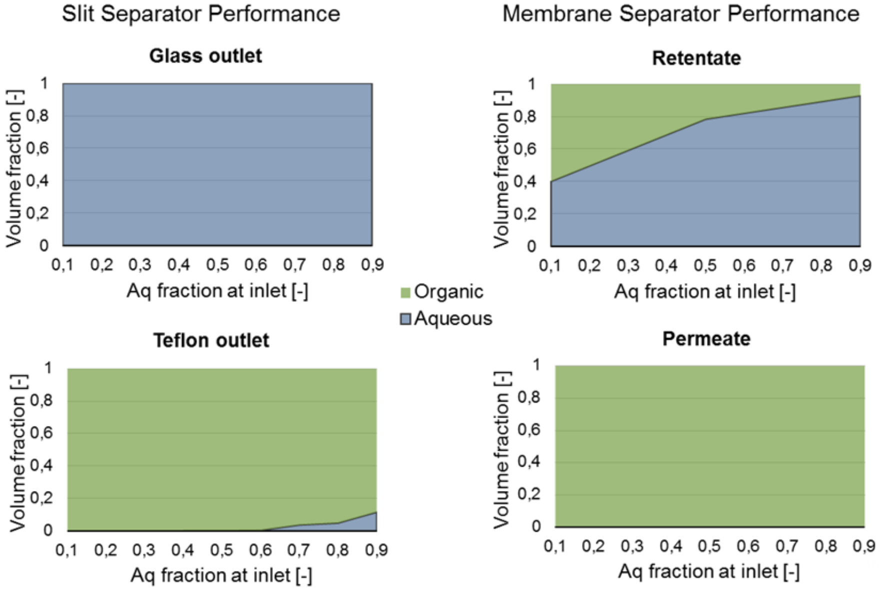

Figure 4.14. Separator performance as a function of aqueous volume fraction for the toluene-water-acetone system – volume fraction of organic phase and aqueous phase in two outlets, left slit shaped separator: top glass outlet and bottom Teflon outlet at total flow rate: 20 ml/min, right membrane separator: top retentate outlet and bottom permeate outlet at total flow rate: 10 ml/min.

4.4.4.2. Butyl acetate-water-acetone system

The interfacial tension has a major influence on the operation of separators using capillary forces. As can be seen from Figure 4.12, the operating window of the separator reduced significantly with the lowering of the interfacial tension from the toluene-water-acetone system to the butyl acetate-water-acetone system. It was also observed by Kralj et al.[54] that by lowering the interfacial tension the maximum operating flow rate decreases significantly.

From Figure 4.12, it is seen that the hydraulic pressure of water in the glass slit will exceed the capillary pressure threshold for a flow rate of about 12 ml/min. After this flow rate it is expected to observe water breakthrough at the Teflon slit. The same can be expected for the toluene to breakthrough at the glass slit above about 20 ml/min. From experiments it was observed that (Figure 4.15, left) at both outlets breakthrough occurred above about 16 ml/min and increased rapidly up to 40 % at 50 ml/min. The experiments were stopped at this flow rate due to high breakthrough. Breakthrough of 20 % occurred at about 32 ml/min which is much lower than 120 ml/min attained for the toluene-water-acetone system indicating the influence of the interfacial tension.

When the membrane separator was used (Figure 4.15, right), similar observation with the toluene-water-acetone was made. It was seen that some of the organic phase was retained in the aqueous phase resulting about 40 % of organic to be lost at the aqueous side. At the permeate side pure organic phase was attained throughout. If it is required to have pure organic phase, than membrane has slightly better performance than the slit separator which has pure organic phase until 16 ml/min but there is significant loss of some organic phase at the aqueous side which could be overcome using an integrated pressure control system.

The result for the butyl acetate-water-acetone system with variation of aqueous volume fraction with the total flow rate fixed at 10 ml/min is given in Figure 4.16. When the slit shaped separator was used (Fig. 4.16, left), similar observation with the toluene-water-acetone system is made but here the effect is seen to be larger. This is because the capillary pressure is lower for this system due to lower interfacial tension system. At aqueous volume fractions above 0.5, water breakthrough in the Teflon slit was observed and it increased up to 20% where maximum 10% breakthrough was observed in the first system. When membrane separator was used (Fig. 4.16, right), again no breakthrough of the aqueous phase through the membrane occurred and at retentate side high amount of organic left with the aqueous phase at low aqueous volume fractions as also observed for the toluene-water-acetone system. With the increase in aqueous volume fraction although the percent loss of organic at the aqueous side is almost the same, the amount that is lost decreases with the decrease in the total organic feed. Since also the aqueous amount increases this results in the decrease in the organic percentage at the retentate side seen in Fig. 4.16, right.

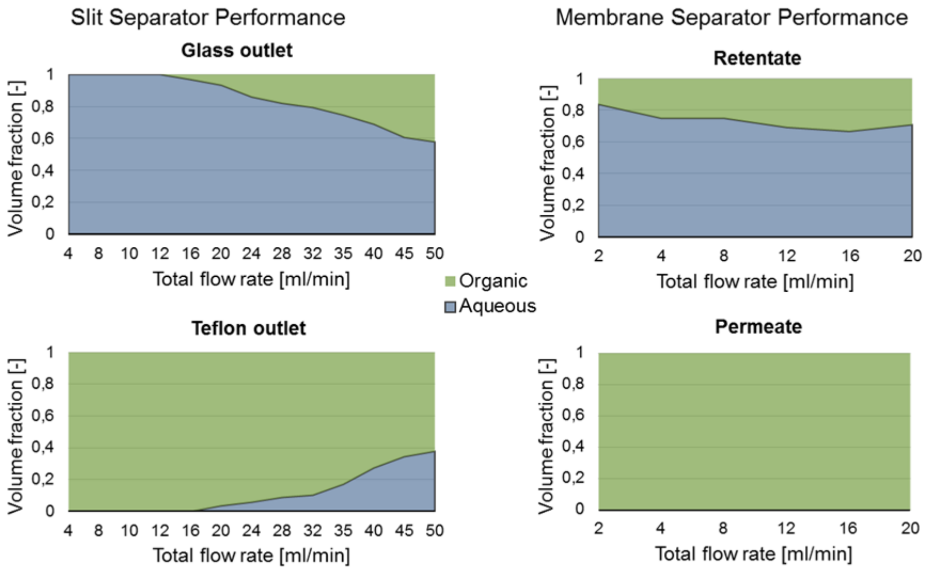

Figure 4.15. Separator performance as a function of total flow rate for the butyl acetate-water-acetone system – volume fraction of organic phase and aqueous phase in two outlets, left slit shaped separator: top glass outlet and bottom Teflon outlet, right membrane separator: top retentate outlet and bottom permeate outlet

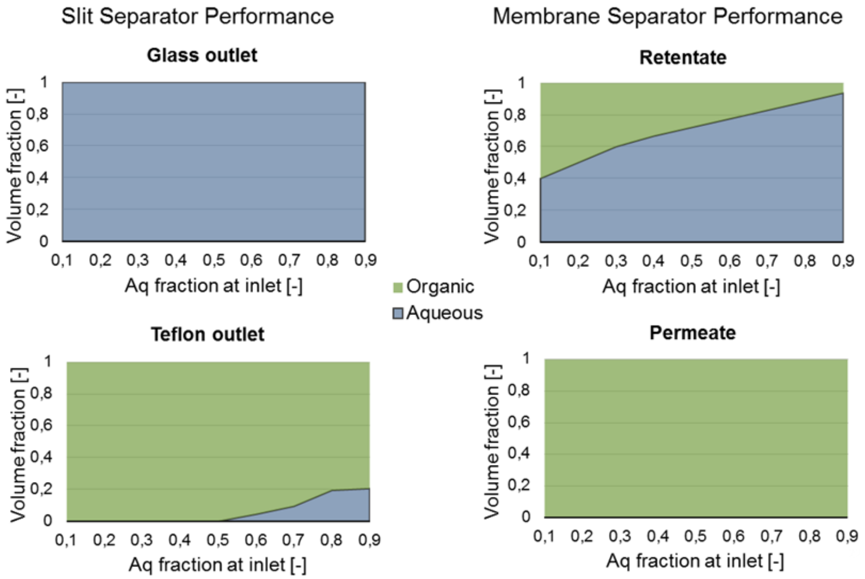

Figure 4.16. Separator performance as a function of aqueous volume fraction for the butyl acetate-water-acetone system – volume fraction of organic phase and aqueous phase in two outlets, left slit shaped separator: top glass outlet and bottom Teflon outlet, right membrane separator: top retentate outlet and bottom permeate outlet, total flow rate: 10 ml/min

4.5. Conclusion

In this chapter a liquid-liquid extraction setup developed using milli-scale CFI (3.2 mm ID, 210 cm length) and phase separator was described. The extraction performance of the setup was tested for the two widely used and EFCE recommended model systems of toluene-water-acetone and n-butyl acetate-water-acetone. We report for the first, to best of our knowledge, the application of CFI for immiscible liquid-liquid mixing. Also, the study of flow separators that can handle flow rates suitable for industrial scale continuous pharmaceutical production is very rare and this was successfully achieved here. For the toluene-water-acetone a flow rate up to 120 ml/min was studied which corresponds to 7.2 l/h and 58 m3/y. It is important to point out that the slug flow regime that is limited to microfluidic systems is maintained even at such pilot scale. The literature review on slug flow reveals that this is the highest flow rate achieved so far. There are several microreactors developed that enables contacting of liquid phases at high flow rate. However, there is very limited number of examples that achieve the phase separation part of liquid-liquid extraction at these flow rates. Most of these examples involve the use of settlers where phase separation is achieved using macro force of gravity and it is slow. In this study, after contacting of the phases the phase separation is achieved immediately using micro effect of capillary force at high throughput. Two separator concepts utilizing capillary forces were investigated that are PTFE membrane separator and slit shaped separator composed of glass and Teflon outlets enabling separation based on wettability.

Flow pattern of two-phase toluene-water and butyl acetate-water systems characterized with high-speed photographic system revealed the dependence of the slug length depends on the ratio of organic and aqueous flow rates. The dimensionless numbers calculated in the frame of 10 ml/min organic flow rate by 10 ml/min aqueous flow rate confirm the presence of slug flow regime with the interfacial tension dominating over inertia and viscous forces. Extraction performances with variation of aqueous volume fraction at constant total flow rate and with variation of total flow rate at equal volume fraction were investigated. For both systems close to thermodynamic extraction efficiency was achieved (96% for first, 100% for second). The extraction efficiency of the setup was compared with a straight tube setup. Straight tube efficiency was seen to drop at higher flow rates due to mass transfer limitation with the reduced contact time. For CFI it was observed that even at much higher flow rates high extraction efficiency was maintained due to intensified secondary flow and flow inversions achieved. The difference in extraction efficiency between CFI and straight tube was seen to be about 20 % at higher flow rates. It was observed that although CFI operated in slug flow regime throughout, parallel flow occurred in the straight tube with the increase in flow rate due to viscous and inertia forces becoming more prominent. It is believed that the centrifugal forces and angular velocity present in CFI acts to overcome these stream wise forces.

Lastly, the performances of the two separators were evaluated. Slit shaped flow separator performed well with the breakthrough occurring at flow rate expected where hydraulic pressure exceeds the capillary pressure threshold. Breakthrough of 20 % occurred at about 120 ml/min for the toluene-water-acetone system whereas it was observed at 32 ml/min for the butyl acetate-water-acetone system indicating the influence of the interfacial tension on the operating window of the separators. With the variation of the aqueous volume fraction it was observed that at high aqueous volume fraction water breakthrough in the Teflon outlet occurs due to increase in hydraulic pressure of the water in the glass slit. The membrane separator flow rate was limited to 20 ml/min. It was seen that some of the organic phase was retained in the aqueous phase while at the permeate side pure organic phase was attained throughout. If pure organic phase is required, then the two separators performed similarly with the slit shaped separator enabling pure organic phase until 26 ml/min for toluene-water-acetone system and 16 ml/min for butyl acetate-water-acetone system. However, there is significant loss of organic phase at the aqueous side which could be overcome by a separator with an integrated pressure controller. With the variation of the aqueous volume fraction it was observed that no breakthrough of the aqueous phase through the membrane occurred but at retentate side at low aqueous volume fractions high amount of organic left at the retentate side due to low amount of fluidic resistance at this side with the low flow rate of aqueous phase. With increase in the aqueous volume fraction this was seen to be reduced due to decrease in the flow rate of the organic phase.

Acknowledgements

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4.6. Appendix

4.6.1. General chemicals information

Chemicals were purchased in their highest purity available from Sigma Aldrich. Methylene blue stock solution was made by dissolving 0.498 gram methylene blue in 100 ml demineralized water (purified with a Millipore Elix UV-5 machine) resulting in 0.016 M solution. Acetone solutions were made by dissolving 24.32 gram acetone in a 250 ml volumetric flask with demineralized water.

4.6.2. General analytical information

Quantitative analysis of the acetone transferred to organic phase was done using GC-FID on a Varian 430-GC with a flame ionization detector using a CP-Sil 8 CB column (length 60 m, diameter 0.25 mm, film thickness 0.1 μm), with helium as the carrier gas. Sample from organic outlet was taken and analyzed for amount of solute. External calibration was performed by making solutions of varying concentrations 0, 2, 4, 6, 8, and 10 wt. % of acetone in butyl acetate. For toluene system calibration was performed with concentrations of 0, 1, 3.5, 5.5, 6.5, 10 and 13.7 wt. % of acetone. (Appendix 4.6.7)

4.6.3. Investigation of liquid-liquid two-phase flow patterns

To study the flow patterns observed high speed imaging system was used. For this visualization experiments acetone was not used. The aqueous phase of water was colored with the methylene blue solution by adding 0.5 ml of the prepared solution to 250 ml of demineralized water. Syringes were filled with the pure liquid phases and placed in separate syringe pumps. The aqueous and organic phases were fed at both equal and unequal flow rate combination in the range of 1-10 ml/min of each phase. As soon as uniform slug flow regime was achieved, flow was recorded by MotionPro X3 high speed camera. The camera was placed at a set distance from the setup to take picture of a straight section of tubing. It was adjusted to capture approximately 3 slugs in an exposure. Two lamps were placed as light source. Several snapshots were taken for each set of flow conditions. Image analysis was done with MotionPro software. Pictures are presented to give an indication of the size of the slugs at that condition. The length of the tube diameter is placed on the pictures as a measure bar to get an estimation of the size and to be able to make comparison of slug lengths with other flow conditions. The absolute lengths of slugs were not calculated.

4.6.4. Determination of extraction efficiency

Experimental procedure

Two 20 ml syringes were willed with 10 wt. % acetone solution and mounted on one syringe pump. One 50 ml syringe was filled with organic feed (either toluene or butyl-acetate) and mounted on to another syringe pump. Experiments were conducted both equal and unequal flow ratios of the phases. To study the effect of flow rate, the flow ratio was kept equal to one and flow rate was increased equally. To study the effect of aqueous volume fraction, aqueous and organic phases were fed at different flow rate combinations with the total flow rate kept equal to 20 ml/min for toluene system and at 10 ml/min for the butyl acetate system. The aqueous volume fraction is defined as the aqueous flow rate divided by the total flow rate. After all the system was filled with uniform slugs, one more residence time was waited before a sample was taken. At least three samples from organic outlet were taken from each set of experiments and analyzed using GC-FID to determine amount of acetone. The mean value was recorded.

Calculation of extraction efficiency

Extraction efficiency is the ratio of the amount of solute transferred to the maximum amount transferable defined by the thermodynamic equilibrium. To calculate extraction efficiency (E) Eq. 4.6 was used:

$$E = \frac{C_{org,out} - C_{org,in}}{C_{org,eq} - C_{org,in}} \times 100 \tag{4.6}$$

where $C_{org,in}$, $C_{org,out}$, and $C_{org,eq}$ are the inlet, outlet and equilibrium concentration of acetone in the organic phase, respectively. The inlet concentration of acetone in the organic phase is zero; all acetone enters with the aqueous phase. The outlet concentration of acetone in the organic phase is determined using GC-FID and the calibration curves as described in the Appendix. The equilibrium concentration was determined with shake flask experiments at different aqueous volume fractions and straight line fitting was done (Appendix 4.6.8). At equal flow rate of the phases (aqueous volume fraction of 0.5) and acetone concentration of 10 wt.% the thermodynamic partition coefficient is given in literature as 0.88 for toluene system and 0.98 for butyl acetate system.[63] The experimentally determined thermodynamic partition coefficients are 0.87 for toluene system and 0.98 for butyl acetate system. This indicates the validity of the experimental method used.

4.6.5. Comparison with straight tube

For comparison of the performance of the CFI with the straight tube, experiments were performed replacing the CFI with a tube of same diameter and length. Due to the long length of the tube required, to be able to fit in the fume hood, the tube was placed as a one large circle. It is assumed that there will be negligible secondary flow effects with such a large coil. The same experimental procedure as CFI setup was followed for determination of extraction efficiency.

4.6.6. Measurement of separator performance

After all the system was filled with uniform slugs and two residence times has passed over the separator, the collector bottles were removed and measuring cylinders of 50 ml were placed at the outlets. This way startup effects were excluded. Visual inspection of the measuring cylinders was done. Since the aqueous phase was colored it was easy to evaluate the separation performance and measure the amount of one phase leaving at the other phase. In case of incomplete separation, volume fraction of the two phases at the two outlets was determined by volumetric measurement.

4.6.7. Calibration curves for GC-FID analysis

To determine the calibration curve for the two systems, known amounts of acetone were dissolved in the organic phase and put into the GC-FID. The area of the acetone peak was then divided by the area of the organic phase peak, this is plotted on the x-axis in Figure 4.17. The acetone concentration is plotted on the y-axis. Appropriate trendlines were fitted to these points using Excel. The goodness of fit of both curves are shown with R^2 and are close or equal to one. This shows that the calibration curves are appropriate to determine the acetone concentration of organic samples from experiments.

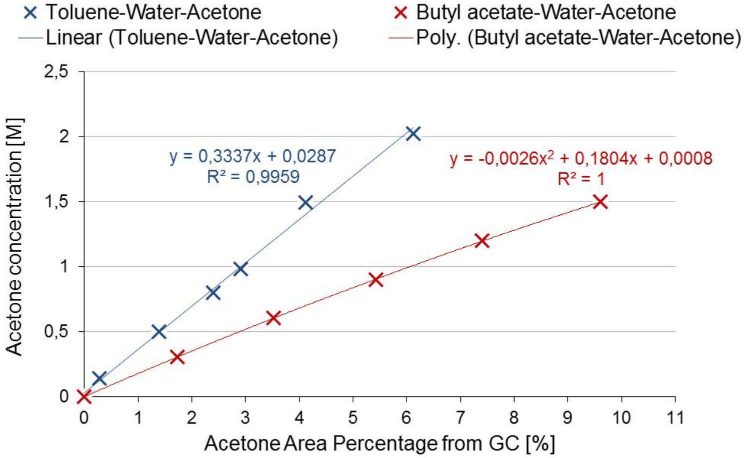

Figure 4.17. Calibration curves for GC-FID

4.6.8. Thermodynamic equilibrium concentration curves

To determine the thermodynamic equilibrium concentration experimentally shake flask method was used. Aqueous phase of 10 wt. % acetone in water was combined with the organic phase at different volumetric fractions of the aqueous phase. After equilibrium was reached sample was taken from the organic phase and analyzed with GC-FID. With the calibration curve explained in the previous section the equilibrium concentration of acetone in the organic phase is determined. This is plotted with respect to the aqueous volume fractions they correspond to. Straight line fitting was done to these points using Excel. The goodness of fit of both curves are shown with R^2 and are close to one. This shows that these curves are appropriate to determine the equilibrium concentration of acetone in organic at different aqueous volume fractions studied.

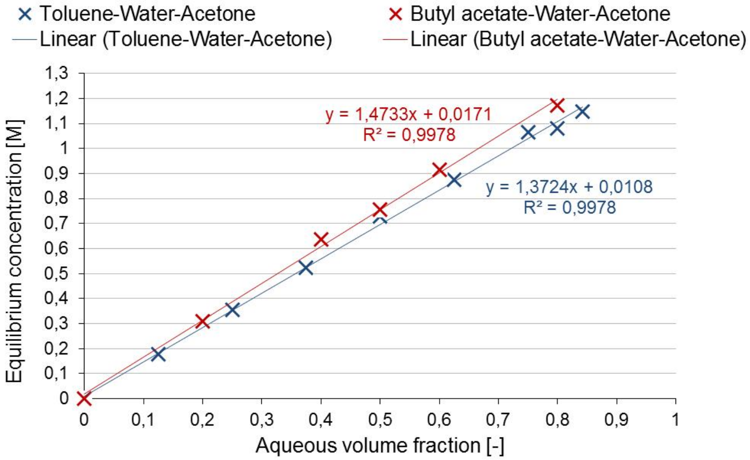

Figure 4.18. Equilibrium concentration curves

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CHAPTER 5

Compact Modular Plants for Fine Chemistry – Modular Process Integration at Pilot Scale

This chapter is based on :

Vural Gursel, I., Hessel, V., Wang, Q., Noël, T. & Lang, J. (2012). Window of opportunity : potential of increase in profitability using modular compact plants and micro-reactor based flow processing. Green Processing and Synthesis, 1(4), 315-336.

Abstract:

Recently much focus has been given to a new type of chemical production plant, with the aim of a much faster time-to-market ("50% idea") and better cash-flow revenue. The main enabling technology is to have the plants pre-manufactured and assembled by a modular construction and to use innovative, smart-scale processing and apparatus technology, in order to achieve a compact overall plant footprint. Focal points in such technology are on the one hand, flow processing, with micro process technology as a cutting-edge cornerstone, and on the other hand, the container framework. Yet, other process-intensified technologies are suitable as well such as milli-flow or upgraded batch technologies. Finally, process robustness and short-time applicability make the decision. In this chapter, a CAPEX and OPEX analysis of the new plant technology is done, at the example of the Evotrainer production platform (meanwhile renamed as the EcoTrainer). This platform is pre-manufactured in serial and provides all the utilities needed around the reactor and e.g. separator to be tailored and inserted. Since the fine-chemical application comprises the envisaged target market of the Evotrainer infrastructure and also since for this application all relevant data were at hand, the cost analysis investigations started with and were

centered around this chemical process. The same procedure was applied as model-based scenarios for market applications in bulk chemistry and pharmacy for comparison. It is shown, in many facets, that the Evotrainer infrastructure based plants indeed have a faster payback and higher earning as compared to conventional technology; particularly when serving high-priced markets. Further, the combination with novel chemical routes or novel processing (Novel Process Windows) is advantageous. Micro process technology is one of the key enablers and was taken here, since the dataset of such technology was readily available to due to past research efforts and there is some general belief in the combination to the so-called "Future Factories". Yet, it stands also for any other process intensification technology which can achieve the same performance level and which is able to satisfy the needs of a producing industry.

5.1. Introduction

5.1.1. Need for faster market and product launch – "window of opportunity"

Europe's chemical industry is under pressure in view of new emerging markets and production capabilities in Asia and the Near East.[1] Lower costs of production, lower taxes, different approval, environmental and safety procedures, and increasingly skilled personnel in Asia allow the chemical industry to grow at a high rate and to increase the global high market share.[2] To improve competitiveness of the chemical industry in Europe and worldwide, new innovative production and plant technologies are needed. Besides, markets are continuously diversifying, as products are increasingly designed for special customer needs.[3] New products have to be developed in even shorter time periods and thus the time to market has to be shortened correspondingly.[4] The current plant concepts used in the chemical industry cannot necessarily satisfy all of these market conditions to the full extent anymore.

To reduce risk over the whole time line from the product idea to the product launch requires a reduction in the capital investment.[5] A critical issue is the numerical ramp up scenario of the product quantity sold. Firstly, intelligent handmade experiments in the lab help to reduce the technical risk of product development and an early-bird provision of test samples helps to make a timely contract with the future customer. Especially in volatile markets, it is highly important to enter at the right time in the "window of opportunity" which is facilitated when engineering is done at an early stage. A window of opportunity denotes a short period of time during which an opportunity must be acted on or missed. This established term in medicine and social sciences, is increasingly used also in the economy for volatile markets, to describe the right time to approach a customer. It may be too early, e.g., if the manufacturing of the product with the targeted high quality and functionality cannot be proven (documented probes on a pilot/production level) or if adherence to a production schedule is not secured. It may be too late when the competitor is already on the market, the client is in contracts with other parties, and product prices decline.[6,7]

5.1.2. Current chemical plant concepts

Bulk chemical industry builds high capacity plants as a consequence of economies of scale. They are optimized for the efficient production of a single product.[8] The plant is built from individually designed equipment in a customized way. Because of their size and the degree of optimization required, design and engineering takes a long time and costs are higher.[9] Also, procurement of the equipment and construction of the plant is lengthy and expensive.[10] These all lead to a long time-to-market. Fine chemical production is carried out batch-wise in multi-purpose plants and is flexible regarding production rate and different products produced.[8] Yet, it is nonetheless inefficient in terms of energy and raw material consumption, as the equipment is not optimized for the requirements of the products and recycling and heat recovery is hard to implement.[11]

When the demand for customized, high-value products in low annual capacities increases and a much shorter market entry is required, these existing plant concepts are not necessarily optimal anymore.

5.1.3. Modular plants, compact and pre-manufactured

Modular compact plants, being partly or fully preconfigured in their modules, parts and interfaces, constitute an innovative approach to address this situation.[12] They are seen as main enablers to cut in half the time it takes to get through the development process from the product idea to the final production process. This was discussed at the 48th Tutzing-Symposium “Die 50%-Idee – Vom Produkt zur Produktionsanlage in der halben Zeit” (translated: The 50% idea – from product to production facility in half the time).[4,13] With having entirely new concepts and apparatus at hand (process intensification), investigations of the advantages of modular design and its economic potential, have gained new momentum and intensified recently. Bramsiepe and Schembecker[12] pointed out the advantage of modular process design in terms of planning process that enables laboratory to production with small effort. Hady and Wozny[14] presented a modular concept with the aim of showing engineering and equipment reuse, creating saving in terms of knowhow and cost. Brodhagen et al.[15] showed that with a shorter time-to-market achieved, modularization is more economical than conventional batch technology. Rottke et al.[16] described an approach to configure plant design using modules, making it easier to determine the cost of different layouts.

Standardization through pre-manufactured modules assembled into highly functional plant environment facilitates a desired lead time reduction to respond to market changes in an efficient manner. It was pointed out by Bramsiepe et al.[9] that with a modular plant concept, elimination of specialized field installation and customized design is possible by standardization, leading to savings in construction and design time and expenditure. Through the reduction of the planning and construction period, the Net Present Value (NPV) of a modular plant was 30 % higher compared to multiproduct batch plant.[11] For the calculation of the capital investment for a modular plant, Shah[17] suggested that the factors which are used to estimate based on total equipment cost should be reduced, but the degree of reduction was not specified.

Evonik Industries have developed a modular, mobile, compact platform that supports an individual chemical process with a highly functionalized infrastructure – the Evotrainer (meanwhile renamed as the EcoTrainer, see Figure 5.1).[18,19] It triggers a far fetching modular plant approach, with a holistic view comprising far beyond the reaction parts. The concept orients particularly on the manufacture of specialty products with tonnage, which are at present typically made as campaign products in conventional multi-product plants.[20] It can be upgraded to a production plant of a capacity of some 100 tons per year. It takes into account the whole process development to make easier the conversion from lab to production by including raw material and product logistics, separation parts, utilities, process control and environmental and safety measures.[21]

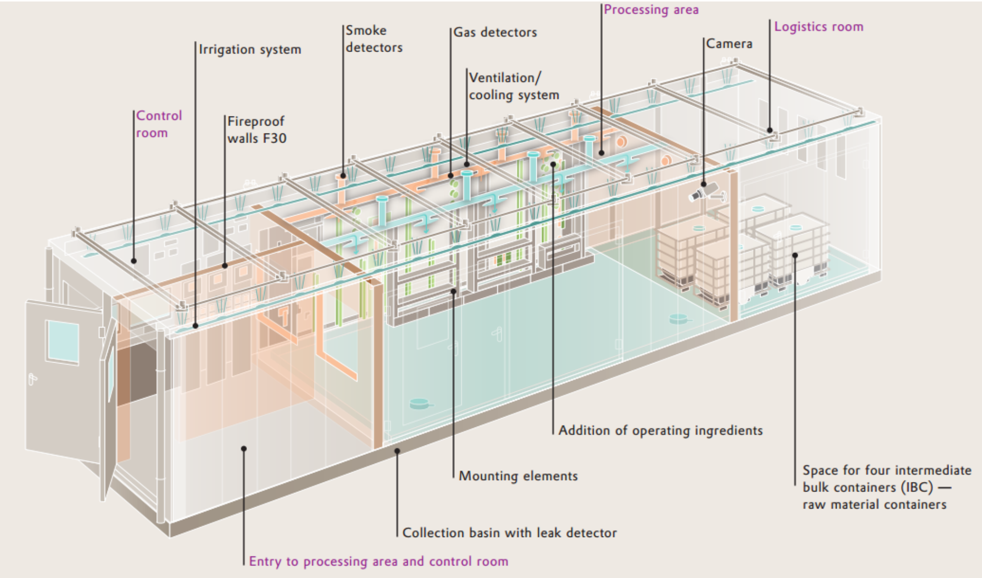


Figure 5.1. The EcoTrainer of Evonik Industries[19]

Standardized infrastructure, utility and process control supports the standardization of modules.[9] The compatibility of the modules offers the opportunity to rearrange the same design to meet the needs of different processes. Design and engineering time is reduced significantly through pre-manufactured modules. Standardization reduces the need for customized equipment, piping and structural design.[17] Thus, efforts for detailed equipment design will be reduced, as well as detailed piping and instrumentation design. The engineering job can be focused to find the optimal configuration of modules for the specific process.[11] Since the engineering task is significantly easier, there is faster transfer from lab to production.

Modular plants are efficient in terms of construction and mounting. Construction time can be significantly reduced by the opportunity of preassembling modules in a workshop where tools and machinery to build will be already available. With the use of modular components it is possible to minimize additional field installation. The different modules will only be plugged together on the production site. Accordingly, the costs for scaffolding, construction tools and rentals and personnel located at the construction site can be minimized. A further advantage of the concept is that construction will not be affected by the weather conditions. Expensive site inspections can be omitted, as testing can be partly done on the preassembled plant in the workshop.[9] The sum of these benefits helps to reduce the investment cost and time-to-market.

Additional benefits can be gained in terms of operating costs as well. Due to modularity, only the interaction between the modules needs to be managed, which lowers the labor requirement. Accordingly, the cost of operating labor and its supervision will be reduced. Also, owing to standardization, the maintenance of modules will be easier and no requirement for special parts makes it less costly.

5.1.3.1. Project workflow compression by modular plants

To be able to bring a new product to market faster than other products produces an opportunity to seize high margins in the early phase of a product launch. Because of the capacity of money to earn further money, the financial gain earned earlier is worth more than the same amount earned later.[22]

In Figure 5.2 the difference between classical project workflow is shown in comparison to the proposed workflow based on modular plants. In a classical project work flow after initial selection of the process to be used, the process flow diagram is prepared. The flowsheet shows the arrangement of the equipment selected, operating conditions and stream flow rates and compositions.[23] The flowsheet is formed by the material and energy balance calculations which are carried out using process simulation. It is used as a basis for the design of instrumentation and control, equipment and piping and structure. Piping and instrument diagrams are made and equipment specification sheets are prepared via detailed design. Using these sheets, the procurement of equipment and materials is done.

The field construction and equipment installation is done and after field inspection and testing, the plant is started up. The workflow based on modular components deviates considerably from classical project workflow. Some major steps are eliminated or extremely simplified. From the process selection, different configurations of the modules are considered and a modular assembly plan is made.[17] With the use of process simulation software, different modular processes are compared and optimal configuration is identified.[11] Then, the step from process flow diagram to final piping and instrument diagram is prepared with minimum effort, due to standard information regarding each module. The modules are constructed in workshops and field installation includes only plugging the modules together.[9] Since the checks of the plant are made before delivery, after installation on site it can be started up. These differences in workflows indicate the saving in engineering and construction time and corresponding cost reduction.

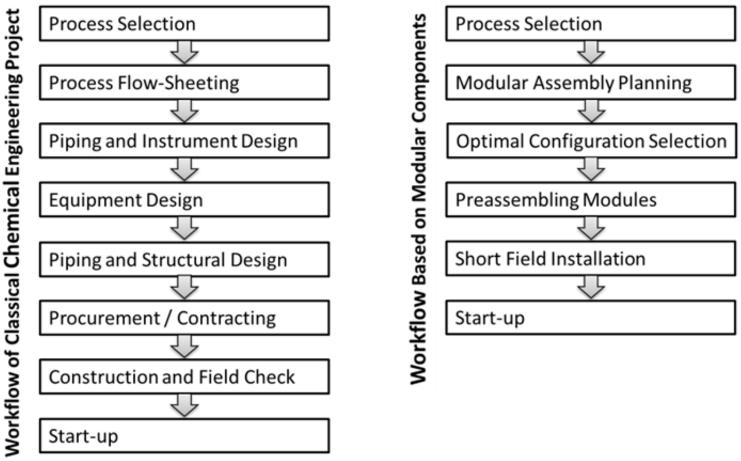


Figure 5.2. Project workflow – Classical workflow vs. workflow based on modular components. It is assumed that the modular components are "off-the-shelf" or benefit from serial manufacture of the modular plant. Otherwise, there would also be work steps as process flow sheeting etc. similar to classical project description.

Figure 5.2 naturally presents a generic, yet ideal picture. Real-case engineering can be more complex and need to take into account additional time-consuming engineering activities to comply with company or governmental specific regulations. It has to be further considered that the modular project is re-using equipment from earlier projects, for which equipment and process and instrumentation diagram (P&ID) design is required, as well as procurement. Thus, an ultimate comparison needs to mirror a first-time built classical project with a modular project where a large part of initial engineering has already been done.

5.1.4. Micro process technology

5.1.4.1. Cost saving potential

Micro process technology provides a potential for improvements to chemical processes regarding economic sustainability. An economic advantage principally can occur from a reduction in capital expenditure (CAPEX) through lower investment and from a reduction in operating costs (OPEX) by introducing this technology. Merck Company together with the Technical University Clausthal presented a four staged potential analysis for the microreaction technology as theoretical, technical, material and economical potential.[24] Cost saving from using a microreactor was discussed for the example reaction of nitration to 3-methyl-4-amido-5-nitro benzoic acid. Roberge et al.[25] presented a cost analysis of continuous vs. batch production for large scale pharmaceutical production. For a large-scale unit, the CAPEX for a microreactor system can be as high as, or even higher than that of the batch process. Regarding OPEX, the raw material costs account for 30–80 %. Higher product yield and quality attained represents the main cost saving potential for microreactors. This also has a direct influence on labor and waste treatment costs.

Krtschil et al. and Azurchem Company made an economic evaluation of the 4-cyanophenylboronic acid formation process.[26] Besides the assessment of the existing microchemical process, capacity increase case scenarios were described. Five- and 10-fold increases in capacity were considered. The plant size per given production rate can be decreased with the order-of-magnitude change in productivity, enabling a reduction of the overall costs to 25 % of the investigated microchemical process with the 10-fold capacity increase.[26] It was also noted that the equipment cost having a low share should have a minor impact on the decision to go for the novel technology.

Hessel et al.[27] performed a cost analysis for the Kolbe-Schmitt synthesis of 2,4-dihydroxy benzoic acid. The base case considered is microreactor production at 4.4 tons/year, and the final product cost is calculated as approximately 91 €/kg (based on a reaction time of about 4 s). A microreactor production under the same conditions and with the same productivity, but being operated at a reaction time of 2 h under reflux conditions, would run into a final product cost of approximately 17,350 €/kg, which is fully out of economic range. For a similar throughput, the operating cost for a 20 L batch-reactor is approximately 107 €/kg. This economy of scale can be seen in relation: a 1 L batch, which matches roughly the space requirements of the microreactor, including tubings (same scale of equipment), accounts to a product cost of approximately 985 €/kg. This one order of magnitude increase in product costs also reflects the economy of scale of chemical industry – in negative manner. For the microstructured reactor with a 10-fold throughput, the operating cost is reduced to approximately 57 €/kg which reflects the economy of numbering up of flow chemistry.[27,28]

5.1.4.2. Plant embedment

It is an aim of this chapter to analyze for the first time the combined benefits of process intensification enabled by smart-scaled process-intensified reaction equipment and of modular compact plants. The first can be upgraded and integrated batch technology or, following a prime industrial trend[29], continuous processing, favorably with small-scale flow equipment, which may be milli-reactors or, when needed, microstructured reactors. This chapter focuses in a methodological way on (virtual) microreactor applications; yet they stand for the use of any similar high-performing reactor technology, and finally, the most robust will be chosen if the performance is similar. The innovative microstructured reactors have so far been implemented in a more conventional plant environment and tailored to the needs of these reactors and process intensification. Thus, so far, it remains unclear which potential dedicated process control, utility, and safety systems may add. Here, it is aimed at a financial answer; the processing advantages need to be determined experimentally through demonstration projects.

5.1.5. Cash flow analysis for chemical plants

The NPV is a central tool in discounted cash flow analysis and is a standard method for using the time value of money to appraise long-term projects.[30] It is used to find the sum of future cash flows discounted back to its present value. Thus, the NPV is sensitive to the discount rate used. The discount rate is the minimum acceptable return that must be achieved by an investment.[30] It is adjusted to compensate for the degree of risk in an investment with the rate increasing with the risk level. Since the modular plant concept lowers the risk in process development, this allows lower discount rates, which depends on risk. This in turn enables a higher NPV to be achieved.

Modular compact plants can be quickly built and applied at any location with approval for chemical manufacture and needed installations, facilities, and piping to take advantage of economical potentials. Producing directly at a customer's site can be attractive regarding adapting the product to varying requirements quickly; also if the product is hazardous to transport.[11] Depending on the process, if raw material consumption is high, production close to the source can be advantageous in terms of transportation costs and availability of resources. Another argument for distributive manufacturing is if the process has high energy demands and is moved to a site where energy is reliably available at a low price. Production in close proximity to an existing plant might also determine the plant location decision. In such Verbund fashion, compact plants can be used to produce derivatives from the product or upgrade a small volume of products.[17] They can also be used for new product production whose market chances are unknown.

A detailed calculation of capital investment and operating cost for a modular plant, to our best knowledge, has not been made so far in open literature quantifying the benefits of modular design. In particular, this has not been done considering the step-change character of process intensification and smart-scale technologies such as microstructured reactors, with the aim of checking if they add to the advantage of modular compact plants.

We would like to express clearly at this point that naturally for a very new technology such as the Evotrainer plant infrastructure, a number of assumptions had to be made. These are listed clearly throughout the text. Wherever possible, in the context of an industrial development, a rationalization of the assumption is made. Clearly those parameters, such as the cost reduction by pre-manufacture or the risk-related lowering of the rent, have a decisive impact on the outcome of the study. These are to be proven by industrial demonstration activities. For all these reasons, we have assigned this study as an investigation towards model-based scenarios (including virtual microreactor applications) making clear that the generic outcome is the main ambition in the sense of a parametric sensitivity and a proof of principle for a new economic model in chemical manufacturing.

5.2. Methodology

5.2.1. Demonstration processes and market applications considered

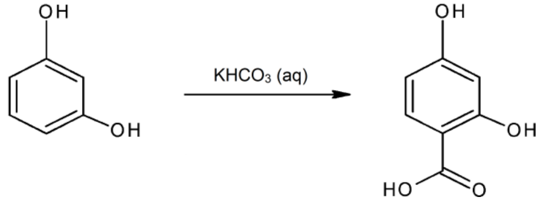
The chemical manufacturing in the compact and premanufactured plant infrastructure was analyzed for three application fields – bulk chemistry, fine chemistry, and pharmacy. These markets have very different production volumes, product prices, added value, plant technologies and more[8], as summarized in Table 5.1. It was clear and expected that the bulk chemical manufacturing in the novel plant infrastructure is economically not efficient. Yet, this case serves as a comparison to complete the picture given here.

Table 5.1. Difference in characteristics of bulk chemicals vs. fine chemicals

Characteristics	Bulk chemical	Fine chemical	Pharmaceutical
Volume (tons/yr)	$10^4 – 10^6$	10^2-10^4	10-10^3
Price ($/kg)	< 10	> 10	> 100
Added value	Low	High	Very high
Processing	Continuous	Batch-wise	Batch-wise
Plants	Dedicated	Multi-purpose	Multi-purpose
Flexibility	Low	High	High
Safety and environmental efforts	Relatively low	High	Relatively high

The fine chemical considered here is 2,4-dihydroxybenzoic acid, which was chosen due to extensive past experience with experimental microreactor work and cost analysis for the respective synthesis, i.e., all relevant cost data (materials, equipment, performance, etc.) were at hand. In the following, the published background is given; cost information is part of the introduction given above. In this study investigations were centered around this fine chemical process. As bulk-chemical, adipic acid manufacturing was considered, for which extended results are at hand. Also, experimental research on the adipic acid synthesis in flow is performed in our group. The pharmaceutical product considered is naproxen, a commercial drug. Reasons for this selection were the general relevance of this product on the pharma market, the fact that patent protection is not given anymore (market prices orient more on function/production rather than on development costs) and, last but not least, that a derivative of this product (naproxcinod) has been made at large scale in flow with microreactors.[31] More details concerning bulk chemistry and pharmacy application are given in results section.

2,4-Dihydroxybenzoic acid is used as an intermediate in the manufacture of dyes, pharmaceuticals and of additives in photography, and cosmetics.[32] It is produced via conversion of resorcinol with aqueous potassium carbonate solution at 100 °C and applying a carbon dioxide pressure of 4.5 bar. A by-product of 2,6-dihydroxybenzoic acid (γ-resorcylic acid) is formed and can be separated by recrystallization.[32]



Scheme 5.1. Reaction scheme of the Kolbe-Schmitt reaction giving 2,4 –dihydroxybenzoic acid

The reaction of resorcinol to 2,4-dihydroxybenzoic acid in aqueous potassium bicarbonate solution at high temperatures and high pressure using a microreactor rig was studied previously.[33] The reaction is shown in Scheme 5.1. The achieved yield was up to 45 %, which compares closely to the batch operation carried out for at least 2 h (only reaction time considered here); much higher yields are difficult to reach due to the reversible nature of the reaction. Microreactor superheated processing at 200 °C and 40 bar in comparison to the batch operation carried out at 100 °C and 1 bar, enabled a reduction of reaction time by a factor of 450 at comparable yields. Cost analysis of the microreactor and batch reactor operation of the realized process was done previously at a production rate of 0.55 kg/h with a five-tube reactor.[27,28] This corresponds to a production rate of 4.4 tons/year assuming an 8000 h/year operation. Also, the production rate with a 10-fold higher throughput (44 tons/year) equivalent to microstructured reactors operating in parallel was considered. It was found in other studies that new approaches such as microwave heating (MW) and using ionic liquids (IL) can increase the yields compared to the conventionally heated process from about 40 % up to 60 % and allow operation at a lower reaction temperature.[34] This improvement in yield can have a profound effect in terms of cost, since synthesis of high-value product is made from expensive raw materials. However, the investment for microwave heating and the high cost of ionic liquid material (due to missing recycling at this point of time) presents economic burden for these processes.

In this study, a capacity of 200 tons/year is selected according to the production capacity of the compact and pre-manufactured plant infrastructure. The process data of raw material and utility requirements are based on the previous experimental data of the microreactor and batch reactor operation at a yield of 45 % for both. Besides these two cases, a virtual case of 60 % yield with the same microreactor operation was considered to take into account the potential of achieving high yields with the use of microreactors, which has been demonstrated for so many reactions[35] (yet the Kolbe-Schmitt reaction here is rather an exception, if not considering the IL- and MW-processing).

5.2.2. Capital investment estimation

The capital needed to supply the required manufacturing and plant facilities is called the fixed capital investment (FCI), while that necessary to start the plant up and operate to the point when income is earned is termed the working capital (WC) with the sum making the total capital investment (TCI).[30] WC is recovered at the end of the plant life. FCI is subdivided into manufacturing FCI, also known as direct cost, and non-manufacturing FCI, also known as indirect cost. Direct costs include purchased equipment, purchased equipment installation, instrumentation and controls, piping, electrical systems, buildings and service facilities.[30] Indirect costs include engineering and supervision costs covering the design of the plant and purchasing, procurement and construction supervision as well as contingency allowance to cover for unforeseen circumstances.[30]

Capital cost estimation is done based on an estimate of the total purchase cost of the major equipment items required for the process and the other costs being estimated as factors of the equipment cost. This method is called the factorial estimate method. After the preparation of the material and energy balances for the process and preparation of the flowsheets, sizing of major equipment items is done. Then an estimation of the purchased cost of equipment is made. In literature log-log plots or correlations for the main types of process equipment based on cost data obtained from vendors are provided[30,36] that are used here for estimation.

For the detailed factorial estimate method used here, the factors allow the total capital investment to be calculated based on information of the purchased equipment cost. These factors are given in literature and are determined for typical chemical plants of three general process types – solid, solid-liquid and liquid processing. Table 5.2 gives the ratio factors that are used here for estimating FCI based on delivered equipment cost. These factors are based on work by Peters et al.[30], where yard improvements, legal expenses and contractor’s fee are neglected in this context. The delivered equipment cost is calculated with a delivery allowance of 10 % of purchased equipment cost.

The compact and pre-manufactured plant infrastructure of the Evotrainer includes instrumentation and controls, electrical systems, building and service facilities in its structure. The associated costs of these in calculating the direct costs with the detailed factorial estimate method are already incurred in the Evotrainer infrastructure. Therefore, the factors used to calculate these in this scenario are eliminated and the corresponding total cost is replaced by the efforts about the Evotrainer infrastructure. Due to the compact structure of the plant and the standardization of units as discussed previously in Section 5.1.3, the associated costs for the purchased equipment installation and piping are adjusted to lower than for a conventional plant, as an estimate by 35 %. Engineering and supervision costs included in the indirect costs are also expected to be significantly lower than for a conventional plant, due to the elimination of customized equipment, piping and structural design as discussed previously in Section 5.1.3. Also, the contingency allowance can be reduced significantly due to the lower risk of design errors. The factors in their estimation are decreased accordingly as an estimate by 50 %.

Table 5.2. Fixed capital investment determination based on detailed factorial estimate method (as given by Peters et al.[30]).

	Solid processing plant	Solid-fluid processing plant	Fluid processing plant
Direct costs			
Delivered equipment cost (E)	1.00	1.00	1.00
Purchased equipment installation	0.45	0.39	0.47
Piping	0.16	0.31	0.68
Instrumentation & controls	0.18	0.26	0.36
Electrical systems	0.10	0.10	0.11
Buildings	0.25	0.29	0.18
Service facilities	0.40	0.55	0.70
Total Direct Plant Cost	2.54	2.90	3.50
Indirect Costs			
Engineering and supervision	0.33	0.32	0.33
Contingency	0.35	0.37	0.44
Total Indirect Plant Cost	0.68	0.69	0.77
Fixed Capital Investment	3.22	3.59	4.27

The corresponding fixed capital investment calculation for the Evotrainer based scenario can be done according to Table 5.3. This table is based on factors used for a solid-fluid processing plant by Peters et al. given in Table 5.2. Since the Evotrainer is a pre-manufactured plant infrastructure, part of the costs for instrumentation and controls, electric systems, buildings, and service facilities are constant and here a fixed value was assumed which shall not be disclosed here due to confidentiality. The working capital is then estimated as 15 % of the TCI.[30] With the knowledge of the fixed capital investment as explained above, the TCI is found.

The fixed cost, mentioned in Table 5.3 and considered for further calculations, stands for the current Evotrainer infrastructure (third generation) with given demands and flexibility on scale and possibly on application and fits to the production targets considered (200 t/a). Yet, future generations of such a modular plant with a much different scale and project task, may have other fixed costs. That would naturally change the outcome of the calculations.

Table 5.3. Fixed capital investment determination based on detailed factorial estimate method for the Evotrainer scenario

	Solid-fluid processing plant
Direct costs	
Delivered equipment cost (E)	1.00
Purchased equipment installation	0.25
Piping	0.20
Instrumentation & controls	Evotrainer
Electrical systems	
Buildings	
Service facilities	
Total Direct Plant Cost	
Indirect Costs	
Engineering and supervision	0.16
Contingency	0.185
Total Indirect Plant Cost	
Fixed Capital Investment	

5.2.3. Operating cost estimation

Operating costs include direct costs and general expenses. Direct costs, also called as manufacturing costs, refer to the costs of producing the product at the production site. In addition to these costs are general expenses for contributing to corporate functions of research and development and selling of the product.[30] The direct costs are divided into variable and fixed operating costs. Variable costs include raw material, utilities and catalysts and solvents.[36] Fixed costs include operating labor, supervision, maintenance, plant overheads, laboratory charges, depreciation, taxes and insurance. General expenses include administrative, distribution and marketing and research and development costs.[30]

The variable cost items are determined based on mass and energy balances and operating labor is determined based on the production rate and the type of processing plant. The other items are estimated based on the known operating cost items and fixed capital investment. This factorial method of estimation of operating cost can be seen in Table 5.4. These factors used for estimation are based on average values given by Peters et al.[30] and Sinnott.[36]

Table 5.4. Operating cost determination based on factorial estimates (as given by Peters et al.[30] and Sinnott[36])

Operating cost items	Factor	Basis
Variable Costs		
Raw materials	-	Required input
Utilities	-	Required input
Catalysts and solvents	-	Required input
Fixed Costs		
Operating labour	-	Required input
Operating supervision	0.15	of operating labor
Maintenance and repairs	0.05	of FCI
Plant overheads	0.50	of operating labor
Laboratory charges	0.15	of operating labor
Local taxes	0.02	of FCI
Insurance	0.01	of FCI
Depreciation / Capital charges	-	Calculated separately
Direct Production Cost	-	Variable + Fixed Costs
General Expenses	0.20	Direct Production Cost
Total Product Cost	-	

The Evotrainer infrastructure enables the reduction of operating costs due to its modularity and compact structure in terms of cost of operating labor and due to standardization of units in terms of cost of maintenance, as discussed previously in Section 5.1.3. The factors in their estimation are decreased accordingly as an estimate by 20 %, which is a rough-cut assumption taken from the very first experience. Since some other cost items, including operating supervision, plant overheads and laboratory charges, are related to operating labor as explained above, their corresponding costs are reduced accordingly as well.

Table 5.5. Annual depreciation rates with modified accelerated cost recovery system (MACRS) depreciation method 5-year recovery period

Recovery year	Depreciation rate, %
1	20.00
2	32.00
3	19.20
4	11.52
5	11.52
6	5.76

Depreciation is calculated separately because it is not the same each year. A depreciation method termed modified accelerated cost recovery system (MACRS) with a 5-year recovery period and half-yearly convention is selected, which is typically preferred for chemical plants.[30] Table 5.5 shows the annual depreciation rates for this method.

5.2.4. Cash flow analysis

A cumulative cash flow diagram allows visualization of the forecasted cumulative new cash flow over the life of a project. It gives an idea of the resources required and timing of the earnings. The cash flow is found by adding depreciation to net profit after taxes and subtracting the TCI:

$$\text{Net profit} = (\text{sales-total operating costs (including depreciation)}) \times (1-\varphi) \quad (5.1)$$

$$\text{Cash flow} = \text{net profit} + \text{depreciation} - \text{total capital investment} \quad (5.2)$$

where φ is income tax rate.

For doing cash flow analysis, the schedule of the project is decided. Generally, for a chemical plant, the construction takes place heavily in the 1st year and in the 2nd year the remaining construction is completed.[36] Accordingly, it is taken here that 30 % of the FCI is spent in the 1st year and 70 % of the FCI is spent in the 2nd year. Then, in the 3rd year, working capital is allocated and the plant starts production. Production at full design capacity does not usually occur in the 3rd year, so that production at 50 % capacity is taken for this year. This gives 50 % of revenue in this year. In terms of the operating cost, 50 % of the variable cost (VC) but 100 % of fixed costs (FC) occur in this year. From the 4th year, production at full capacity takes place until the end of project, with 100 % of annual revenue and 100 % of operating costs. For this evaluation 8 years of operation is considered with the end of the project at the 10th year, due to 2 years of construction. At the end of the project working capital is recovered by the sale of materials and supplies. The cash flow schedule is given in Table 5.6.

Due to the reduction of the planning and construction period, it was assumed that the construction of the Evotrainer plant can be achieved in 1 year. So, 100 % of FCI is spent in 1st year and in the 2nd year, working capital is allocated and the plant starts production. Production at full design capacity does not usually occur in the 2nd year, so 50 % of VC and 50 % of revenue is taken but 100 % of FC occur this year. From the 3rd year, production at full capacity takes place. The end of the project is at the 9th year, with 8 years of operation selected here. The cash flow schedule is given in Table 5.7.

Table 5.6. Cash flow schedule for the conventional plant

Year	FCI, %	WC, %	VC %	FC, %	Revenue, %
1	30	0	0	0	0
2	70	0	0	0	0
3	0	100	50	100	50
4-10	0	0	100	100	100

Table 5.7. Cash flow schedule for the Evotrainer plant

Year	FCI, %	WC, %	VC %	FC, %	Revenue, %
1	100	0	0	0	0
2	0	100	50	100	50
3-9	0	0	100	100	100

The cash flows show the value in the year in which they occur, so they stand for the future worth of the projected industrial manufacture. Since cash flows occur in different years throughout the project, it is necessary to convert them to equivalent values. This is done by discounting future cash flows to a particular point in time. In this way, the time value of money is taken into consideration. The time value of money is related to the capacity of money to earn money. The money earned in any year can be reinvested as soon as it is available and can start to earn a return. NPV calculation is made here to assess the profitability of a projected industrial manufacture. The net cash flow in each year of the project is brought to its present value at the start of the projected industrial manufacture by discounting it at a chosen discount rate. The NPV is then found as the sum of the present values of the future cash flows[30] :

$$NPV = \sum_{n=1}^{n=t} \frac{CF_n}{(1+i)^n} \tag{5.3}$$

where is CF_n cash flow in year n, t is project life in years and i is discount rate.

The value of NPV is strongly dependent on the discount rate chosen. It will have a lower value if a higher discount rate is selected. The appropriate discount rate to use is determined from the minimum acceptable rate of return. It is the rate of earning that must be achieved in order for it to be acceptable to the investor, given its risk and opportunity cost of forgoing other projects.[30] The discount rate is determined based on the rate from safe investment such as on government bonds (8 %) and adjusted to account for uncertainties associated with a new project. With the increase in risk for the project, the risk premium added on top of the risk-free rate increases.

5.3. Results and Discussion

Since the fine-chemical application comprises the envisaged target market of the Evotrainer infrastructure and also since for this application all relevant data were at hand, the cost analysis investigations started with and were centered around this chemical process. From the earnings made and common data on the compact and premanufactured plant Evotrainer infrastructure gathered, the same procedure was applied to the bulk-chemical (adipic acid) and pharmaceutical (naproxen) applications for comparison.

5.3.1. Capital investment estimation of fine chemical

The process equipment for the 2,4-dihydroxybenzoic acid manufacture used included pumps for feeding the reactor at the required pressure, a mixer for mixing the reactants, heat exchangers for heating the reactor feed and cooling the reactor effluent and a reactor unit supplied with heating.[33] The choice of apparatus refers to flow equipment in the case of microreactor operation and to batch equipment in the case of batch operation. For the microreactor operation, the reaction conditions are 200 °C and 40 bar, whereas for the batch operation, 100 °C and 1 bar were used. Besides the reaction part downstream processes are considered as well. After cooling to about 60 °C, water is added to the suspension until complete dissolution of the solid is achieved. Then, the resulting mixture is acidified with hydrochloric acid at room temperature. Then, by cooling to about 15 °C, crystals are formed which are then filtered and dried. The product is attained with about 99 % purity. For the downstream processes, the same batch equipment was used for both operation types (batch/flow) consisting of a dissolving tank, crystallizer, filter and dryer.

In addition to the normal flow process with the standard yield, a virtual flow process with a higher (60 %) yield, termed “micro 60 %”, was investigated as well. This refers to the proven capability of microreactors to increase selectivity, which actually was also found for the Kolbe-Schmitt synthesis, yet with use of microwaves (which was not considered as equipment here).[34]

Thus, equipment cost estimates are made for three processes (batch, micro, micro 60 %). The equipment for the reaction part is based on the costs of lab set-ups determined previously for 4.4 tons/year production.[27] For the batch operation, scaling up of the batch reactor and apparatus is done and for the flow operation, the microreactors are numbered up. The downstream equipment is simulated with Aspen and their respective costs are determined using the literature.[36] The microreactor operation has a higher cost than the batch operation, due to the higher cost of flow equipment in comparison to batch equipment. However, the difference is not so high (about 25 %), mainly because the downstream equipment used is the same. The equipment cost for the microreactor operation with 60 % yield is estimated to be 10 % lower than the microreactor operation with 45 % yield, since a lower amount of raw material goes through to achieve the same amount of product, making it possible to use smaller equipment.

Applying the methodology described in Section 5.2.2, the detailed factorial estimate method based on the total purchased equipment cost, the FCI for the three processes (batch, micro, micro 60 %) is determined for the conventional plant and the Evotrainer plant. With the three process types taking place in two plant types, a corresponding six cases are considered in this evaluation.

The cost of the Evotrainer infrastructure, comprising the costs of instrumentation and controls, electrical systems, building and service facilities, were estimated. The sum of these costs calculated separately with factorial estimates for the conventional plant is slightly higher than that of the cost of the Evotrainer infrastructure. The other direct costs of installation and piping are considerably lower for the Evotrainer plant regarding the factors used, as explained in Section 5.2.2.

Also, the indirect costs of engineering and supervision and contingency allowance are lower due to lower factors used. This makes the capital investment for the Evotrainer plant around 15 % lower than that for the conventional plant. Figure 5.3 shows the FCI estimated for the six cases showing the direct and indirect plant costs separately.

It should be noted here that batch operation in the conventional plant has a very close capital investment with the microreactor operation in the Evotrainer plant. This shows the opportunity of using Evotrainer infrastructure for applying micro process technology to be competitive, with conventional operation in terms of capital investment which cannot be achieved normally due to the higher cost of more advanced flow reactors.

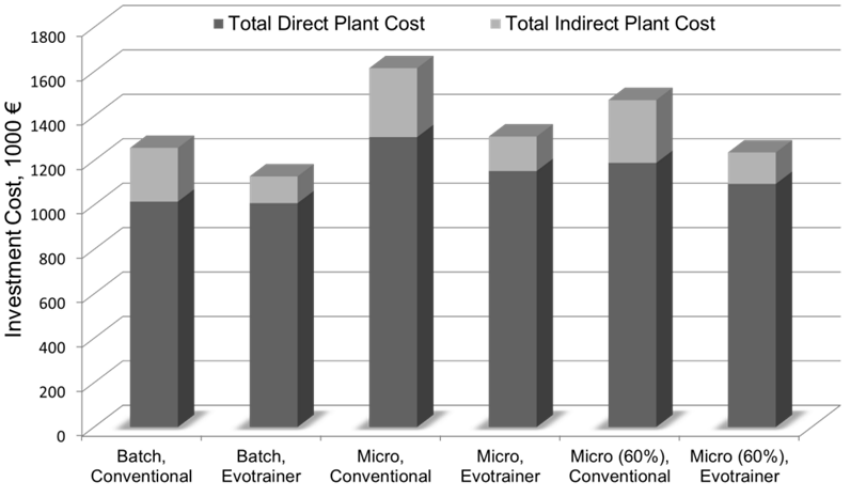


Figure 5.3. Fixed capital investment estimated for the six cases considered

5.3.2. Operating cost estimation of fine chemical

The operating cost estimation is started with estimation of raw material, utility and operating labor costs. The raw material requirement is derived from the experimental data for the 45 % yield for the micro and batch operations and for the 60 % yield it is estimated by stoichiometry. A five- to six-fold excess of potassium bicarbonate to resorcinol is used conventionally. However, for the microreactor operation, this could be reduced to three-fold excess, enabling saving in terms of raw material cost. The microreactor operation with

60 % yield has a considerably lower raw material cost, due to lower raw material requirement. The raw material costs are based on wholesale price information.[37] The operating labor is estimated based on rule of thumb of solid-fluid plants as 10 employee-hours per ton of product.[30] For the microreactor operation 1.5 times lower labor of 6.6 employee-hours per ton of product is taken, partly accounting for a faster product manufacture by estimation. An average common labor rate of 34 €/employee-hour is taken based on the Engineering News Record.[38] This corresponds to one to two operators, which is a reasonable estimate for such a small plant of 200 tons/year production.

The other operating costs are determined by factors of the known values as described in Section 5.2.3. Figure 5.4 shows the operating costs estimated for the six cases split into the variable costs, fixed costs and general expenses.

Since the Kolbe-Schmitt synthesis presents the case of a synthesis of high-value product from relatively expensive raw materials, the raw material cost dominates the operating costs. The raw material costs constitute around 66 % of the operating costs and the total variable costs sum up to around 80 %. Accordingly, the share of other operating cost items is low. The use of an Evotrainer infrastructure affects the operating labor and maintenance. However, since these cost categories have a low share in the overall operating cost, the effect of the Evotrainer infrastructure is seen as very small for this process example. For process examples with cheaper raw material the effect of the Evotrainer plant would be larger. It is seen that compared to batch, lower operating cost values can be achieved with the microreactor. Also, the increase in yield in the microreactor operation with 60 % yield case enables a profound reduction of the operating costs, due to the raw material cost reduction, which has a big effect on the overall operating cost.

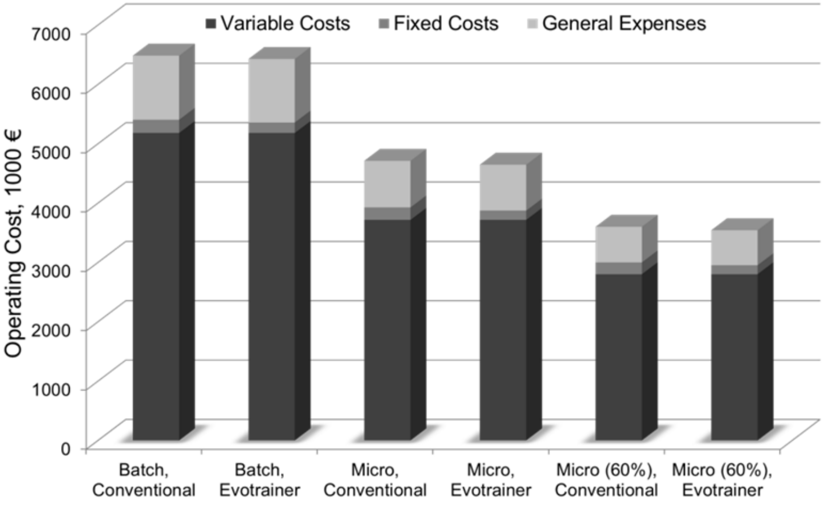


Figure 5.4. Operating cost estimated for the six cases considered

5.3.3. Cash flow analysis of fine chemical

In Table 5.8, the cash flow analysis is given for the case of batch process in a conventional plant. The schedule of the project is as described in Section 5.2.4 and Table 5.6 for the conventional plant. In the 3rd year, the working capital is allocated and the plant starts production at 50 % capacity. After the 3rd year, 100 % of revenue is earned and 100 % of operating cost (OC) is spent. With the eight years of operation selected the end of the project is at the 10th year. At the end of the project, the working capital is released and taken as a positive increment to the cash flow.

The revenue, that is the income earned from the sales of the product, is found by sales price 58 €/kg[37] multiplied by the amount of 200,000 kg of product produced. The annual depreciation charge is calculated with rates of MACRS depreciation method given in Table 5.5 for the recovery period. Gross profit is calculated as the difference between the revenue and the operating cost, including depreciation. The net profit is calculated as gross profit after taxes with Eq. 5.1. Then, the cash flow (CF) is found using Eq. 5.2. The cumulative cash is calculated to see the cash position over the life cycle of the project. The present value (PV) of the cash flow in each year is then determined by multiplying with PV factor for the discount rate selected which is calculated as $(1+i)^{-n}$. The NPV up to year n is the cumulative sum of all the present values of cash flows up to that year as given in Eq. 5.3. For the case of batch process in a conventional plant with the discount rate of 15 % the NPV is found as 9076 × 10^3 €. Cash flow analysis tables for the other cases are given in the appendix.

Table 5.8. Cash flow analysis for the case of batch process in a conventional plant (all cost values in the unit of 10^3 €)

End of Year	1	2	3	4	5	6	7	8	9	10
FCI	-377	-880								
WC			-222							222
Fraction of Capacity			0.5	1	1	1	1	1	1	1
Annual Revenue			5800	11600	11600	11600	11600	11600	11600	11600
Annual OC w/o depr.			-3892	-6482	-6482	-6482	-6482	-6482	-6482	-6482
Annual Depreciation			-251	-402	-241	-145	-145	-72		
Annual Gross Profit			1657	4716	4877	4973	4973	5046	5118	5118
Annual Net Profit			1077	3065	3170	3233	3233	3280	3327	3327
Annual CF	-377	-880	1106	3467	3411	3377	3377	3352	3327	3548
Cumulative CF	-377	-1257	-150	3317	6728	10106	13483	16835	20162	23710
PV factor (15 %)	0.87	0.76	0.66	0.57	0.50	0.43	0.38	0.33	0.28	0.25
PV of annual CF	-328	-668	730	1976	1706	1452	1283	1106	931	887
PV cumulative CF	-328	-996	-266	1710	3416	4868	6151	7258	8189	9076

The important consideration here is the selection of the discount rate as explained previously in Section 5.2.4, which is the minimum acceptable rate of return suitable for each case. For a low level of risk in investment, a lower rate can be selected. Since with the Evotrainer plants there is a lower risk in bringing the product from idea to production, a lower discount rate can be used. That is evident from Figure 5.2, with its fewer respective steps in development and the more straight forward combined development from laboratory to production in this pre-manufactured facility, mentioned in the corresponding text.

As micro process technology is fairly new technology, it can be considered to have a higher risk than the established process technology of batch production. Accordingly, a higher rate is selected for micro processes. The discount rates selected for the different cases based on the level of risk estimation are given in Table 5.9. The known conventional batch process rate of return was taken as 15 % and by estimation reduced by 3 % when being operated in a container. The risk increase by use of micro process technology was considered with a 5 % higher rate.

Table 5.9. Minimum acceptable rate of return (discount rate, i) selected for the cases

Case	Discount rate, %
Batch, Conventional	15
Batch, Evotrainer	12
Micro, Conventional	20
Micro, Evotrainer	17

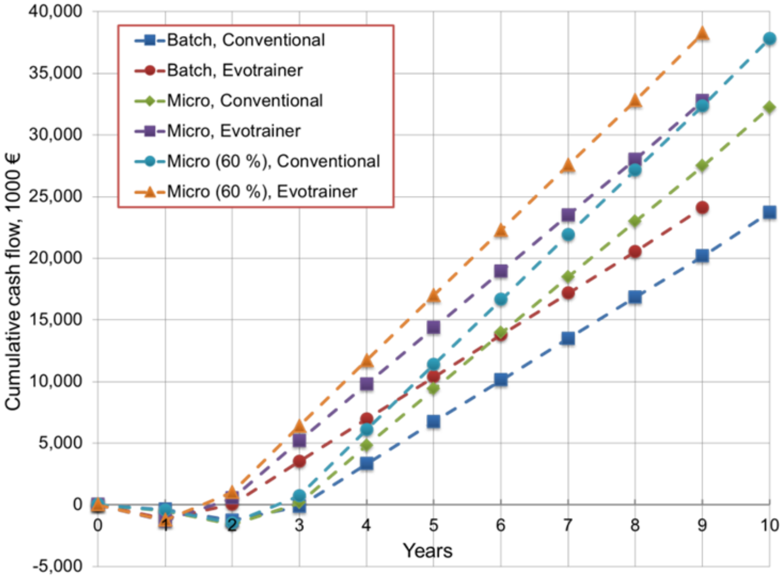


Figure 5.5. Cumulative cash flow diagram for the six cases considered

The diagram of cumulative cash flow over the course of the project life for the six cases is given in Figure 5.5. It is seen that in comparison to the conventional plant, the Evotrainer plant enables a higher cumulative cash flow for each process case. Also, the capital investment is repaid quicker with the reduction of the construction period. The microreactor operation with 60 % yield has the lowest operating cost and highest cash flows are attained accordingly. Due to synthesis of the high value product, the reduction in operating costs has a significant effect. This makes the investment cost difference a minor influence. Accordingly, the batch operation has the lowest cash flow, because of its higher operating cost and cannot profit from its lowest capital investment.

Cumulative cash flow diagrams do not take into account the time value of money. Accordingly, NPV calculation is made. As explained before, with a higher discount rate, lower NPV values can be achieved for the same investment consideration. The resulting NPV for the six cases using discount rates given in Table 5.9 is given in Figure 5.6.

The reduction of risk achieved with the compact and pre-manufactured Evotrainer plant enables higher NPV values to be achieved for each process considered. In comparison to the conventional plant for the reaction studied, with the use of the Evotrainer infrastructure, an increase in NPV of around 40 % is obtained for each process type. Regarding the process type, although the microreactor processes have a higher discount rate, a still higher NPV than with the batch process can be achieved due to lower operating cost.

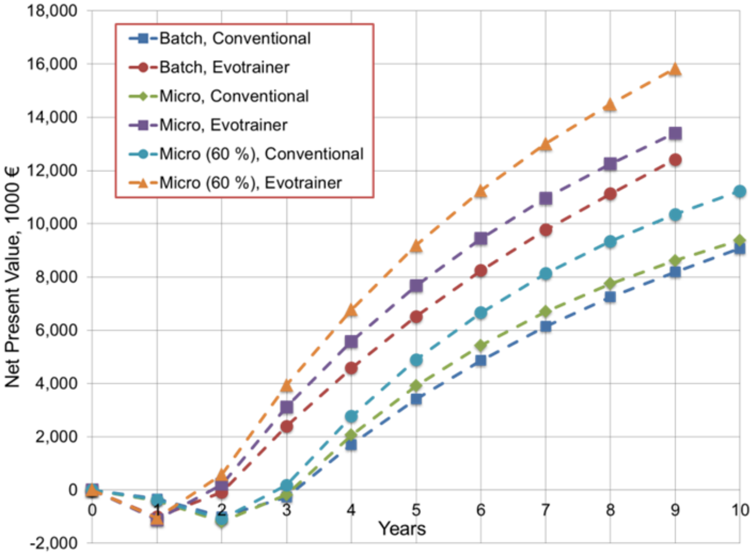


Figure 5.6. Net Present Value for the six cases considered at different discount rates

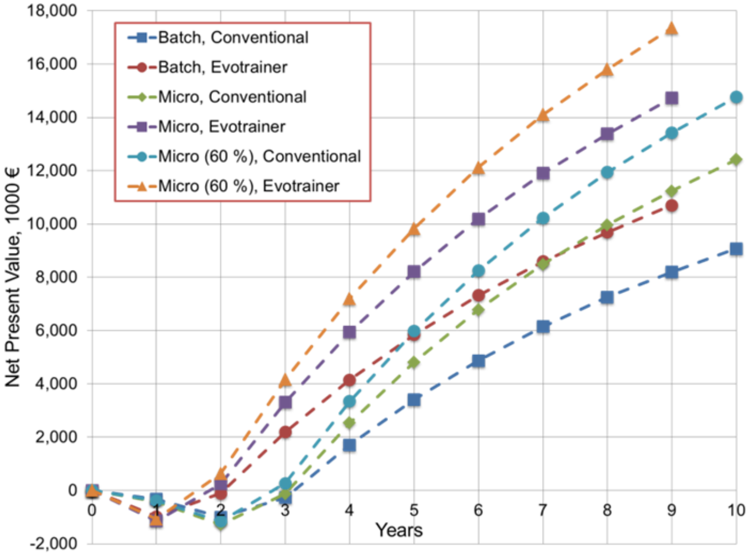


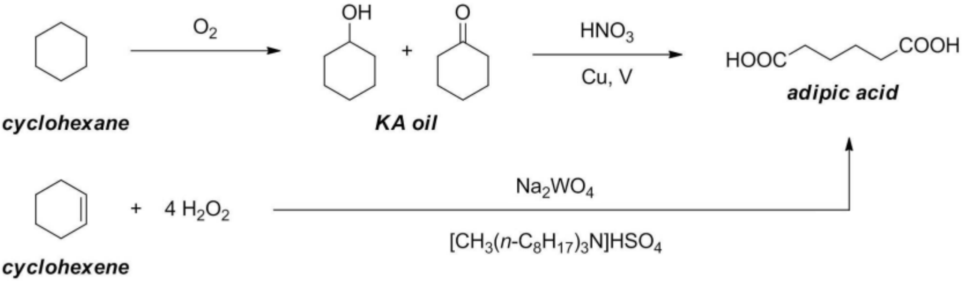
Figure 5.7. Net Present Value for the six cases considered at same discount rate of 15 %

To eliminate the effect of discount rates selected, the NPV calculation is also done by using a 15 % rate for all cases. Accordingly, the discount rate used for batch, Evotrainer case is increased, batch, conventional case is kept the same and the other cases are decreased compared to the cases given in Figure 5.6. The resulting NPV for the six cases is given in Figure 5.7. Due to the changed discount rates the NPV of batch, Evotrainer case decreased compared to Figure 5.6.

In Figure 5.7, the same discount rate is considered and accordingly the same risk level is taken. That is why the high difference in NPV seen in Figure 5.6 achieved with the Evotrainer infrastructure owing to lower risk, is not seen in Figure 5.7. However, using the same risk level, the Evotrainer plant still enables higher NPV values. In comparison to the conventional plant the Evotrainer infrastructure gives around 18 % higher NPV at same risk level. This difference is due to a lower operating cost achieved with the Evotrainer plant and the reduction in the construction period that enables higher financial gain to be achieved since the money earned earlier is worth more than that earned later. Considering the process type, the microreactor process is seen to have a higher NPV, due to the profound effect of the reduction in the operating cost achieved.

5.3.4. Comparison of chemical product classes – bulk chemical, fine chemical and pharmaceutical

As bulk-chemical, adipic acid manufacturing was considered, for which extended results are at hand. Recently, a one-step oxidation of cyclohexene to adipic acid by 30% hydrogen peroxide (H_2O_2) has been reported.[39] We investigated the process design intensification through the microreactors and flow processing of this one-step adipic acid synthesis. Further analysis of this can be found in Chapters 7 and 8. For this route, the use of microreactor technology is selected to overcome limits in interfacial transfer, to safely handle hydrogen peroxide, to explore new, harsher process chemistries, and to test for better selectivity at much reduced reaction times (transport and chemical intensification fields). Current commercial production processes for adipic acid are carried out in two steps: the first step involves the production of so-called KA oil (a mixture of cyclohexanone, the ketone or K component, and cyclohexanol, the alcohol or A component). The second stage involves the oxidation of the KA oil to adipic acid, with an excess of strong nitric acid. The reaction scheme of the two routes are given in Scheme 5.2.



Scheme 5.2. Reaction scheme of commercial 2-step and one-step adipic acid synthesis

Here, four cases are considered at a capacity of 200 tons/year according to the production capacity of the Evotrainer infrastructure: two-step commercial process in conventional or Evotrainer plant and 1-step micro process in conventional or Evotrainer plant. The investment, operating cost and revenue that are used in making cash flow analysis for these cases are based on the previous study of the two-step and one-step operations through process simulation.[40] The investment cost calculation is done with the same factorial estimate method as used above, based on the total purchase equipment cost estimated for the two-step process and the one-step micro process. Due to a more compact plant design achieved with the one-step micro process, a significant reduction in capital cost occurs. A higher impact of using the Evotrainer infrastructure is seen for the two-step process in the reduction of the capital cost.

The variable operating cost calculation is then done based on the mass and energy balance that enables determination of the raw material and utility costs. The operating labor is estimated as 10 employee-hours per ton of product for commercial and 6.6 employee-hours per ton of product for the microreactor operation. The other operating costs are determined by factors of the known values, carrying out the same methodology as before. The revenue is calculated using the wholesale price of 3000 €/ton.[41] The cash flow and thereafter the NPV calculations are done as explained for the previous example. Cash flow analysis tables for these cases are given in the appendix. Again, the same discount rates given in Table 5.9

are used for analysis where batch representing the commercial operation in this bulk-chemical process example.

The total operating cost is greater than the revenue for this process example, showing that it is not worth investing at this very low production rate. Accordingly, minus NPV values are attained showing that the margin is not enough to recover the investment (see Figure 5.8). Actually, a production capacity of 130,000–450,000 tons/year defines the commercial range seen for adipic acid synthesis.[36] At a higher production rate, the effect of the fixed operating costs decreases, enabling higher margins to be achieved.

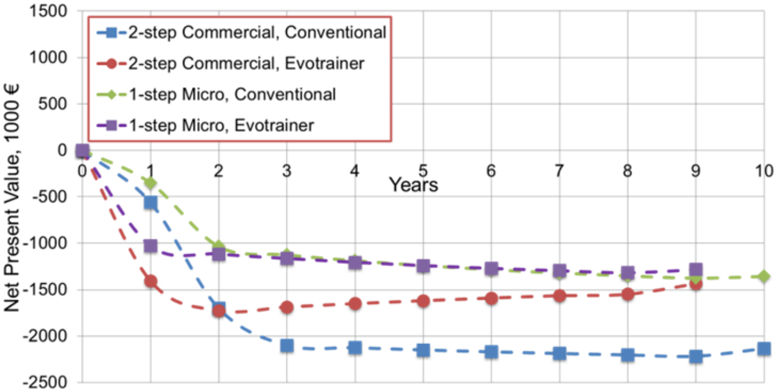
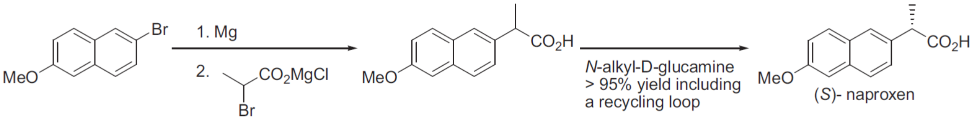


Figure 5.8. Net Present Value for adipic acid synthesis (bulk-chemical case)

The pharmaceutical product considered is naproxen. It is a nonsteroidal anti-inflammatory drug. It is used to relieve pain from various conditions such as headaches, muscle aches, tendonitis, dental pain, and menstrual cramps. It also reduces pain, swelling, and joint stiffness caused by arthritis, bursitis, and gout attacks.[42] It was introduced to the market in 1976 and the patent expired in December of 1993. The Syntex manufacturing process used today has the starting material 2-bromo-6-methoxynaphtelene (BMN), which is converted to a Grignard reagent which is then coupled with a salt of bromopropionic acid. This way, the corresponding *d,l*-acid is produced with a yield > 90 %. This is then efficiently resolved using N-alkylglucamine (> 95 %).[43] The reaction scheme is given in Scheme 5.3.



Scheme 5.3. Reaction scheme of naproxen synthesis

The investment cost of this process is determined based on the equipment required for the Grignard reaction step and the resolution step, with a racemization-recycling loop. The equipment includes a reactor and related parts, a mixer for mixing the resolving agent, a heater, a filter for separation of the insoluble salt and a separator for recovery and recycle of the resolving agent.

Regarding the operating cost, again the major share refers to the raw material cost due to the production of a high value product use of relatively expensive raw materials. There are various alternatives to produce naproxen, and production with the starting material BMN enables the lowest operating cost, with BMN being the least expensive.[43] Due to the labor intensive resolution step, the operating labor is estimated as 20 employee-hours per ton of product. The other operating costs are determined by factors of the known values carrying out the same methodology as before. The revenue is based on a wholesale price of naproxen at 25 kg of approximately $10,000.[44] Here, two cases are considered at a capacity of 200 tons/year according to the production capacity of the Evotrainer infrastructure: naproxen synthesis with micro in conventional or Evotrainer plant. Cash flow analysis tables for these cases are given in the appendix. Since micro use is considered 20 % discount rate is taken for the conventional plant and 17 % discount rate is used for the Evotrainer plant as in previous cases.

The selection of naproxen as an example is motivated by a well-published industrial application example of micro process technology. In 2009, the development was started to get a new drug, naproxcinod to treat patients with osteoarthritis, to market; it reached Phase III studies.[31] Naproxcinod is a naproxen derivative which contains a nitrate group as a substituent. Compounds containing a nitrate group are difficult to make, as nitration reactions must be handled carefully due to producing products that can violently decompose. Highly diluted, biphasic conditions and specialized safety equipment are necessary to realize this type of processing in a classical batch manufacturing process. Beyond this safety issue, the selectivity in nitration reactions and work-up are to be considered to permit extraction and neutralization of the nitrated product. A microreactor system enabled this eco-efficient production at a few hundred tons capacity of naproxcinod per year and combined three main steps: the nitration reaction, neutralization and work-up.[31] Thus, it would have been of interest to evaluate the use of microreactors for the synthesis of naproxcinod as a further step from the naproxen process described above. However, due to lack of data about this process, naproxen has been studied here.

The resulting NPV calculation for the pharmaceutical cases is given in Figure 5.9 together with fine-chemical micro process cases and adipic acid 1-step micro process cases for comparison.

It is evident that the operation of a much more costly product, such as naproxen, has a very positive effect on the cash-flow. Using a compact and pre-manufactured plant infrastructure, already after 1 year, a substantial payback and earning is achieved, while a similar trend is observed with conventional plant technology only after 2 years. The overall earnings over the years with pharma products are much higher as compared to the two other application cases. Thus, a GMP-type upgrading of the Evotrainer infrastructure technology provides a promising business case.

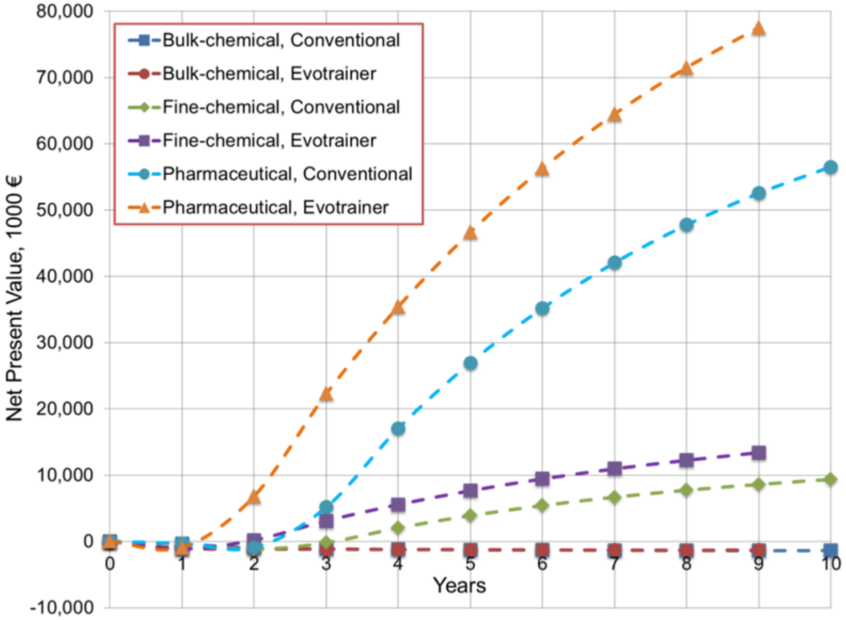


Figure 5.9. Net Present Value comparison of the three chemical product classes

5.4. Conclusion

A detailed calculation of capital investment and operating cost for a modular plant is made for the first time, quantifying the benefits of modular design. For the evaluation, Evonik's new compact and pre-manufactured production platform, termed the Evotrainer (meanwhile renamed as the EcoTrainer), was considered. Standardization through pre-manufactured modules assembled into a highly functional plant environment, facilitates savings in the design and construction time and expenditure. Additional benefits can be gained in terms of the operating costs as well, regarding operating labor and maintenance. A detailed factorial estimate method, which is used in making an economic analysis for conventional plants, is employed to make an analysis for the plant based on the Evotrainer infrastructure. Regarding the advantages gained with the Evotrainer plant, these factors are either replaced with the cost of the Evotrainer infrastructure or reduced, since the latter already includes instrumentation and controls, electrical systems, and building and service facilities in its structure. The study also considers the step-change character of process intensification and smart-scale technologies, such as microstructured reactors, together with modular compact plants; the latter also stand for any other modern robust high-performance equipment to hand in the chemical industry. As stated in the introduction, the main generic aim of this study was to provide parametric sensitivity and a proof of principle for a new economic model in chemical manufacturing using model based scenarios (including virtual microreactor applications). Therefore, several assumptions were made that are stated in the text.

The chemical manufacturing in the compact plant infrastructure (e.g., framed in a container-like module) was analyzed for three virtual microreactor applications. These model-based scenarios for market applications in bulk chemistry, fine chemistry and pharmacy, take into consideration all possible markets regarding production volumes, product prices etc. The fine chemical considered was 2,4-dihydroxybenzoic acid, which was chosen due to extensive past experience with experimental microreactor work. CAPEX and OPEX calculations and a following cash flow analysis were carried out. In comparison to the conventional plant, with the use of the Evotrainer infrastructure based plant, an increase in NPV of around 40 % was obtained; using a lower discount rate for the Evotrainer plant, it has a lower risk in bringing the product from idea to production. However, with the use of the same risk level, the Evotrainer plant still enables higher NPV values (e.g., 18 % for the fine chemical case considered at 200 t/a and the same discount rate of 15%). This difference is due to the lower operating cost achieved with the Evotrainer plant and the reduction in the construction period. Considering the process type, microreactor (or generally intensified) processes were seen to have a higher NPV than that of the batch processes, due to the profound effect of the reduction in operating cost achieved. It was seen that the Evotrainer infrastructure and micro process technology can be synergistic in costs.

The study carried out for the bulk chemical (adipic acid) did not give favorable results as expected, indicating that bulk chemical manufacturing in the Evotrainer based plant is economically generally not efficient. In the pharma case (naproxen), a high positive effect on the cash-flow was seen due to higher value-added making it attractive to be produced in the Evotrainer based plant.

5.5. Appendix: Cash flow analysis tables

Fine-chemical:

Table 5.10. Cash flow analysis for the case of batch process in a Evotrainer plant – fine-chemical (all cost values in the unit of 10^3 €)

End of Year	1	2	3	4	5	6	7	8	9
FCI	-1128								
WC		-199							199
Fraction of Capacity		0.5	1	1	1	1	1	1	1
Annual Revenue		5800	11600	11600	11600	11600	11600	11600	11600
Annual OC w/o depr.		-3837	-6427	-6427	-6427	-6427	-6427	-6427	-6427
Annual Depreciation		-226	-361	-217	-130	-130	-65		
Annual Gross Profit		1737	4812	4956	5043	5043	5108	5173	5173
Annual Net Profit		1129	3128	3222	3278	3278	3320	3362	3362
Annual CF	-1128	1156	3489	3438	3408	3408	3385	3362	3561
Cumulative CF	-1128	28	3516	6954	10362	13770	17155	20518	24079
PV factor (12 %)	0.89	0.80	0.71	0.64	0.57	0.51	0.45	0.40	0.36
PV of annual CF	-1007	921	2483	2185	1934	1727	1531	1358	1284
PV cumulative CF	-1007	-86	2397	4582	6516	8242	9774	11132	12416

Table 5.11. Cash flow analysis for the case of micro process in a conventional plant – fine-chemical (all cost values in the unit of 10^3 €)

End of Year	1	2	3	4	5	6	7	8	9	10
FCI	-485	-1131								
WC			-285							285
Fraction of Capacity			0.5	1	1	1	1	1	1	1
Annual Revenue			5800	11600	11600	11600	11600	11600	11600	11600
Annual OC w/o depr.			-2853	-4710	-4710	-4710	-4710	-4710	-4710	-4710
Annual Depreciation			-323	-517	-310	-186	-186	-93		
Annual Gross Profit			2624	6373	6580	6704	6704	6797	6890	6890
Annual Net Profit			1706	4142	4277	4357	4357	4418	4478	4478
Annual CF	-485	-1131	1744	4659	4587	4544	4544	4511	4478	4763
Cumulative CF	-485	-1616	128	4788	9375	13918	18462	22972	27451	32214
PV factor (20 %)	0.83	0.69	0.58	0.48	0.40	0.33	0.28	0.23	0.19	0.16
PV of annual CF	-404	-785	1009	2247	1843	1522	1268	1049	868	769
PV cumulative CF	-404	-1189	-180	2067	3910	5432	6700	7749	8617	9386

Table 5.12. Cash flow analysis for the case of micro process in a Evotrainer plant – fine-chemical (all cost values in the unit of 10^3 €)

End of Year	1	2	3	4	5	6	7	8	9
FCI	-1308								
WC		-231							231
Fraction of Capacity		0.5	1	1	1	1	1	1	1
Annual Revenue		5800	11600	11600	11600	11600	11600	11600	11600
Annual OC w/o depr.		-2788	-4646	-4646	-4646	-4646	-4646	-4646	-4646
Annual Depreciation		-262	-418	-251	-151	-151	-75		
Annual Gross Profit		2750	6536	6703	6804	6804	6879	6954	6954
Annual Net Profit		1788	4248	4357	4422	4422	4471	4520	4520
Annual CF	-1308	1819	4667	4608	4573	4573	4547	4520	4751
Cumulative CF	-1308	511	5178	9786	14359	18932	23479	27999	32750
PV factor (17 %)	0.85	0.73	0.62	0.53	0.46	0.39	0.33	0.28	0.24
PV of annual CF	-1118	1328	2914	2459	2086	1783	1515	1287	1156
PV cumulative CF	-1118	211	3125	5584	7670	9452	10967	12255	13411

Table 5.13. Cash flow analysis for the case of micro 60 % process in a conventional plant – fine-chemical (all cost values in the unit of 10^3 €)

End of Year	1	2	3	4	5	6	7	8	9	10
FCI	-442	-1030								
WC			-260							260
Fraction of Capacity			0.5	1	1	1	1	1	1	1
Annual Revenue			5800	11600	11600	11600	11600	11600	11600	11600
Annual OC w/o depr.			-2198	-3598	-3598	-3598	-3598	-3598	-3598	-3598
Annual Depreciation			-294	-471	-283	-170	-170	-85		
Annual Gross Profit			3308	7531	7720	7833	7833	7917	8002	8002
Annual Net Profit			2150	4895	5018	5091	5091	5146	5201	5201
Annual CF	-442	-1030	2185	5366	5300	5261	5261	5231	5201	5461
Cumulative CF	-442	-1472	713	6079	11379	16640	21901	27132	32333	37794
PV factor (20 %)	0.83	0.69	0.58	0.48	0.40	0.33	0.28	0.23	0.19	0.16
PV of annual CF	-368	-716	1264	2588	2130	1762	1468	1217	1008	882
PV cumulative CF	-368	-1083	181	2769	4899	6660	8129	9345	10353	11235

Table 5.14. Cash flow analysis for the case of micro 60 % process in a Evotrainer plant – fine-chemical (all cost values in the unit of 10^3 €)

End of Year	1	2	3	4	5	6	7	8	9
FCI	-1236								
WC		-218							218
Fraction of Capacity		0.5	1	1	1	1	1	1	1
Annual Revenue		5800	11600	11600	11600	11600	11600	11600	11600
Annual OC w/o depr.		-2141	-3541	-3541	-3541	-3541	-3541	-3541	-3541
Annual Depreciation		-247	-396	-237	-142	-142	-71		
Annual Gross Profit		3412	7663	7822	7917	7917	7988	8059	8059
Annual Net Profit		2218	4981	5084	5146	5146	5192	5238	5238
Annual CF	-1236	2247	5377	5321	5288	5288	5263	5238	5456
Cumulative CF	-1236	1011	6387	11709	16997	22285	27548	32787	38243
PV factor (17 %)	0.85	0.73	0.62	0.53	0.46	0.39	0.33	0.28	0.24
PV of annual CF	-1056	1641	3357	2840	2412	2062	1754	1492	1328
PV cumulative CF	-1056	585	3942	6782	9194	11255	13009	14501	15829

Bulk-chemical :

Table 5.15. Cash flow analysis for the case of 2-step commercial process in a conventional plant – bulk-chemical (all cost values in the unit of 10^3 €)

End of Year	1	2	3	4	5	6	7	8	9	10
FCI	-646	-1508								
WC			-380							380
Fraction of Capacity			0.5	1	1	1	1	1	1	1
Annual Revenue			300	600	600	600	600	600	600	600
Annual OC w/o depr.			-524	-647	-647	-647	-647	-647	-647	-647
Annual Depreciation			-431	-689	-414	-248	-248	-124		
Annual Gross Profit			-655	-736	-461	-295	-295	-171	-47	-47
Annual Net Profit			-655	-736	-461	-295	-295	-171	-47	-47
Annual CF	-646	-1508	-604	-47	-47	-47	-47	-47	-47	333
Cumulative CF	-646	-2154	-2758	-2806	-2853	-2900	-2947	-2994	-3041	-2709
PV factor (15 %)	0.87	0.76	0.66	0.57	0.50	0.43	0.38	0.33	0.28	0.25
PV of annual CF	-562	-1140	-397	-27	-23	-20	-18	-15	-13	82
PV cumulative CF	-562	-1702	-2099	-2126	-2150	-2170	-2188	-2203	-2217	-2135

Table 5.16. Cash flow analysis for the case of 2-step commercial process in a Evotrainer plant – bulk-chemical (all cost values in the unit of 10^3 €)

End of Year	1	2	3	4	5	6	7	8	9
FCI	-1577								
WC		-278							278
Fraction of Capacity		0.5	1	1	1	1	1	1	1
Annual Revenue		300	600	600	600	600	600	600	600
Annual OC w/o depr.		-421	-544	-544	-544	-544	-544	-544	-544
Annual Depreciation		-315	-505	-303	-182	-182	-91		
Annual Gross Profit		-436	-448	-247	-125	-125	-35	56.23	56.23
Annual Net Profit		-436	-448	-247	-125	-125	-35	36.55	36.55
Annual CF	-1577	-399	56.23	56.23	56.23	56.23	56.23	36.55	314.55
Cumulative CF	-1577	-1976	-1920	-1864	-1807	-1751	-1695	-1658	-1344
PV factor (12 %)	0.89	0.80	0.71	0.64	0.57	0.51	0.45	0.40	0.36
PV of annual CF	-1408	-318	40.03	35.74	31.91	28.49	25.44	14.76	113.43
PV cumulative CF	-1408	-1726	-1686	-1650	-1619	-1590	-1565	-1550	-1436

Table 5.17. Cash flow analysis for the case of 1-step micro process in a conventional plant – bulk-chemical (all cost values in the unit of 10^3 €)

End of Year	1	2	3	4	5	6	7	8	9	10
FCI	-422	-985								
WC			-248							248
Fraction of Capacity			0.5	1	1	1	1	1	1	1
Annual Revenue			300	600	600	600	600	600	600	600
Annual OC w/o depr.			-208	-730	-730	-730	-730	-730	-730	-730
Annual Depreciation			-244	-391	-234	-141	-141	-70		
Annual Gross Profit			-152	-521	-365	-271	-271	-201	-130	-130
Annual Net Profit			-152	-521	-365	-271	-271	-201	-130	-130
Annual CF	-422	-985	-156	-130	-130	-130	-130	-130	-130	118
Cumulative CF	-422	-1407	-1563	-1694	-1824	-1954	-2085	-2215	-2345	-2228
PV factor (20 %)	0.83	0.69	0.58	0.48	0.40	0.33	0.28	0.23	0.19	0.16
PV of annual CF	-352	-684	-90	-63	-52	-44	-36	-30	-25	19
PV cumulative CF	-352	-1036	-1126	-1189	-1241	-1285	-1321	-1352	-1377	-1358

Table 5.18. Cash flow analysis for the case of 1-step micro process in a Evotrainer plant – bulk-chemical (all cost values in the unit of 10^3 €)

End of Year	1	2	3	4	5	6	7	8	9
FCI	-1204								
WC		-212							212
Fraction of Capacity		0.5	1	1	1	1	1	1	1
Annual Revenue		300	600	600	600	600	600	600	600
Annual OC w/o depr.		-208	-677	-677	-677	-677	-677	-677	-677
Annual Depreciation		-216	-345	-207	-124	-124	-62		
Annual Gross Profit		-123	-422	-284	-201	-201	-139	-77	-77
Annual Net Profit		-123	-422	-284	-201	-201	-139	-77	-77
Annual CF	-1204	-120	-77	-77	-77	-77	-77	-77	135
Cumulative CF	-1204	-1324	-1401	-1478	-1555	-1631	-1708	-1785	-1650
PV factor (17 %)	0.85	0.73	0.62	0.53	0.46	0.39	0.33	0.28	0.24
PV of annual CF	-1029	-88	-48	-41	-35	-30	-26	-22	33
PV cumulative CF	-1029	-1116	-1164	-1206	-1241	-1271	-1296	-1318	-1285

Pharmaceutical :

Table 5.19. Cash flow analysis for the case of naproxen process in a conventional plant – pharmaceutical (all cost values in the unit of 10^3 €)

End of Year	1	2	3	4	5	6	7	8	9	10
FCI	-371	-865								
WC			-218							218
Fraction of Capacity			0,5	1	1	1	1	1	1	1
Annual Revenue			32300	64600	64600	64600	64600	64600	64600	64600
Annual OC w/o depr.			-15889	-26849	-26849	-26849	-26849	-26849	-26849	-26849
Annual Depreciation			-247	-395	-237	-142	-142	-71		
Annual Gross Profit			16164	37356	37514	37609	37609	37680	37751	37751
Annual Net Profit			10507	24281	24384	24446	24446	24492	24538	24538
Annual CF	-371	-865	10536	24677	24621	24588	24588	24563	24538	24756
Cumulative CF	-371	-1235	9301	33978	58599	83187	107775	132339	156877	181633
PV factor (20 %)	0,83	0,69	0,58	0,48	0,40	0,33	0,28	0,23	0,19	0,16
PV of annual CF	-309	-600	6097	11900	9895	8235	6862	5713	4756	3998
PV cumulative CF	-309	-909	5188	17088	26983	35218	42080	47793	52548	56546

Table 5.20. Cash flow analysis for the case of naproxen process in a Evotrainer plant – pharmaceutical (all cost values in the unit of 10^3 €)

End of Year	1	2	3	4	5	6	7	8	9
FCI	-1050								
WC		-185							185
Fraction of Capacity		0,5	1,0	1	1	1	1	1	1
Annual Revenue		32300	64600	64600	64600	64600	64600	64600	64600
Annual OC w/o depr.		-15785	-26745	-26745	-26745	-26745	-26745	-26745	-26745
Annual Depreciation		-210	-336	-202	-121	-121	-60		
Annual Gross Profit		16305	37519	37653	37734	37734	37795	37855	37855
Annual Net Profit		10598	24387	24475	24527	24527	24566	24606	24606
Annual CF	-1050	10623	24723	24676	24648	24648	24627	24606	24791
Cumulative CF	-1050	9573	34296	58973	83621	108269	132896	157501	182292
PV factor (17 %)	0,85	0,73	0,62	0,53	0,46	0,39	0,33	0,28	0,24
PV of annual CF	-897	7760	15437	13169	11242	9609	8206	7007	6034
PV cumulative CF	-897	6863	22299	35468	46710	56319	64524	71532	77566

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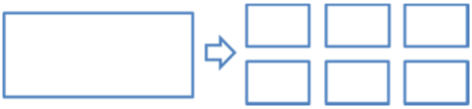

CHAPTER 6

Decentralized Biofuel Production – Modular Process Integration at Commercial Scale

This chapter is based on :

Vural Gursel, I., Wang, Q., Noël, T., Hessel, V., Kolb, G. & van Veen, A. (2014). Heat-integrated novel process of liquid fuel production from bio resources – Process simulation and costing study. Chemical Engineering Transactions, 39, 931-936.

Abstract:

Innovative ways of providing novel sustainable solutions to reduce the emissions and consumption of exhaustible resources is called for. Production of liquid fuels from bioresources satisfies this call and it is aimed to be achieved with BIOGO project. Proposed process involves coupled reforming of biogas and bio oil followed by methanol production which is then converted to gasoline. This novel route through methanol eliminates challenging separation steps of Fischer-Tropsh process. Decentralized production in modularized small scale plants with process intensified equipment is considered. Preliminary techno-economic analysis is carried out here to analyze the feasibility of the process. Process simulation reveals that carbon efficiency of 56 % and energy efficiency of 42 % can be achieved. Cost calculations show that with the total cost of production of gasoline at € 0.5/L; it is economically competitive with petroleum-based production and more economical than Fischer-Tropsh process. Comparison of 35 decentralized small modular plants with one centralized large scale plant reveals that the reduced construction time and operating cost of decentralized plants can outweigh the higher investment cost.

6.1. Introduction

Concerns about the depletion of fossil fuel reserves, increased energy demand, society's pressure for clean and sustainable production make use of bioresources as energy source an attractive solution. Although, recently there has been increasing research on renewable energy sources, still around 90 % of the world energy needs are met with non-renewable sources.[1]

Bioenergy is the largest source of renewable energy and can provide heat, electricity as well as transport fuels. International Energy Agency foresees that biofuels contribution to total transport fuel could increase from 2 % today to 27 % by 2050.[1] The scenario suggests that this will be possible by advanced biofuel technologies that are not yet commercially available. These advanced (second generation) biofuels manufactured from various types of biomass, which are not competitive to food production, can substitute current fossil derived gasoline and diesel fuels.[2] The two main catalytic processes for biomass to liquid fuel production are Fischer-Tropsch (FT) and Methanol-to-hydrocarbons processes. FT is an established process already applied on large scale worldwide in coal and natural gas based plants.[2] There is one commercial methanol to gasoline plant using methanol produced from natural gas.[3] Methanol to olefins process is also developed. A further development is the Mobil olefins to gasoline/diesel process. They are at demonstration phase.[3]

BIOGO, a new project funded by the European commission, proposes to combine bio oil and biogas sources to produce syngas which is then converted to methanol. The methanol produced as intermediate is finally transformed into liquid fuels with a sharper product distribution than the ones from the FT process. The novelty of this route comes also from coupled syngas generation. Decentralized production in modular plant environment utilizing flow reactors is considered. In this chapter, results from the preliminary study done to analyze feasibility of the proposed novel process is presented with process simulation and cost analysis.

6.2. Methodology

Important problems associated with synthesis from biomass are; it is widely distributed, and its composition and amount differs with location and season. Due to its large water content its transportation is costly. Also large stocks of biomass needs to be stored near the production plant because of its low energy density. Therefore, decentralized fuel production is found preferable in this project. Moreover, production in modular plants is taken to benefit from feed flexibility, scalability and faster time-to-market.[4] They are formed by pre-manufactured modules assembled into highly functional plant environment that facilitates piping, utility, control and safety requirements in its infrastructure.[5]

For ease of transportation and storage, biomass is usually densified by torrefaction or pyrolysis.[6] With fast pyrolysis biomass is converted to liquid bio oil.[7] Bio oil is up to 10 times the energy density of biomass and it has diverse chemical composition, typically with low hydrogen (7 %) and high oxygen (45 %) content.[8] Another bio source of energy is biogas. Biogas is produced by decomposition of organic matter mainly of plant and animal wastes or landfills. It is primarily methane and carbon dioxide along with other trace gases.[9] For liquid fuel production, these bioresources need to be converted to syngas. The two main syngas production processes are partial oxidation and steam reforming. Conventionally steam reforming occurs in catalytic fixed bed reactors placed in direct-fired furnaces.[10] Long contact times are required due to heat transfer limitations. In this project coupling of exothermic partial oxidation with endothermic steam reforming in a microchannel plate heat exchanger reactor is considered.[11] This reactor design provides intensive mixing and enhanced mass and heat transfer that allows very short contact times.[12]

Fischer-Tropsch (FT) synthesis from syngas irrespective of operating conditions cannot produce uniquely diesel and gasoline. Therefore, FT product upgrading is required that involves challenging separation steps of many side products. Methanol produced from syngas can either be converted to gasoline or olefins.[3] Product upgrading is simpler. There is significantly less gaseous products and light saturates and also no heavy products that require cracking. BIOGO project is formed accordingly for decentralized liquid fuel production from bioresources of biogas and bio oil through methanol synthesis in modularized small scale plants with process intensified equipment including microreactors. To analyse the feasibility of the proposed project, a preliminary techno-economic analysis is performed. First, the process scheme is developed and a mass and energy balance is done. This is carried out with Aspen Plus™ modeling. Production capacity of 117.6 t/d gasoline is selected according to the production capacity of a small scale plant.[13] In this way the viability of the proposed process scheme can be shown. Second, cost analysis is done by first estimating capital and operating costs. Accordingly cost of production of gasoline is calculated for rate of return of 10 % and 20-year plant life. This can assist to compare this route with values from FT synthesis and conventional fossil based production. Also, the economics of decentralized small scale production is assessed in comparison with large scale plant with a discounted cash flow analysis.

6.3. Results and Discussion

6.3.1. Process simulation

The preliminary study to assess the BIOGO project is started with a process simulation done with Aspen Plus™. Biomass handling and drying, pyrolysis, biogas cleaning, air separation and wastewater treatment are not included in the process simulation but are taken into account in cost calculations. The process flow diagram of generation of liquid fuel from biogas and bio oil is given in Figure 6.1.

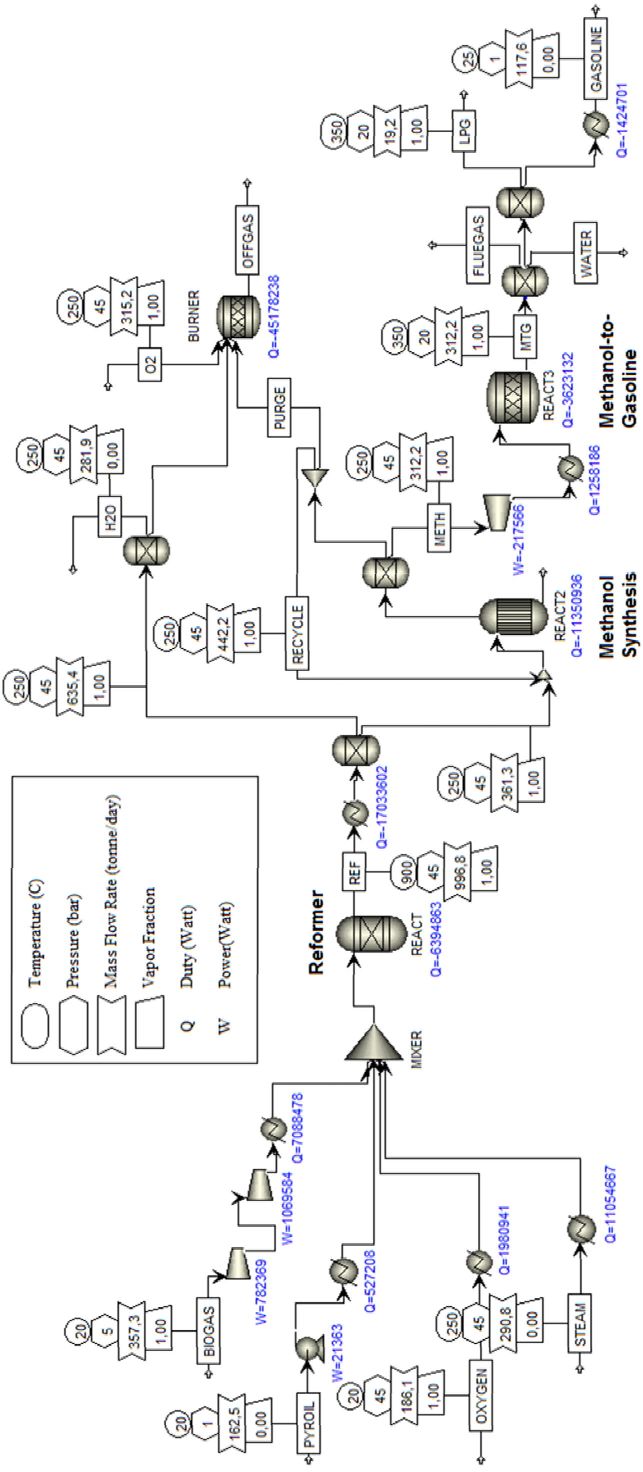

Figure 6.1. Process flow diagram of liquid fuel production from biogas and bio oil

Biogas is fed together with bio oil from fast pyrolysis to the reformer in 4:1 mole ratio. High feed temperature is required to achieve a high yield of syngas and to inhibit coke formation. The reformer temperature is set to 900 °C and pressure to 45 bar to achieve high methane conversion. Coupled reforming of the two streams enables high hydrogen content of the biogas to be utilized by bio oil. The rapid and intimate heat transfer eliminates coke formation. Pure oxygen is input to the reformer to provide the heat required for the reforming reactions. Its amount is adjusted to limit formation of carbon dioxide (CO_2) instead of carbon monoxide (CO). Steam is manipulated to achieve a hydrogen to carbon monoxide (H_2/CO) ratio of two. Therefore, further reverse water-gas-shift reaction is not required. The reformer outlet gas is separated from water, carbon dioxide and methane. Water can be recycled after treatment to the reformer. The methane left after reforming is sent to a combustion unit with oxygen to recover energy.

The syngas composed of H_2 and CO is fed to methanol synthesis. This is an equilibrium reaction with two moles of H_2 and one mole of CO converted to one mole of methanol. The reactor temperature and pressure are set to 250 °C and 45 bar respectively. Recycle is employed to maximize yield of methanol. Because of water-gas-shift reaction, some CO is converted to CO_2 which needs to be taken into consideration. The syngas mixture is typically adjusted to contain 4 – 8 mole % CO_2 for maximum selectivity and a stoichiometric ratio defined as $(\mathrm{H_2} - \mathrm{CO_2})/(\mathrm{CO} + \mathrm{CO_2})$ of two is preferred for methanol synthesis.[2] The recycle is adjusted to get this stoichiometric ratio equal to two and the combined syngas with recycle contains 6 mole % CO_2. 10 % of the recycle syngas stream is purged to prevent accumulation. This purge stream is used as fuel gas and fed to combustion unit.

The methanol product has a composition of 2.8 mole % water and 97.2 mole % methanol. It is fed to the methanol to gasoline reactor. The inlet conditions are adjusted to 350 °C and 20 bar.[2] The methanol is converted to 56 wt. % water and 44 wt. % hydrocarbons. 100 % methanol conversion is assumed. The hydrocarbon product composition is modelled based on typical composition in literature.[3] Hydrocarbon composition is 1.5 wt. % light gas, 5 wt. % C_3, 11.5 wt. % C_4, and 82 wt. % C_5+. The crude hydrocarbons are separated into finished liquid fuel products of which 86 wt. % is gasoline, 14 wt. % is LPG and the balance is fuel gas.

Using methanol as intermediate ensures a high conversion to liquid fuels. The light gas formation is much lower than FT synthesis. These light gas streams would need to be recompressed and recycled leading to extra energy requirement and loss of sellable product. A process route via methanol therefore avoids challenging gas separations and recycle which are required for conventional FT route. Thus, a more compact process scheme is achieved.

6.3.2. Mass, carbon and energy balance

Mass, carbon and energy balance from simulation is presented in Table 6.1. The inputs to the process simulation are biogas, bio oil and oxygen while the outputs are gasoline, LPG, CO_2 and water. Although there is also water inlet to the system, the net balance of water is written on the table indicating outlet water streams are more than enough to satisfy the inlet water by recycle. 100 % balance is attained. In the carbon balance carbon is input to the process by biogas and bio oil and exits the process via gasoline, LPG and CO_2. The carbon conversion efficiency to liquid fuels is calculated as 55.8 % which is slightly higher than reported in previous biomass to liquid studies.[13] This is mainly due to reduced separation requirement of the product in this process enhancing carbon utilization. 100 % of carbon is accounted for. Energy balance is given in Table 6.1 on a LHV basis. The energy efficiency of the process to liquid fuels is calculated by dividing the total energy output of gasoline and diesel by the total energy input to the process from biogas and bio oil. This energy efficiency is calculated as 41.8 %.

Table 6.1. Overall mass, carbon and energy balance

	Mass Balance t/d	Carbon Balance kmol/h	Energy Balance MW
Inputs			
Biogas	357.3	484.7	108.1
Bio oil	162.5	230.0	61.6
Oxygen	453.0	0.0	0.0
Outputs			
Gasoline	117.6	343.3	61.0
LPG	19.2	55.3	10.1
CO_2	501.5	316.1	0.0
Water	334.5	0.0	0.0

6.3.3. Cost analysis

The sections of the plant include biomass pyrolysis, coupled reforming, methanol synthesis, methanol to gasoline (MTG) conversion process. Combustion unit is used to recover heat. Oxygen is produced on site with air separation unit. Water is recycled inside the unit with water treatment. Water treatment unit also includes steam turbine to generate electricity from waste heat in the process. Therefore, system is self-sufficient without external utility requirement. The direct costs of the units are calculated using estimates from several literature sources. Biomass pre-processing, fast pyrolysis and combustion unit costs are estimated using a scaling factor of 0.7 to values from Wright et al.[14] The other unit costs are estimated using cost parameters given in Baliban et al.[15,16] Chemical engineering plant cost index is used to bring the unit costs to Q4 2013 (567.3). For conversion to euro from dollars 1.33 exchange rate is taken. The total direct cost includes cost of equipment, installation, instrumentation, piping and service facilities. The indirect costs of engineering and construction expenses and contingency are expected to be lower with modular plants since engineering and construction time and expenditure is much reduced with standardization and pre-manufacturing. Accordingly, indirect costs are estimated to be 50 % lower than conventional plants. The fixed capital investment is calculated as sum of total direct cost plus the indirect cost as given in Table 6.2. This is converted to annual basis to be incorporated into cost of production. Annual capital charge is calculated by multiplying the investment with a factor that depends on rate of return and plant life. For the selected rate of return of 10 % and plant life of 20 years the factor used is 0.117.[17] The other contributions to total cost of production come from raw materials, operating & maintenance (O&M) cost and LPG. LPG is sold as by-product so indicated as negative value. The cost parameters used in calculation are also given in Table 6.2.

Table 6.2. Breakdown of investment cost (left), total cost of production and cost parameters (right)

	MM€
Biomass pre-processing	3
Biomass fast pyrolysis	5
Combined reforming	20
Syngas separation	7
Methanol synthesis	5
MTG process	7
LPG - gasoline separation	3
Combustion	13
Air separation	9
Wastewater treatment	2
Total Direct Cost	75
Indirect Cost	12
Fixed Capital Investment	87

	MM€/yr	€/L
Biomass	5	0.10
Biogas	11	0.21
O&M	3	0.07
Capital charge	10	0.20
LPG	-4	-0.07
Total Cost of Production	26	0.50

Item	Cost parameters
Biomass	€ 62.0per dry ton
Biogas	€ 0.12per Nm^3
LPG	€ 0.32per litre

The total cost of production is calculated both in MM€/yr and in €/L using gasoline lower heating value of 32 MJ/L. The latter value represents the price of gasoline from which this process becomes economically competitive. The current gasoline price is 0.56 €/L (given regular gasoline spot price of 2.8 \$/gal[18]) is higher than 0.50 €/L estimated in this study indicating this process can be competitive with petroleum-based process. It should be noted that the estimations are sensitive to the cost parameters selected in the study. Baliban et al.

found a similar value for MTG process (0.51 €/L gasoline) and a higher value for FT process (0.59 €/L gasoline equivalent) at same production capacity.[13] The FT process cost of production is higher mainly due to higher investment cost required for this process with higher separation demand.

Higher capacities up to 50 times the capacity used in this study (5,880 t/d gasoline) was also studied. The investment and fixed operating cost information of this large scale plant is taken from Baliban et al.[13] to make comparison of decentralized plants with a centralized large scale plant. Due to seasonality large scale plants can't run at full capacity. 70 % capacity usage is assumed in this study, so one large plant of 5,880 t/d gasoline total capacity is compared with 35 plants of 117.6 t/d gasoline capacity each. Large scale plants collect biomass typically from 80 km radius so the associated transportation cost is added to the biomass cost giving 75 €/t. One year construction time is taken for small-plants and three year for the large plant. The plant-life is taken as 20 years. The resulting net present value (NPV) calculation is given in Figure 6.2.

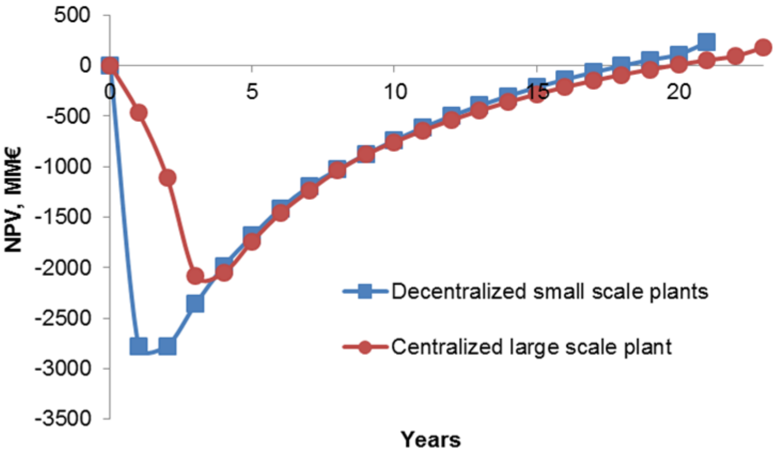

Figure 6.2. Net Present Value of decentralized small-scale plants and centralized large plant

The investment cost is higher for decentralized plants because of economies of scale. However, due to lower construction time, financial gain is earned earlier and due to time value of money this gives higher NPV. Also, operating cost is lower due to no added transportation cost for biomass. It is seen that these positive effects can outweigh the negative effect of higher investment requirement.

6.4. Conclusion

In the proposed novel production plant process integration (reaction coupling), process simplification (elimination of complex separation steps), modular processing and process intensification (microreactor utilization) is achieved. Syngas can be generated with coupled reforming at a stoichiometric ratio suitable to directly feed to methanol synthesis while simultaneously avoiding coke and minimizing methane formation. Neither challenging gas separation nor extensive light gas recycle loops are required in contrast to Fischer-Tropsch based routes. Therefore a compact process design is attained. Carbon efficiency to liquid fuels of 56 % and energy efficiency to liquid fuels of 42 % is achieved. Cost calculation reveals that with the price parameters used this proposed novel process is economically competitive with petroleum-based process and is more economical than FT process. Capital cost reduction is possible due to lower requirement of product separation and upgrading, also with lowered indirect costs with modular processing. Transportation which has associated costs and emissions is reduced by decentralized production. Discounted cash flow analysis show that decentralized plants can be preferable to large scale plants because they can be built in shorter time with faster time-to-market. Also due to seasonality and presence of variety of bioresources feed flexibility and capacity adaptation is important and can be achieved with these plants Liquid fuels produced from bioresources cause lower greenhouse gas emissions since carbon dioxide is captured by the feedstock and it offsets carbon dioxide emission from burning fuel. The introduction of environmental regulations such as carbon tax will improve the economics of biomass to liquid processes and can enable the shift from fossil-based processes. This chapter gives an ex-ante analysis before start of the BIOGO project activities and more coming insight can lead to a differentiated picture.

Acknowledgements

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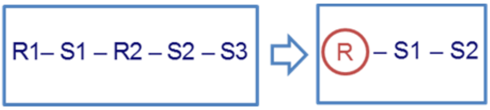

CHAPTER 7

Bulk Chemistry Process Simplification – End-to-end Process Integration at Commercial Scale

This chapter is based on :

Vural Gursel, I., Wang, Q., Noël, T. & Hessel, V. (2012). Process-design intensification : direct synthesis of adipic acid in flow. Chemical Engineering Transactions, 29, 565-570.
Vural Gursel, I., Wang, Q., Noël, T., Hessel, V. & Tinge, J.T. (2013). Improving energy efficiency of process of direct adipic acid synthesis in flow using pinch analysis. Industrial and Engineering Chemistry Research, 52(23), 7827-7835.
Wang, Q., Vural Gursel, I., Shang, M. & Hessel, V. (2013). Life cycle assessment for the direct synthesis of adipic acid in microreactors and benchmarking to commercial process. Chemical Engineering Journal, 234, 300-311.

Abstract:

Synergy of micro dimensions and harsh operating conditions results in a three-step intensification within a reaction system: transport, chemical and process-design intensification. Transport intensification that improves mass and heat transfer has been vastly demonstrated. Emerging chemical intensification uses highly intensified, unusual and typically harsh process conditions to boost micro-processing (high-T, high-p, high-c, safety). Process-design intensification is a new field in micro processing and it heads for integrated and simplified smart-scaled (micro-meso) flow process design in a holistic picture. The latter two constitute Novel Process Windows. As a demonstration example, direct adipic acid synthesis is considered which is an important intermediate for the nylon industry. It provides an innovative alternative to the conventional process currently used. The conventional process occurs in two steps from oxidation of cyclohexane by air followed by nitration oxidation. The direct route is from cyclohexene and uses hydrogen peroxide as oxidant. This results in higher adipic acid yield and simplified process. Drawbacks of the direct synthesis are long reaction time and increased safety issues, which

can be overcome by using microreactors. The reaction rate is increased by the largely improved mass transfer and the use of higher temperature. Based on laboratory flow experiments a full-chain process simulation was made for the direct route using Aspen Plus. This was used to make cost, energy and environmental analysis of this new process. Moreover, comparison with the two-step process was made to benchmark the flow process against conventional technology. Profound simplification of the process scheme of direct process leads to fewer unit operations enabling reduction of investment cost, although the microreactor cost is higher than those of conventional reactors. Through simplification or elimination of energy intensive separation units energy requirement can be reduced significantly. Life cycle assessment (LCA) shows that for a number of impact categories the direct process is greener; yet there are also categories for which the conventional route is more environmentally sustainable.

7.1. Introduction

Microreaction technology has attracted much attention in last 20 years because of its high capability in mass transfer and heat transfer, as well as its process window widening, e.g. to allow safe operation even in explosive regimes or with toxic or hazardous reactants or intermediates.[1–3] Nearly all microreactor studies are on the synthetic/reaction engineering level; the process design aspect, especially for a larger productivity scale (>1000 t/y) is missing in scientific literature. In such context, this chapter studies how microreaction technology donates to the end-to-end process integration for a bulk chemical process.

Process-design intensification through microreaction technology is new in literature and it is studied for the first time at the example of direct adipic acid synthesis.[4,5] Process-design intensification benefits from interdisciplinary integration of chemistry, micro process technology and process engineering. A step change improvement can be realized via bringing new chemical transformations such as direct synthesis on a full-process level. Such direct chemistries have the potential to reduce the cascades of separation units considerably. A decreased number of apparatus combined with a decreased size results in a smaller plant foot-print. The new flow-based process design then can have an entirely new cost, energy and sustainability structure.

Adipic acid is an important precursor for the production of nylon 6,6.[6] According to the market report[7], the global synthetic adipic acid market was worth USD 4,898.5 million in 2010 and is expected to reach USD 8,063.1 million in 2018. The conventional way to produce adipic acid comprises the two-step catalyzed air / nitric acid oxidation of cyclohexane (see Figure 7.1, top).[8] The first step involves the production of so-called KA oil (a mixture of cyclohexanone, the ketone or K component, and cyclohexanol, the alcohol or A component). In general, KA oil is produced by air oxidation of cyclohexane. In order to ensure the high selectivity to KA oil of over 75 % in the first air-oxidation step, it is necessary to keep the conversion of cyclohexane very low, to 4-6%.[9] To cope with that, capital and energy intensive distillation equipment is needed to separate and recycle unconverted cyclohexane from the product stream. The second stage involves oxidation of the KA oil with nitric acid where adipic acid is obtained in 92-96 % yield.[10] The high concentration (50-60 wt. %) and large consumption of nitric acid causes serious problems, since nitric acid is highly corrosive.[10] Moreover, nitric acid oxidation produces significant quantities of nitrous oxide (N_2O) and NO_x (NO, NO_2, and higher oxides) gases.[11] Accordingly abatement technologies are adapted to reduce these emissions to the environment. Generally thermal decomposition is used where high amount of energy is required.[12] Despite the efficient recovery still large amounts are emitted. N_2O emission from this process, which is considered to cause global warming and ozone depletion[13], corresponds to 5 to 8 % of the total amount released by man worldwide.[14]

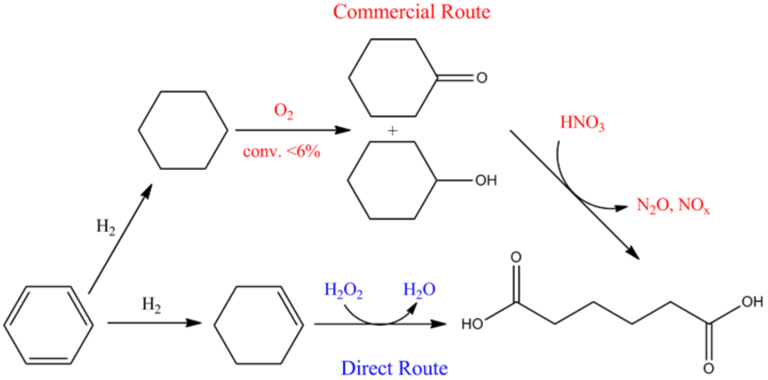

Figure 7.1. Reaction scheme of commercial two-step route and direct route for adipic acid synthesis

Accordingly, an ideal process would proceed at higher conversion and without the use of nitric acid. The solution can be a selective direct process with an oxidant that causes no emission to be removed. A direct route by the one-step all-air oxidation of cyclohexane is researched for this purpose[15–18], yet this is so far not in commercial use.

In virtually the same manner and now using another oxidant, a direct route was realized through the oxidation of cyclohexene with hydrogen peroxide in batch or membrane reactors[19–21] (see Figure 7.1, bottom). This direct route is process simplified (one-step) and has higher yield as compared to the conventional route. Also water is produced as by-product instead of nitrous gases in conventional process. Sato et al. described the direct oxidation of cyclohexene to adipic acid by 30% hydrogen peroxide (H_2O_2) with Na_2WO_4 and $[CH_3(n\text{-}C_8H_{17})_3N]HSO_4$ as phase-transfer catalyst.[19] This aqueous, organic biphasic reaction was seen to enable high yield (93 %) in batch experiments under conditions that are entirely free of organic solvents and halides.[19,22] Jiang et al. studied alternative phase transfer catalysts due to $[CH_3(n\text{-}C_8H_{17})_3N]HSO_4$ being expensive and tedious to synthesize. Deng et al. reported the use of peroxytungstate-organic complex catalyst for the direct oxidation of cyclohexene to adipic acid without any phase transfer catalyst.[20]

It has to be noted that the terminology “direct synthesis” is only valid in the strict sense at a lab-scale. On an industrial level, cyclohexane and cyclohexene are produced from the hydrogenation of benzene comprising an additional step as shown in Figure 7.1.

This is a highly exothermic reaction and, in co-amplification with the much accelerated decomposition of H_2O_2[23], heat management is especially demanding at high process temperatures and high production capacity. For these demands for intensified mass/heat transfer and safety operation, batch reactors are not optimal; instead another type of reactor which can safely handle such highly exothermic and severe reaction conditions is required. Given that profile, one largely preferred solution is the use of microreactors.[24]

Recently, in our group we showed, for the first time, the feasibility of carrying out the direct oxidation of cyclohexene with H_2O_2 to produce adipic acid in continuous micro-flow.[25] The reaction rate is significantly increased in the micro-flow consisting of a milli packed bed reactor with micro interstices between the beads forming a microchannel network. The yield improved from upto 50% by increasing the reaction temperature from 90°C to 100°C. But with a further increase of temperature from 100°C to 110°C, the yield decreased. Decomposition of H_2O_2 at elevated temperature lowers the concentration of H_2O_2 which decreases reaction rate and yield.

The yield of 50% is satisfactory, but not so high to simply give a straightforwardly intuitive and unequivocal argument to commercialize such process, while the H_2O_2 decomposition adds further problem. For such situation, holistic guidance in terms of economic, energy and environmental analysis are needed in order to determine the process feasibility and what needs to be done to optimize it. Accordingly, in this study process simulation of the direct route and two-step conventional route was carried out. Comparison of the two routes were made based on cost of equipment and energy requirement calculation and environmental impact determination by means of life cycle assessment (LCA).

One of the important goal is to facilitate finding the right path from the starting point of the process development curve towards a new full-chain continuous flow process design, by implementing the needs of the latter from the first moment of investigations. Holistic process route selection is becoming more and more important, as largely increasing number of holistic process papers in the scientific engineering literature over the last 8 years shows.[3] We see such investigation also as aid for the industrial management and it has accordingly entered the decision making of bulk-chemical industry.[26]

7.2. Methodology

7.2.1. Process model development

Since, the direct route is not yet commercially applied for adipic acid synthesis, a flow diagram and the process conditions were not available – this is exactly where innovation through the new flow process design has to set in. The reaction characteristics of this process based on laboratory experiments were considered together with the downstream equipment of the nitric acid oxidation process (second step of commercial route) to propose the full-chain process for the direct route.

In the direct oxidation process, cyclohexene, hydrogen peroxide together with sodium tungstate and phase transfer catalyst are fed to the oxidation reactor. The biphasic reaction takes place at 90°C and 1 bar. Cyclohexene is converted to water soluble adipic acid. The reactor effluent goes through a separator to remove the organic phase containing unreacted cyclohexene and by-products. The resulting aqueous stream is treated analogous to reactor effluent stream in the nitric acid oxidation process to recover adipic acid. First it is fed to a crude crystallizer operated at 50°C. The crystals are removed by a filter. And the mother liquor is sent to concentrating still to remove some of the produced water. The remaining stream goes through a purge crystallizer operated at 30°C to recover any remaining adipic acid. The purity of the crude adipic acid is high (99%) therefore recrystallization with water done for nitric acid oxidation process is not required.[27] The combined crystals are dried and the final product is attained.

Process simulations were done using Aspen Plus^{TM} for the commercial route (two-step air and nitric acid oxidation of cyclohexane) and for the direct synthesis route following the proposed process. The commercial route was simulated with data from the industrial production process from relevant patents and literature.[6,8–10,28–32] The direct route is simulated with data on the reaction based on laboratory flow experiments and for the downstream equipment the properties proposed above is used. Conversion of cyclohexene of 40 % based on primary result and 50 % based on current result were taken in simulation of the direct route. Since the experiments are ongoing, it is likely that it can be improved further. Therefore, also conversion of 98 % was simulated which reflects the best performance achieved for the direct route in literature in batch experiments. The capacity selected is 400 kton/year based on average adipic acid production plants.[33]

7.2.2. Energy analysis

The power, heating and cooling requirements of the processes were determined from the process simulations that were carried out for both routes. Heat integration that is typically employed in industrial plants is not considered here. Another chapter is devoted to heat integration study for the direct route (Chapter 8). In this chapter the aim is to get an idea of the energy requirements of the direct route and compare it with the requirements in conventional process.

7.2.3. Cost analysis

For further comparison of the routes cost analysis was carried out. This was done so by comparing the total purchased cost of equipment for the two routes based on the sizing information from the process simulations done. Equipment costs for major equipment were estimated using Aspen Process Economic Analyzer[34], log-log plots of equipment costs from books[35–37] and internet[38]. Chemical engineering plant cost index was used to bring the unit costs to Q4 2013 (567.3). For conversion to euro from dollars 1.33 exchange rate was taken.

7.2.4. Environmental analysis – LCA methodology

Environmental sustainable development needs methods and tools to measure and compare the environmental impacts as a result of the production processes. A preferred tool is LCA which is a method for evaluating the environmental impacts of a material, product, process, system or service throughout its entire life cycle holistically, i.e. from 'cradle to factory gate', 'cradle to grave' or even from 'cradle to cradle'. The LCA work in this study was conducted with regard to standards of ISO 14040[39] and its related guidelines[40]. The impact categories considered in this study are based on CML2001 method[41].

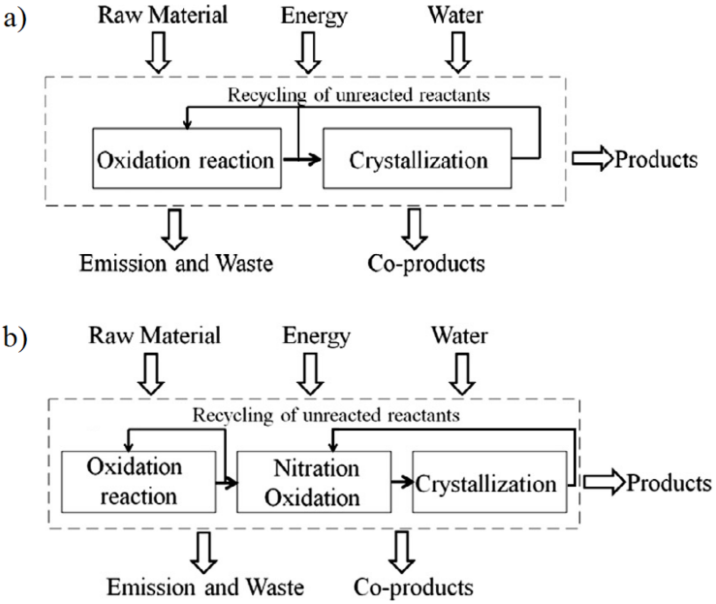

Figure 7.2. System boundary of a) direct synthesis, b) conventional synthesis (the dotted lines indicate system boundaries, full process equipment such as distillation not shown for reason of graphical simplicity)

LCA as considered in this study refers to a “cradle to factory gate” analysis, which means starting from raw materials and end up with final products. The boundaries for the direct micro-flow route synthesis and two-step conventional synthesis are shown in Figure 7.2.

The inventory data were adopted from the Ecoinvent v2.2 database incorporated in Umberto 5.6. The functional unit is “1 kg adipic acid”. The by-products produced in the process were treated as waste, so no allocation was needed in this study. Only the material flow and energy flow were considered while the transportation of raw materials was not considered in the study. The mass and energy flows are collected from process simulation of the two routes for inventory analysis.

Life cycle impact assessment is a means of examining and interpreting the inventory data from an environmental perspective. The impact categories[42] considered here is based on the CML2001 method[41] incorporated in Umberto 5.6. The impact categories in the present study are: acidification potential, average European (AP), global warm potential: climate change in 20 years (GWP 20a), eutrophication potential, average European (EP), freshwater aquatic ecotoxicity in 20 years (FAETP 20a), human toxicity in 20 years (HTP 20a), marine aquatic ecotoxicity in 20 years (MAETP 20a), photochemical oxidant creation potential (POCP), depletion of abiotic resources, terrestrial ecotoxicity in 20 years (TAETP 20a).

Since the inventory data for cyclohexene is not available in database, a sub process to produce cyclohexene by the partial hydrogenation of benzene is built.[43] In this study, an ideal conversion with 100 % and selectivity with 85 % are assumed in order to simplify the LCA analysis. In the real process, however, to achieve high selectivity low conversion is required. So the environmental profile does not include the energy consumed by separation and recycle of unreacted benzene. Under such simplification of the sub-process, the proportion of cyclohexene contribution to the impact categories will be lower than that in real case.

7.3. Results and Discussion

7.3.1. Process simulation

As explained above process simulations were done using Aspen Plus™ for the conventional route (two-step air and nitric acid oxidation of cyclohexane) based on the industrial production process and for the direct route following the proposed process. The process flow diagram of the conventional synthesis is given in Figure 7.3 and process flow diagram of the direct synthesis is given in Figure 7.4 for 50% conversion of cyclohexene case. As can be seen from the process flowsheets of the two routes, the direct route leads to a more compact plant design. With the reduction in step in synthesis there is requirement of fewer process units: only one reactor is needed and energy intensive separation units are either eliminated or simplified.

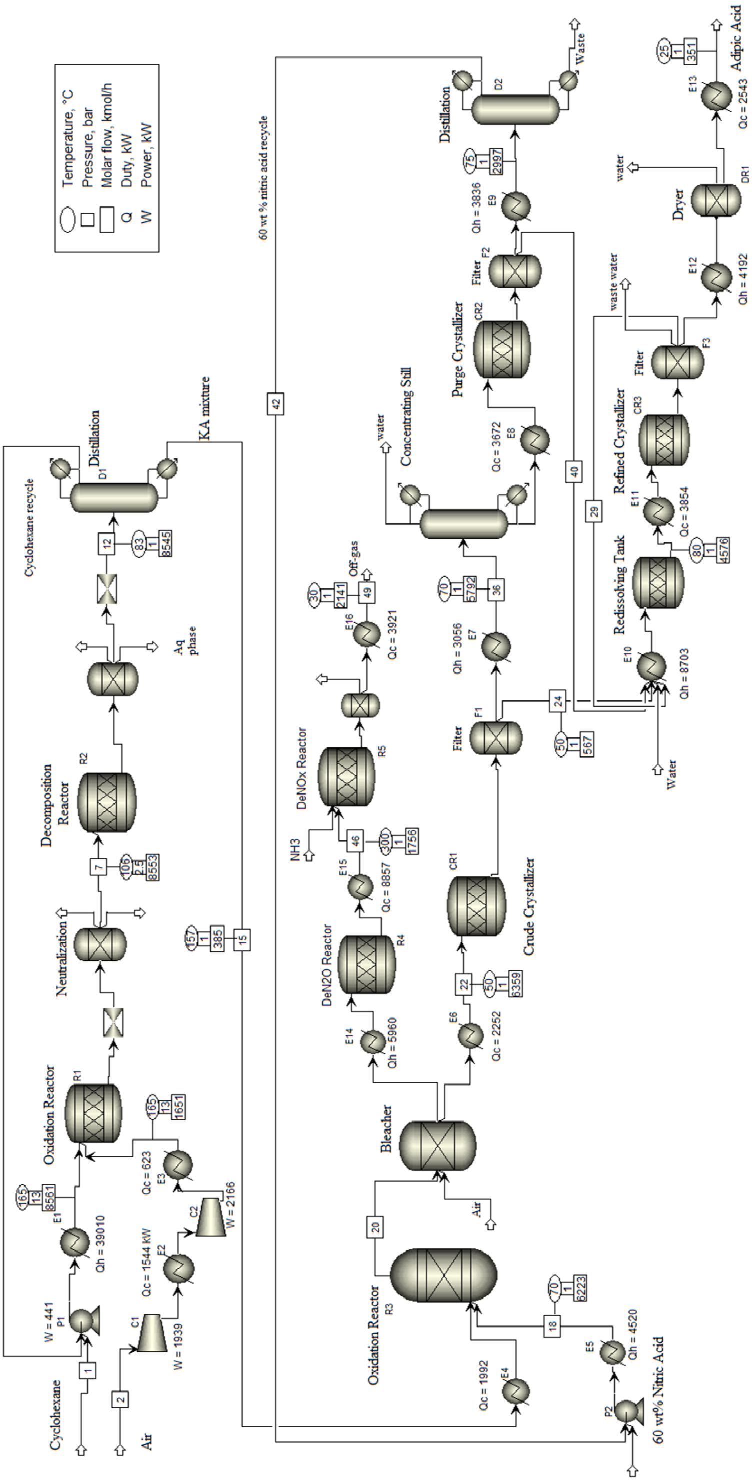

Figure 7.3. Process flowsheet of Aspen Plus simulation of conventional synthesis

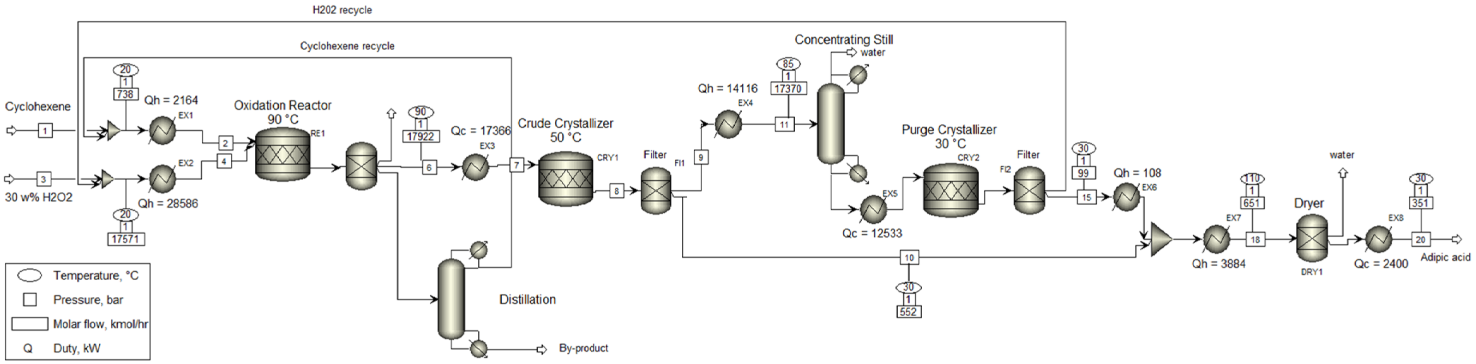

Figure 7.4. Process flowsheet of Aspen Plus simulation of direct synthesis at 50 % conversion

In the conventional route there is requirement of 5 reactors (air oxidation, decomposition, nitric acid oxidation, N_2O and NO_x decomposition reactors) whereas in the direct route there is requirement of only one which is the oxidation reactor. The purity of the crude adipic acid is found high in direct synthesis[27] therefore recrystallization is not required omitting redissolving and refined crystallization units. The low cyclohexane conversion in the conventional route demands high recycle ratio, whereas in the direct flow route conversions per pass are much higher. In the conventional route also NO_x and N_2O treatment is required. With water being the only by-product in the direct route waste treatment is simplified as well.

7.3.2. Energy requirements

The power, heating and cooling requirements of the conventional route and direct route are determined based on the process simulation. Also the effect of change in conversion for the direct route on the energy requirements is analyzed by making simulations at conversion levels of 40%, 50% and 98%. These are given in Table 7.1. Power requirement is the total requirement of compressors and pumps. Cooling requirement is the total duty of the heat exchangers that enable cooling. Heating requirement is the total duty of the heat exchangers that enable heating.

Table 7.1. Power, cooling and heating requirements of conventional and direct route at different conversion levels

	Conventional Route	Direct Route 40%	Direct Route 50%	Direct Route 98%
Power requirement, kW	4,546	0	0	0
Cooling requirement, kW	29,258	42,189	32,299	13,281
Heating requirement, kW	69,277	60,105	48,859	26,773
Total, kW	103,081	102,294	81,158	40,054

With the elimination of compressors and working at atmospheric pressure the power requirement for the direct route is 0. In real life for the transfer of liquids also power is required but simulation only considers the power requirement when higher pressure operation is involved requiring pressure differential.

For the conventional route, there is requirement of large heat input to reheat the large amount of recycled cyclohexane to the reaction temperature due to low conversion by pass. For the direct route, there is requirement of 4.4 moles of H_2O_2 per mole of cyclohexene. Also H_2O_2 concentration of <60% is required because the use, storage and transportation of higher concentration of H_2O_2 are not desirable for safety reasons.[19] Therefore together with the reactants and products large volume of water needs to be heated and cooled in the process. There are large heating and cooling requirements for this reason. It is seen that for the 40% conversion case, there is close total energy requirement with the conventional route although there are much less process units involved. However, with the increase in conversion the energy requirements are very much reduced. With the 50% conversion achieved currently and with the ongoing studies for further improvement, it can be said that direct route is more energy efficient than the conventional route.

7.3.3. Equipment cost estimation

A list of major equipment and their rough cost estimates for the two routes are provided in Table 7.2. The costs for the direct route is representative of 40-50 % conversion. This table depicts the difference of the two routes due to the simplification of the process design achieved with direct route. In the list for the conventional route there are 22 major equipment whereas in the list given for the direct route there are 10. It is also shows that the capital investment can be reduced even with the use of more expensive microreactor technology. The total purchase cost of equipment was seen to be cut approximately in half.

Table 7.2. List of major equipment and their cost estimates for the conventional route and the direct route

Conventional Route		Direct Route	
List of Equipment	Cost Estimates, M€	List of Equipment	Cost Estimates, M€
Pump	1.00	Pumps	0.80
Compressors	7.50	Oxidation reactor	8.00
Oxidation reactors	1.75	Phase separator	0.75
Decomposition reactor	1.00	Distillation	1.00
Neutralization vessel	0.80	Crude crystallizer	1.75
Distillation	1.50	1st Centrifuge/Filter	1.60
Pump	0.40	Concentrating still	1.50
Oxidation reactor	1.50	Purge crystallizer	1.50
Bleacher	0.80	2nd Centrifuge/Filter	1.25
Compressors	6.30	Dryer	0.75
DeN_2O reactor	1.50		
DeNO_x reactor	1.50		
Crude crystallizer	2.25		
1st Centrifuge/Filter	1.95		
Concentrating still	1.50		
Purge crystallizer	1.75		
2nd Centrifuge/Filter	1.60		
Distillation	1.75		
Redissolving tank	0.45		
Refined crystallizer	1.50		
3rd Centrifuge/Filter	1.25		
Dryer	0.75		
Total Purchase Cost	40.30	Total Purchase Cost	18.90

In the conventional route there is requirement of costly compressors to compress the air to be fed into the oxidation reactor and also for the transfer of nitrous gases to treatment. It has been seen that elimination of the compressor in the direct route with the use of liquid hydrogen peroxide as oxidant has a big impact in terms of costs.

Also, the reduction in number of steps in synthesis leads to lower number of downstream units (separators). Correspondingly the total cost of equipment for separators has decreased in comparison to the two-step route. Figure 7.5, left shows graphically the breakdown of the costs of equipment. In this figure, the effect of elimination of compressors and the reduction of downstream equipment in the direct route can be clearly seen.

It is seen that the total cost for reactors is similar for the two routes with microreactor being used in the direct route. Therefore, application of microreactor technology with process-design intensification is justified. Although flow reactors have higher cost than conventional reactors applying them to a simplified process design does not result in higher capital expenditure.

From Figure 7.5, right the share of costs can be seen within process equipment groups of auxiliary equipment (pumps and compressors), separators (crystallizers, centrifuges, distillation columns, separator vessels and dryers) and reactors. It is seen that for the conventional route auxiliary equipment and separators have higher cost share (about 40 %) than reactors (about 20 %). In the direct route with the elimination of compressors auxiliary equipment have a low share. With the reduction in cost of separation equipment the share of reactors is seen to be larger for the direct route (about 40 %) showing shift in plant footprint toward more reaction dominated.

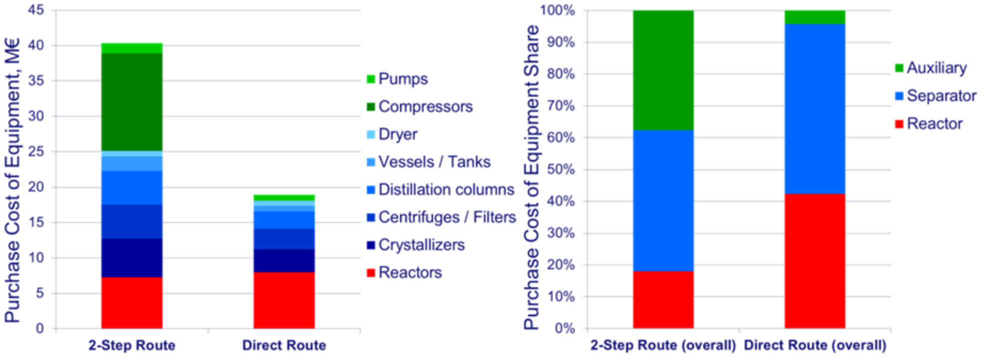

Figure 7.5. Total purchase cost of equipment (left) and share of equipment costs (right) comparison of 2-step conventional and direct route

The analysis solidified the dream of pioneers in continuous small-scale plant design, Benson and Rinard, who predicted that separation will be much reduced due to advances in flow reactor performance. Rinard made detailed analysis of a micro-reactor plant concept which he termed mini-plant production. Important criteria in this concept are JIT (just-in-time) production, zero holdup, inherent safety, modularity and the KISS (keep it simple, stupid principle) principle.[44,45] Benson and Ponton proposed the concept of distributed small-plant manufacturing referring to small scale, intrinsically safe and highly automated plants[46]

7.3.4. Life cycle assessment

The environmental profile for the direct route is detailed for impacts that were mentioned above in 7.2.4. (see Figure 7.6). Even at a glance it is obvious that the production of H_2O_2 dominates most of these impact categories. This is because H_2O_2 production is an energy and pollution intensive process. 95% of all H_2O_2 is produced on an industrial scale by the Anthraquinone oxidation (AO) process, which was developed by BASF. It involves the sequential hydrogenation and oxidation of an Anthraquinone precursor dissolved in a mixture of organic solvents followed by liquid–liquid extraction to recover H_2O_2.[47] The high energy input and generated waste has negative effect on environmental and production costs.[48] Also, the transport, storage, and handling of bulk H_2O_2 involve hazards. Moreover, H_2 as raw material for producing H_2O_2 is also made in an energy intensive process, mostly by the steam reforming of methane to generate H_2. It is seen that the H_2O_2 impact is therefore much dominant (>50%) for all toxicity-related impacts (FAETP 20a, HTP 20a, MAETP 20a and TAETP 20a).

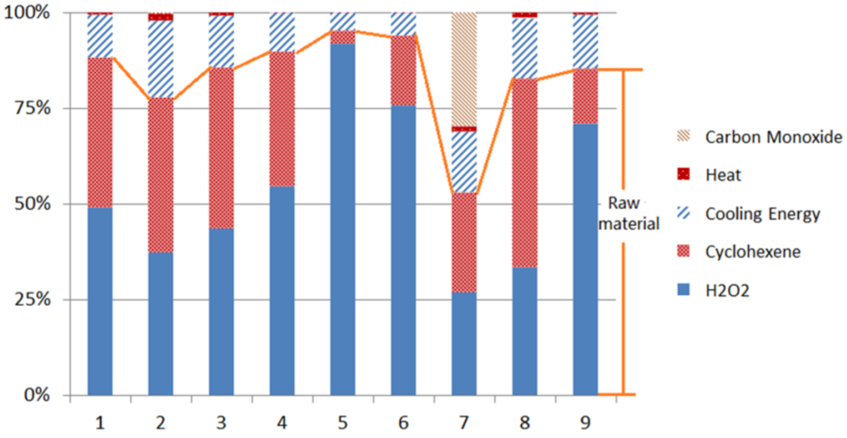

Figure 7.6. Environmental profile of the direct synthesis 50% conversion (functional unit: 1 kg adipic acid) 1. AP 2. GWP 20a 3. EP 4. FAETP 20a 5. HTP 20a 6. MAETP 20a 7. POCP 8. Depletion of abiotic resources 9. TAETP 20a. The line drawn separates raw material- from process technology contributions.

The second most dominant factor for most impact categories is cyclohexene. Cyclohexene has much lower impact on all toxicity-related impacts. It is relatively strong for the other impacts. Cyclohexene and H_2O_2 are the raw materials, the other contributions can be considered as process technology related. The strong raw material impact – clearly visible by the line drawn in Figure 7.6 – is dominant at all impact categories.

For the two-step conventional synthesis, the dominating contribution for most of the impact categories also comes from raw materials (see Figure 7.7). The nitrogen oxides is the dominating parameter for AP and EP, while the waste treatment is the dominating parameter for POCP.

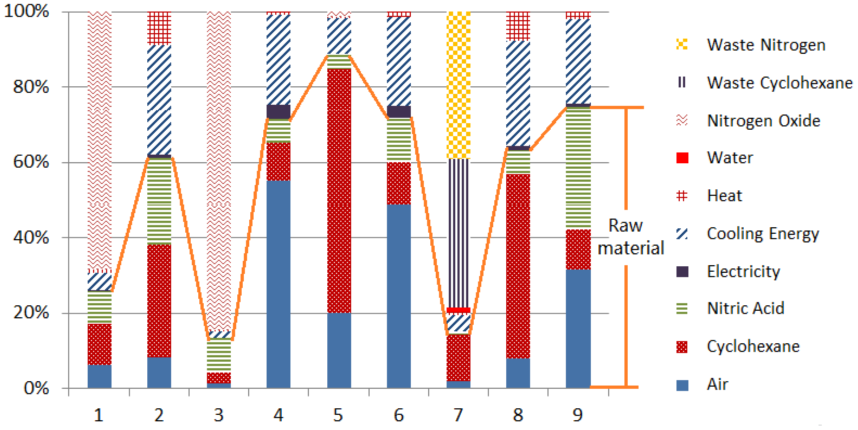

Figure 7.7. Environmental profile of the two-step conventional synthesis (functional unit: 1 kg adipic acid) 1. AP 2. GWP 20a 3. EP 4. FAETP 20a 5. HTP 20a 6. MAETP 20a 7. POCP 8. Depletion of abiotic resources 9. TAETP 20a. The line drawn separates raw material- from process technology contributions.

So far shares of material- and process-related contributions have been compared in a relative manner, normalized to 100%. In addition, a quantitative benchmarking between process options will give insight about the total amount for each impact category. Besides the 40% and 50% conversion levels taken from experimental results for the direct route, a respectively higher conversion (98%) was also taken into consideration reflecting batch conversion of direct route.

The comparison between the direct route (DR) and two-step conventional route (CR) shows lower GWP for the direct route (see Figure 7.8). Because the recycling of unreacted reactants is considered in the LCA, the GWP caused by the raw material consumption is almost the same which is around 6 kg CO_2-eq/kg adipic acid with different conversion of cyclohexene from 40% to 98%. The difference in GWP performances of two routes becomes even larger when including nitrous oxide emission in the total GWP sum-up (denoted as CR2 in Figure 7.8). The GWP of emission 1 kg N_2O equals to emission 270 kg CO_2 according to the eco-efficiency analysis by BASF.[49] Then, the GWP for conventional route increases from 6.7 to 16.7 kg CO_2-eq/kg adipic acid.

Although from the GWP point of view the direct synthesis is better compared to the two-step synthesis, it is also worse for some other impact categories. The human toxicity potential (HTP) of the direct synthesis is found to be higher compared to the two-step route (see Figure 7.9). In the direct route, the contribution of H_2O_2 to HTP is above 90%. In the two-step conventional route, cyclohexane is the main contributor to HTP, while the nitric acid has only small share. The total HTP of the conventional route is smaller than the direct route. Improved conversion does not help here as explained in the discussion of GWP as the unconverted raw material is always recycled.

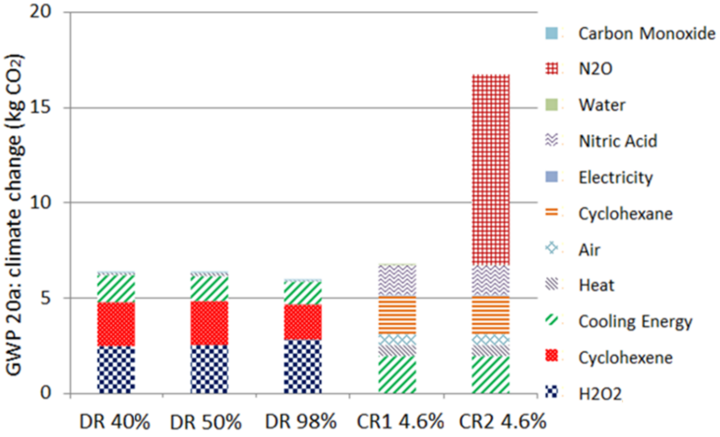

Figure 7.8. GWP for direct route with different cyclohexene conversion (40%, 50% and 98%) and also for the two-step conventional route. DR: direct route, CR1: conventional route without considering the emission of N_2O, CR2: conventional route considering N_2O emission

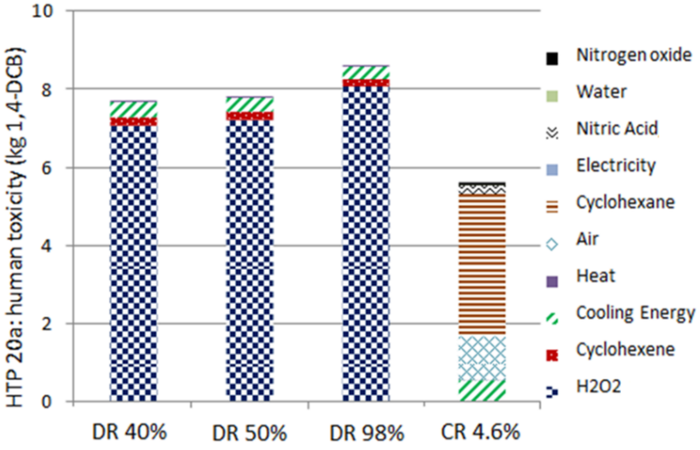

Figure 7.9. HTP for direct route with different cyclohexene conversion (40%, 50% and 98%) and also for the two-step conventional route. DR: direct route, CR1: conventional route

Figures 7.8 and 7.9 show that H_2O_2 is not "green" as claimed by chemists[22] because of its comparable GWP contribution as cyclohexene and high contribution in HTP. It is green in an atom economy and waste context (only water emission), but not in a more holistic view "from cradle to factory gate".

In order to compare the direct micro-flow and the two-step conventional routes holistically, radar figures with normalized quantitative information are an appropriate presentation approach (see Figure 7.10). The whole LCA sometimes is in (strong) favour for the direct micro-flow process, sometimes for the two-step conventional process. It is a typical multi-criteria decision. It is already seen from the findings given above; yet is spotlighted in Figure 7.10 giving results from 9 impact categories. The direct route shows much better results for the impact categories of AP, EP and POCP. The two-step conventional route has visible better results in the impact categories of FAETP, HTP and MAETP.

It is also seen that even radical process improvements (such as increasing conversion up to 98%) cannot change the overall environmental profile and advantage/disadvantage of a certain process. Exceptions are given when both the direct and conventional process have similar data on one impact. Then the smart changes possible by process intensification in direct route can have decisive character.

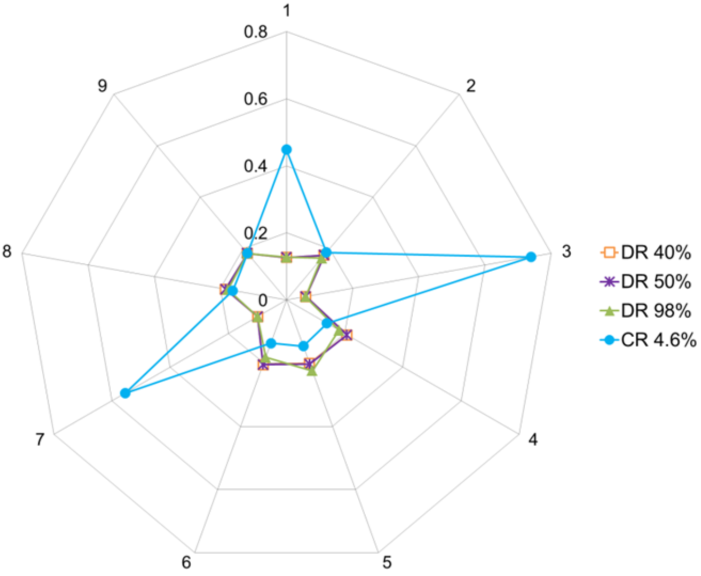

Figure 7.10. Comparison of all LCA impact categories for the direct route at different cyclohexene conversion (40%, 50% and 98%) and the two-step conventional route. 1. AP 2. GWP 20a 3. EP 4. FAETP 20a 5. HTP 20a 6. MAETP 20a 7. POCP 8. Depletion of abiotic resources 9. TAETP 20a.

7.4. Conclusion

Adipic acid can be obtained by the direct synthesis from cyclohexene using H_2O_2 as oxidant with chances for simplified process as compared to the two-step conventional process used commercially in industry. Direct synthesis in batch, however, suffers from long reaction time and safety concerns. That can be overcome by applying a micro-flow reactor for which the yield was recently increased to 50% by processing at 100 °C in 20 minutes. For the direct micro-flow process still the yield needs to be much further optimized and scale-up remains a not-tackled issue so far. Nonetheless, it is the ambition of this chapter to answer in an early stage of process development (ex-ante), if such new direct micro-flow process is feasible through economic, energy and environmental analysis. Process-design intensification through microreaction technology is new in literature and it is studied for the first time at the example of direct adipic acid synthesis.

In order to make comparison, process simulations were done using Aspen Plus^{TM} for the conventional route (two-step air and nitric acid oxidation of cyclohexane) based on the industrial production process and for the direct route following the proposed process and data on the reaction based on laboratory flow experiments. It is demonstrated that the direct flow process leads to more compact plant design owing to the need of much less process units (one reactor, less number of downstream units). Energy requirements of the two routes are determined based on the process simulation. Direct route at different cyclohexene conversion levels (40%, 50% and 98%) is considered. It is seen that due to low cyclohexane conversion and requirement of compressors, the conventional route has high energy requirement. Direct route at 50% conversion, which reflects result of current flow experiments, has 20% lower energy requirement than the conventional route.

The capital investment is then much lower for the direct route as seen from the cost of equipment calculations owing to the elimination of compressors and the reduction of downstream equipment. The cost of the more advanced flow reactor is higher but it is compensated by requiring only one in comparison with 5 reactors in conventional route. With the cost of separation equipment being lower, the share of reactor costs is seen to be larger for the direct route. Process-design intensification which is seen to enable reduction in investment costs can thus lower the main decision barrier in the management of chemical industry towards new technologies.

With LCA analysis it was seen that the production of H_2O_2 dominates most of the impacts in direct route. It was found that the direct route is better in GWP, especially evident when N_2O-impact on GWP is considered. It also shows much better results for the impact categories of AP, EP and POCP. Yet, the new proposed route has worse profile in HTP and some other impact categories (FAETP, MAETP) compared to the conventional route. Thus, the overall environmental picture is complex and there is not one better and greener process.

This direct route will be economically and environmentally attractive when low cost H_2O_2 production methods become available. When considered from cradle to process gate, the Anthraquinone process for H_2O_2 production is an energy and pollution intensive process. Only by replacing it through an environmental sustainable process, which can be the direct H_2O_2 synthesis out of the elements, the direct route will become "green" on all levels i.e. creating a double-direct route to adipic acid. Such an in situ or on-site synthesis using H_2 and O_2 in industry can also reduce the cost of H_2O_2 production, making its use economically favorable. Also changes in legislation and taxation policy regarding N_2O emission can be effective for the switch to this direct process.

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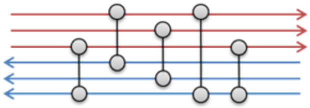

CHAPTER 8

Bulk Chemistry Heat Integration – End-to-end Process Integration at Commercial Scale

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This chapter is based on :

Vural Gursel, I., Wang, Q., Noël, T., Hessel, V. & Tinge, J.T. (2013). Improving energy efficiency of process of direct adipic acid synthesis in flow using pinch analysis. Industrial and Engineering Chemistry Research, 52(23), 7827-7835.
Vural Gursel, I., Wang, Q., Noël, T. & Hessel, V. (2013). Implementation of heat integration for efficient process design of direct adipic synthesis in flow. Chemical Engineering Transactions, 35, 775-780.

Abstract:

An energy efficient process is searched for the novel direct micro-flow route of adipic acid synthesis introduced in the previous chapter. For systematically and holistically analyzing the process and in particular its heat integration, pinch analysis is employed. Three conversion cases of 40%, 50% and 98% is considered. With the use of the Aspen Energy Analyzer the available energy recovery potential is determined and a new heat exchanger network is designed with minimum total annual cost. Compared with the initial heat exchanger network where energy requirements are supplied with utility streams, the improved heat exchanger network designed enables 50-70 % saving in operating cost which enables to pay back the extra capital cost requirement in less than one year in all cases. The benefit of heat integration is seen to be reduced with increased conversion due to the reduced heat load in the process. The heat exchanger selection is also very important design consideration. The pinch analysis is restricted to shell and tube heat exchangers, however the utilization of compact heat exchangers (including microchannel-based) which have proven advantages in thermal effectiveness, safety and reduced size can enable further

benefits in terms of total plant cost and plant complexity. Also, the opportunity to have lower operable temperature approach gives the possibility to lower the utility requirement by 20%. As a consequence, for operation of flow processes using micro-meso reactors at large scale, the utility/energy support and heat exchanger selection should be taken into consideration. Such holistic thinking has not been detailed and justified so far for micro- or similar smart-scale flow reactors, to our best knowledge.

8.1. Introduction

Process-design intensification is a new field in micro processing and it considers a completely new process design that has a new cost, energy and sustainability structure.[1–5] The investigation is started with process simplification at reaction level, which is given by replacing multi-step by direct synthesis. The demonstration example is the direct oxidation of cyclohexene with hydrogen peroxide for adipic acid synthesis. In previous studies it has been shown that the direct route enables reduction of number of process units considerably which results in the total purchase cost of equipment to be cut approximately in half and energy requirements to be reduced compared with the two-step commercial route.[3] Also life cycle assessment revealed that direct route can not be considered totally green due to energy and pollution intensive process of H_2O_2 production.[4]

Heat integration is typically employed in industrial plants to enable heat recovery by matching hot and cold process streams. This chapter focuses on its application for the direct route. In the microreactor literature it is common to consider one unit and intensify its operation. However, we consider the chemical process as a whole in a holistic context. Pinch analysis is taken here therefore to evaluate the entire process.[6] It enables heat integration by maximization of process-to-process heat recovery considering the whole heat exchanger network.

In the process simulation a basic design approach is used where the heating and cooling requirements are satisfied by the use of external utility streams such as LP steam and cooling water respectively. By employing heat integration, reduction of utility loads and consequently operating costs can be achieved. However, energy recovery always involves additional heat exchangers and hence higher capital cost. Therefore, an optimization is required so that total cost is minimized. The design of the aimed heat exchanger network is not easy considering the fact that most processes involve a large number of process and utility streams. Pinch analysis presents a powerful technique in solving these energy saving problems.[7] Initially developed by Linnhoff [8,9], this can be applied now with speed and efficiency with the use of available software programs such as Aspen Energy Analyzer.[10]

In the present work, the effort of process-design intensification is combined with pinch analysis to enable energy efficient simplified flow process design on production scale for the direct synthesis of adipic acid. Further, the importance of heat exchanger selection is highlighted with information regarding compact (including microchannel-based) heat exchangers. Software programs are restricted to conventional shell and tube heat exchangers due to lack of readily available data on compact heat exchangers. This is because of their currently limited industrial application. However, it is shown that with the use of compact heat exchangers, due to their higher heat transfer coefficient, reduced space requirement and increased safety compared to shell and tube heat exchangers, it is possible to achieve operating cost as well as capital cost reduction which can add to the benefits achieved by heat integration.[11,12]

8.2. Methodology

For the application of pinch analysis to the direct flow oxidation process a stepwise procedure is followed (Figure 8.1).

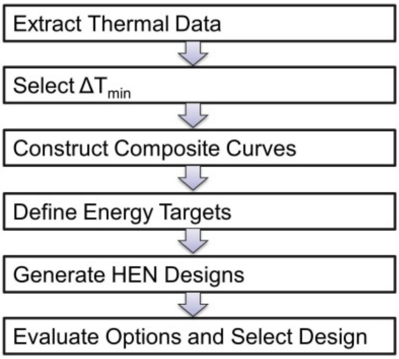

Figure 8.1. Steps of pinch analysis

The software program of Aspen Energy Analyzer is employed to carry out these steps of pinch analysis. The first step is the identification of hot, cold and utility streams in the process and extraction of thermal data that are supply temperature, target temperature and heat duty from process heat and material balance. The Aspen Plus^{TM} simulation of the direct flow oxidation process is used to extract the thermal data and they are given as input to the Aspen Energy Analyzer. Heating and cooling utilities must also be specified. For this process LP (low pressure) steam is hot enough to satisfy the heating load of the unit and cooling water is cold enough to satisfy the cooling load of the unit. Accordingly, the utilities selected for this process are LP steam and cooling water. Aspen Energy Analyzer includes a default utility database of utilities typically available on the process site. The cooling water is specified with 20°C inlet and 25°C outlet temperature. The LP steam is specified with 125 °C inlet and 124°C outlet temperature.

In order to make economical evaluation some cost data are also required, these are given in Table 8.1. Utility cost and base operating time are needed to calculate operating cost saving and heat exchanger cost is needed to estimate the investment cost. For estimating the installed cost of a shell and tube heat exchanger of carbon steel material the equation given in Table 8.1 is used where A is exchanger area in m^2.

Table 8.1. Cost data for pinch analysis

Utility cost*	€/GJ
LP Steam	11.24
Cooling Water	0.28
Operating time	8000 h/year
Heat Exchanger Cost	€
Equation**	$37614 + 916\ A^{0.81}$

* Utility cost modified from Turton et al.[13] based on current prices.

** Coefficients updated from Hall et al.[14] ($A \leq 550m^2$) based on Nelson-Farrar cost index for heat exchangers[15], 1 € = 1.25 $.

Temperatures of hot and cold streams at any point in the heat exchanger must always have a minimum temperature difference which is defined as ΔT_{min}. The next step is the selection of this ΔT_{min}. It is related to the thermal effectiveness of the heat exchanger used. Rule-of-thumb ΔT_{min} values have been developed from experience for various types of processes for shell and tube heat exchangers. High temperature processes (over 300°C) use ΔT_{min} of over 20°C, while low temperature processes (around 0°C) use ΔT_{min} of under 5°C. Processes at medium temperature use ΔT_{min} of typically 10°C[16]. Accordingly, in this study a ΔT_{min} value of 10°C is selected.

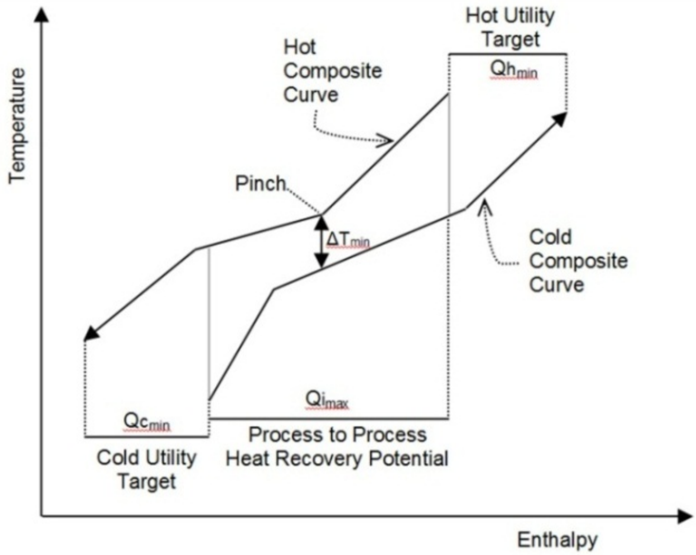

Figure 8.2. Combined composite curves on a temperature vs. enthalpy plot

With the knowledge of thermal data and ΔT_{min} composite curves are constructed with the use of Aspen Energy Analyzer. Composite curves consist of hot composite curve and cold composite curve placed together on a single temperature – enthalpy plot[7] (see Figure 8.2). The hot composite curve represents the sum of all the heat sources (hot streams) within the process whereas the cold composite curve represents the sum of all the heat sinks (cold streams) within the process.[6] These curves are separated by ΔT_{min} and where it is observed is referred to as pinch.[17] Composite curves provide a counter-current picture of heat transfer and can be used to define energy targets for the process. Heat recovery is possible in the region where the hot composite overlaps with the cold composite curve and this region indicates maximum heat integration potential.[18] The remaining heating and cooling needs are supplied by the utilities. The enthalpy difference at the upper end of the curves indicates minimum hot utility target. Similarly, the enthalpy difference at the lower end of the curves indicates minimum cold utility target.

The pinch principles are central to the procedure for designing the heat exchanger network. The main focus is to minimize the total annual cost by taking into account the energy targets (minimum hot and cold utility) of the process. Aspen Energy Analyzer is used for performing optimal heat exchanger network design. It recommends several near optimum heat exchanger network designs with its embedded optimization algorithm.[10,19] The resulting heat exchanger network designs are presented graphically with a grid diagram which shows the coupling of hot and cold streams, so the process-to-process heat exchange.

The generated design options are compared based on minimum total annual cost and the one that gives the minimum is selected. For calculating total annual cost, the capital cost is multiplied by an annualization factor in order to set it on the same basis as the operating cost. Then the addition of the operating cost and the annualized capital cost yields the total annual cost (Equation 8.1). The annualization factor is calculated with Equation 8.2[20]:

$$\text{Total annual cost (TAC)} = \text{Operating cost} + \text{Capital cost} \times \text{Annualization factor} \tag{8.1}$$

$$\text{Annualization factor} = \frac{r(1+r)^n}{(1+r)^n - 1} \tag{8.2}$$

where r is interest rate and n is the plant life. For the selected plant life of 10 years and interest rate of 10 % the annualization factor calculated is 0.162745.

In the following section, the pinch analysis performed with Aspen Energy Analyzer for the direct flow oxidation process will be described following the steps described above.

The effect of change in conversion for the direct route on the energy requirements is analyzed by making simulations at conversion levels of 40%, 50% and 98%. Conversion of cyclohexene of 40 % is based on primary result from laboratory flow experiment and 50 % is based on the current result achieved. Since the experiments are ongoing, it is likely that it can be improved further. Therefore, also conversion of 98 % was simulated which reflects the best performance achieved for the direct route in literature in batch experiments and represents the superficial best performance.

8.3. Results and Discussion

8.3.1. Data extraction

The thermal data of supply and target temperature of hot and cold streams as well as heat duty for the direct flow oxidation process is extracted from the process simulation and is given in Table 8.2 for the 40% conversion case. Heating and cooling utilities selected were LP steam and cooling water respectively.

Table 8.2. Thermal data of hot and cold streams of the direct flow oxidation process

Stream Number	Stream Name	Stream Type	Supply Temp (°C)	Target Temp (°C)	Heat Duty (kW)
1	Cyclohexene	Cold	20	90	2,705
2	30% H_2O_2	Cold	20	90	35,719
3	Cryst. 1 feed	Hot	90	50	21,450
4	Mother liquor	Cold	50	85	17,688
5	Cryst. 2 feed	Hot	85	30	18,339
6	Mixer feed	Cold	30	50	108
7	Dryer feed	Cold	50	110	3,884
8	Product	Hot	110	30	2,400

8.3.2. Defining energy targets

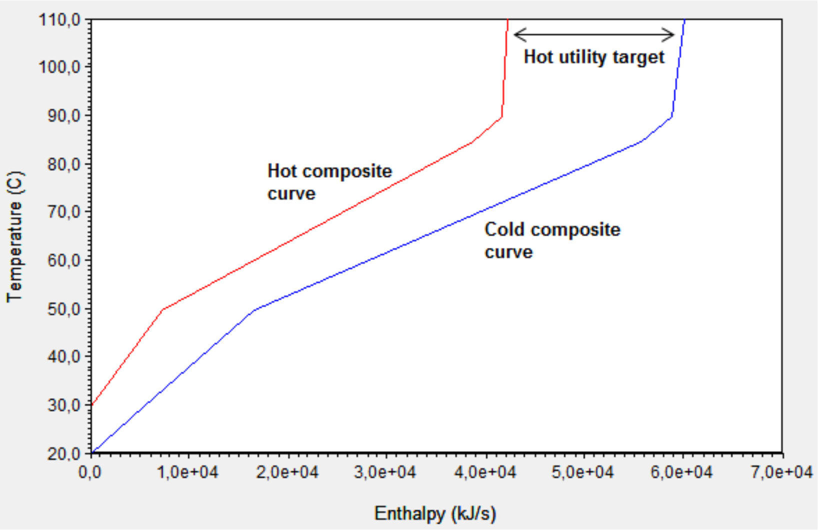

Figure 8.3. Combined composite curves of direct flow oxidation process

The hot and cold composite curves are constructed with the input thermal data and ΔT_{min} value of 10°C. In Figure 8.3 this is given for the 40% conversion case. It is seen that the minimum cold utility target is 0 and the minimum hot utility target is calculated using Aspen Energy Analyzer as 17,916 kW for the 40% conversion case. For the other two conversion cases the minimum cold utility target is also 0. The hot utility target for the 50% conversion case is 16,560 kW and for the 98% conversion case it is 13,492 kW. The heat exchanger network designs to be generated will be based on these targets for minimum energy consumption.

8.3.3. Initial heat exchanger network

The initial network for direct flow oxidation process has all the heating and cooling requirements of process streams satisfied by utility streams. The heat exchanger network based on this basic design can be conveniently revealed by a grid diagram (see Figure 8.4, top) that shows how individual process streams and utility streams of LP steam and cooling water are matched with heat exchangers.

Hot process streams flow direction is from left to right and cold process streams run from right to left. A red marking of a heat exchanger indicates a heater with the use of hot utility and a blue marking of a heat exchanger indicates a cooler with the use of cold utility. If process-to-process heat exchanger was available it would have been shown with a grey colour. It is seen that this heat exchanger network can be improved with process-to-process heat exchange.

8.3.4. Designing heat exchanger network with pinch analysis

Aspen Energy Analyzer is used to generate heat exchanger network (HEN) design options to satisfy most closely the energy targets. It has an embedded optimization algorithm that minimizes the total annual cost subject to these constraints. Table 8.3 gives the total heat exchanger area, capital investment, hot utility duty, cold utility duty and annual operating cost results for the generated best two design options for the three conversion cases.

Table 8.3. Generated best two HEN design options of direct flow oxidation process for three conversion cases

Design options	Area (m^2)	Capital cost (10^6 €)	Hot utility (kW)	Cold utility (kW)	Operating cost (10^6 €/y)
40 % Design 1	43,515	13.02	18,516	600	6.00
40 % Design 2	48,124	14.26	17,916	0	5.80
50 % Design 1	30,084	9.12	16,560	0	5.36
50 % Design 2	29,315	8.89	16,851	291	5.46
98 % Design 1	9,400	3.24	13,492	0	4.37
98 % Design 2	8,642	3.01	14,150	658	4.59

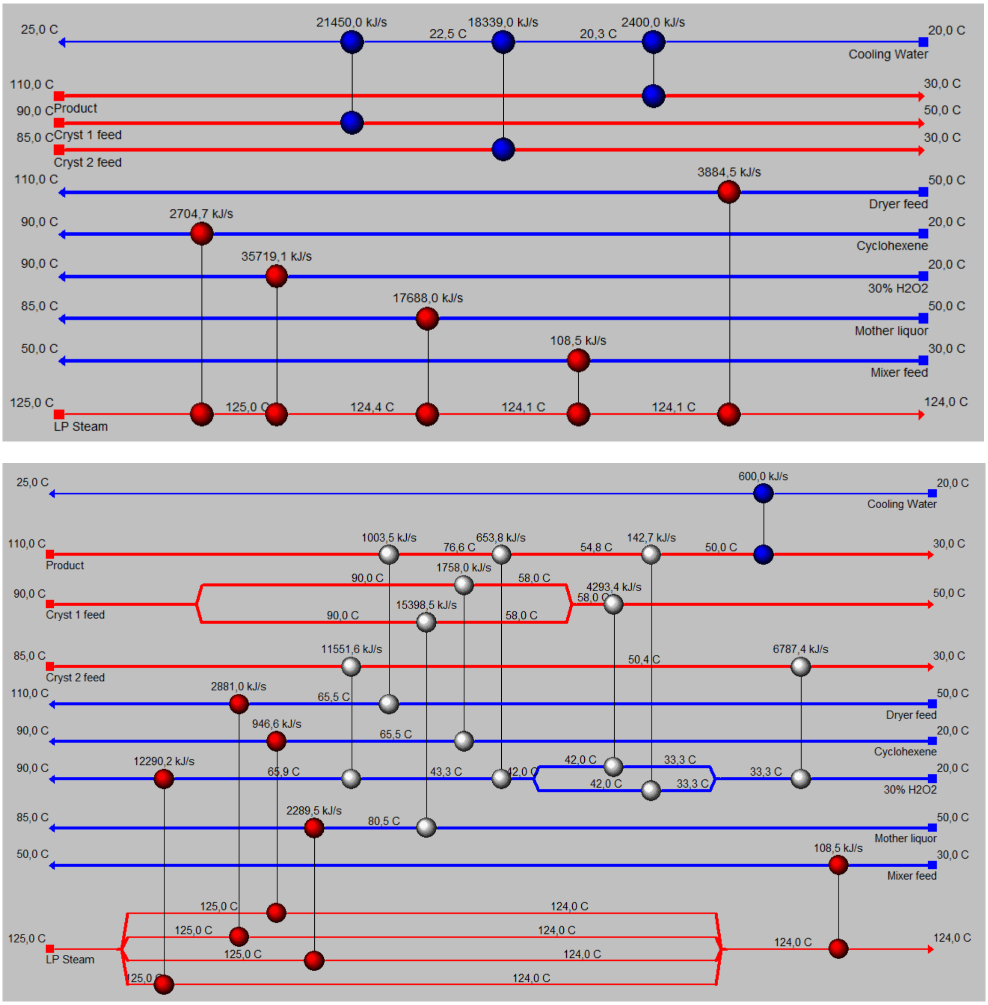

Figure 8.4. Grid diagram of initial heat exchanger network (top) and improved heat exchanger network (bottom) for the direct flow oxidation process (40% conversion case)

It is seen that for example for 40 % conversion case, design 2 enables satisfying minimum energy targets but at a higher capital cost. In order to be able to select the best design option for each conversion case, total annual cost (TAC) calculation needs to be made. It is found using Eq. 8.1 and 8.2 explained above. The calculated TAC of the design options for the three conversion cases is given in Table 8.4. Design 1 is found to be the best design option with minimum TAC for all three conversion cases. The HEN of design 1 for 40% conversion case is presented with a grid diagram in Figure 8.4, bottom. For this design there are fourteen heat exchangers. Eight of the heat exchangers achieve process-to-process heat recovery which indicates the improved energy efficiency of the direct flow oxidation process. Of the remaining six, five is supplied with hot utility of LP steam and one is supplied with cold utility of cooling water. The improved HEN of direct flow oxidation process for the other conversion cases of 50% and 98% are given in the appendix.

Table 8.4. TAC of best two HEN design options of direct flow oxidation process for three conversion cases

	40 % Design 1	40 % Design 2	50 % Design 1	50 % Design 2	98 % Design 1	98% Design 2
TAC, 10^6 €/y	8.117	8.120	6.845	6.904	4.894	5.077

The generated improved HEN results are compared with the results of the initial network without heat integration as seen in Table 8.5. In order to achieve process-to-process heat exchange more heat exchangers are required in the improved HEN, resulting in increased capital cost. However, the hot and cold utility requirements are very much reduced indicating a reduced operating cost. The operating cost for 40 %, 50 % and 98 % conversion is calculated to be reduced by 70 %, 68 % and 50 % respectively. With the increase in conversion the heat load in the system is reduced creating less room for improvement. Accordingly, the benefit achieved with heat integration is seen to be reduced.

Table 8.5. Comparison of improved HEN with initial HEN for three conversion cases

	Area (m^2)	Capital cost (10^6 €)	Hot utility (kW)	Cold utility (kW)	Operating cost (10^6 €/y)
40 % Initial HEN	11,836	3.73	60,105	42,189	19.80
40 % New HEN	43,515	13.02	18,516	600	6.00
50 % Initial HEN	9,257	2.99	48,859	32,299	16.08
50 % New HEN	30,084	9.12	16,560	0	5.36
98 % Initial HEN	4,278	1.60	26,773	13,281	8.77
98 % New HEN	9,400	3.24	13,492	0	4.37

Pay-back time can be calculated to see how long it takes for the operating cost saving to pay back the extra capital cost requirement. This is given in Table 8.6. It is seen that with the improvement of the HEN major saving in operating cost is achieved which enables to pay back the extra capital cost requirement in less than one year (4.5 – 8 month) in all cases. These results indicate that that heat integration is a useful technique for efficient design of processes as it results in more sustainable and economical condition.

Table 8.6. Pay-back time for three conversion cases

Conversion Case	Capital cost (10^6 €)	Operating cost saving (10^6 €/y)	Pay-back time (months)
40 %	13.02	13.80	11.3
50 %	9.12	10.72	10.2
98 %	3.24	4.41	8.8

To estimate the cost of plant or inside battery limit (ISBL) investment, besides cost of equipment, the cost of equipment delivery, installation, piping, instrumentation, electrical and civil work should also be taken into consideration.[21] The total purchase cost of equipment for the direct route representative of 40-50% conversion was estimated in Chapter 7 as 18.9 M€. The total delivered cost of equipment (E) is found to be 25 M€ adding 15% delivery cost to the purchased equipment cost and 15% contingency on estimation. ISBL can be estimated with factorial estimation where typical factors for the other cost contributors based on delivered cost of equipment are present in literature and are given in Table 8.7. The sum of these factors is 2.2 for a fluids-solids process type[21] making the ISBL cost 3.2 times the total delivered cost of equipment. The ISBL cost calculated in this way is found to be approximately 80 M€.

The fixed capital investment can also be estimated with a factorial estimation which is the sum of ISBL cost, offsite cost, engineering cost and contingency. Offsite (OS) cost can be calculated as 40% of ISBL cost.[21] Engineering cost then can be calculated as 25% and contingency as 10 % of ISBL plus offsite cost.[21] The fixed capital investment is then found as 1.89 times the ISBL cost. The capital investment calculated in this way amounts to approximately 150 M€ (see Table 8.7). It can be seen that the annual operating cost saving achieved with pinch analysis of 13.8 M€ for 40% conversion case can enable to pay out the plant cost (ISBL) of 80 M€ in approximately 6 years.

Table 8.7. Plant cost estimation

	Fraction		Cost, M€
Total delivered cost of equipment(E)	1.0	of E	25.0
Purchased equipment installation	0.5	of E	12.5
Piping	0.6	of E	15.0
Instrumentation & controls	0.3	of E	7.5
Electrical systems	0.2	of E	5.0
Civil work	0.3	of E	7.5
Structures and buildings	0.2	of E	5.0
Lagging and paint	0.1	of E	2.5
ISBL Investment	3.2	of E	**80.0**
Offsite cost (OS)	0.4	of ISBL	32.0
Engineering cost	0.25	of (ISBL+OS)	28.0
Contingency charges	0.1	of (ISBL+OS)	11.2
Fixed Capital Investment	1.89	of ISBL	**151.2**

8.4. Design Considerations – Compact Heat Exchangers

Pinch analysis presents a novel approach that integrates the design of heat exchange system to the design of the core process. It is seen in section 8.3 that with its application major reduction in utility consumption and correspondingly operating cost saving can be achieved. Another important consideration in process design is heat exchanger selection. However, current design procedures are mainly based on the use of shell and tube heat exchangers. This is because software programs handle only this heat exchanger type[17]. This is mainly due to lack of readily available data on compact heat exchangers because of their currently limited industrial application.

Numerous articles have been published regarding the advantages of compact heat exchangers which are characterized by having a high area density; the ratio of heat transfer surface to heat exchanger volume.[11,12] A typical shell and tube exchanger has an area density of around 100 m^2/m^3 on one fluid side.[12] A compact heat exchanger has an area density over 700 m^2/m^3 in gas side of a gas-liquid heat exchanger and over 400 m^2/m^3 for liquid-liquid heat exchanger.[12] Micro heat exchangers being the most compact have an area density greater than 10,000 m^2/m^3.[11]

8.4.1. Commercial microchannel-based heat exchanger examples

The microchannel-based heat exchanger technology enables enhanced heat transfer realized from large area density and heat transfer coefficients that are much higher than typically seen in conventional heat exchangers.[22] This feature allows the microchannel heat exchangers to be compact and lightweight. By arranging microchannel in pure counter current flow pattern, high thermal effectiveness of 99 % is possible.[23] In contrast to 6-8°C or even 10°C approach of conventional shell and tube heat exchangers, a less-than 1°C temperature approach is available which can enable significant operating cost saving.[24]

IMM develops prototype micro heat exchangers suitable for pilot or small scale production plants. Laser-welded (WT-series) and brazed (HX-series) type micro heat exchangers are available.[25] They are developed for liquid/liquid, gas/liquid or gas/gas applications. Counter- or co-current flow regimes are possible. The core elements are chemically etched microstructured plates in many cases, but rolled or embossed devices are on their way to reduce the fabrication cost.[25] As the name implies, they are joined by high precision laser-welding or brazing technology forming a stack of aligned plates. They enable enhanced heat transfer with their high inner specific surface. The brazed series are suitable for applications at high temperature (up to 800°C) and pressure (up to 500 bar).[25] When coated with catalyst, the heat exchangers can also be used as chemical reactors.

Printed circuit heat exchanger (PCHE) is an established micro- and millichannel heat exchanger technology commercially manufactured by Heatric Company.[26] The core matrices are formed by chemically milling microchannels (under 200 μm) or millichannels (up to 3 mm) into flat metal plates and then diffusion bonding the plates together into a single block.[23] The complete heat exchanger is composed by welding together as many of these blocks as the thermal duty required. Diffusion bonding is a solid state joining process which gives parent metal strength and ductility throughout the entire exchanger[23]. No gaskets or braze materials are required for the assembly making the potential for leakage and corrosion reduced to minimum.[26] Because of the compactness provided by its design they are up to 85% smaller and lighter than an equivalent shell and tube heat exchanger.[26] Obviously, this reduction will cut the material and installation cost noticeably. Flexibility is another feature of PCHE. The standard construction material is stainless steel but it can be constructed out of a range of materials to meet process requirements. In this way they have very large temperature capability from cryogenic (-200°C) to 900°C.[11] With its structure it can operate at pressures of more than 600 bar.[26] They are also able to incorporate multiple process streams into a single unit reducing exchanger and piping complexity simplifying process control.[26] They can also incorporate additional unit operations such as chemical reaction, mass transfer and mixing.[26]

8.4.2. The benefits of compact heat exchangers

A major advantage of compact heat exchangers is their high thermal effectiveness. The effectiveness can be defined as the ratio of the actual heat transfer to the maximum possible heat transfer[11]. A higher effectiveness implies a closer temperature approach (see Figure 8.5). This gives possibility of further operating cost saving as explained in section 8.4.3.

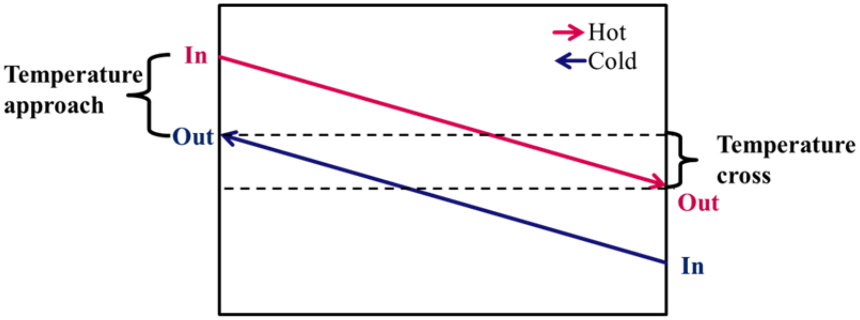

Figure 8.5. Schematic representation of temperature approach and temperature cross

Most compact heat exchangers allow the application of pure countercurrent flow which enables better use of temperature driving force.[27] It is most valuable when there is a temperature cross (see Figure 8.5). For shell and tube heat exchangers the solution is to use multiple shells in series whereas in case of compact this can be achieved with single heat exchanger.[27] This gives possibility of capital cost reduction as explained in section 8.4.3.

Another major advantage of compact heat exchangers is their reduced size and weight.[11] Figure 8.6 shows for the same heat transfer duty reduction in size and weight compared to shell and tube heat exchanger. This makes installation easier and less costly. For shell and tube heat exchangers the installation factor is approximately 3 whereas it ranges from 1.5 to 2 for compact heat exchangers depending on the size of the unit.[27] Thus compact heat exchangers can be cheaper in view of the total installed cost; especially in the case when the heat exchanger has to be made from expensive material. Also, for a new plant design a reduction in plant size can be achieved reducing investment cost.

Figure 8.6. Size and weight comparison of a PCHE (front) and a shell and tube heat exchanger for same duty[28]

Compact heat exchangers also have improved safety. They have much reduced hold-up which makes handling hazardous fluids safer.[11] The tube rupture hazard in shell and tube heat exchangers is eliminated.[26] They are also less prone to fouling and are able to cope with rapid temperature changes.[29]

Shell and tube heat exchangers handle only one hot stream and one cold stream. Some compact heat exchangers (plate-fin and printed circuit) can enable multi-streaming.[11] Figure 8.7 depicts the multi-streaming possibility with a PCHE. This enables additional to reduced plant complexity, major reduction in heat exchange area and accordingly cost.

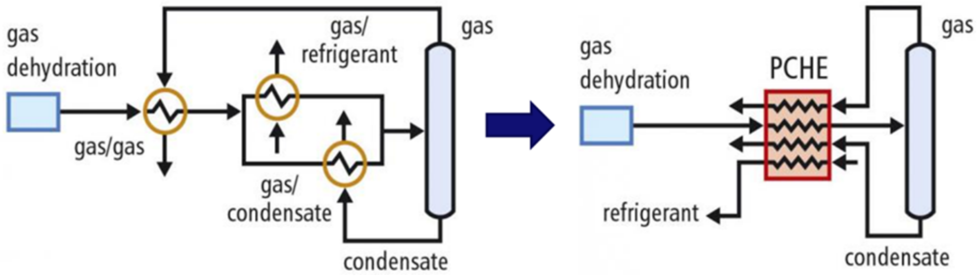

Figure 8.7. Multi-streaming possibility enables PCHE to replace three conventional units[28]

Many of these benefits of compact heat exchangers can only be realized if the heat exchanger selection is handled at the earliest stages of plant design. Especially the saving in terms of weight and space cannot be seen if the plant layout is already set for shell and tube heat exchanger. The installed cost should be taken into consideration rather than the purchase cost since this gives the effect on total cost. Also, the heat exchanger network design would be different with the improved thermal effectiveness (closer approach temperature), pure counter flow and multi-streaming. Therefore, in view of total plant cost the most economic heat recovery can be achieved if the selection of heat exchanger is undertaken from the beginning considering available heat exchanger technologies. It is believed that, as the compact heat exchangers become more widely known and applied there will an increasing demand toward them for general application instead of shell and tube heat exchangers. Using such innovative tools means considering the effect of process intensification also on the utility side aiming at decreasing the size of the plant, thereby rendering a true holistic picture of the intensification.

8.4.3. Heat exchanger network design change implications

With the pure counter current flow achieved with compact heat exchangers major advantage in terms of capital cost can be attained in case of temperature cross. Whenever there is a temperature cross (cold stream heated to a temperature greater that the outlet temperature of the hot stream) the duty is split into multiple shells in series for shell and tube heat exchanger design.[17] For the direct flow oxidation process studied here three heat exchangers have a high number of shells due to presence of temperature cross for the 40% conversion case and they make the major part of the capital cost requirement. These heat exchangers are presented in Table 8.8 for 40% conversion case. Their total cost is found to contribute to more than 80% of the total capital cost requirement given in Table 8.6.

Table 8.8. Heat exchangers with temperature cross of direct flow oxidation process of new HEN (40 % conversion case)

Heat exchanger	Area (m^2)	Capital cost (10^6 €)	Number of shells	Hot T in (°C)	Hot T out (°C)	Cold T in (°C)	Cold T out (°C)
1	5514	1.6	12	50	30	20	33
2	10712	3.1	24	85	50	43	66
3	20734	5.9	44	90	58	50	80

With the use of microchannel-based heat exchangers, series of shells used for shell and tube design can be replaced with single compact heat exchanger. This major reduction in the heat transfer area results in smaller units to be used in plant which reduces plant complexity, making operation and control easier and maintenance cheaper. It also enables capital cost saving by replacing number of units with a single small unit. It is estimated that in this way the capital cost requirement of heat exchangers can be cut at least by half. This also indicates that the operating cost saving will enable to pay back the extra capital cost in even shorter time.

It was explained that with the high thermal effectiveness of compact heat exchangers temperature approach can be reduced. This has the potential to reduce the operating cost by bringing the composite curves closer to each other increasing the process-to-process heat integration.

For the direct flow oxidation process studied here there is total overlap of the composite curves at ΔT_{min} of 10°C as can be seen in Figure 8.3. In these cases of total overlap the positive effect of decreasing ΔT_{min} value on reduced operating cost cannot be seen. In case of partial overlap this reduction in temperature approach will enable reduction of utility and correspondingly operating cost. It can therefore be said that the use of microchannel-based heat exchangers will be advantageous only in this case. This situation is shown for one process example (from Aspen tutorial guide[19]) in Figure 8.8.

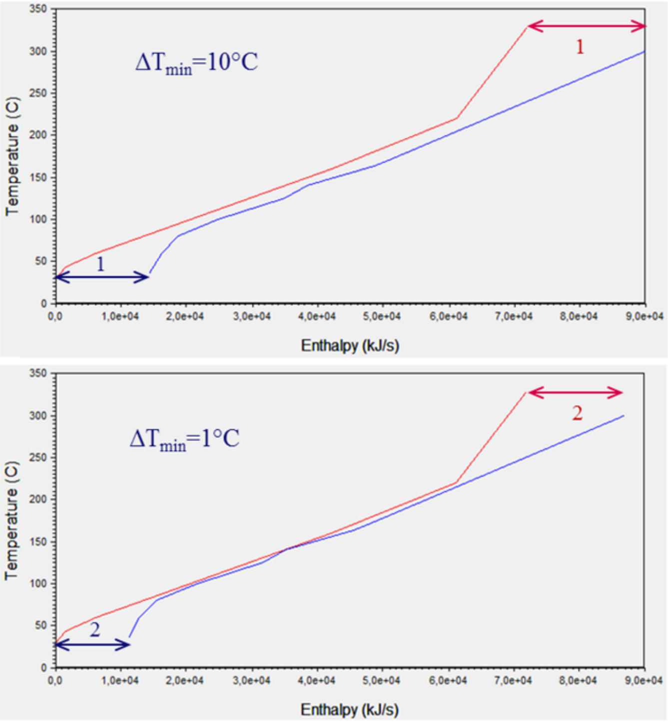

Figure 8.8. Combined composite curves of Aspen tutorial guide example process with ΔT_{min} = 10 °C (top), ΔT_{min} = 1 °C (bottom)

In top figure the composite curves at ΔT_{min} of 10°C and at bottom figure the composite curves at ΔT_{min} of 1°C is shown. The cold and hot composite curves have partial overlap and with the reduction of approach temperature they get closer enabling higher process-to-process heat recovery and thus lower utility requirement. In Figure 8.8, cold utility requirement is shown with a blue two sided arrow and hot utility requirement is shown with a red two sided arrow. Also, ΔT_{min} of 10°C is denoted as 1, ΔT_{min} of 1°C is denoted as 2. Same denotation is used in Figure 8.9. The reduction in utility requirements are given in Figure 8.9. Decreasing ΔT_{min} from 10°C to 1°C enables about 20% reduction in both hot and cold utility resulting in operating cost saving.

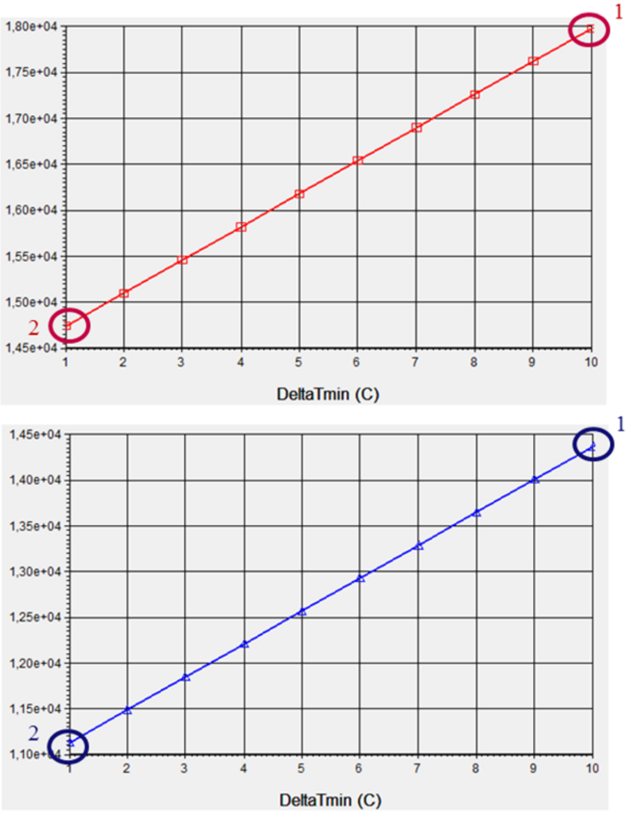

Figure 8.9. Hot utility (top) and cold utility (bottom) requirements vs. ΔT_{min} for Aspen tutorial guide example process

8.5. Conclusion

This chapter shows that intensification on the utility side is of primary relevance for process design intensification of flow processes in micro- or similar smart-scaled reactors at large capacity, beyond fine chemistry. As such, it probably can constitute a strong pillar in the overall process-design intensification.

The direct oxidation of cyclohexene with hydrogen peroxide for adipic acid synthesis was taken as the example for process-design intensification to investigate its potential for process simplification. It was seen in previous chapter through process simulation that this direct route leads to a more compact plant design. To design an energy efficient heat exchanger network for this novel direct flow route in this chapter pinch analysis and the software Aspen Energy Analyzer is employed. The design is selected from the alternatives provided by the software by making a total annual cost calculation. By following the stepwise procedure of such pinch analysis an improved heat exchanger network design is achieved for the three conversion cases considered: 40% (representing primary result), 50% (representing current improved result) and 98% (representing superficial best performance). Compared with the basic design where the heating and cooling requirements are satisfied by the use of utilities, the improved design enables 50-70 % operating cost saving. It is calculated that this saving pays back the extra capital requirement for the heat exchangers in 4.5 – 8 months.

Heat exchanger selection is also a very important design consideration which should be handled at the earliest stages of plant design so that in view of total plant cost the most economic heat recovery can be achieved. However, the current software programs are restricted to conventional shell and tube heat exchangers due to lack of readily available data on compact heat exchangers. Compact heat exchangers have proven advantages in terms of thermal effectiveness, safety, size and weight. With their improved heat transfer that enable operation with approach temperature as low as 1°C, they give the possibility to reduce the utility requirement by 20%. They can also enable saving in the total plant cost and enable a reduction in plant complexity with the pure countercurrent flow achieved. For the case of temperature cross they can achieve the additional capital cost to be halved. As their application increase in industry and their benefits are most widely recognized it is believed that there will be an increasing demand towards them.

In conclusion, the use of microprocess or other smart-scaled technology can achieve considerable capital cost and energy consumption reduction through process-design intensification lowering the management’s main decision barrier towards new technologies. Yet, considerable challenges are expected when releasing the theoretical potential into industrial practice.

8.6. Appendix

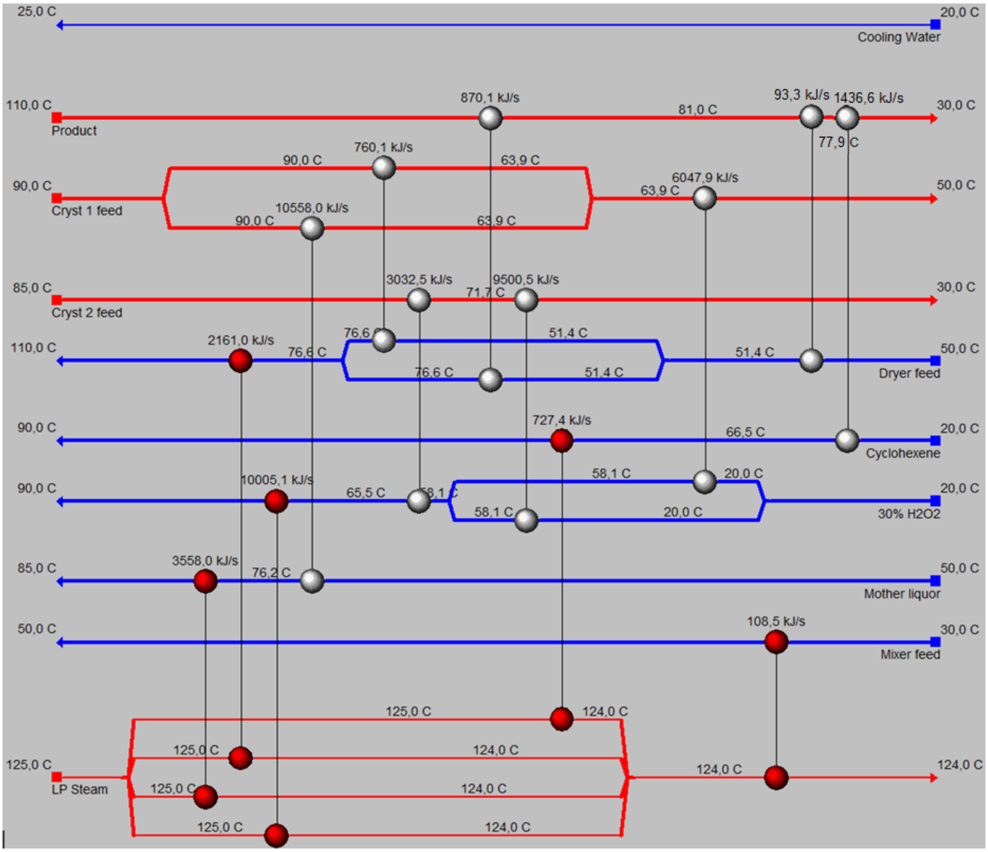

Figure 8.7. Grid diagram of improved heat exchanger network for the direct flow oxidation process for 50% conversion case

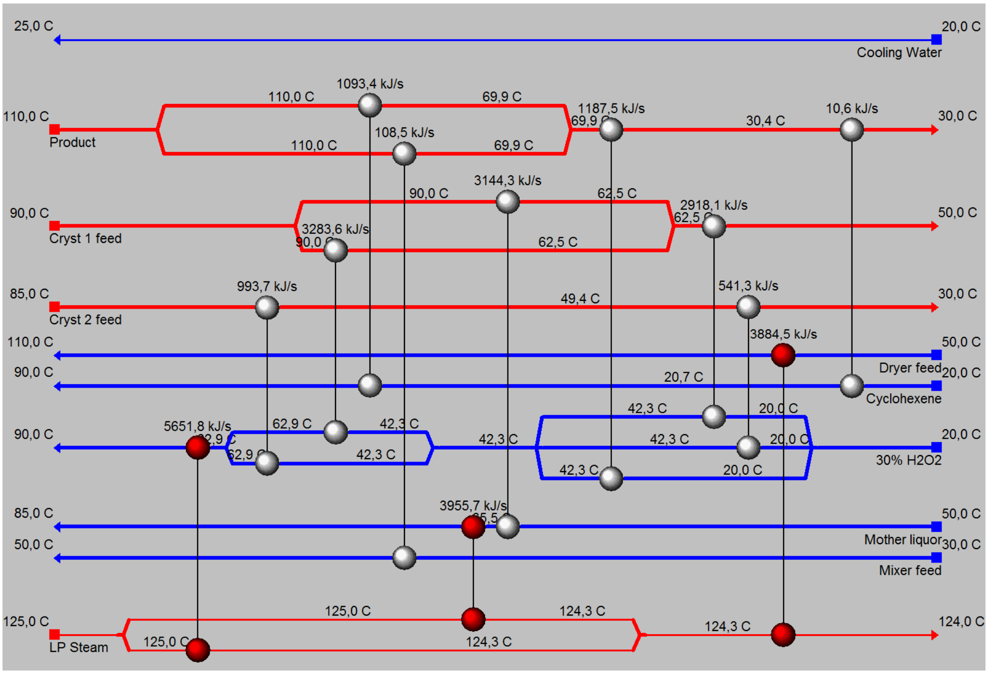

Figure 8.8. Grid diagram of improved heat exchanger network for the direct flow oxidation process for 98% conversion case

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CHAPTER 9

Conclusions and Recommendations

9.1. Conclusions

Research Highlights in this Œuvre at a Glance:

- Process-design intensification was predicted for the first time by the ERC Advanced Grant in 2010 and the research presented here is the first manifest of that concept.
- Theoretical potential analysis of process development time reduction for case scenarios in fine and bulk chemistry was done as a function of the three intensification fields and plant modularity. Before in literature, only the latter was predicted.
- A continuous metal scavenging unit was developed and coupled to a CuAAC click reaction in flow enabling to reach pharma-grade purity level (ppm) in 1 stage of extraction
- Coupled reaction-separation in flow has very few demonstrations and this was successfully conducted here; even at the example of a one-pot synthesis.
- Scale-up of liquid-liquid extraction unit was done using milli-scale CFI and a phase separator, and gave ~20% higher extraction efficiency compared to straight tube setup.
- The use of the CFI for immiscible liquid-liquid mixing and its application for liquid-liquid extraction was reported for the first time
- The study of flow separators that can handle flow rates suitable for pilot scale pharmaceutical production is very rare and this was successfully achieved here
- Slug flow regime was maintained at 7.2 l/h (highest reported in literature) and the micro effect of capillary force was able to be used for phase separation at such high flow rate
- A detailed cash flow analysis for a modular plant was reported for the first time to quantify the benefits and to make comparison with conventional plants
- The combination of smart-scaled process-intensified equipment with modular compact plants was analyzed and they were found synergistic in costs
- An initial techno-economic analysis was done to analyze the feasibility of a novel process for biofuel production considering decentralized production in modular plants; also here in literature only rare information is given.
- The process simplification potential of a direct adipic acid synthesis route was investigated by cost, energy and environmental analysis at world-scale capacity
- The latter involved a comprehensive end-to-end Aspen simulation analysis of using small-scale flow processing at world-scale capacity for the first time.
- Heat integration for the direct adipic acid synthesis was achieved with pinch analysis and compared to initial design significant utility cost saving is attained

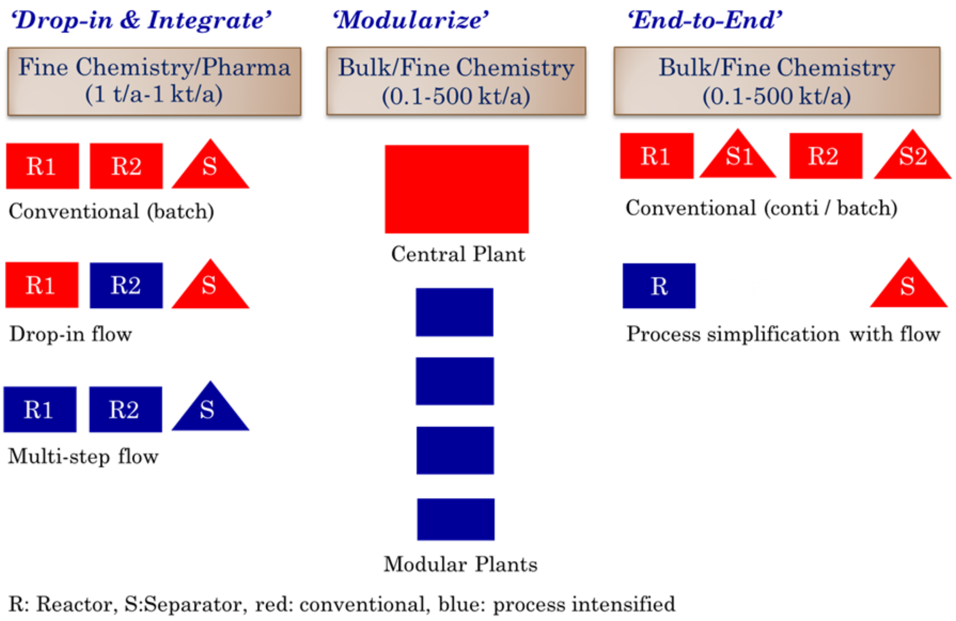

Figure 9.1. A schematic representation of the three main parts of this thesis

From intensified reactor to intensified process engineering

Chapter 1 outlines the synergy of micro dimensions and harsh operating conditions which results in a three-step intensification within a reaction system: transport, chemical and process-design intensification. Transport intensification that improves mass and heat transfer has been vastly demonstrated. Emerging chemical intensification uses highly intensified, unusual and typically harsh process conditions to boost micro-processing (high-T, high-p, high-c, safety). This was predicted first in 2005 by Hessel[1] and resulted finally in the ERC Advanced Grant in which this work was done. Process-design intensification was in this grant and particular in this thesis explored as a new field in micro processing. It heads for integrated and simplified smart-scaled (micro-meso) flow process design in a holistic picture. The latter two constitute Novel Process Windows.

After having seen almost two decades of flow-related developments of micromixers, microreactors, micro heat exchangers, and recently microseparators, the time was ripe for the next round of the implementation of microreactor and flow techniques. This is devoted towards bringing all of the above-mentioned devices together (drop-in & integrate), scaling these up to industrial productivity and embedding them in a modern Future Factory type plant environment (modularize) with an overarching process and plant approach. A final, yet still too less exploited consideration is the chance for radical changes in process design by process simplification (end-to-end), e.g. by newly developed chemical transformations such as direct synthesis in flow. These concepts are schematically given in Figure 9.1.

Potential of process development time reduction through flow processing

In Chapter 2, case scenarios are considered with stepwise intensification covering the three intensification fields of flow processing and the use of modular plants. Such paradigm changes in process development can enable a faster development to the final production plant through reduction in the number of apparatus in the plant, reduction in apparatus size, and higher predictability in the scale-out of the apparatus. Their effect is shown in a generic (impact-wise) manner giving an idea of their impact on the process development time in bulk and fine chemistry. The distribution into individual impacts allows to assess which approaches in intensification ensure already today a good practice in fastened process development, which are better used in near future, and which do not save time in process development at all. It is seen that time savings in process development are likely for fine-chemical applications up to the border of bulk-chemical processes; but that for true bulk-chemical applications, the cost and sustainability arguments are the main motivation for investigation.

Connected reaction and metal separation in flow

One possibility to bring step-change improvement in chemical production was seen to be through enabling multi-step synthesis in flow which is especially attractive to facilitate switch to continuous processing for fine chemistry/pharmaceutical production. The essential base unit hereto is coupled reaction-separation. Chapter 3 describes accordingly the development of a continuous metal separation unit which enables liquid-liquid extraction based on slug flow using chelating agents and phase separation with a porous fluoropolymer membrane. Its performance was optimized by investigating the use of different types of copper catalysts and metal scavengers together with variation of metal scavenger concentration and pH. It was successfully coupled to the copper-catalyzed azide-alkyne cycloaddition reaction studied in one-pot (eliminating the need to isolate and handle potentially explosive azide). The triazole product was attained in flow with yield of up to 92% and the level of purity requirement for pharmaceuticals of 15 ppm was met in one stage of extraction.

Scale-up of flow extraction unit utilizing CFI

The vision is to achieve such multi-step synthesis in flow on pilot scale. This calls for scale-up of separation units. This study is rare in micro flow literature and was conducted in Chapter 4. A liquid-liquid extraction setup was developed using milli-scale CFI (3.2 mm ID, 210 cm length) and a phase separator. Two separator concepts were investigated: a PTFE membrane flow separator and a slit shaped flow separator composed of glass and Teflon rectangular capillaries. The extraction performance of the setup was tested for the two widely used and EFCE recommended model systems of toluene-water-acetone and n-butyl acetate-water-acetone. For toluene-water-acetone, a flow rate up to 120 ml/min was studied which corresponds to 7.2 l/h and 58 m^3/y. It is important to point out that the slug flow regime that is considered limited to microfluidics is maintained even at such pilot scale. For both systems close to thermodynamic extraction efficiency was achieved (96% for first, 100% for second). Compared to a straight tube, the CFI showed 20 % higher performance at high flow rates most likely due to the Dean vortices which is intensified by the flow inversions in the CFI. In straight tube, parallel flow developed at higher flow rates whereas the CFI kept operating in the slug flow regime.

Compact modular plants

Another possibility to bring step change improvement in chemical production is the use of compact, modular plants. They are seen as key to faster market introduction of a new product (50% idea) by shortening time-to-market resulting in higher cash flows. In Chapter 5, a detailed calculation of capital investment and operating cost for a modular plant was done, at the example of Evotrainer production platform of Evonik Industries, quantifying the benefits of modular design. The step-change character of process intensification and smart-scale technologies such as microstructured reactors is considered, in particular to check if they add to the advantage of modular compact plants. For a fine chemical example, six scenarios were considered: two plant type (conventional, Evotrainer) and three processes (batch, micro, virtual micro of high yield). In comparison to the conventional plant, the use of the Evotrainer infrastructure resulted in significant higher Net Present Value (NPV) to be achieved with the reduction in construction period. Considering the process type, microreactor (or generally intensified) processes were seen to have a higher NPV than that of the batch processes, due to the profound effect of the reduction in operating cost achieved. It was seen therefore that the modular plants and micro process technology can be synergistic in costs.

Decentralized production with modular plants

The modular plants are also beneficial because of their flexibility and scalability. Therefore, they are ideally suited for decentralized production such as biomass conversion processes (‘Chemistry on Wheels’; Evonik promotion name[2]). This is because biomass is widely distributed and its composition and overall amount differs from location and season. Therefore, decentralized production close to resource is beneficial to save from transportation and storage costs. Yet, plant modularity at small scale has its price (seemingly violating the economy of scale) and thus holistic cost calculations, which show if the total cost is positive or negative, are rare for decentralized biomass plants. Finally the plant has to meet current gasoline fuel prices, costing enables a check if the goal was reached.

With such motivation, a holistic cost calculation was done for the application case of decentralized biofuel production in Chapter 6. It involves an initial techno-economic analysis to analyze the feasibility of a novel process for biofuel production. Process integration and intensification was achieved by coupling of reforming of biogas and bio oil in a microchannel plate heat exchanger. In this process via methanol, neither challenging gas separation nor extensive light gas recycle loops were required in contrast to Fischer-Tropsch based routes. Therefore a compact process design was attained with high carbon and energy efficiency. Cost calculations showed that these benefits can outweigh the higher investment cost of decentralized plants especially with the use of modular plants that are flexible to production capacity and that can be built in short time. Cost calculations showed that with the total cost of production of gasoline at € 0.5/L; this biofuel production process can be economically competitive with petroleum-based and Fischer-Tropsch process.

Process simplification of a bulk chemical synthesis

Finally, a step change improvement can be realized by bringing direct chemistries on a full-process level. The demonstration example taken was the direct adipic acid synthesis which is an important intermediate for the nylon-6,6 industry. Chapter 7 described the investigation of the process simplification potential of this direct route by cost, energy and environmental analysis. To propose the flow diagram and conditions for this direct route, the reaction characteristics were considered together with the downstream equipment of the two-step commercial route. A reduction in step of synthesis led to a compact plant design owing to the need of much less process units (one reactor, less number of downstream units) compared to the commercial route carried out in two-steps. This resulted in the total purchase cost of equipment to be halved although a more advanced and very costly flow reactor was used. Process-design intensification which is seen to enable reduction in investment costs can thus lower the main decision barrier in the management of chemical industry towards new technologies. The analysis solidified the dream of pioneers in continuous small-scale plant design, Benson and Rinard, who predicted that separation will be much reduced due to advances in flow reactor performance.[3–5]

Through simplification or elimination of energy intensive separation units, energy requirement was also reduced significantly. Life cycle assessment showed that for a number of impact categories the direct process shows much better results especially evident when N_2O-impact on GWP is considered; yet there are also categories for which the conventional route is more environmentally sustainable. The main limitation of the direct route was found to be the energy and pollution intensive Anthraquinone process for the production of raw material of H_2O_2. Since consideration from cradle to gate is made this production method of the raw material is also affecting the results for the direct route.

Heat integration on the process simplified bulk chemical synthesis

Furthermore, to design an energy efficient process for this route pinch analysis was employed in Chapter 8. A new heat exchanger network was designed by enabling heat integration with process-to-process heat exchange. Compared with the initial heat exchanger network where energy requirements are supplied with utility streams, the improved heat exchanger network enabled up to 70 % saving in utility cost which enabled to pay back the extra capital cost requirement in less than one year.

Overall impact of this research

Overall, the research provides insight at different production scales what chemical plant of tomorrow and the future may look like – seen through the goggles of micro-flow chemical intensification envisioned to intensified process-design scale. The analysis accordingly was done in the hierarchy of scales as follows. Multi-step synthesis for continuous fine chemical production is now in lab development. Compact modular plants used to shorten time-to-market and to achieve decentralized production is now in pilot operation for industrial application cases. Bulk chemistry process change can enable step change improvement by bringing a new chemical transformation on a full-process level. However, such exploration of new reaction pathways and their respective new equipment designs to implement new process condition will naturally require much time to be realized, more a question of decades than of years.

9.2. Recommendations

Extension of metal scavenging experiments in flow

In Chapter 3, copper scavenging with continuous liquid-liquid microextraction unit was described to achieve metal catalyst separation in flow. This study can be extended to test the metal scavenging performance of the unit for other homogeneous metal catalysts. It can therefore be applied to other metal catalysed reactions such as palladium. PGM noble metals have become rare and recycling is a must here. In this sense, the new extraction concept may be used in applications beyond chemistry such as in mining and metallurgy.

In this study the recovery of the chelating agent EDTA was achieved offline and it was reused. A further study could be done to develop this scavenger recovery and recycle system in continuous flow. In this way besides the reaction and separation taking place together in flow recycle could be achieved as well. Kinetic analysis of metal scavenging has been performed in literature for batch operation.[6–8] A possibility can be to extend this study to investigate kinetic analysis of metal scavenging for a flow process.

Flow regime investigation

In Chapter 4, a milli-scale coiled flow inverter was used in combination with a phase separator and liquid-liquid extraction was achieved in slug flow regime. It was observed that parallel flow regime developed in straight tube with increase in flow rate as also found in literature. Further analysis would be beneficial to understand why the slug flow regime can be preserved with CFI at higher flow rates. As a continuation to that, it would be interesting to find the limit for the CFI where the switch to parallel flow occurs.

Accordingly, a flow regime map can be made for the CFI showing at what flow rate and aqueous volume fraction what type of flow regime is observed. In this study the flow rate of 7.2 l/h was the maximum flow rate achievable with the two syringe pumps used. Therefore, larger capacity pumps would be required to make this further investigation and one possibility could be to use peristaltic pumps.

Further scale-up of the flow extraction unit

In this study CFI with internal diameter of 3.2 mm was used. Scale-up of the extraction system can be studied by using several of these CFIs in parallel or by developing a CFI of a larger internal diameter. It would be interesting to apply this unit to a fine chemistry or pharmaceutical production process of industrial importance enabling multi-step synthesis at high throughput. The extraction is composed of two parts of mixing and phase separation. It would not be expected to have problems in achieving high flow rates in mixing part which is achieved with CFI in this case. Main limitation to achieving such high flow rates would come from the phase separation part. In this study highest flow rate in literature is achieved using micro effect of capillary force to achieve separation with a slit shaped flow separator composed of glass and Teflon rectangular capillaries. So, further development of such units is required to achieve higher throughput. It was not possible to have flow rate above 20 ml/min with the membrane separator. Development of a membrane separator with an integrated pressure controller like the device of Adamo et al.[9] that can handle high flow rates required could be the solution to this problem. This pressure control apart from higher flow rates could also extend the applicability of the separator to lower interfacial tension systems.

Validation of assumptions on modular plants with industry

The main generic aim of Chapter 5 was to provide parametric sensitivity and a proof of principle for a new economic model in chemical manufacturing of compact modular plants using model based scenarios (including virtual microreactor applications). Therefore, for such a very new technology several assumptions had to be made that are stated in the text. Clearly, the assumption of cost reductions that could be achieved with modular plants need to be proven by industrial demonstration activities. These are underway in European Union’s large scale projects on Future Factories.

Extension of the techno-economic study and performing sensitivity analysis

An initial, preliminary techno-economic analysis for a novel process of liquid fuel production from bioresources was performed in Chapter 6 to analyse the feasibility of the proposed project. This was carried out before the start of the project activities of the new project funded by the European commission of BIOGO. Methanol to gasoline converter product composition is modelled based on typical composition in literature. The applicability of such composition needs to be verified for biofuel production. The cost of gasoline production is very much dependent on the capital cost estimation and the cost parameters used in the study. A complete PhD project is now devoted to the comprehensive assessment of this process therefore a further more detailed work will follow. It is recommended to perform sensitivity analysis here to investigate the effect of several parameters such as cost parameters and process conditions on the economics of this process. Such analysis is performed in the techno-economic studies carried out by the National Renewable Energy Laboratory (NREL) which can be used as a guideline. [10,11]

Validation of the new bulk chemistry process design and additional sensitivity analysis

In Chapter 7 and 8, direct adipic acid synthesis route was studied. Since this direct synthesis is currently only studied at the reactor level and at lab scale, the downstream equipment and large scale synthesis was proposed in this study to assess the potential of this route in full-chain process level holistically. The cost, energy and environmental analysis were done based on the process simulation made following this proposed process. Therefore, the results are subject to the validity of the process simulation. This study was conducted in consultation with Dr. Johan Tinge from DSM. However, a more detailed analysis to reflect real life application finally needs in-flow from data of industry. Also, a sensitivity analysis was made in terms of only conversion in this study. It would be good to expand the sensitivity analysis to investigate the effect of other process parameters.

New hydrogen peroxide production process investigation

The main limitation of this route was found to be the raw material of hydrogen peroxide. It results in high raw material cost making this route economically infeasible. Its current production through Anthraquinone process is energy and pollution intensive. This direct route will be economically and environmentally attractive when low cost H_2O_2 production methods become available. H_2O_2 synthesis from its elements of H_2 and O_2 directly can be the solution to reduce the costs. It will also enable the direct route to be considered green on all levels with the H_2O_2 production also produced in a green way. Therefore, a further study can be made to investigate such double direct route to adipic acid.

Process design intensification studies beyond and following this research package

Process-design intensification, as per definition, is a step-change technology. Thus, it is far from existing practice and largely not implemented in educational curriculum, standard books, standard software and process-design tools. Moreover, current performances, known to experts, may be not representative of the full potential. Selection of process data needs so much care. Validated data are generally lacking. Sometimes extrapolation needs to be made, which again needs validation. Current process simulation, cost, energy and environmental analysis given in Chapters 5 through 8 may therefore be far from intrinsic and theoretical potential. The technology is simply too young and too less documented.

Nonetheless and hopefully with the improvements mentioned above, the overall future aim naturally is to realise a fully-assembled development for one intensified flow process, meaning to perform all the single objectives given here in the chapters in one process frame. This thesis could not achieve such total picture for the reasons given above, and rather provided different selected frames and facets which on their own have still high innovation.

Thus, the last recommendation is to bring the visions here into reality and to make the Plant of the Future to the Plant of Tomorrow, i.e. to realise a demonstration example for such fully-assembled process development. Due to the need to involve production scale, this needs large-TRL development by public-private partnerships with strong industrial involvement and lead (TRL = Technology Readiness Level).

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List of Publications

Journal Articles

1. Vural Gursel, I., Kurt, S.K., Aalders, J., Wang, Q., Noël, T., Nigam, K.D.P., Kockmann, N. & Hessel, V. (2015) Utilization of milli-scale coiled flow inverter in combination with phase separator for continuous flow liquid-liquid extraction processes. Chemical Engineering Journal, 283, 855-868.
2. Kurt, S.K., Vural Gursel, I., Nigam, K.D.P., Hessel, V. & Kockmann, N. (2015). Liquid-liquid extraction system with microstructured coiled flow inverter and other capillary setups for single-stage extraction applications, Chemical Engineering Journal, 284, 764-777.
3. Vural Gursel, I., Noël, T., Wang, Q. & Hessel, V. (2015) Separation/recycling methods of homogeneous transition metal catalysts in continuous flow. Green Chemistry, 17, 2012-2026.
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5. Vural Gursel, I., Wang, Q., Noël, T., Hessel, V., Kolb, G. & van Veen, A. (2014). Heat-integrated novel process of liquid fuel production from bio resources – Process simulation and costing study. Chemical Engineering Transactions, 39, 931-936.
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Conference Contributions

Oral Presentations

1. Vural Gursel, I. (2015) Milli-scale coiled flow inverter coupled to phase separator for continuous liquid-liquid extraction applications. Autumn Session of the Dutch Process Intensification Network (PIN-NL), 18 November 2015, Helmond, The Netherlands.
2. Vural Gursel, I., Aldiansyah, F., Aalders, A., Wang, Q., Noël, T., Hessel, V. & Nigam, K.D.P. (2014). Continuous metal scavenging and coupling to one-pot click reaction in flow. NPS-14: 'Fundamentally Innovative', 3-5 November 2014, Utrecht, The Netherlands.
3. Vural Gursel, I., Aldiansyah, F., Wang, Q., Noël, T. & Hessel, V. (2014). Continuous metal scavenging in flow coupled to one-pot click reaction. 21st International Congress of Chemical and Process Engineering CHISA 2014, 23-27 August 2014, Prague, Czech Republic.
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Poster Presentations

1. Vural Gursel, I., Wang, Q., Noël, T., Hessel, V., & Nigam, K.D.P. (2015). Milli-scale continuous extraction with coiled flow inverter connected to phase separator. 10th European Conference of Chemical Engineering (ECCE10), 27 September - 1 October 2015, Nice, France.

2. Vural Gursel, I., Wang, Q., Noël, T., Kolb, G., Hessel, V., & van Veen, A. (2014). Process simulation and cost analysis for novel process of liquid fuel production from bioresources. International Conference on MicroREaction Technology (IMRET13), 23-25 June 2014, Budapest, Hungary.

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5. Vural Gursel, I., Wang, Q. & Hessel, V. (2011). Coupling of chemically intensified microreactors to microseparators. Netherlands Process Technology Meeting (NPS-11), 24-26 October 2011, Arnhem, The Netherlands

Future Publications

Journal Article

Vural Gursel, I., Kockmann, N. & Hessel, V. (2016). Multiphase flow in microstructured devices - flow separation concepts and their integration into process flow networks. Chemical Engineering Science, in preparation.

Upon invitation to contribute to Chemical Engineering Science special issue - Multiphase Microfluidic Engineering

Book

Vural Gursel, I. & Hessel, V. "Modular Compact Intensified Plants", Wiley-VCH Verlag GmbH & Co. KGaA, proposal accepted, in preparation.

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About the Author

Iris Vural Gürsel was born on 07.06.1986 in Eskisehir, Turkey. She finished Koc High School in Istanbul, Turkey in 2004 as class of 2004 Valedictorian with GPA of 5.00/5.00. She obtained her BSc. degree in Chemical Engineering in 2008 at Bogazici University in Istanbul, Turkey. She graduated with high honour with GPA 3.86/4.00 ranking 2nd in the department. She was employed between 2008 and 2011 at Turkish Petroleum Refineries Cooperation (TUPRAS). She worked at the TUPRAS Izmit Refinery as a Process Engineer at Technical Services and R&D Department. While working, she studied MSc in Engineering and Technology Management at Bogazici University from 2008 to 2010. In 2010, she completed her MSc with high honour ranked 1st with GPA 4.00/4.00.

In August 2011, she moved to the Netherlands and started her PhD project at Eindhoven University of Technology in the group of Micro Flow Chemistry & Process Technology. Her PhD project on Process Simplification and Integration is under the ERC advanced grant awarded "Novel Process Windows – Boosted Chemistry". The results of her research are presented in this dissertation and are currently given as output in 12 peer reviewed journal papers. She has presented her studies orally or with poster in several national and international conferences. She was awarded 3rd prize for Best Poster in PRES 2012 conference. She wants to pursue a career in academics and as a next step she is carrying out postdoctoral research at Utrecht University, Copernicus Institute of Sustainable Development, group of Energy & Resources to further her career. Her postdoctoral research is on Sustainability assessment of chemicals and fuels produced from biomass within CatchBio project.