# Ex-ante life cycle evaluation of new process platforms

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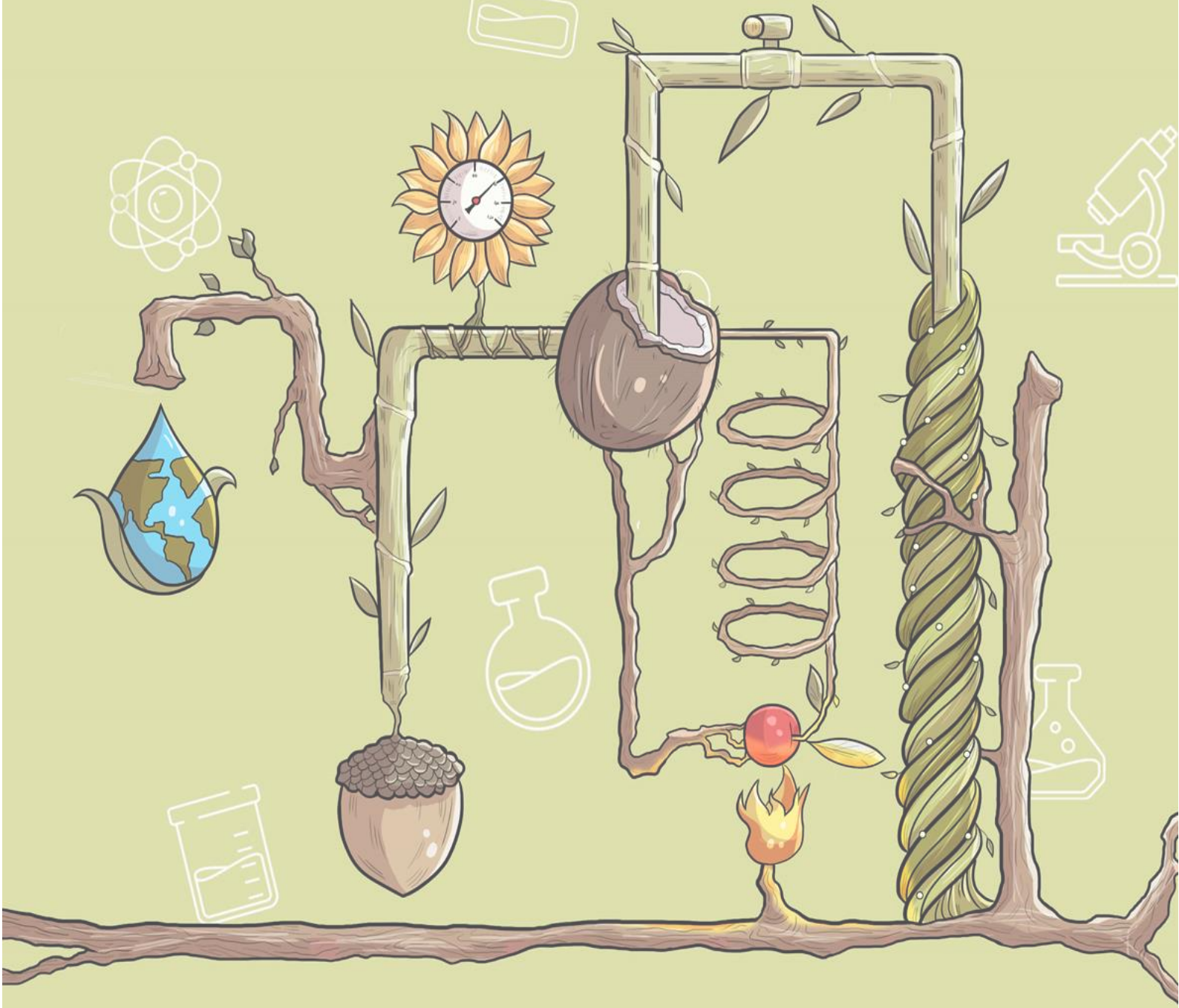
## for pharmaceutical cascades in flow



Olivia Maria Morales Gonzalez

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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, in het openbaar te verdedigen op dinsdag 5 juli 2022 om 11:00 uur

door

Olivia Maria Morales Gonzalez

geboren te Tehuacan, Mexico

Dit proefschrift is goedgekeurd door de promotoren en de samenstelling van de promotiecommissie is als volgt:

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*Het onderzoek of ontwerp dat in dit proefschrift wordt beschreven is uitgevoerd in overeenstemming met de TU/e Gedragscode Wetenschapsbeoefening.*

This research was founded by the EU project ONE–FLOW, under the gran agreement number 737266 of the European Commission's framework H2020 FET–Open Grant.

**Ex–ante life cycle evaluation of new process platforms**

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Olivia Maria Morales Gonzalez

Technische Universiteit Eindhoven, 2022

A catalogue record is available from the Eindhoven University of Technology Library

ISBN: 978-90-386-5542-0

Cover designed by Andrea Lindero (@chika.lindero)

Printed by Proefschrift specialist

To everyone that made this possible

"But ask the beasts, and they will teach you; the birds of the heavens, and they will tell you; or the bushes of the earth, and they will teach you; and the fish of the sea will declare to you…"

Book of Job 12:7–10

# SUMMARY

The increasing environmental awareness and observed climate change as consequence of anthropogenic emissions, have influenced the different industrial sectors to move towards sustainable production pathways. In particular, the pharmaceutical industry has undergone significant changes to reduce its environmental impact. The most significant change is the transition from a batch production towards a more efficient, flexible, robust, and sustainable flow production. This change is being driven due to the low capacity of production achieved with batch processes, the possibility of drugs shortages as the population keeps growing, and the waste issues related.

Among other challenges of the pharmaceutical industry is waste production. The manufacture of Active Pharmaceutical Ingredients involves multiple sequences that consist of a rection units followed by a separation train. Compared with the reaction, the separation procedure can be three times longer, due to the multiple separation steps needed to achieve the purification desired. These separations are also often conducted in a batch fashion, and it is considered that they compromise between 40% to 90% of the mass intensity of the process. This high demand of resources causes the pharmaceutical industry to produce 250 times more waste than the oil industry. Solvents have, among all the materials used, the largest contribution to the waste issues. Moreover, many of them are toxic and hazardous.

Due to this waste issues, it is necessary to develop new process options. In that sense, there is no "one–size–fits–all" approach, and multiple options need to be developed for the number of products in the pharmaceutical industry. Inspiration can be taken from nature, where multiple reactions and purification steps are conducted within the same structure continuously, e.g., in a cell.

New process pathways need to be carefully investigated coupling the technical development with environmental and economic assessments. A Life Cycle Assessment (LCA) can be applied to a process or product at different stages of development. It is of great advantage when it is applied at early stages of development as it can aid in the development and changes are easier to implement. The same holds true for economic assessments coupled with process optimization.

In this work, it has been investigated new process options, namely the use of high process conditions and automated purification with ionic liquids and polymeric nanoreactors. These are introduced as alternative platforms to overcome future and present sustainable and economic challenges in the pharmaceutical industry. However, due to their emergent nature

it is necessary to conduct a deep assessment before they reach higher technological readiness levels.

**Chapter 1** presents a detailed introduction of the environmental challenges that the pharmaceutical industry is facing, and key areas of research. Then a comprehensive overview of three new process pathways discussed in the following chapter is given. The processes pathways discussed are Novel Process Windows which uses chemical intensification through harsh conditions to boost micro–process technologies and flow chemistry to produce fine chemicals and pharmaceuticals. The second pathway described is the use of Polymersomes nanoreactors as a catalysis compartmentalization strategy. The last pathway is the Functional Solvent Factory, which is a process pathway based on a new synthetic technological factory to move from a discontinuous and intermittent synthesis–purification process towards compartmentalized flow chemistry based on switchable solvents.

**Chapter 2** reports the life cycle assessment of the production of vitamin $D_3$ through novel process windows and benchmark it against a state–of–the–art process. The production of vitamin $D_3$ was conducted in microflow by combining UV photoirradiation and high–p,T (photo–high–p,T) processing. Followed by the continuous crystallization to purify the product. Foreground data was used to model the experimental continuous setup, and multiple scenarios for the state–of–the–art process were developed using background data. Then the process scenarios were modeled in ASPEN Plus. Mass and energy balances were implemented in Umberto LCA software. The ReCiPe method was used to estimate the environmental impacts of the examined processes. LCA results showed that the continuous process is mainly driven due to the use of acetonitrile and t–BME, both solvents. In comparison with the state–of–the–art, the continuous process presents a significant reduction in the environmental impact. Even considering high recycling rates (95%) of solvent in the case of the state–of–the–art, the impact of the state–of–the–art is around double the continuous process.

**Chapter 3** presents the results of the techno–economic evaluation of the production of Cross–linked Enzyme nano–Aggregates (c–CLEnA) at lab scale. These are bowl–shaped polymeric vesicles used as supports, with the advantage of high activity retention and ease of recycling. The assessment was conducted at lab scale to find hot spots for optimization as supports generally represent a large fraction of the cost in the case of enzymatic processes. Moreover, an ex–ante economic assessment is needed before moving to larger scales of production. An estimated cost per 0.5 ml of CalB loaded c–CLEnA of 139€ was obtained, mainly driven by the CAPEX. This cost was benchmarked against traditional cross–linked supports, which production is simpler compared with the c–CLEnA, but higher leakage has

been observed. Therefore, it is necessary to assess the tradeoffs of both catalyst compartmentalization strategies. It was found that c–CLEnA needs to be recycled around 20 times to obtain an economic benefit compared to traditional cross–linked supports. Finally, process changes were discussed to improve the economic performance before scaling up.

**Chapter 4** introduces in detail the concept of the "Functional Solvent Factory (FSF)" and the main key performance indicator of this, the solubility. Due to the importance of the solvent, a tailored methodology was developed to aid in the selection of the solvent. The methodology is complemented with the sustainability aspects of solubility–based selection. Then an ex–ante process design for the synthesis of benzyl azide under the FSF conditions was created. Two processes scenarios were developed based on literature due to the low TRL of this concept and were modeled in Aspen Plus. Each route shows some of the benefits that the FSF aims for, particularly automated separation, as well as investigated the possible downsides. For example, when automated separation is not achieved at 100%, and a separation train is needed. The particulars of this separation train, as well as the complexity, were checked for the worst–case scenario to find the trade–offs of high purification rates. Then KPIs were identified, namely reaction conditions and IL stability/purity.

**Chapter 5** reports an ex–ante life cycle assessment of the case study developed in chapter 4, with the aim to identify hot spots based on the KPIs previously defined and the potential improvements. In addition, two processes were developed to compare the results of the FSF. These processes were a state–of–the–art (batch) and a solvent–less (continuous), selected due to their market implementation (batch scenario), and the industrial interest based on the environmental and economic benefits of a solvent–less process. The data from Chapter 4, namely mass and energy balances, was used. Then this data was implemented in Umberto LCA. The ReCiPe method was used to estimate the environmental impacts of the examined processes. The assessment was conducted in first place to the two types of functional solvent factories worst–case scenarios, where it was identified that the impacts are mainly attributed to the IL. Then they were compared against the benchmark processes. In both cases, the impact was larger than benchmark cases. Particularly, the solvent–less case obtained the lowest environmental impact.

Despite the results, the focus was on collecting the data needed for further stages of development, and for other solvent factories. Then, the optimized scenarios, with the ideal FSF processes were assessed and compared against their corresponding worst case scenario and the state–of–the–art. With these changes the environmental profile decreased considerably showing the advantages of the functional solvent factory concept. Moreover,

with these assessments, valuable lessons were learned. To bring this platform to the market is necessary a) to optimize the use of ionic liquids, b) low amounts of functional solvents, c) low processing temperatures, d) high recyclability and e) avoid contamination of the ionic liquids. These were found to be the most important performance indicators, that will influence the future development of this platform.

The processes were further optimized and modeled in Aspen Plus to obtain the statistical data needed to perform an uncertainty assessment, presented in **Chapter 6**. Uncertainty assessments are very important for the case of emergent technologies to validate the environmental assessments. In a comparative LCA for emergent technologies, despite the data completion, the result can remain subject to uncertainty from the missing or inaccurate data, inaccuracy, temporal or spatial variability, and other factors. To address these uncertainties, stochastic parameters with probability distributions instead of fixed values and the propagation of the sampling was conducted using Monte Carlo simulations. Then the overlap area approach was used to assess the results of these comparative LCAs. The results concluded that the functional solvent factory Type 1 shows a lower environmental profile compared with Type 2, except for two categories Human toxicity and Water depletion. In these two categories is not possible to differentiate which of the two solvent factories is the best–case scenario. Furthermore, the result points out the importance of the selection and management of the ILs, as they have the largest contribution to these categories.

Finally, in **Chapter 7** the concluding remarks of the main findings of this work are discussed in brief, and recommendations for future research are given based on the outcomes of the assessment here conducted.

# CONTENTS

# CHAPTER 1. INTRODUCTION

This chapter highlights the motivation behind the development of new process pathways for the synthesis of pharmaceuticals and fine chemicals. First the reader is introduced to the challenges faced by the pharmaceutical and fine chemical industry, and the environmental consequences accompanied by these challenges. Afterward, the new process pathways are introduced and the scientific research behind these developments are discussed. Finally, a general outline of this thesis is presented to guide the reader along each of the topics explored here.

## 1.1 INTRODUCTION

The increased societal awareness to protect and safeguard our planet has made it imperative for scientists and industries to develop and apply sustainable technologies, which can lead to a green production of chemicals[1]. This entails more environmentally friendly chemistry, in which reusing and eliminating chemicals with a negative environmental impact is the goal. These measures are embedded within the term "Sustainable Chemistry", which also sets the pathway for sustainable production[2].

From an industrial point of view, these process technologies should also satisfy the needs for reducing development times, growing demand, and ensuring profitability[1]. Novel green chemistry approaches should therefore always be combined with a cost advantageous strategy, to ensure the implementation of a new technology[3,4].

One special class of chemicals is medicines. They play a key role in the treatment and prevention of diseases[5]. Their synthesis consists in multistep processes that involve a synthetic step followed by a, often complex, purification train[6]. The number of necessary processes until the product is obtained with the specific purity can comprise up to 40 steps[7]. This large number of steps results in a very high environmental impact.

Since the 80's, the waste problems of the fine chemical industry have been acknowledged, which even led some companies to close operations[8]. To compare the environmental burden of different process pathways multiple tools, also known as green metrics, have been developed[9]. Examples of this are the Product Environmental Foot Print (PEF) which aims to assess the environmental performance of products[10]; Process Mass Intensity (PMI), which asses the total mass of materials used per mass of product obtained[5]; or the *E*– Factor (environmental factor) that provides with an estimate over the ratio between resources consumed and waste produced[11]. These assessments revealed that the amount of waste produced in the pharmaceutical industry is over 250 fold larger, proportionately, compared to the oil industry[12]. The pharmaceutical industry is also considered an energy intensive industry with the use of up to 4.3 ± 3 $GJ_{exergy}/mol_{API}$ [7]. In terms of material use, the largest environmental impact is due to the use of solvents, with a 67.2 ± 12.7% contribution to the overall impact[7]. In 2008, up to 88 kt of waste solvent were produced in the US alone, of which 83% were endorsed to the top ten solvents used in the pharmaceutical industry. In 2015, the demand for solvents was over 20 million tonnes[13]. Solvents are used only in a relatively small volume in the reaction itself, but they are used in great amounts as separating agents, auxiliary fluid, propellants, and for cleaning[14]. These operations also account for 60% of the energy use of the pharmaceutical industry[15].

Organic solvents in particular are of high concern regarding their environmental, health, and safety (EHS) effects[15]. Characteristics like toxicity, hazardous level, the need for special handling, and post treatment are factors of importance when selecting a solvent for a process[16].

These problems and other challenges have led the American Chemistry Society (ACS), the Green Chemistry Institute® (GCI), and several global pharmaceutical corporations to fund the ACS GCI Pharmaceutical Roundtable[17]. The aim of the Roundtable is to achieve a greener production in the pharmaceutical industry. They established green goals and targets based on key engineering areas of focus, which are: continuous processing, bioprocess, separation and reaction technologies, solvent selection, recycling and optimization, process intensification, integration of Life Cycle Assessment (LCA), integration of chemistry and engineering, scale up aspects, process energy intensity, and mass and energy integration[17]. Continuous processing was selected and targeted by the Food and Drug Administration (FDA) to promote the change from batch to flow in the pharmaceutical industry[18–20]. Continuous processing is recommended for its capacity to address the issues around the economic constraints of batch production[21,22]. Then the roundtable, motivated by the legislative authority, in this case the FDA, moved continuous manufacturing to the top of the key green engineering research areas[17]. In addition to continuous production, emphasis was given to solvent research[23], and biocatalysts[24].

The approach towards solvents has focused on minimization, i.e. use of lower volumes, and (green)selection. Solvent–free synthesis is an example of minimization, or in this case complete elimination. These systems are considered one of the most sustainable options, with the capacity to address key environmental issues of the pharma industry[15]. Some advantages of solvent–free conditions are the potential waste reduction, low cost, and relative simplicity for industrial implementation[25]. As well, these systems have been used successfully in the high–volume chemical industry. However, not all organic reactions can be conducted under solvent–free conditions[26].

The second crucial element for green chemistry is catalysis[3,4]. The catalyst can make the chemical process more sustainable; however, it is important to consider the costs and emissions associated with the production of the catalyst when assessing the entire process. Thus, its section is key in the design of a sustainable chemical process, and its prolonged utilization is necessary for a low environmental impact.

After its use, it is necessary to recover the catalyst. In that respect, heterogeneous catalysis has advantages over homogeneous systems facilitating the recovery of the catalyst from the

reaction mixture[27]. For instance, a supported heterogeneous catalyst facilitates the use and reuse of the material multiple times. However, quite often restrictions in terms of activity and mass transfer limitations of the reactants and/or products may be associated with porous supports[28–30].

Industrial bio–catalysis has become an attractive solution for greener production, and the immobilization of enzymes has been exploited over the years[31]. The interest in biocatalysts grew due to the high product selectivity, and milder operating conditions, which overall contribute to safer processes and a lower environmental impact than traditional metal–catalysts[32]. Within the biotechnology field, enzymatic processing is considered one of the most promising and greener alternatives[33].

In 2012, the use of enzymes on an industrial scale in terms of environmental assessment was reported[33]. Those results showed that implementing enzymatic processes in place of thermochemical processes reduced the impact in the categories of global warming, acidification, and photochemical ozone formation, while saving energy and agricultural raw materials. Moreover, enzymes do not need functional group protection. This would allow their implementation in a wide range of synthetic routes, and thereby increase the environmental efficiency. Unfortunately, industrial use of enzymes is still limited by the low operational stability and difficult recovery–reuse processes due to the excessive purification needed[34,35].

Traditionally enzymes are obtained by micro–organisms such as bacteria or yeast[33]. Before they can be utilized, enzymes often must be purified. This purification process is complex as the enzymes can be easily denatured by foaming, drying, contact with solvents, or heating. The purification process also requires many steps, which increases their production cost[36,37]. Therefore, given the complexity and costs of these operations, immobilization strategies are implemented to facilitate enzyme reuse and to make the entire process more efficient[31].

The term immobilization is used when the enzyme is transformed from a soluble (homogenous) species to a supported species. This is done by attaching the enzyme onto an insoluble carrier or by encapsulation[34,38–41]. Immobilization can increase the enzyme activity in organic solvents; moreover, it facilitates product recovery, minimizes the contamination of the enzyme and enables an efficient recovery and re–use of the enzyme[35,41]. From a process perspective, benefits like enhanced performance, thermal stability of the enzyme and longer operation conditions are observed[34,38]. These advantages can be beneficial for the economics of the process[41]. However, immobilization has some drawbacks such as lower enzyme activity and diminished accessibility to the substrate[37]. Moreover, there is an additional cost associated to the support[41]. Commonly, the most used immobilization strategies are chemical (or physical)

binding of the enzyme to the carrier[39]; physical entrapment[34], or the formation of insoluble aggregates of enzymes via cross–linking[42]. The properties of the enzyme will depend on the type support used and the enzyme itself[34,35].

To make the synthesis of fine chemicals more efficient, meet the needs of the market and obtain a low environmental impact is necessary to explore and develop new processing pathways. Inspiration can be taken from nature, where multistep processes take place within the same medium without interruption, as it occurs in cells (see Fig. 1.1). There is a local dynamic enviroment where cells interact with other cells and other non–cellular components, and within this internal machinery there are constant changes in time and space that allow the continuous processing of nutrients [43].

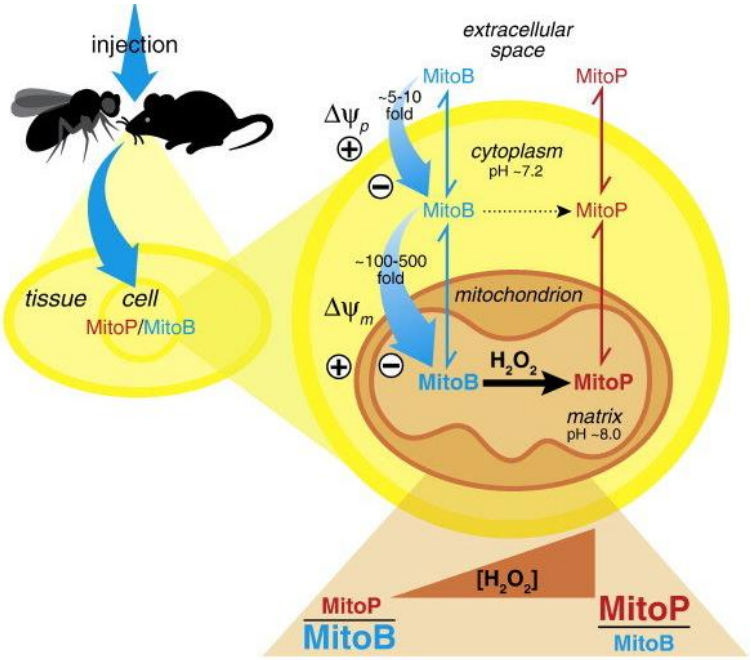



**Figure 1.1.** Hydrogen peroxide formation withing the mitochondria of a cell triggered by the injection of MitoB[44].

Inspired by nature the project ONE–FLOW[65] was created, with the aim of developing a flow cascade machinery to perform multiple reactions in one–step. To achieve a horizontal hierarchy, compartmentalization strategies were developed. As novel processes pathways, it is necessary to complement these with a LCA studies and assessment of economic viability. Coupling these studies at early stages of development can improve their future performance, as well changes are easily to implement[45]. In this thesis the environmental and techno–economic assessments of the strategies developed within ONE–FLOW project, are presented.

Focusing particularly on two of the ONE–FLOW strategies, namely Cross–linked Polymersomes and the Functional Solvent Factory. In addition, the first part of this thesis addresses another strategy for sustainable production in the pharmaceutical industry, the Novel Process Windows strategy.

## 1.2 NOVEL PROCESS WINDOWS

The possibility to work in harsh conditions (see Fig. 1.2), also called Novel Process Windows (NPW)[46,47], was enabled by the use of continuous processing. Such NPW intensification allows to shorten residence times and therefore increasing productivity and optimizing the sustainability of the process. Thus continuous processing allowed the possibility NPW and green chemistry to reduce the complexity of multistep synthesis[48].

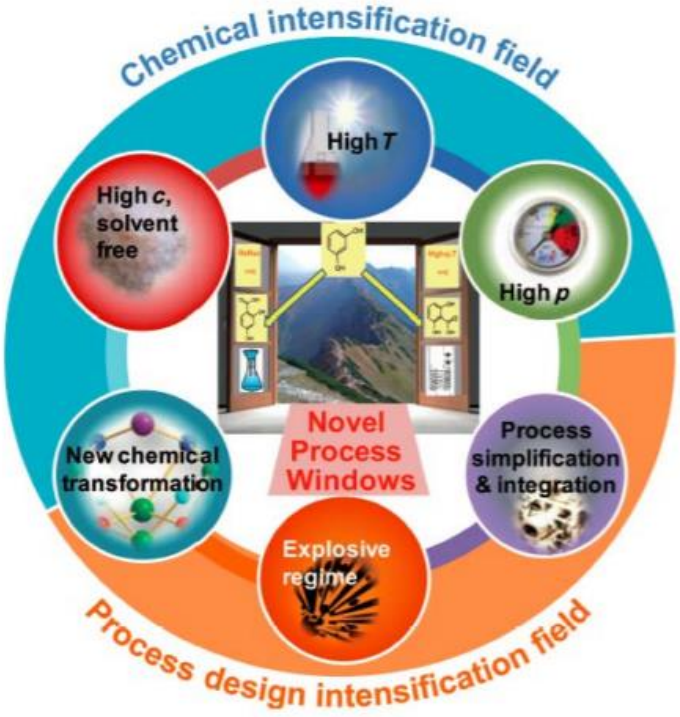



**Figure 1.2.** Schematic representation of the conditions applied under Novel Process windows[48].

Microreactors have contributed to this development. They play an important role in continuous processing by improving mixing and heat transfer, facilitating scale–up and lowering space–time demand[49]. In addition the synthesis can be conducted at higher temperatures and higher pressures[47].

NPW is a highly promising strategy for the greening of the pharmaceutical industry, e.g., microreactors as a key component in modular plants (containers) which are seen as part of the 50% idea (half time reduction of process development by a faster transition from lab to pilot to production)[50]. Cost benefits are obtained from the higher yields, purity, shorter reaction time, and reduce significatively the environmental impact of the processes[51]. Furthermore, the use of raw materials is reduced, purification stages are minimized, and the need for end of pipe solutions is avoided[52].

Flow chemistry intensifies a wide spectrum of chemical reactions making them faster by boosting the activation via novel process windows. An example where NPW is applied and process improvement were obtained is presented in the synthetize Rufinamide in a continuous flow reactor under solvent– and catalyst–free conditions[53,54]. The continuous production showed improvements in the sustainability profile in terms of life cycle assessment with respect to batch processing given by process simplification and process integration.

In Chapter 2, the LCA synthesis of Vitamin $D_3$, under NPW conditions is presented. This process was conducted in micro–flow by combining UV–photoirradiation and high–p,T (photo–high–p,T) processing. The process was coupled with an integrated continuous crystallization and its feasibility has been proven and reported. The potential environmental impacts were assessed there from a cradle–to–gate perspective.

## 1.3 COMPARTMENTALIZED– CROSS–LINKED ENZYME NANO–AGGREGATES

Enzymatic entrapment can be done in a polymeric network, such as a polymersome. A polymersome is defined as porous nano–capsules or polymeric vesicles[55,56]. Entrapment options have been acknowledged due to their capacity to protect enzymatic species and decrease leakage during the reaction[57]. The drawbacks of this strategy are the mass transfer limitations linked to the use of supports and the low capacity of enzyme loading[34,35].

Creating micro–sized objects by crosslinking enzymes (without the introduction of supports) is another interesting alternative for enzyme immobilization. It is very a versatile option, and easy to achieve. Examples of three ways of preparing these are presented in Fig 1.3. However, the use of cross–linking often leads to the reduction of the enzyme's activity attributed to the difficult accessibility of the substrate to the enzyme active site and the restricted mobility upon protein folding[34,35].

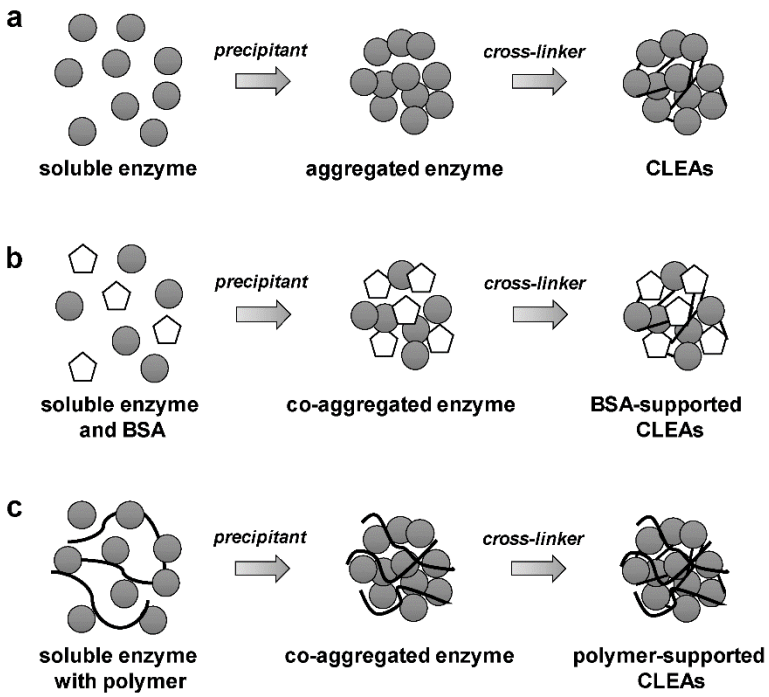



**Figure 1.3.** Schematic representation of three ways to prepare of crosslinked enzymes (CLEAs): a) General cross–linking; b) via bovine serum albumin (BSA); and c) ionic–polymer[58].

The formation of insoluble crosslinked enzymatic aggregates (CLEAs) without any support might give rise to inhomogeneity in the size distribution of the final aggregates since the size of the cross–linked proteins cannot be specified; these CLEAs often lack mechanical stability which could be an issue in continuous operations. However, despite the drawbacks, their operational stability, high recycling potential and high range of application with several enzymes, make CLEAs suitable for industrial applications[37,59] and consequently, there is a growing interest in implementing them at industrial scale.

Polymeric nanoreactors appear as an innovative and environmentally friendly tool for conventional catalytic systems[60,61]. The use of polymeric nanoreactors in an aqueous dispersion enables reactions to proceed in water thanks to compartmentalization[62] and makes it possible to perform sequential reactions in one pot[63]. Stomatocytes nanoreactors, bowl–shaped polymersomes, with an additional internal cavity, have been found to be suitable for bioconversions, and the inclusion of one or more enzymes has been demonstrated[64]. Moreover, the ability of stomatocytes to retain enzymes without posing additional barriers to substrate diffusion makes them an appealing class of nanoreactors to be exploited for several applications[65].

Compartmentalized– crosslinked enzymatic nano–aggregates (c–CLEnA), are a sub–class of nanoreactors. These nanoreactors can be derived from stomatocytes upon cross–linking the loaded enzymes. The cross–linker normally is a small molecule, able to bridge together multiple enzymatic species. c–CLEnA can be utilized in continuous flow processing and has shown to be resistant to leaching for a long period. The introduction of c–CLEnAs as an effective immobilization method could enable reactions to proceed in media that is not suitable for the enzyme but is favorable for the reaction. Besides, c–CLEnAs have the capacity to encapsulate one or more enzymatic species with a high encapsulation efficiency[60]. Their ability to be used and reused in–flow makes them interesting for industrial catalysis, and from the green chemistry perspective[66].

Despite the advantages of c–CLEnAs, their production process is still more complex. In Chapter 3, c–CLEnAs are studied from a techno–economic point of view, to provide a guide for the optimization of their synthesis from a cost perspective. An evaluation in terms of recyclability vs cost is presented comparing c–CLEnAs with lose enzymes and crosslinked enzymes.

## 1.4 FUNCTIONAL SOLVENT FACTORY

The term "Functional Solvent Factory" (FSF) was given to the systems where multiphase liquids that perform the role of reactors and purification units are used[67,68]. This term is introduced in detail in Chapter 4.

It aims to reduce the high environmental impact due to the solvents used to conduct the reaction and purification steps. In this strategy, neoteric solvents are used to conduct the reaction and purification within the same system, ideally without the need for post–processing or purification[9] as shown in Fig. 1.2. In these systems it is possible to incorporate supramolecular entities within, such as Pickering emulsions[69], polymersomes[70], or a combination thereof[71] to increase reaction–separation performance. Altogether can enable multiple reactions, such as catalytic cascades, to be conducted within one continuous–flow stream, as aimed in One–Flow project.

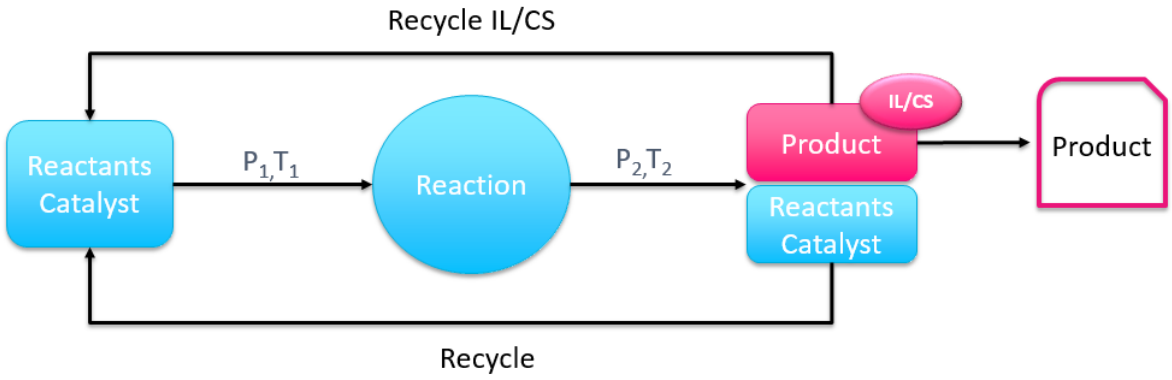



**Figure 1.4.** Simplified scheme of the ONE–FLOW Functional Solvent Factory. IL stands for ionic liquid and CS for common solvent, P and T refers to the process conditions [72].

Neoteric solvents have been proposed to replace organic solvents. They comprise supercritical carbon dioxide ($ScCO_2$), and ionic liquids (ILs), which are believed to be greener and with the potential to enhance and optimize reactions[73]. Supercritical $CO_2$ is mainly used for purification[74]. For example, used to separate the product from the catalyst[75]. In some cases, it can also be used as a solvent for spray coating. $ScCO_2$ has been attempted many times in chemical reactions, yet such processes have rarely been seen and passed pilot scale[74]. An advantage of supercritical $CO_2$ is that it comes as a byproduct/waste from ammonia manufacturing or from breweries, therefore $CO_2$ is not released to the environment contributing to global warming. On the other hand, it has some limitations such as the high quadrupole moment (uneven charge distribution) and that it is chemically not completely inert, i.e. it can react with certain nucleophiles[25].

The term Ionic liquid (IL) is used to refer to a number of compounds with unique physiochemical properties[76]. They are considered green solvents with an environmentally benign nature[73] due to their low vapor pressure[77], which reduces the risk of atmospheric contamination[78].

Besides the environmental benefits, ILs have proven to boost processes. In many laboratory–scale cases ILs caused an increase in selectivity, facilitated product purification and catalyst and solvent recycling. They can also reduce the need for catalyst and/or solvent. However, they can be toxic, non–biodegradable, unstable, and under high temperature and low pressure they can evaporate[79]. Because of the previous reasons, any implementation of IL needs to be carefully assessed, including their production and the impact they have in the process before considering them greener than conventional solvents[78].

More than a million ionic liquids can be prepared at the lab, but only three hundred of them are commercially available. Due to their wide range of applications and tuneability they are considered the solvents of the future[78]. Furthermore, their designer capability has made them interesting for extraction or purification processes. The anion of the IL can tune miscibility with solvents enabling multiphase systems. The chain length of the cation also has an influence on the polarity, viscosity, density, and surface tension of the IL[77]. For example, biphasic systems with IL have been observed when they are mixed with water. A water–IL system was used in the Mizoroki–Heck reaction. The IL stabilized the catalyst without the need for a ligand and allowed the recovery of the catalyst in the IL–phase by the addition of hexane[76]. Due to the large number of ILs, their selection is of high importance. In Chapter 4 a methodology to select the solvent for the specific case of the FSF is presented, wherein solubility was coupled with LCA to aid in the selection process of a solvent. A tailored methodology was needed as solvent selection methodologies focus on conventional solvents such as Methanol[16]. Simultaneously aspects like compatibility could be addressed and non–conventional solvents can be explored.

The introduction of ILs at industrial scale[79] has been triggered by the simplification achieved in the process[80], allowing the recyclability of catalyst, and product purification by the development of multiphase systems[78]. The BASF BASIL process is an example of an industrial process (see Fig. 1.3). This process taught that the usage of alternative solvents at industrial scale needs the push of process intensification which is translated into economical[81], and environmental advantages[82]. In this process, 1–methylimidazolim chloride creates a biphasic mixture[78] making easier the recyclability of the ionic liquid and increasing the yield by 30%[79]. Another industrial process where the use of ionic liquid enhanced the activity of the catalyst, and the formation of a second phase facilitated the recyclability of the catalyst is the Dimersol process by IFP. Among the advantages observed are better selectivity, higher yields and the use of a smaller reactor compared with the homogenous system[79]. Finally, Evonik Industries developed a hydrazination process where the use of imidazolium and pyridinium based IL allowed the recovery of the catalyst, and a simple separation of the product with 99% conversion achieved[78]. All the processes described show ways in which the use of IL facilitated the recycling of the catalyst or reduced the need for a purification train.

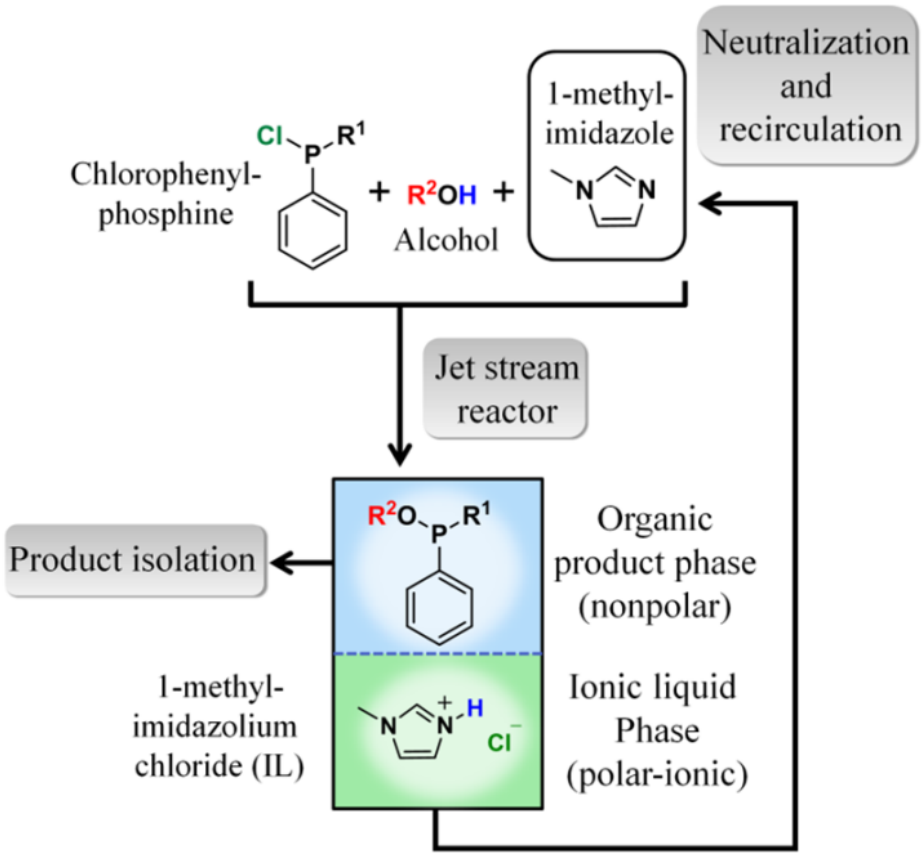



**Figure 1.4.** Scheme of the BASIL™ process. The IL 1–methylimidazolium chloride, liquid at the reaction conditions, forms a biphasic system which allows an easy work up as the upper phase contains thereby the solvent–free product[83].

Despite the examples depicted, complete separation of the products or catalyst via ionic liquids in continuous systems is still infrequent. There are other process pathways such as *In–Situ* Product Removal (ISPR), which has been proposed to increase the yield and productivity of bioprocesses[84]. In Situ Product Removal is based on a two–phase system, where the product and enzyme are separated based on their solubility[85].

Following ISPR and multiphase extraction approaches[86] as a generalized concept, the FSF concept was created to go one step further to conduct catalytic cascades processing while preventing intermediate purification steps. This new process concept utilizes periodic (segmented) multi–phase flows as compartments for the desired set of reactants, catalysts, and products. These compartments can be combined on demand with other compartments and by preferential solubility each reaction partner finds its right place, to facilitate further (down)processing[87].

In the ideal case of exclusive solubility, meaning 100% of one molecular species in one phase and none of the other, such a flow process system could eliminate the need for further product separation and catalysts recovery steps[67]. Advanced compartmentalization is provided by tri–[88] or four–phasic solvent systems[89]. These multiphase technologies with designer solvents, particularly ionic liquids are known[90]. Their integrated reaction–separation performance has also been reported before[91].

Due to the emergent nature of the FSF a case study was developed as a conceptual case to assess the environmental performance of functional ILs. In Chapter 4 this case study is described in detail. Simulations conducted in Aspen Plus were used to assess different routes with different degrees of separation and varied complexity of the separation train. Evaluating the different degrees of separation achieved is necessary to identify key parameters for design. Then, the results of this conceptual case, namely mass and energy balances were used to conduct a life cycle assessment reported in Chapter 5. This LCA showed that in the simplest case, i.e. only product recovery without recovering the catalyst, the impact is higher than other process approaches. Moreover, is necessary to ensure high recyclability rates of the IL, as the IL is one of the main drivers of the environmental impact. Furthermore, the lessons learned here can be used for further process design and the design of other FSF. Lastly, with emergent technologies many uncertainties arise, these uncertainties were explored in Chapter 6. Most of the uncertainties were due to the nature of the conceptual case, an explorative case, rather than an extensively defined production factory as is the case of high TRL level technologies. Besides the uncertainties, a confirmation of the critical role of the IL in the process was observed not only driving the impact but also the uncertainties.

Finally, in Chapter 7 the main findings of this research are summarized and recommendations for future research on these topics are presented. In closing, a short discussion on the different pathways assessed here for their potential to make more sustainable the pharmaceutical and fine chemical industry.

The results presented here aim to assess the environmental impact and economic feasibility of the proposed pathways. Assessing how these processes are compared to others in the market is necessary, and beneficial at the early stages of development, as changes can be implemented easily. The scope of this thesis is on the big picture of the environmental and economic impact that these processes may have. The only case where the assessment is focused on a particular process is in Chapter 2. The rest of the chapters aim to get the big picture of the environmental and the economic advantages and drawbacks of the ONE–FLOW approach in order to guide future developments.

**REFERENCES**


1 P. L. Heider, S. C. Born, S. Basak, B. Benyahia, R. Lakerveld, H. Zhang, R. Hogan, L. Buchbinder, A. Wolfe, S. Mascia, J. M. B. Evans, T. F. Jamison and K. F. Jensen, *Org. Process Res. Dev.*, 2014, **18**, 402–409.

2 C. Blum, D. Bunke, M. Hungsberg, E. Roelofs, A. Joas, R. Joas, M. Blepp and H. C. Stolzenberg, *Sustain. Chem. Pharm.*, 2017, **5**, 94–104.

3 P. T. Anastas, M. M. Kirchhoff and T. C. Williamson, *Appl. Catal. A Gen.*, 2001, **221**, 3–13.

4 V. Polshettiwar and R. S. Varma, *Green Chem.*, 2010, **12**, 743.

5 C. Jimenez–Gonzalez, C. S. Ponder, Q. B. Broxterman and J. B. Manley, *Org. Process Res. Dev.*, 2011, **15**, 912–917.

6 J. A. Moulijn and A. Stankiewicz, *Encycl. Sustain. Technol.*, 2017, 509–518.

7 W. De Soete, S. Debaveye, S. De Meester, G. Van Der Vorst, W. Aelterman, B. Heirman, P. Cappuyns and J. Dewulf, *Environ. Sci. Technol.*, 2014, **48**, 12247–12255.

8 F. Roschangar, J. Colberg, P. J. Dunn, F. Gallou, J. D. Hayler, S. G. Koenig, M. E. Kopach, D. K. Leahy, I. Mergelsberg, J. L. Tucker, R. A. Sheldon and C. H. Senanayake, *Green Chem.*, 2017, **19**, 281–285.

9 V. Hessel, D. Kralisch and U. Krtschil, *Energy Environ. Sci.*, 2008, **1**, 467.

10 A. Lehmann, V. Bach and M. Finkbeiner, *Integr. Environ. Assess. Manag.*, 2015, **11**, 417–424.

11 F. Tieves, F. Tonin, E. Fernández–Fueyo, J. M. Robbins, B. Bommarius, A. S. Bommarius, M. Alcalde and F. Hollmann, *Tetrahedron*, 2019, **75**, 1311–1314.

12 R. A. Sheldon, *Green Chem.*, 2017, **19**, 18–43.

13 M. J. Raymond, C. S. Slater and M. J. Savelski, *Green Chem.*, 2010, **12**, 1826.

14 S. Abou–Shehada, J. H. Clark, G. Paggiola and J. Sherwood, *Chem. Eng. Process. Process Intensif.*, 2016, **99**, 88–96.

15 C. Jimenez–Gonzalez, *Curr. Opin. Green Sustain. Chem.*, 2019, **18**, 66–71.

16 J. H. Clark and S. J. Tavener, *Org. Process Res. Dev.*, 2007, **11**, 149–155.

17 C. Jiménez–González, P. Poechlauer, Q. B. Broxterman, B. S. Yang, D. Am Ende, J. Baird,

C. Bertsch, R. E. Hannah, P. Dell'Orco, H. Noorman, S. Yee, R. Reintjens, A. Wells, V. Massonneau and J. Manley, *Org. Process Res. Dev.*, 2011, **15**, 900–911.

18 R. L. Hartman, J. P. McMullen and K. F. Jensen, *Angew. Chemie – Int. Ed.*, 2011, **50**, 7502–7519.

19 S. L. Lee, T. F. O'Connor, X. Yang, C. N. Cruz, S. Chatterjee, R. D. Madurawe, C. M. V. Moore, L. X. Yu and J. Woodcock, *J. Pharm. Innov.*, 2015, **10**, 191–199.

20 R. Porta, M. Benaglia and A. Puglisi, *Org. Process Res. Dev.*, 2016, **20**, 2–25.

21 B. Benyahia, R. Lakerveld and P. I. Barton, *Ind. Eng. Chem. Res.*, 2012, **51**, 15393–15412.

22 L. Malet-Sanz and F. Susanne, *J. Med. Chem.*, 2012, **55**, 4062–4098.

23 D. J. C. Constable, C. Jimenez-Gonzalez and R. K. Henderson, *Org. Process Res. Dev.*, 2007, **11**, 133–137.

24 S. Kim, C. Jiménez-González and B. E. Dale, *Int. J. Life Cycle Assess.*, 2009, **14**, 392–400.

25 M. Lancaster, in *Green Chemistry: An Introductory Text*, RSC Paperbacks, 2002, pp. 130–165.

26 K. Tanaka and F. Toda, *Chem. Rev.*, 2000, **100**, 1025–1074.

27 X. S. Zhao, X. Y. Bao, W. Guo and F. Y. Lee, *Mater. Today*, 2006, **9**, 32–39.

28 I. Denčić, S. De Vaan, T. Noël, J. Meuldijk, M. De Croon and V. Hessel, *Ind. Eng. Chem. Res.*, 2013, **52**, 10951–10960.

29 F. H. M. Dekker, A. Bliek, F. Kapteijn and J. a. Moulijn, *Chem. Eng. Sci.*, 1995, **50**, 3573–3580.

30 D. Rotticci, T. Norin and K. Hult, *Org. Lett.*, 2000, **2**, 1373–1376.

31 L. Cao, *Immobilized Enzymes*, Elsevier B.V., Second Edi., 2011, vol. 2.

32 P. Tufvesson, J. Lima-Ramos, M. Nordblad and J. M. Woodley, *Org. Process Res. Dev.*, 2011, **15**, 266–274.

33 K. R. Jegannathan and P. H. Nielsen, *J. Clean. Prod.*, 2013, **42**, 228–240.

34 R. A. Sheldon and S. van Pelt, *Chem. Soc. Rev.*, 2013, **42**, 6223–6235.

35 N. Miletić, A. Nastasović and K. Loos, *Bioresour. Technol.*, 2012, **115**, 126–135.

36 P. Vijayaraghavan, S. R. F. Raj and S. G. P. Vincent, eds. G. S. Dhillon and S. B. T.–A.–I. W. as F. for E. P. Kaur, Academic Press, San Diego, 2016, pp. 95–110.

37 A. A. Homaei, R. Sariri, F. Vianello and R. Stevanato, *J. Chem. Biol.*, 2013, **6**, 185–205.

38 P. Grunwald, *Catalysts*, 2018, 396.

39 S. Datta, L. R. Christena and Y. R. S. Rajaram, *3 Biotech*, 2013, **3**, 1–9.

40 F. Cozzi, *Adv. Synth. Catal.*, 2006, **348**, 1367–1390.

41 I. Eş, J. D. G. Vieira and A. C. Amaral, *Appl. Microbiol. Biotechnol.*, 2015, **99**, 2065–2082.

42 R. A. Sheldon, *Catalysts*, 2019, **9**, 1–31.

43 J. P. Sluka, A. Shirinifardy, M. Swat, A. Cosmanescu, R. W. Heiland and J. A. Glazier, *Bioinformatics*, 2014, **30**, 2367–2374.

44 A. Logan, H. M. Cochemé, P. B. Li Pun, N. Apostolova, R. A. J. Smith, L. Larsen, D. S. Larsen, A. M. James, I. M. Fearnley, S. Rogatti, T. A. Prime, P. G. Finichiu, A. Dare, E. T. Chouchani, V. R. Pell, C. Methner, C. Quin, S. J. McQuaker, T. Krieg, R. C. Hartley and M. P. Murphy, *Biochim. Biophys. Acta – Gen. Subj.*, 2014, **1840**, 923–930.

45 S. M. Moni, R. Mahmud, K. High and M. Carbajales-Dale, *J. Ind. Ecol.*, 2019, 1–12.

46 V. Hessel, *Chem. Int.*, 2018, **40**, 12–16.

47 V. Hessel, B. Cortese and M. H. J. M. de Croon, *Chem. Eng. Sci.*, 2011, **66**, 1426–1448.

48 V. Hessel, D. Kralisch, N. Kockmann, T. Noël and Q. Wang, *Chem. Sustain. Energy Mater.*, 2013, **6**, 746–789.

49 M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, *Chem. Rev.*, 2017, **117**, 11796–11893.

50 I. V. Gürsel, V. Hessel, Q. Wang, T. Noël and J. Lang, *Green Process. Synth.*, 2012, **1**, 315–336.

51 M. Hempel, *Chem. Eng. Technol.*, 2009, **32**, 1651–1654.

52 S. J. Haswell and P. Watts, *Green Chem.*, 2003, **5**, 240–249.

53 S. Borukhova, T. Noël, B. Metten, E. de Vos and V. Hessel, *Green Chem.*, 2016, **18**, 4947–4953.

54 D. Ott, S. Borukhova and V. Hessel, *Green Chem.*, 2016, **18**, 1096–1116.

55 F. Golombek and K. Castiglione, *Biotechnol. J.*, 2020, **15**, 1–10.

56 M. V. Dinu, I. A. Dinu, S. S. Saxer, W. Meier, U. Pieles and N. Bruns, *Biomacromolecules*, 2021, **22**, 134–145.

57 D. Weiser, F. Nagy, G. Bánóczi, M. Oláh, A. Farkas, A. Szilágyi, K. László, Á. Gellért, G. Marosi, S. Kemény and L. Poppe, *Green Chem.*, 2017, **19**, 3927–3937.

58 H. Yamaguchi, Y. Kiyota and M. Miyazaki, *Catalysts*, 2018, **8**, 4–6.

59 B. H. Lipshutz, N. A. Isley, J. C. Fennewald and E. D. Slack, *Angew. Chemie Int. Ed.*, 2013, **52**, 10952–10958.

60 M. T. De Martino, F. Tonin, N. A. Yewdall, M. Abdelghani, D. S. Williams, U. Hanefeld, F. P. J. T. Rutjes, L. K. E. A. Abdelmohsen and J. C. M. Van Hest, *Chem. Sci.*, 2020, **11**, 2765–2769.

61 M. C. M. van Oers, W. S. Veldmate, J. C. M. van Hest and F. P. J. T. Rutjes, *Polym. Chem.*, 2015, **6**, 5358–5361.

62 M. C. M. van Oers, L. K. E. A. Abdelmohsen, F. P. J. T. Rutjes and J. C. M. van Hest, *Chem. Commun.*, 2014, **50**, 4040–4043.

63 S. F. M. Van Dongen, M. Nallani, J. J. L. M. Cornelissen, R. J. M. Nolte and J. C. M. Van Hest, *Chem. – A Eur. J.*, 2009, **15**, 1107–1114.

64 L. K. E. A. Abdelmohsen, M. Nijemeisland, G. M. Pawar, G. J. A. Janssen, R. J. M. Nolte, J. C. M. Van Hest and D. A. Wilson, *ACS Nano*, 2016, **10**, 2652–2660.

65 M. Nijemeisland, L. K. E. A. Abdelmohsen, W. T. S. Huck, D. A. Wilson and J. C. M. Van Hest, *ACS Cent. Sci.*, 2016, **2**, 843–849.

66 S. V. Ley, *Chem. Rec.*, 2012, **12**, 378–390.

67 C. Zhang, Z. Song, C. Jin, J. Nijhuis, T. Zhou, T. Noël, H. Gröger, K. Sundmacher, J. van Hest and V. Hessel, *Chem. Eng. J.*, 2019, **385**, 123399.

68 ONE–FLOW Research Project, https://one–flow.org/vision.

69 B. P. Binks and J. H. Clint, *Langmuir*, 2002, **18**, 1270–1273.

70 H. Che and J. C. M. van Hest, *J. Mater. Chem. B*, 2016, **4**, 4632–4647.

71 M. Wang, M. Wang, S. Zhang and J. Chen, *React. Chem. Eng.*, 2019, **4**, 1459–1465.

72 O. M. Morales-Gonzalez, C. Zhang, S. Li and V. Hessel, *Chem. Eng. Sci. X*, , DOI:10.1016/j.cesx.2019.100024.

73 P. G. Jessop, R. R. Stanley, R. A. Brown, C. A. Eckert, C. L. Liotta, T. T. Ngo and P. Pollet, *Green Chem.*, 2003, **5**, 123–128.

74 M. J. Earle, S. P. Katdare and K. R. Seddon, *Org. Lett.*, 2004, **6**, 707–710.

75 N. J. Meehan, A. J. Sandee, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. Van Leeuwen and M. Poliakoff, *Chem. Commun.*, 2000, 1497–1498.

76 F. Bellina and C. Chiappe, *Molecules*, 2010, **15**, 2211–2245.

77 S. K. Shukla, S. Pandey and S. Pandey, *J. Chromatogr. A*, 2018, **1559**, 44–61.

78 A. J. Greer, J. Jacquemin and C. Hardacre, *Industrial Applications of Ionic Liquids*, 2020, vol. 25.

79 N. V. Plechkova and K. R. Seddon, *Chem. Soc. Rev.*, 2008, **37**, 123–150.

80 D. R. Shonnard, A. Kicherer and P. Saling, *Environ. Sci. Technol.*, 2003, **37**, 5340–5348.

81 Pharmaceutical Technology, Ionic Liquids in the Chemical Synthesis of Pharmaceuticals.

82 P. Saling, R. Maisch, M. Silvani and N. König, *Int. J. Life Cycle Assess.*, 2005, **10**, 364–371.

83 D. Rauber, F. Philippi, J. Seibert, J. Huwer, H. Natter and R. Hempelmann, *World J. Chem. Educ.*, 2019, **7**, 153–165.

84 A. Freeman, J. M. Woodley and M. D. Lilly, *Bio/Technology*, 1993, **11**, 1007–1012.

85 A. Pohar, I. Plazl and P. Žnidaršič-Plazl, *Lab Chip*, 2009, **9**, 3385–3390.

86 A. Stankiewicz and J. A. Moulijn, *Re-Engineering the Chemical Processing Plant Process Intensification*, 1st edn., 2018.

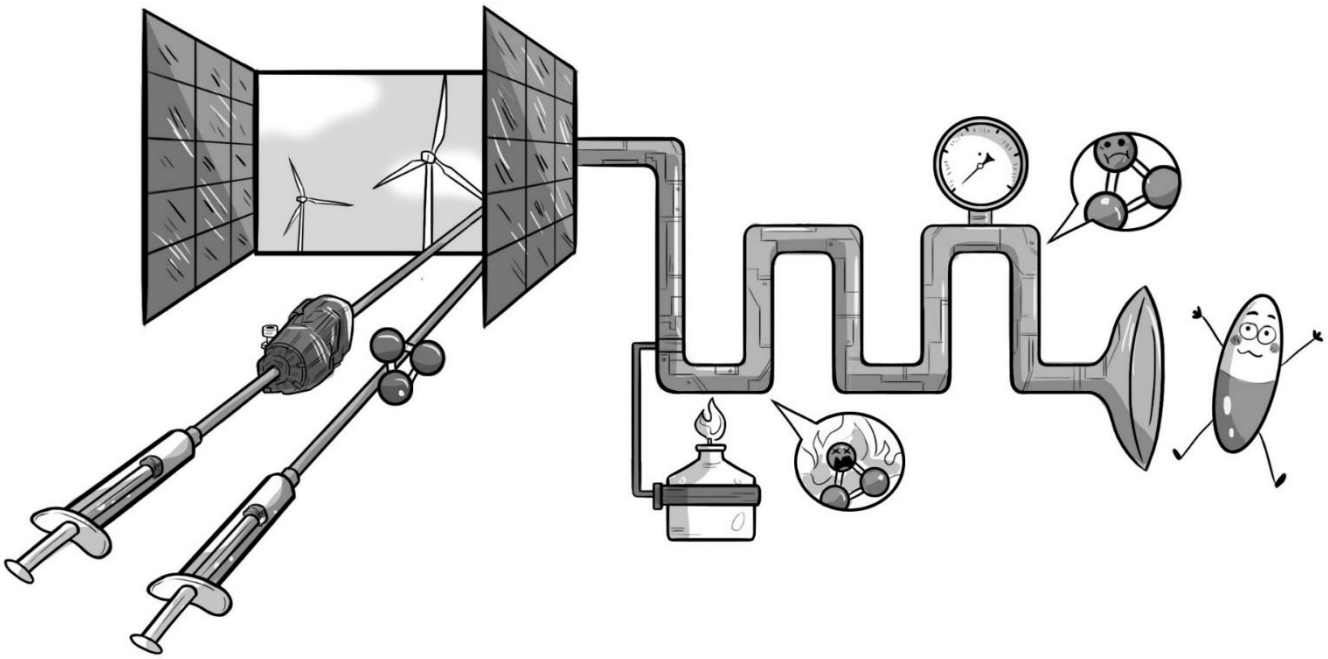
87 C. Zhang, Z. Song, C. Jin, J. Nijhuis, T. Zhou, T. Noël, H. Gröger, K. Sundmacher, J. van Hest and V. Hessel, *Chem. Eng. J.*, 2020, **385**, 123399.

88 D. O. Katole and G. D. Yadav, *Mol. Catal.*, 2019, **466**, 112–121.

89 G. Li, D. Zhou, Q.-Q. Xu, G.-Y. Qiao and J.-Z. Yin, *J. Mol. Liq.*, 2019, **284**, 102–109.

90 B. Subramaniam, *Ind. Eng. Chem. Res.*, 2010, **49**, 10218–10229.

91 R. Villa, E. Alvarez, R. Porcar, E. Garcia-Verdugo, S. V. Luis and P. Lozano, *Green Chem.*, 2019, **21**, 6527–6544.



# CHAPTER 2. LIFE CYCLE ASSESSMENT OF VITAMIN $D_3$ SYNTHESIS AND PURIFICATION – FROM BATCH TO PHOTO–HIGH P,T

This chapter presents the Life Cycle Assessment (LCA) of the synthesis of Vitamin $D_3$ using Novel Process Windows (NPW). NPW were applied to develop an optimized and simplified process for the synthesis of crystalline Vitamin $D_3$. This process was conducted in micro–flow combining UV–photoirradiation and high–p,T (photo–high–p,T) processing. Then, it was coupled with an integrated continuous crystallization, for complete continuous processing.

The potential environmental impacts were assessed from a cradle–to–gate perspective and benchmarked against batch production. Both processes, continuous and batch, were modelled in Aspen Plus using foreground data from the experimental continuous setup, and background data from different patents. The assessment was performed in the software Umberto NXL LCA using the ReCiPe Midpoint 2008 method. The results discussed the advantages of this process and the areas for further optimization. Then the comparison against batch processes is presented. The results show the promising effect of using NPW, not only in terms of process technology but also environmentally.

This chapter is based in the following paper:

Morales–Gonzalez, O. M., Escribà–Gelonch, M., & Hessel, V. (2019). Life cycle assessment of vitamin $D_3$ synthesis: from batch to photo–high p,T. International Journal of Life Cycle Assessment, 24(12), 2111–2127.

## 2.1 INTRODUCTION

Vitamin $D_3$ is a secosteroid[1] discovered over 100 years ago. Nowadays is one of the most relevant nutrients[2] required for the optimal functioning of many organs, particularly the cardiovascular system[3]. Its deficiency is a worldwide problem[4] that affects both mankind and indoor raised animals[5]. Therefore, the efficient and economical production of dietary supplements and the fortification of food with this vitamin have become of great interest[1,6].

Driven by the advantages that continuous processing offers, and the motivation of the Food and Drug Administration (FDA)[7–9] and the American Chemistry Society Green Chemistry Institute® (ACS GCI) Pharmaceutical Roundtable[10] new processes should be developed for the continuous synthesis of medicines and vitamins. Continuous processing can promote and trigger innovation as well as address the issues around the economic constraints[11,12].

Microreaction technology plays an important role in continuous processing, as it improves mixing and heat transfer, facilitates scale–up, and has lower space–time demand[13]. Microreactors have contributed to the transfer from batch to continuous processing. Besides the above requirements, microreactors can also enable the possibility to work in harsh conditions, also called Novel Process Windows (NPW)[14,15]. NPW intensification can reduce the residence time, thus increasing productivity and allowing a more sustainable synthesis. NPW are considered highly promising for the greening of the pharmaceutical industry, e.g. microreactors as key components in modular plants (containers) which are seen as part of the *so–called* 50% idea (half time reduction of process development by a faster transition from lab to pilot to production)[16]. Cost benefits come from higher yields, purity and shorter reaction time, with a significant reduction in the environmental impact of the processes[17] due to the use of fewer materials, minimization of purification stages, and avoiding the need for end of pipe solutions[18]. An example of previous process improvements is shown in Ott et al. (2016) and Brukohova et al. (2016)[19,20] where NPW were applied to synthesize Rufinamide in a continuous flow reactor under solvent– and catalyst–free conditions. The continuous production showed improvements in the sustainability profile over the life cycle of the process, with respect to a batch process given by the process simplification integration achieved.

Due to the benefits observed in the integration of continuous processing and NPW, a continuous process for the synthesis[21,22] and crystallization[23] of Vitamin $D_3$ ($VD_3$) using NPW was developed. The combination of these two steps, synthesis and crystallization, forms the first fully continuous process for the synthesis of crystalline Vitamin $D_3$, to the best of the knowledge of the author. High pressure and high temperature were used together with UV–

photoactivation. High pressure was used to ensure a single liquid phase over the process, and the UV–laser irradiation allowed pulsed operation in the femto–second order. This faster pulsing, faster than the lifetime excitation of the molecule, has the potential of higher selectivity and thus changed the chemical pathway, which would occur under normal (not pulsed UV–irradiation) conditions.

The reaction mechanism for the synthesis of Vitamin $D_3$ is elucidated in Figure 2.1. Provitamin $D_3$, also known as 7–dehydrocholesterol (7DHC), a by–product obtained after cleansing the wool[5] is irradiated with UV light to produce Pre Vitamin $D_3$. The optimal wavelength for the conversion of 7DHC is 296 nm, although a spectrum from 280–320 nm can also be applied for the synthesis. The light source can vary, but the most common source in the industry is a Hg lamp in a quartz reactor. Other options are Bromine and Laser light[5,21]. The photo–isomerization step is not selective. Therefore, to minimize the formation of undesired isomers, i.e. tachysterol and lumisterol[5] (as shown in Figure 2.1), and to ease the separation of the products is necessary to stop the reaction at low conversions (max. 20–30%)[24,25]. Finally the irradiation is followed by a thermally driven step to isomerize Pre Vitamin $D_3$ to Vitamin $D_3$ and conclude the synthesis[5,26].

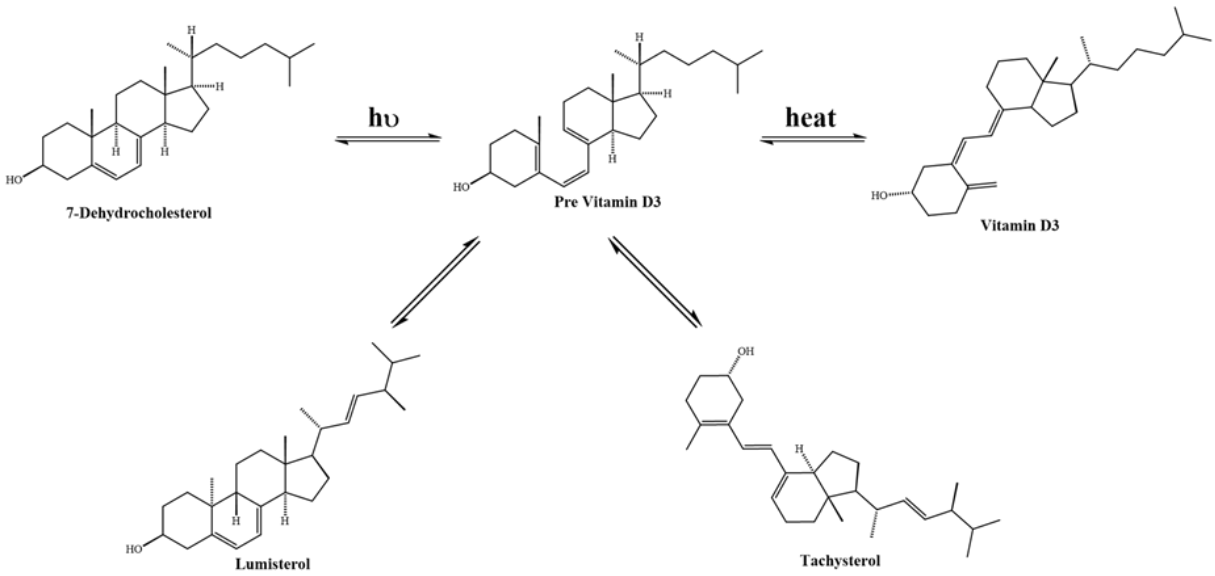



**Fig. 2.1** Reaction mechanism for the synthesis of Vitamin $D_3$

In recent years, environmental assessment, particularly life cycle assessments (LCA), have become of high importance for the evaluation of a process[27]. Life cycle assessment is a methodological framework used to evaluate the environmental burden of a product through

its whole life cycle[28]. As far as the environmental assessment of Vitamin $D_3$ is concerned, there is not any LCA reported. In this chapter a life cycle assessment of the continuous process for Vitamin $D_3$ production is presented and compared with the conventional batch synthesis. A scenario–based assessment was selected due to the increasing relevance of scenarios, to make a comprehensive and detailed assessment, and to identify hot spots for improvement[29]. The focus of the following is not entirely on the new way of conducting the chemical reaction (flow chemistry) but also on the downstream separation and purification. Here solvents play a major role in lowering the environmental profile. Solvents, in general, are the determining process factor throughout this thesis.

## 2.2 METHODOLOGY

### 2.2.1 Goal and Scope

The goal of this LCA study is to assess the environmental impacts and to compare the intensified continuous production of crystalline Vitamin $D_3$ with respect to the conventional batch production. The scope of this study encompasses the synthesis of Vitamin $D_3$ from the irradiation of 7DHC, the purification of the Vitamin $D_3$ resin and crystallization of the resin to obtain crystalline Vitamin $D_3$. The purification of the by–products, namely the extraction of tachysterol and lumisterol, is excluded since this step was not developed for the continuous process.

### 2.2.2 System boundaries

The system boundaries of the Vitamin $D_3$ production examined in this LCA study have been defined based on a "cradle–to–gate" approach, which considers the materials, energy flows and emissions associated with the extraction of the raw materials until the product is obtained[30]. End of life and downstream processing (i.e. waste management) were excluded for both the continuous (NPW) and the batch production. The system boundaries are presented in Figure 2.2.

The LCA does not include the impact associated with the manufacturing of the equipment such as reactors or heat exchangers and the transport of the raw material.

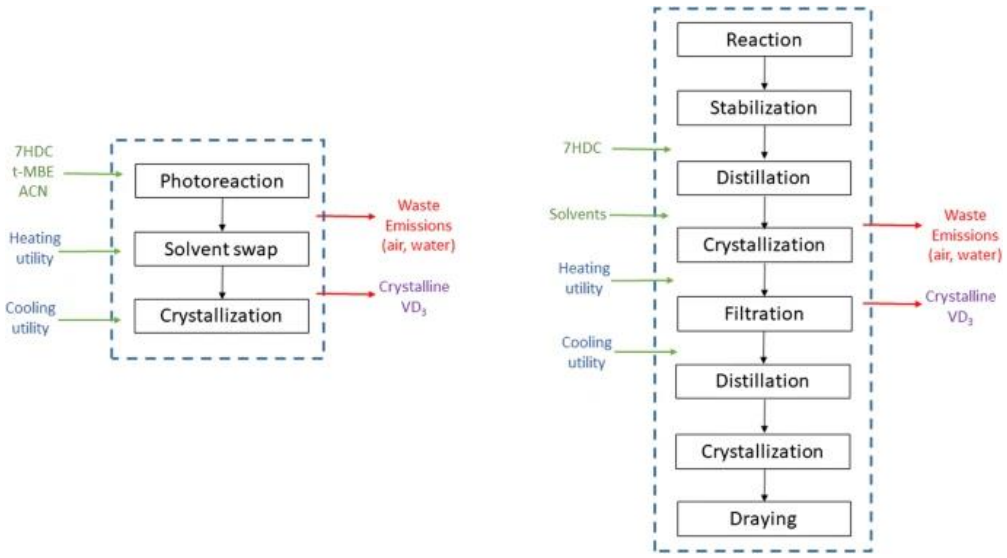



**Fig. 2.2** System boundaries of Vitamin $D_3$ processes Continuous (left) and Batch (right).

### 2.2.3 Life Cycle Inventory (LCI)

To build the inventory, the functional unit was defined as 1 g of product, i.e. crystalline Vitamin $D_3$. All LCI analyses are referred to this amount of product.

Foreground data from the laboratory was used to develop the workflow sheet of the continuous process. Secondary data was used for the batch processes from which five scenarios were developed.

To compile the data to build the inventories Aspen Plus V9 software was used to model the continuous and batch processes. These simulations were developed to produce the amount of product declared in the functional unit.

Below it is described the continuous process and how it was implemented in Aspen Plus. Then the batch scenarios are presented. Using different scenarios for the industrial process was necessary to reduce the uncertainty caused by the lack of metadata[31]. Likewise, the use of scenarios can be used to assess the influence or sensitivity of the input parameters[32,33]. After that, it is detailed how the scenarios were implemented in Aspen Plus.

#### *Continuous Process*

The first approach to continuous processing was proposed by Fuse et al. (2010)[24]; where a two–stage continuous microreactor was employed. Recently, an intensification of the process was achieved using either a UV–Lamp or a Laser[21,22], with the aid of microreactors operation in harsh conditions. There UV photo–radiation was combined with high pressure and high temperature (photo–high–p,T, see Figure 2.3). The solvent selected for the process was tert–butyl methyl ether

(t–MBE). Other solvents like diethyl ether, can form dangerous peroxides.

The intensified process is conducted as follows: a solution of 7DHC (0.22 M) in t–BME is pumped through a quartz made coil with a pressure of 32 bar, achieving max. 240 ºC in the irradiation chamber. The reaction is conducted using an HOK 400 W UV lamp. After the reaction, the solution flows out of the chamber and cools down immediately. Conversion of 42% with a 17% yield is achieved, and the resin obtained can be used for animal feed after 7DHC recovery[23].

The resin is crystallized to obtain a human–compatible Vitamin $D_3$. Coupling the photochemical synthesis with a continuous crystallization setup, allowed continuous processing[6,23]. A solvent swap is conducted after the solution leaves the photoreactor, where t–BME is swapped with acetonitrile (ACN) inflow at 40 ºC and 290 mbar. The new solvent (ACN) enables the separation of Vitamin $D_3$ from the resin. Removal of the unreacted 7DHC is achieved by precipitation and subsequent filtration. Crystallized 7DHC can be recycled and reused in the synthesis step. In addition, the solution becomes supersaturated once it cools down to room temperature, as can be observed in the temperature profile shown in Escriba–Gelonch et al. (2018)[23].

Then the solution is pumped to the crystallization section where the capillary is submerged in a cooling bath with a temperature of 7 ºC for 1 min. Crystals are formed and filtered. Ahead of the filter, the permeated ACN–Vitamin $D_3$ solution can be recycled back to the cooling bath. This recycling step enhances the super saturation and the recovery of Vitamin $D_3$ crystals that were too small to be removed by the filter in the first pass.

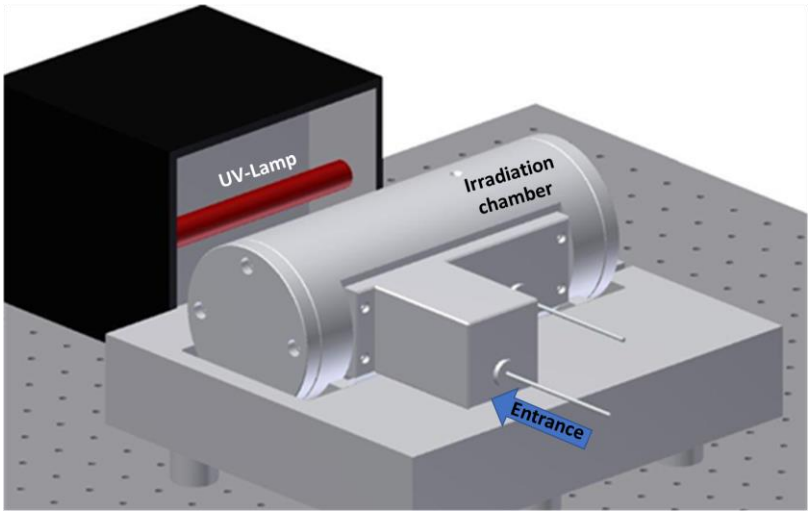



**Fig. 2.3** 3D design view of the High–p, T micro photoreactor. At the entrance it is located the preheating chamber follow by the irradiation chamber (in Fig. 2.4 area enclosed in purple). Behind the chamber it is located the UV–Lamp.

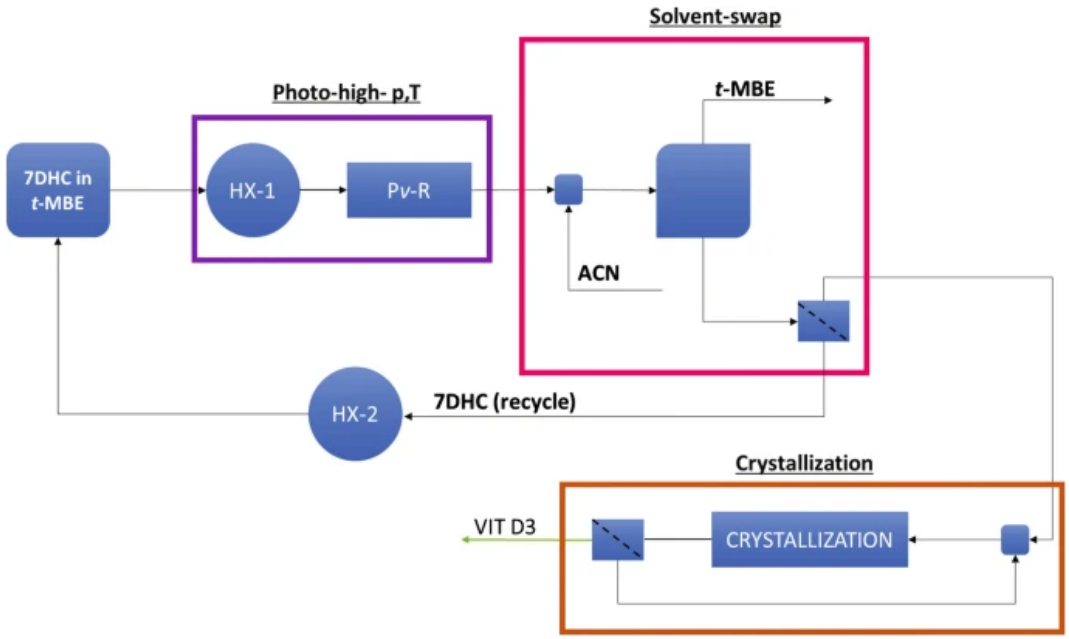



**Fig. 2.4** Flow diagram of the fully continuous–flow process for the synthesis and crystallization of Vitamin $D_3$.

Figure 2.4 presents the flow diagram of the continuous process. It also indicates the stages and materials of the process; whereby stages, it is meant the photoreaction (photo–high–p,T) in purple, the solvent swap in pink and the crystallization in orange.

### *Modelling in Aspen Plus*

To model the intensified flow process in Aspen Plus the following assumptions were made: (i) photoreactions were not simulated considering the limitations of the software Aspen Plus, (ii) the ambient temperature was defined as 20 ºC, (iii) the crystallization process was simplified due to the lack of data in the batch case and to avoid inconsistencies in data quality caused by having a more detailed simulation for continuous case compared to the batch, and (iv) steady state.

The method selected was UNIQUAC following Aspen recommendations[34] and literature[35–37]. UNIQUAC is an activity coefficient property method used for liquid and gas–liquid interactions. UNIFAC, also an activity coefficient method, was used to estimate missing binary interaction parameters between components. These methods are already incorporated into the property methods from Aspen Plus. All binary systems were modelled as mentioned except for the case of the t–MBE–acetonitrile binary system, where thermodynamic properties were modelled according to literature[36].

Most of the components were present in Aspen databases. The only component that is not

present in the database at the time of the study was the 7DHC. The proxy Beta–Cholesterol was used instead.

The photoreactor in the continuous process was modelled with a heat exchanger that represents the heating chamber of the reactor. The energy of the UV laser was not considered. After the reactor, the mixture cools down to ambient temperature, this process is done without the need for a heat exchanger. But for the simulation it was needed to use a heat exchanger to cool down before the solvent swap; however, its cooling requirement was not considered in the final energy balance. A conceptual design was done for the solvent swap using the Fenske–Underwood–Gilliland method, and the parameters obtained were implemented in a RadFrac unit. The configuration of the RadFrac unit was a column of 35 stages, with a total condenser, a reflux ratio of 3.1 and a distillate to feed ratio of 0.25. For the crystallizer a heat exchanger was used. No reactive system, crystallization or precipitation were considered due to the lack on data of the batch process. The filters were modelled using separators and the mixers with a stream mixer.

### *Batch Industrial Process*

The reliability of the data has a large impact on the applicability of the life cycle assessment. To guarantee consistency within the data used, data quality indicators[38] were considered during the data collection. For data completeness, different scenarios for the batch process were developed to model possible pathways of production. From Pfoertner (1971) and Hirsh (2011) the synthesis scenarios were obtained[5,39]. These consisted of the reaction of 7DHC to Vitamin $D_3$ (resin) and the purification of the resin, to remove 7DHC. Five scenarios were obtained out of these patents, as shown in Fig. 2.5.

Hirsch (2011) process details were used to improve temporal correlation since data from Pfoertner (1971), Marbet (1972)[40] and Schaaf et al. (1967)[41] dates from the 70s. Data from Hirsch (2011) has a temporal correlation smaller than ten years, and with this it could be confirmed that the process to obtain Vitamin $D_3$ has barely changed. This improved the overall temporal correlation. Finally, the use of computer simulations enabled to score the reliability at the same level.

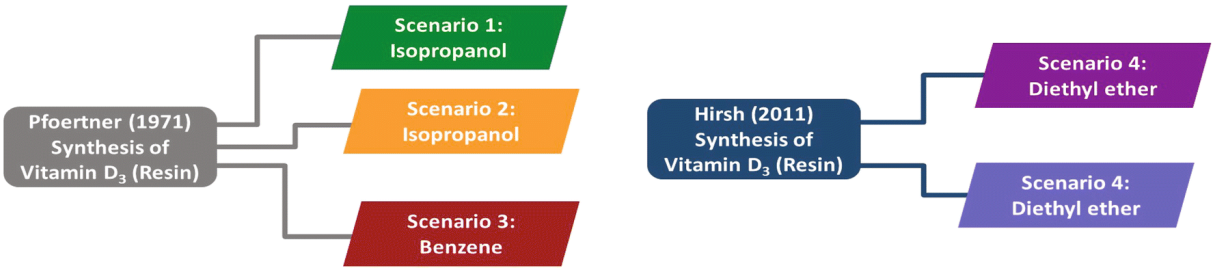



**Fig. 2.5** Tree diagram of the scenarios used to model the synthesis of Vitamin $D_3$ (resin).

From Marbet (1972)[40] and Schaaf et al. (1967)[41] the data to model the crystallization step was obtained. The crystallization process uses the resin, which is obtained from the synthesis scenarios, to obtain crystalline vitamin $D_3$. Three crystallization scenarios were selected to model different crystallization pathways (see Fig. 2.6).

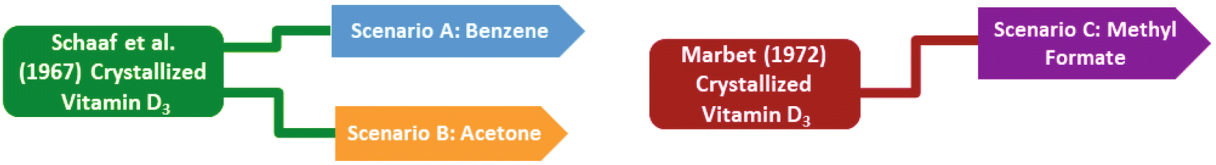



**Fig. 2.6** Tree diagram of the scenarios used to model the crystallization of the resin to obtain crystalline vitamin D3.

These scenarios were combined (see Fig. 2.7) to ensemble the complete process from the synthesis of the resin to crystalline Vitamin $D_3$. This gives a total of 15 scenarios, which will be compared against the continuous process.

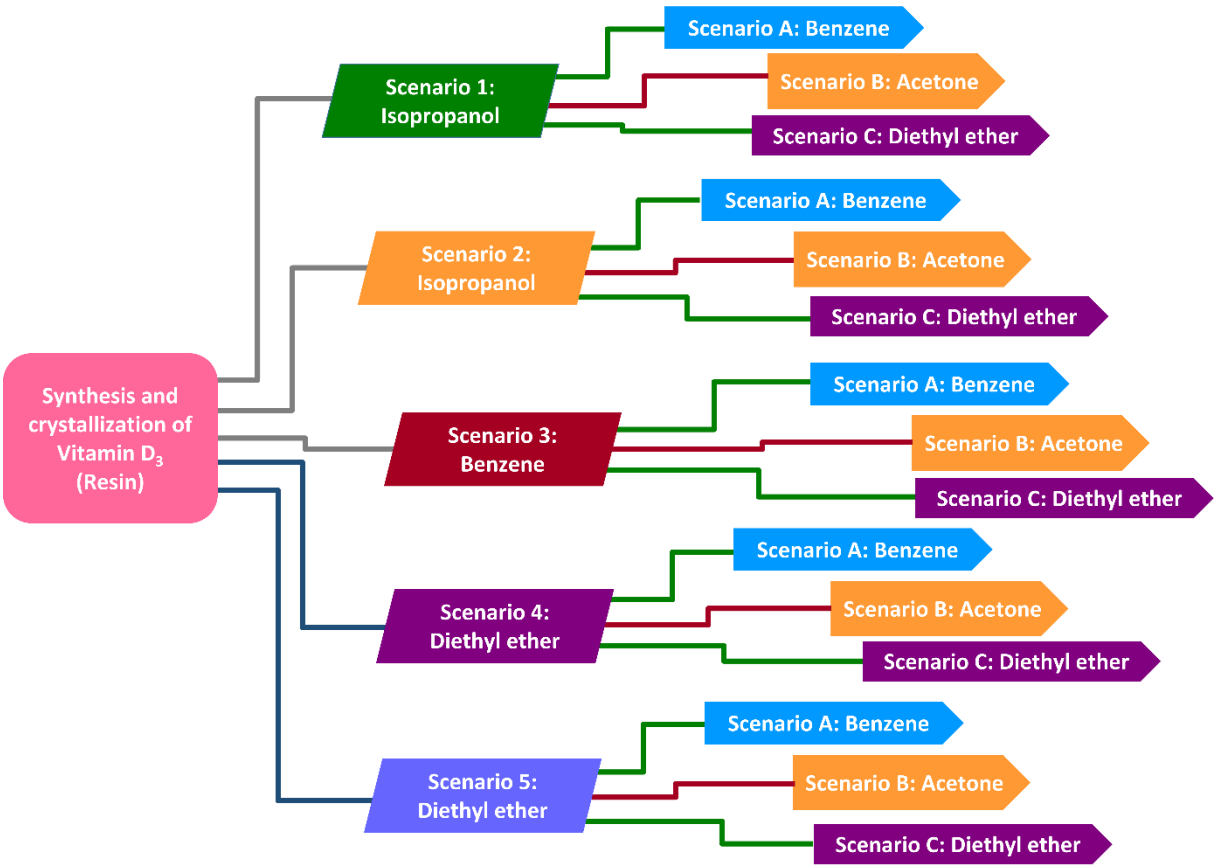



**Fig. 2.7** Tree diagram of the scenarios used to model the synthesis and crystallization of Vitamin $D_3$ starting from 7DHC. For future references the scenarios will be called by number and letter, i.e. "Scenario 3B" will be used to refer to the scenario where the synthesis of vitamin $D_3$ resin is in benzene[39] and the crystallization is in acetone[41].

The conditions to model Scenarios 1 and 2 were obtained from examples one of Pfoertner (1971) and Scenario 3 from example four of the same patent. Example one describes the following process: 2.5 g. of 7DHC is dissolved in 2.5 L of solvent (isopropanol or benzene) and irradiated at constant temperature for 2 h. Different temperatures are provided and the best– and worst–case scenarios were selected, these correspond to the temperatures of 50 °C and 70 °C. The first temperature, 50 °C or the best scenario, is used for Scenario 1; and the worst case, 70 °C, was used for Scenario 2. Afterward, the mixture is heated to 80 °C for 2 h without irradiation. The solvent is evaporated under vacuum, and the residue is dissolved in hot methanol. Because the temperature was not specified, it was defined to be 37 °C due to the availability of solubility data at this temperature. Then it is cooled down to –6 °C to crystallize and remove unreacted 7DHC. Scenario 3 describes the synthetic procedure using Benzene. The process is the same, the only difference besides the solvent is the irradiation temperature, which is conducted at 73 °C.

Scenarios 4 and 5 were modelled from the process described in Hirsh (2011). There, is reported

a similar process for the synthesis of Vitamin $D_3$. The irradiation is conducted in diethyl ether at 30 °C for 2 h. The conversion achieved can be between 20–30%, therefore just like in the case of isopropanol the best– and worst–case scenarios were selected. Conversion of 20% was used for Scenario 4 and 30 % conversion for Scenario 5. After the reaction, butylated hydroxyanisole or butylated hydroxytoluene is added to stabilize the Vitamin $D_3$ against oxidation. Then, the solvent is distilled, and the product is dissolved in methanol. The temperature of the methanol was not specified, so 37 °C was selected as well. The mixture is cooled down to –6 °C and the unreacted 7DHC is recovered. Afterward, the solvent is evaporated, and the resin is recovered.

Once the resin is obtained the next step is the crystallization. The crystallization Scenarios A and B were modelled following the description of examples two and three –respectively– from Schaaf et al. (1967). In example two the resin is dissolved in benzene, then acetonitrile is added, which makes the solution cloudy and causes the formation of a flocculent. The flocculent separates immediately and is removed by filtration. The solution is then cooled to 5 °C for one hour and seeded. The temperature is maintained for 48 h to form the crystals. To recover the crystals, the solution is further cooled down to –15 °C and washed with acetonitrile at –15 °C. The yield of crystallized Vitamin $D_3$ is 74%. In example three, the resin is dissolved in equal amounts of acetone and acetonitrile. Then the solution is cooled to 5 °C for a period of 48 h. Afterward, the solution is cooled to –5 °C, the crystals are filtrated and washed with acetonitrile at –5 °C. The final yield of crystallized Vitamin $D_3$ is 90%.

Finally, Scenario C is modelled from the description of example two of Marbet (1972). According to example two from Marbet (1972), the resin obtained is dissolved in methyl formate at ambient temperature. The solution is cooled down to 12 °C and seeded, then it is further cooled down to 0 °C. Once the crystals start to form it is cooled to –20 °C and left for 12 h. Then the crystals are filtered and washed with methyl formate at –20 °C.

*Modelling in Aspen Plus*

Mass and energy balances were obtained from the simulations in Aspen plus. The results obtained are according to the declared unit.

The following assumptions were made: (i) photoreactions were not simulated considering the limitations of the software Aspen Plus, (ii) the power of the mercury lamp was not considered, (iii) the ambient temperature was defined as 20 ºC.

The integrated method UNIQUAC was selected as the base method to calculate thermodynamic and transport properties. Missing parameters were estimated by the UNIFAC method. These methods are already incorporated into the property methods from Aspen Plus.

Most of the components were present in Aspen databases. The only component that was not present in the databases at the time of the study was the 7DHC. The proxy Beta–Cholesterol was used instead.

### *Synthesis scenarios*

The following description applies to Scenario 1, 2, and 3.

To model the reaction a Batch Reactor was used. The operating specifications constant temperature, pressure and operating time were specified. Since 7HDC and Vitamin $D_3$ are isomers and because of the limitations of the software Aspen Plus the photoreaction was not modelled, and therefore no reactive system was implemented.

After the reaction, the stabilization of the products at higher temperature was simulated in a batch reactor. The operating specifications were constant Temperature with fixed pressure and operating time. For the next step, i.e. the distillation, a flash separator was used to model a single stage distillation.

To bring the methanol to the specified temperature (37 °C) a heater was used. The crystallizer to remove the 7DHC was also modelled with a heat exchanger. No crystallization or precipitation was modelled due to the lack of data. To remove the 7DHC a separator was placed instead of a filter. It was assumed that 100% of unreacted 7DHC could be removed in this step. After, methanol was removed by distillation, using a flash separator.

The next description applies to Scenario 4 and 5.

The irradiation was modelled with a batch reactor using the same conditions as in Scenarios 1, 2 and 3. After, a stabilizer was added to the mixture. Only butylated hydroxytoluene was present in Aspen's databases, thus this component was selected. After the stabilization, the solvent was distilled using a flash separator to simulate a single stage distillation. The following steps (mix with methanol and removal of unreacted 7DHC) were modelled just like in Scenarios 1, 2 and 3.

### *Crystallization scenarios*

#### Scenario A

The resin was mixed with benzene and acetonitrile, and a flocculent is formed. The patent does not specify what is the flocculent composition, so it was assumed that it contained resin (Vitamin $D_3$) with traces of the solvents (1% of each solvent). This was considering the yield declared by the patent. The flocculent was removed using a Sep module. Then, to model the crystallization cooling batch reactors were used. The operating specifications were constant temperature with

fixed pressure and operating time. No reactive system, crystallization or precipitation were considered due to the lack of data. Filtration at –15 °C was modelled in 2 stages, first a heater was used to cool it down to –15 °C and then a separator was used to remove 100% of the crystals. Acetonitrile, used to wash the crystals, was cooled down with a heater and then filtered with a separator. Finally, the crystals were dried using a heater.

Scenario B

Cooling was modelled using a batch reactor. The operating specifications were constant temperature with fixed pressure and operating time. No reactive system, crystallization nor precipitation was considered due to the lack of data. The second cooling step was simulated in a heater, and the crystals were filtrated using the separator module with 100 % efficiency. The acetonitrile used to wash the crystals was cooled with a heater and then filtered with a separator. Finally, the crystals were dried using a heater.

Scenario C

The cooling steps were modelled using a heater. Only the crystallization at –20 °C for 12 h was done in a batch reactor. The operating specifications for the batch reactor were constant temperature with fixed pressure and operating time. No reactive system, crystallization nor precipitation was considered due to the lack of data. A 75 % yield of crystals was assumed due to the lack of data.

### 2.2.4 Impact Assessment

The LCA study was conducted using Umberto NXT LCA software, from which the environmental impacts were obtained. Mass and energy balances from the continuous process and batch scenarios obtained from Aspen plus were implemented in Umberto NXT LCA, which are presented in Table 2.1 and 2.2 respectively.

Background data was mostly available from the database Ecoinvent 2.2, if possible, Dutch (NL) or European (RER) data were used for consistency on the geographic point. If a material was not present in the database, a similar material or proxy was used. This was the case for butylated hydroxytoluene and 7DHC. Fatty alcohol of plant–based origin was selected to replace 7DHC considering the resemblance in their environmental impacts such as land use and water consumption of ovine with crops, whereas butylated hydroxyanisole was replaced by a proxy (ethyl benzene). Transportation and cleaning procedures were excluded from the assessment in both cases. For more details a description of the inventory is present in Table 3.

Emissions to air and water were calculated following the guidelines present in Hischier et al. (2005)[42].

The impact categories used in this study are from the ReCiPe Midpoint 2008[43] from the hierarchic

perspective, namely: Climate Change (GWP), Fossil Depletion (FDP), Freshwater Ecotoxicity (FETPinf), Freshwater eutrophication (FEP), Human toxicity (HTPinf), Natural land transformation (NLTP), Ozone Depletion (ODPinf), Particulate matter formation (PMFP), Photochemical oxidant formation (POFP), and Water depletion (WDP).

**Table 2.1** Data inventory of continuous process, i.e. mass and energy balances to produce 1g of crystalline Vitamin $D_3$.

| Component | Input | Output |
|---|---|---|
| 7DHC [g] | 1.00 | 0.5* |
| MTBE [g] | 16 | |
| Acetonitrile [g] | 23.1 | |
| Heating [kJ] | 99.5 | |
| Cooling [kJ] | 89 | |
| MTBE (waste) [g] | | 15.7 |
| Acetonitrile (waste) [g] | | 22.6 |
| MTBE (emissions) [g] | | 0.3 |
| Acetonitrile (emissions) [g] | | 0.4 |

*Recycled

**Table 2.2** Data inventory of batch scenarios, i.e. mass and energy balances to produce 1g of crystalline Vitamin $D_3$

| | Scenario 1 | | | Scenario 2 | | | Scenario 3 | | | Scenario 4 | | | Scenario 5 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Component | Inflow [g] | Outflow [g] | Component | Inflow [g] | Outflow [g] | Component | Inflow [g] | Outflow [g] | Component | Inflow [g] | Outflow [g] | Component | Inflow [g] | Outflow [g] |
| Scenario A | 7-dhc | 2.5 | 2.1 | 7-dhc | 2.6 | 1.3 | 7-dhc | 4.4 | 3.1 | 7-dhc | 6.75 | 5.4 | 7-dhc | 4.5 | 3.16 |
| | Resin Vitamin $D_3$ | | 0.35 | Resin Vitamin $D_3$ | | 0.35 | Resin Vitamin $D_3$ | | 0.35 | Resin Vitamin $D_3$ | | 0.35 | Resin Vitamin $D_3$ | | 0.35 |
| | Isopropanol | 1944.5 | | Isopropanol | 2077.9 | | Benzene | 3481.4 | | Butylated Hydroxyanisole | 0.01 | | Butylated Hydroxyanisole | 0.01 | |
| | Methanol | 317.8 | | Methanol | 318 | | Methanol | 318 | | Diethyl ether | 4815.5 | | Diethyl ether | 3210.3 | |
| | Benzene | 2.4 | | Benzene | 2.35 | | Acetonitrile | 8.67 | | Methanol | 318 | | Methanol | 318 | |
| | Acetonitrile | 8.67 | | Acetonitrile | 8.67 | | Heating [kJ] | 6274.3 | | Benzene | 2.35 | | Benzene | 2.35 | |
| | Heating [kJ] | 2896.7 | | Heating [kJ] | 3141.7 | | Cooling [kJ] | 40.1 | | Acetonitrile | 8.67 | | Acetonitrile | 8.67 | |
| | Cooling [kJ] | 40.1 | | Cooling [kJ] | 40.1 | | Benzene (waste) | | 3411.7 | Heating [kJ] | 2492 | | Heating [kJ] | 2416 | |
| | Isopropanol (waste) | | 1905.6 | Isopropanol (waste) | | 2036.4 | Methanol (waste) | | 311.6 | Cooling [kJ] | 40.1 | | Cooling [kJ] | 40.1 | |
| | Methanol (waste) | | 311.5 | Methanol (waste) | | 311.6 | Acetonitrile (waste) | | 8.5 | Diethyl ether (waste) | | 4719.1 | Diethyl ether (waste) | | 3146.1 |
| | Benzene (waste) | | 2.3 | Benzene (waste) | | 2.3 | Benzene(emissions) | | 69.6 | Methanol (waste) | | 311.6 | Methanol (waste) | | 311.6 |
| | Acetonitrile (waste) | | 8.5 | Acetonitrile (waste) | | 8.5 | Methanol (emissions) | | 6.4 | Benzene (waste) | | 2.3 | Benzene (waste) | | 2.3 |
| | Isopropanol (emissions) | | 38.9 | Isopropanol (emissions) | | 41.6 | Acetonitrile (emissions) | | 0.2 | Acetonitrile (waste) | | 8.5 | Acetonitrile (waste) | | 8.5 |
| | Methanol (emissions) | | 6.4 | Methanol (emissions) | | 6.4 | | | | Diethyl ether (emissions) | | 96.3 | Diethyl ether (emissions) | | 64.2 |
| | Benzene (emissions) | | 0.05 | Benzene (emissions) | | 0.05 | | | | Methanol (emissions) | | 6.4 | Methanol (emissions) | | 6.4 |
| | Acetonitrile (emissions) | | 0.2 | Acetonitrile (emissions) | | 0.2 | | | | Benzene (emissions) | | 0.05 | Benzene (emissions) | | 0.05 |
| | | | | | | | | | | Acetonitrile (emissions) | | 0.2 | Acetonitrile (emissions) | | 0.2 |

| | Scenario 1 | | | Scenario 2 | | | Scenario 3 | | | Scenario 4 | | | Scenario 5 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Component | Inflow [g] | Outflow [g] | Component | Inflow [g] | Outflow [g] | Component | Inflow [g] | Outflow [g] | Component | Inflow [g] | Outflow [g] | Component | Inflow [g] | Outflow [g] |
| **Scenario B** | 7–dhc | 2 | 0.9 | 7–dhc | 2.2 | 1.1 | 7–dhc | 3.6 | 2.5 | 7–dhc | 5.5 | 4.4 | 7–dhc | 3.7 | 2.6 |
| | Resin Vitamin $D_3$ | | 0.1 | Resin Vitamin $D_3$ | | 0.1 | Resin Vitamin $D_3$ | | 0.1 | Resin Vitamin $D_3$ | | 0.1 | Resin Vitamin $D_3$ | | 0.1 |
| | Isopropanol | 1584.4 | | Isopropanol | 1693.1 | | Benzene | 2834.8 | | Butylated Hydroxyanisole | 0.01 | | Butylated Hydroxyanisole | 0.01 | |
| | Methanol | 259 | | Methanol | 259.1 | | Methanol | 259 | | Diethyl ether | 3923.7 | | Diethyl ether | 2615.8 | |
| | Acetone | 3.6 | 3.6 | Acetone | 3.6 | | Acetone | 3.6 | | Methanol | 258.0 | | Methanol | 258.0 | |
| | Acetonitrile | 7.1 | 7.11 | Acetonitrile | 7.1 | | Acetonitrile | 7.1 | | Acetone | 3.6 | | Acetone | 3.6 | |
| | Heating [kJ] | 2664.2 | | Heating [kJ] | 3064.9 | | Heating [kJ] | 6197.3 | | Acetonitrile | 7.1 | | Acetonitrile | 7.1 | |
| | Cooling [kJ] | 44.3 | | Cooling [kJ] | 44.3 | | Cooling [kJ] | 44.3 | | Heating [kJ] | 2370.0 | | Heating [kJ] | 2348 | |
| | Isopropanol (waste) | | 1552.7 | Isopropanol (waste) | | 1659.3 | Benzene (waste) | | 2778.1 | Cooling [kJ] | 44.3 | | Cooling [kJ] | 44.3 | |
| | Methanol (waste) | | 253.8 | Methanol (waste) | | 253.9 | Methanol (waste) | | 253.8 | Diethyl ether (waste) | | 3845.2 | Diethyl ether (waste) | | 2563.5 |
| | Acetone (waste) | | 3.5 | Acetone (waste) | | 3.5 | Acetone (waste) | | 3.5 | Methanol (waste) | | 252.8 | Methanol (waste) | | 252.8 |
| | Acetonitrile (waste) | | 7.0 | Acetonitrile (waste) | | 7.0 | Acetonitrile (waste) | | 7.0 | Acetone (waste) | | 3.5 | Acetone (waste) | | 3.5 |
| | Isopropanol (emissions) | | 31.7 | Isopropanol (emissions) | | 33.9 | Benzene(emissions) | | 56.7 | Acetonitrile (waste) | | 7.0 | Acetonitrile (waste) | | 7.0 |
| | Methanol (emissions) | | 5.2 | Methanol (emissions) | | 5.2 | Methanol (emissions) | | 5.2 | Diethyl ether (emissions) | | 3609.8 | Diethyl ether (emissions) | | 52.3 |
| | Benzene (emissions) | | 0.1 | Benzene (emissions) | | 0.1 | Acetone (emissions) | | 0.1 | Methanol (emissions) | | 237.4 | Methanol (emissions) | | 5.2 |
| | Acetonitrile (emissions) | | 0.1 | Acetonitrile (emissions) | | 0.1 | Acetonitrile (emissions) | | 0.1 | Acetone (emissions) | | 3.3 | Acetone (emissions) | | 0.1 |
| | | | | | | | | | | Acetonitrile (emissions) | | 6.5 | Acetonitrile (emissions) | | 0.1 |

| | Scenario 1 | | | Scenario 2 | | | Scenario 3 | | | Scenario 4 | | | Scenario 5 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Component | Inflow [g] | Outflow [g] | Component | Inflow [g] | Outflow [g] | Component | Inflow [g] | Outflow [g] | Component | Inflow [g] | Outflow [g] | Component | Inflow [g] | Outflow [g] |
| Scenario C | 7–dhc | 2.5 | 1.1 | 7–dhc | 2.6 | 1.3 | 7–dhc | 4.4262 | 3.1 | 7–dhc | 6.75 | 5.4 | 7–dhc | 4.5 | 3.2 |
| | Resin Vitamin $D_3$ | | 0.35 | Resin Vitamin $D_3$ | | 0.35 | Resin Vitamin $D_3$ | | 0.35 | Resin Vitamin $D_3$ | | 0.35 | Resin Vitamin $D_3$ | | 0.35 |
| | Isopropanol | 1944.5 | | Isopropanol | 2077.9 | | Benzene | 3479 | | Butylated Hydroxyanisole | 0.0135 | | Butylated Hydroxyanisole | 0.01 | |
| | Methanol | 317.8 | | Methanol | 318 | | Methanol | 318 | | Diethyl ether | 4815.5 | | Diethyl ether | 3210.3 | |
| | Methyl Formate | 5.61 | | Methyl Formate | 5.6 | | Methyl Formate | 5.6 | | Methanol | 318 | | Methanol | 318 | |
| | Heating [kJ] | 2895.9 | | Heating [kJ] | 3141.7 | | Heating [kJ] | 6274.3 | | Methyl Formate | 5.61 | | Methyl Formate | 5.61 | |
| | Cooling [kJ] | 77.45 | | Cooling [kJ] | 77.5 | | Cooling [kJ] | 77.5 | | Heating [kJ] | 2492 | | Heating [kJ] | 2416 | |
| | Isopropanol (waste) | | 1905.6 | Isopropanol (waste) | | 2036.4 | Benzene (waste) | | 3409.4 | Cooling [kJ] | 77.45 | | Cooling [kJ] | 77.45 | |
| | Methanol (waste) | | 311.5 | Methanol (waste) | | 311.6 | Methanol (waste) | | 311.6 | Diethyl ether (waste) | | 4719.1 | Diethyl ether (waste) | | 3146 |
| | Methyl Formate (waste) | | 5.5 | Methyl Formate (waste) | | 5.5 | Methyl Formate (waste) | | 5.5 | Methanol (waste) | | 311.6 | Methanol (waste) | | 311.6 |
| | Isopropanol (emissions) | | 38.9 | Isopropanol (emissions) | | 41.56 | Benzene (emissions) | | 69.6 | Methyl Formate (waste) | | 5.5 | Methyl Formate (waste) | | 5.5 |
| | Methanol (emissions) | | 6.4 | Methanol (emissions) | | 6.36 | Methanol (emissions) | | 6.4 | Diethyl ether (emissions) | | 96.3 | Diethyl ether (emissions) | | 64.2 |
| | Methyl Formate (emissions) | | 0.1 | Methyl Formate (emissions) | | 0.11 | Methyl Formate (emissions) | | 0.1 | Methanol (emissions) | | 6.36 | Methanol (emissions) | | 6.4 |
| | | | | | | | | | | Methyl Formate (emissions) | | 0.1 | Methyl Formate (emissions) | | 0.1 |

**Table 2.3** Details of Inventory Units used from Ecoinvent 2.2

| Material/ Energy input | Description of inventory data from Ecoinvent 2.2 |
|---|---|
| 7–DHC* | Fatty alcohol (vegetable origin) [RER] |
| MTBE | Methyl ter–butyl eter, at plant [RER] |
| ACN | Acetonitrile, at plant [RER] |
| Isopropanol | Isopropanol, at plant [RER] |
| Methanol | Methanol, from synthetic gas, at plant [CH] |
| Benzene | Benzene, at plant [RER] |
| Diethyl ether | Diethyl ether, at plant [RER] |
| Acetone | Acetone, liquid, at plant [RER] |
| Formic acid | Formic acid, at plant [RER] |
| Ethyl benzene | Ethyl benzene, at plant [RER] |
| MTBE (waste) | T– Butyl methyl ether [water/river] |
| ACN (waste) | Acetonitrile [water/river] |
| Isopropanol (waste) | 2–propanol [water/river] |
| Methanol (waste) | Methanol [water/river] |
| Benzene (waste) | Benzene [water/river] |
| Diethyl ether** | t–Butyl methyl ether [water/river] |
| Acetone (waste) | Acetonitrile [water/river] |
| Formic Acid (waste) | Formic Acid [water/ground–, long term] |
| Ethyl benzene | Benzene, ethyl– [water/river] |
| MTBE (emissions) | T– Butyl methyl ether [air/high population density] |
| ACN (emissions) | Acetonitrile [air/ high population density] |
| Isopropanol (emissions) | 2–propanol [air/high population density] |
| Methanol (emissions) | Methanol [air/high population density] |
| Benzene (emissions) | Benzene [air/high population density] |
| Diethyl ether | Diethyl ether [air/high population density] |
| Acetone (emissions) | Acetone [air/high population density] |
| Formic Acid (emissions) | Formic Acid [air/high population density] |
| Ethyl benzene | Benzene, ethyl – [air/high population density] |
| Electrical Energy | Electricity, natural gas, at power plat [NL] |
| Heat | Heat, unspecific, in chemical plant [RER] |
| Cooling Energy | Cooling energy, natural gas, at cogen unit with absortion chiller 100 KW [CH] |

*A proxy was used.

**A proxy was used for diethyl ether in the case of waste (impact on water reservoirs) due to the absence of this component in the data base.

## 2.3 RESULTS

The discussion is structured in two sections. The first section analyses the flow process with the purpose of finding the areas for improvement. The second section compares the flow NPW process with diverse batch processes (comparative assertion).

### 2.3.1 Continuous Process

Results in the categories selected are presented in Table 2.4. The main contributors to each category are present in Figure 2.8. The results are established upon the individual environmental impact of the materials and energy exchanges, along with the emissions and waste generated in the process allocated to the product. As can be deduced from Figure 2.8, the solvents in the process represent a large share of the environmental impact. This finding is in agreement with previous results[27], which concluded that solvents are greatly responsible for the environmental impact of pharmaceutical processes. Despite the use of NPW, solvents still dominate the environmental impact of the process.

**Table 2.4** LCIA results of intensified process

| Impact category | |
|---|---|
| Climate Change [kg $CO_2$ to air] | $2.5 \cdot 10^{-01}$ |
| Fossil Depletion [kg Oil] | $1.75 \cdot 10^{-01}$ |
| Freshwater Ecotoxicity [kg 1,4–DCB to freshwater] | $2.84 \cdot 10^{-04}$ |
| Freshwater eutrophication [kg (P to freshwater] | $5.14 \cdot 10^{-06}$ |
| Human toxicity [1,4–DCB to urban air] | $1.19 \cdot 10^{-02}$ |
| Natural land transformation [$m^2$ natural land] | $1.89 \cdot 10^{-04}$ |
| Ozone depletion [kg CFC–11 to air] | $1.70 \cdot 10^{-08}$ |
| Particulate matter formation [kg $PM_{10}$ to air] | $2.78 \cdot 10^{-04}$ |
| Photochemical oxidant formation [kg (NMVOC to urban air] | $7.48 \cdot 10^{-04}$ |
| Water depletion [$m^3$ water] | $1.16 \cdot 10^{-03}$ |

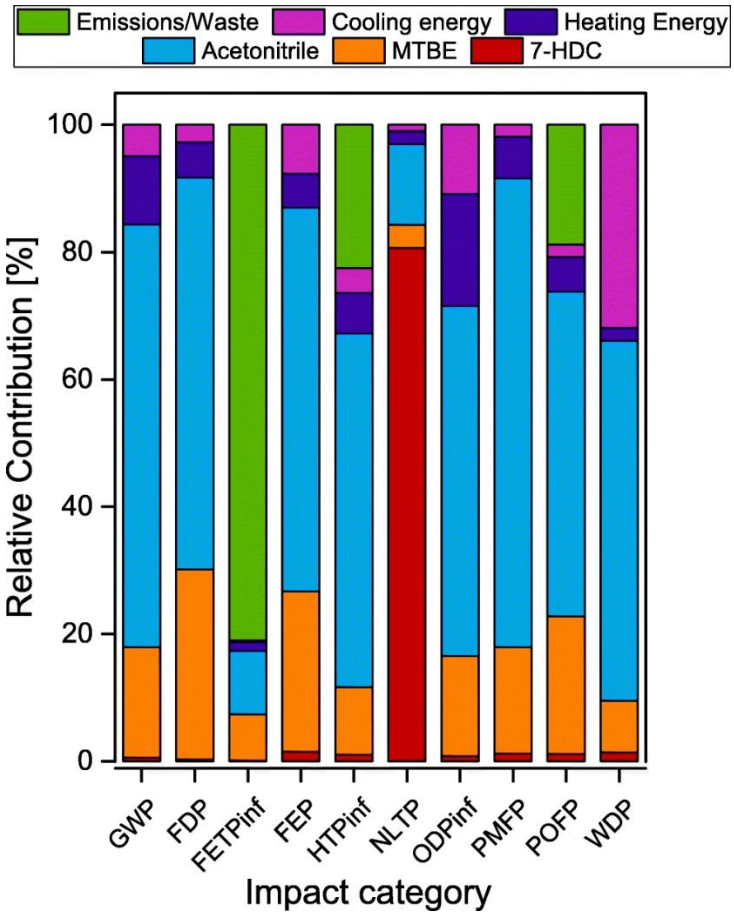



**Fig. 2.8** Normalized LCIA profile of the intensified process

Acetonitrile has the highest contribution in eight out of the ten categories. Large amounts of this solvent are required in comparison with the other solvents or reactants. Hence, among the three stages of the process, i.e. photosynthesis, solvent–swap and crystallization, the solvent swap is the hot spot to improve. t–BME is the material (solvent) with the second highest contribution in five out of the ten categories. These two solvents have a large environmental impact because the process lacks the capacity of recycling them. It is affecting FETPinf category as more than 80% of the impact is caused by emissions and waste solvent. Although the crystallization has a closed loop, the solvent swap does not have. Closing the loop in the solvent swap is therefore a necessary step to improve the environmental footprint of the process. However, this step has not been implemented due to the percentage of ACN present in the t–BME after it has been removed in the solvent swap step.

The energy exchanges, i.e. heating and cooling, have a minor contribution except for the ODP and WDP categories. These contributions are the result of the combustion of fossil fuels to produce energy; the release of recalcitrant chemicals with a long atmospheric life such as

chlorine or bromine during the production, the use of refrigerating agents, and the use of water for cooling purposes.

Finally, the NLTP category is largely dominated by 7DHC. Although the material used from the database has a vegetable origin, the impact in this category can be comparable to the impact of livestock which also requires and consumes large amounts of green areas.

### 2.3.2 Comparison with batch process

Life cycle impacts of batch scenarios were normalized with respect to the continuous intensified process. The results of the comparison of the continuous process with the batch scenarios are shown in Figures 2.9–2.12.

From the results, it clearly appears that the continuous process has a lower environmental impact compared to any of the batch scenarios evaluated. Input materials, in particular solvents, are dominant in the life cycle impact of both continuous and batch. This has been also reported in other publications[44], and in the case of the batch scenarios presented here, these solvents affect greatly their environmental impact.

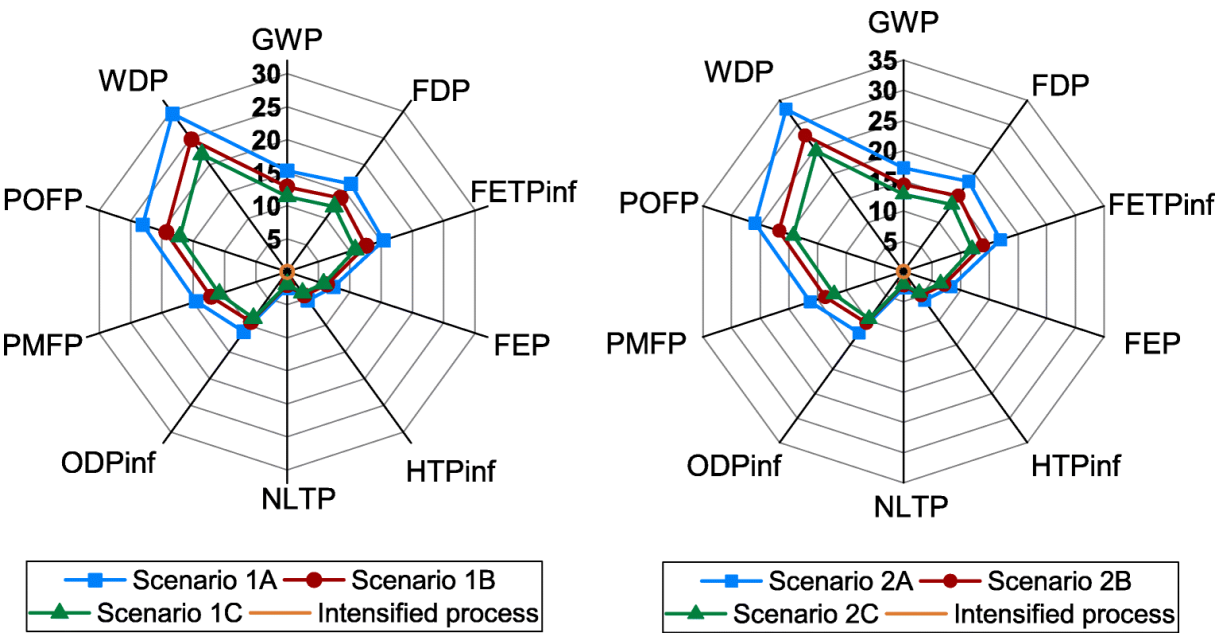



**Fig. 2.9** Life cycle profiles of continuous and batch Scenarios 1A, 1B, 1C (left) and 2A, 2B, and 2C (right).

Figure 2.9 shows the scenarios where the synthesis is conducted in isopropanol. The greatest difference is in the WDP category, the continuous process has a lower water depletion impact

by a factor of 30–22 fold and 33–25 fold (depending on Scenario 1 or 2). In the batch Scenarios 1A, 1B, 1C, 2A, 2B, and 2C the impact categories are driven by the solvent isopropanol. When this solvent is prepared through the catalytic hydrogenation of acetone[45], the hydrogenation has a large impact due to the large requirements of water and energy. Little difference is observed in the NLTP category, which as mentioned before is mainly monopolized by the 7DHC. Hence, the small difference in the amount of 7DHC needed is reflected in a similar impact. The other two categories with low impact are HTP, only 4 to 6 fold higher (lowest and highest limits); and FEP being 6–7 fold higher (lowest and highest limits). This result is remarkable despite the differences in the mass of solvents needed; nonetheless, highlights the importance of solvent selection, isopropanol has a lower impact in these categories than acetonitrile, which is used greatly in the continuous process.

Between Scenarios 1 and 2, Scenario 1 has the lowest environmental impact in all the categories because the overall conversion achieved in Scenario 1 is higher at a lower temperature. The disadvantage of Scenario 1 is that in this process higher amounts of tachysterol compared to Scenario 2 are obtained; however, tachysterol purification was not considered in the scope of this LCA study.

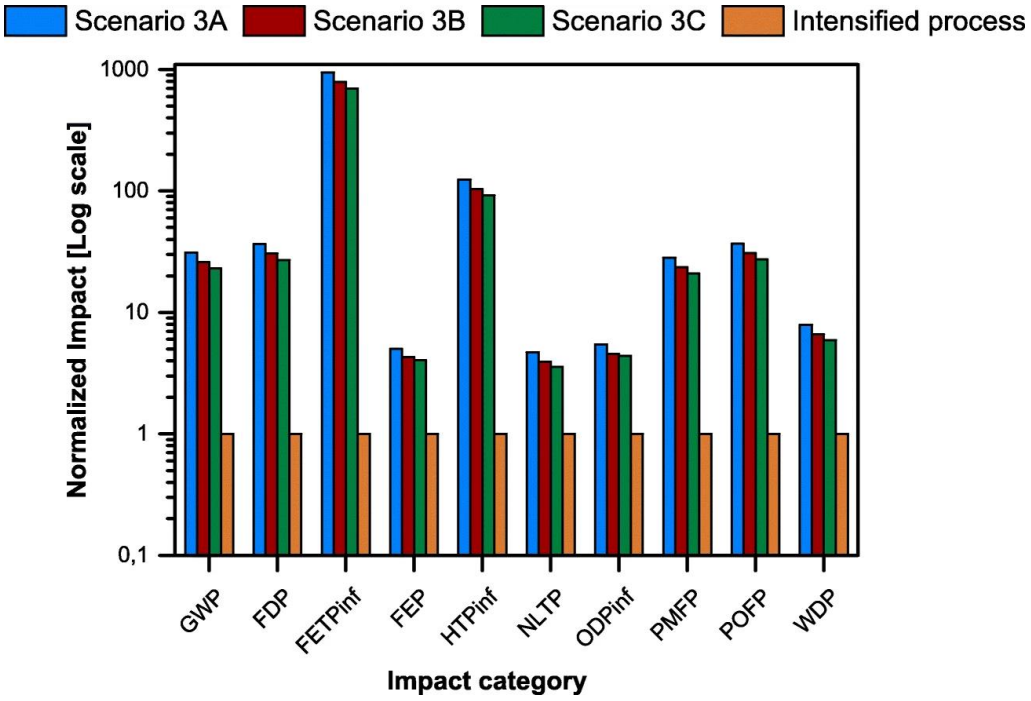



**Fig. 2.10** Life cycle profiles of continuous and batch Scenarios 3A, 3B, 3C (left), scaled view (right).

Figure 2.10 presents the comparison of the intensified process with the batch process when the solvent used in the synthesis is benzene. The scenario using benzene is the most dangerous scenario for humankind because benzene is a carcinogenic solvent (carcinogenic group I) and exposure to this solvent should be limited. This is reflected in the HTPinf category, with the human toxicity being 92–124 times that of the continuous processes, depending on the scenario. Moreover, in terms of safety, the occupational exposure level recommended by the OSHA (Occupational Safety and Health Administration) is 1 ppm [46], which is very low compared to isopropanol (500 ppm) [47]or diethyl ether (400 ppm) [48]. This indicates that other solvents are better alternatives especially in the human safety aspect. The process also represents a concern to the environment with high freshwater ecotoxicity caused by the benzene waste. Therefore, special measures need to be taken to avoid water contact and contamination. The categories that respect the air compartment: GWP, FDP, PMFP, POFP are also affected by the big amounts of benzene used. An increment of 23–31 fold, 27–36 fold, 21–28 fold and 27–37 fold, respectively, is observed in these categories. On the other side eutrophication and ozone depletion do not represent a big concern, as it is only 4–5 times greater, despite the difference in the mass of solvents used.

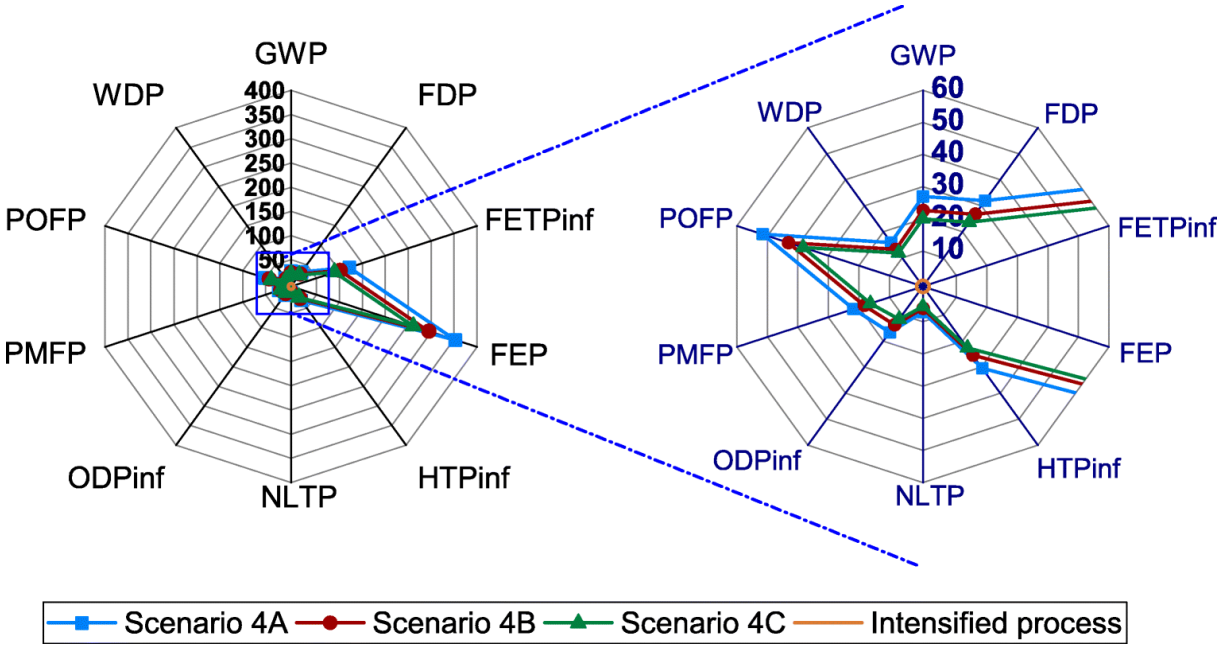



**Fig. 2.11** Life cycle profiles of continuous and batch Scenarios 4A, 4B, 4C (left), scaled view (right).

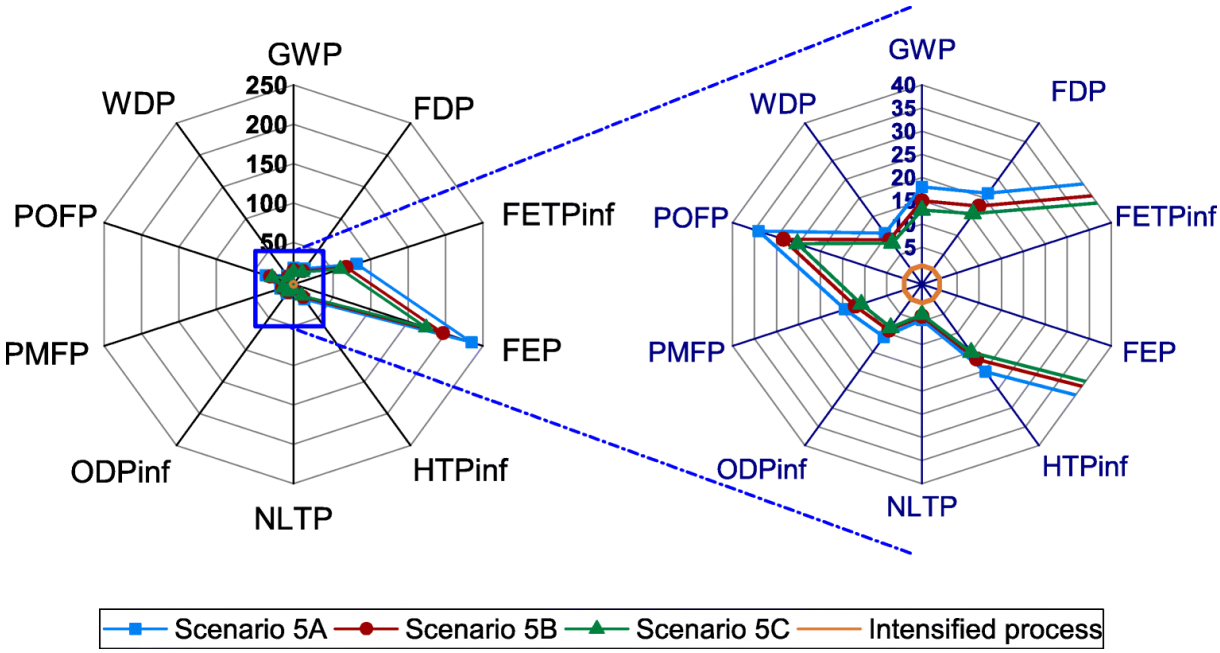



**Fig. 2.12** Life cycle profiles of continuous and batch Scenarios 5A, 5B, 5C (left), scaled view (right).

Finally, Fig. 2.11 and 2.12 presents the comparison of the continuous process with the batch scenarios where diethyl ether is used in the synthesis of the resin. The results of Scenario 4(A, B, and C) in worst that in the case of Scenario 5 (A, B, and C); which is expected based on the higher conversion achieved in Scenario 4. The categories with a larger environmental impact are FEP and FETP. FEP increases by 60 (Scenario 5 lowest value) – 122 (Scenario 4 highest) and FETP by 174 (Scenario 5 lowest value) –352 (Scenario 4 highest). These categories are greatly affected when no solvent waste management strategy is implemented. As far as safety is concerned, this solvent is also peroxidizable[22]; therefore, it is necessary to take important safety measures to avoid risks. The continuous process also shows a better result in the POFP category, reducing the impact from 25–52 times. Lower amounts of solvents are needed, thus lower amounts of volatile components are emitted. In the rest of the categories, the continuous process shows an environmental impact 10 to 25 times smaller.

All the batch scenarios are offset with respect to the continuous ones due to the high dilution used. This is in agreement with previous LCA studies[49,50] where the ecological impact is largely driven by the input materials, which, in the case of the pharmaceutical industry, corresponds largely to the use of solvents[51]. Henderson et al. (2008) studied the production of 7–aminocephalosporic acid, a base for many antibiotics. They found that a great part of the impact is caused by raw materials, and the best option for reducing the impact is recycling[49].

### 2.3.3 Solvent recovery case study

The large difference between the impact of the continuous process and the batch processes poses the question of whether recycling the solvents would reduce this marked contrast. Solvents recycling is a preferred practice over waste management[49,52]. Therefore, there is a great emphasis on solvent recovery to reduce the cost associated with its purchase and disposal. Due to the importance of solvent recovery, this last section will elaborate on the recovery of the solvent for the batch case. In the literature, it is stated that solvents used in the synthesis, such as isopropanol or benzene (Scenarios 1, 2, 3, 4, and 5), can be recycled[5]. However, it is not mentioned how many times and what impact the use of recycled solvent has in the process. Moreover, it would be possible that the solvents would need extra purification[53] before being recycled.

As shown before, the largest disadvantage of the batch process is the use of a diluted system for the reaction. The lowest environmental impact for the batch process is obtained when isopropanol is used as a solvent for the synthesis, with scenarios 1A, 2A, and 3A as the best cases. These scenarios are taken to conduct a further sensitivity analysis. Being the impact dominated by isopropanol, it was decided to investigate the potential effect of the recovery of this solvent.

To assess the impact of solvent recovery, the following assumptions were considered due to the lack of data about recycling and recovering the solvent in the synthesis of Vitamin $D_3$. The first assumption was the use of internal recycling to avoid transportation and post–treatment emissions. Furthermore, from the simulation, it was found that the distillation of isopropanol from the product yields high–purity isopropanol (99.999%). Due to this high purity, it was assumed that the isopropanol can be recycled without further treatment.

Pharmaceutical companies have reported recovery of the solvents from 20% to 60%. According to the Toxic Release Inventory (TRI), the amount of solvent recovered has increased to 70%[53]. Based on these percentages, the amount of solvent recovery was variated from 10% to 25%, 50%, 75%, and 95%. Then, this solvent was mixed with the corresponding fraction of fresh solvent and used in the process. Finally, it was also assumed that the reuse of solvent had no impact on the conversion and selectivity of the reaction. With these considerations, the best–case scenarios were developed. The results are presented in Fig. 2.13.

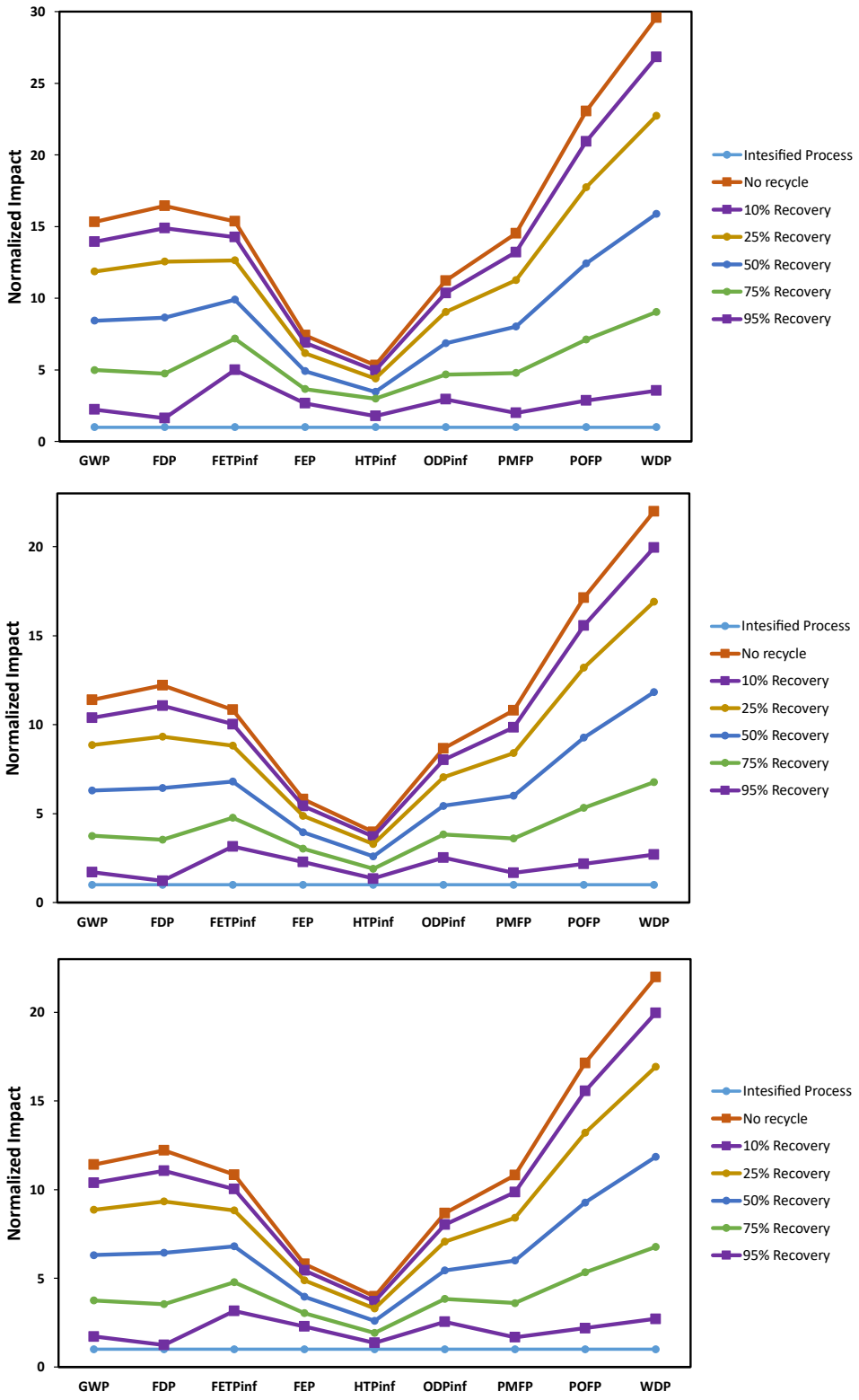



**Fig. 2.13** Life cycle profiles of batch Scenarios 1A (top), 1B (center), and 1C (bottom) at the theoretical scenarios for recovery of isopropanol for the categories of Climate Change (GWP), Fossil Depletion (FDP), Freshwater Ecotoxicity (FETPinf), Freshwater eutrophication (FEP), Human toxicity (HTPinf), Ozone Depletion (ODPinf), Particulate matter formation (PMFP), Photochemical oxidant formation (POFP), and Water depletion (WDP).

The assessment showed that more than 95% recovery is needed to have a process comparable, yet not equal, to the continuous intensified option. In all the categories, an improvement was observed except for the NLTP. This category as mentioned before is dominated by the 7DHC, and without a change in the conversion, it would not be impacted. For that reason, this category was not plotted. However, despite isopropanol recycling, the life cycle impact is still greater. This means that other solvents in the batch process would have to be recovered and recycled without the need for extra purification. This may be possible for methanol since it can be obtained with 99.993% purity. Consequently, methanol recyclability was explored as well. It was assumed that 95% of methanol can be recovered and recycled. This together with a case where 95% of isopropanol can be recovered was assessed, and the results are displayed in Fig. 2.14.

As it can be observed, three categories benefit from this recovery, namely FETPinf, FEP, and HTPinf, particularly for Scenarios 1C and 1B. In these categories, the impact is lower or equal to that of the continuous process. However, the other categories still display a higher environmental impact. The rest of the solvents are mixed; therefore, their recovery would need energy and produce emissions. This must be assessed more carefully to see if their recovery is worthy, or if their disposal would be a better alternative. Moreover, the impact on the process needs to be evaluated.

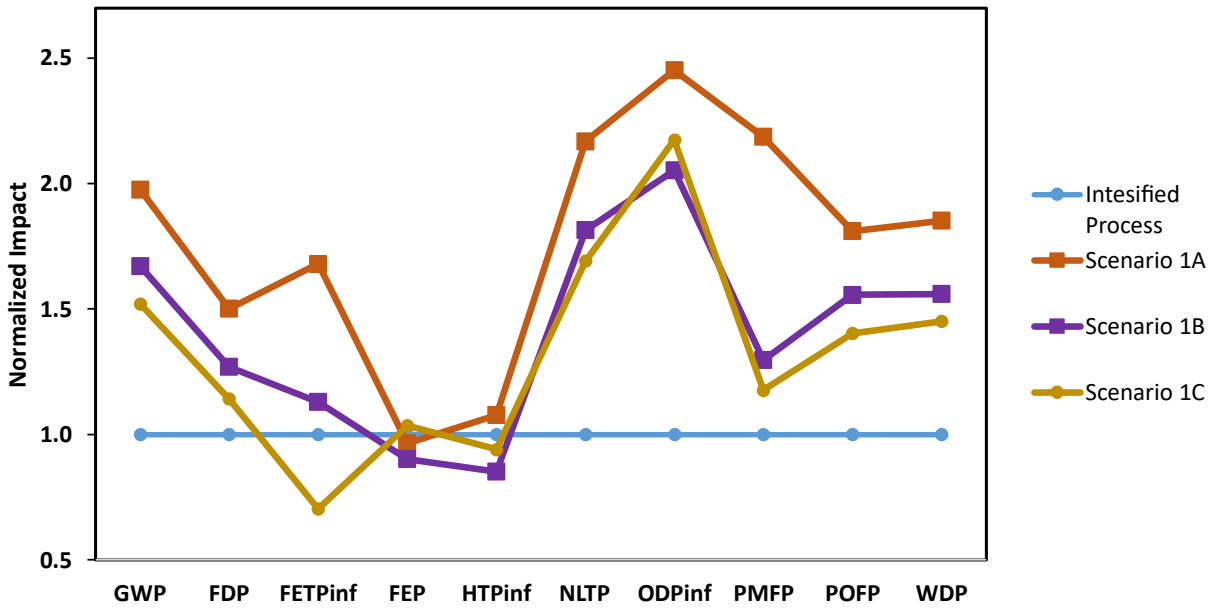



**Fig. 2.14** Life cycle profiles of batch Scenarios 1A, 1B, and 1C at different theoretical scenarios for recovery of methanol for the categories of Climate Change (GWP), Fossil Depletion (FDP), Freshwater Ecotoxicity (FETPinf), Freshwater eutrophication (FEP), Human toxicity (HTPinf), Natural land transformation (NLTP), Ozone Depletion (ODPinf), Particulate matter formation (PMFP), Photochemical oxidant formation (POFP), and Water depletion (WDP).

Another alternative that was not presented here is solvent management. Several alternatives for solvent management have been addressed before[53,54] with distillation being the most common.

Besides solvent management, cleaning cycles were not considered. However, as discussed in Lee et al. (2016), the impact of cleaning is larger in the case of batch processes[44]. This is due to the need for a higher number of washes, which is translated not only into more solvents but also in more energy needed to heat the solvents.

In addition to the higher environmental impact of the batch processes, another great disadvantage of the industrial processes is the duration. The synthesis alone is 2 h, and the crystallization consumes over 48 h. These results in a process of over 50 h length, without even considering dead times (e.g. cleaning)[55].

## 2.4 CONCLUSIONS

The continuous and intensified production of Vitamin $D_3$ was assessed to evaluate its environmental impact. Moreover, it was benchmarked against different batch scenarios,

which were constructed by assembling data from patents. The life cycle assessment illustrated clear differences between the continuous process and the batch processes. The continuous process exhibits a lower environmental impact in all the categories evaluated and optimized use of materials. In addition, the process offers the possibility of working under anoxic conditions, which enhances the resistance of the components and avoids the degradation of Vitamin $D_3$. However, the continuous process can benefit from the implementation of recycling loops for the two solvents used (i.e., t–BME and acetonitrile).

The difference in the environmental footprint is minimized when solvent recycling is implemented in the batch scenarios. Solvent recycling in the batch case was considered, assuming the best–case scenario. The results showed that it is necessary to recover both isopropanol and methanol, in very high yields (>95%). Moreover, is necessary to recycle them without further treatment. Although the best–case scenario was assumed, only three categories showed a better environmental impact. The rest still display a higher impact.

Other advantages of the continuous intensified process that were not discussed here are the smaller equipment size (and hence, potentially smaller plant environmental impact), and the need for less cleaning. On the other side higher automatization is needed, which may be negative, increasing the environmental impact (higher energy demand) but potentially increasing any safety concern[44].

Nevertheless, it is important to consider that an important aspect was disregarded within the scope of the present LCA study, namely the power lamp, which was not considered in the assessment due to the lack of data for an accurate temporal correlation. Taking these aspects into consideration could possibly diminish the sustainability advantage of the continuous process. Future work is needed to address missing process steps (i.e., recycle loops) and incorporate them into the LCA study.

## REFERENCES


1 F. Mahmoodani, C. O. Perera, B. Fedrizzi, G. Abernethy and H. Chen, *Food Chem.*, 2017, **219**, 373–381.

2 S. Khadilkar, *J. Obstet. Gynecol. India*, 2013, **63**, 147–150.

3 J. H. Lee, J. H. O'Keefe, D. Bell, D. D. Hensrud and M. F. Holick, *J. Am. Coll. Cardiol.*, 2008, **52**, 1949–1956.

4 Z. Fanari, S. Hammami, M. B. Hammami, S. Hammami and A. Abdellatif, *J. Saudi Hear. Assoc.*, 2015, **27**, 264–271.

5 A. L. Hirsch, *Industrial aspects of vitamin D*, Elsevier, Third Edit., 2011.

6 H. Gruber-Woelfler, M. Escribà-Gelonch, T. Noël, M. C. Maier and V. Hessel, *Chem. Eng. Technol.*, 2017, **40**, 2016–2024.

7 R. L. Hartman, J. P. McMullen and K. F. Jensen, *Angew. Chemie – Int. Ed.*, 2011, **50**, 7502–7519.

8 S. L. Lee, T. F. O'Connor, X. Yang, C. N. Cruz, S. Chatterjee, R. D. Madurawe, C. M. V. Moore, L. X. Yu and J. Woodcock, *J. Pharm. Innov.*, 2015, **10**, 191–199.

9 R. Porta, M. Benaglia and A. Puglisi, *Org. Process Res. Dev.*, 2016, **20**, 2–25.

10 C. Jiménez-González, P. Poechlauer, Q. B. Broxterman, B. S. Yang, D. Am Ende, J. Baird, C. Bertsch, R. E. Hannah, P. Dell'Orco, H. Noorman, S. Yee, R. Reintjens, A. Wells, V. Massonneau and J. Manley, *Org. Process Res. Dev.*, 2011, **15**, 900–911.

11 B. Benyahia, R. Lakerveld and P. I. Barton, *Ind. Eng. Chem. Res.*, 2012, **51**, 15393–15412.

12 L. Malet-Sanz and F. Susanne, *J. Med. Chem.*, 2012, **55**, 4062–4098.

13 M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, *Chem. Rev.*, 2017, **117**, 11796–11893.

14 V. Hessel, B. Cortese and M. H. J. M. de Croon, *Chem. Eng. Sci.*, 2011, **66**, 1426–1448.

15 V. Hessel, *Chem. Int.*, 2018, **40**, 12–16.

16 I. V. Gürsel, V. Hessel, Q. Wang, T. Noël and J. Lang, *Green Process. Synth.*, 2012, **1**, 315–336.

17 M. Hempel, *Chem. Eng. Technol.*, 2009, **32**, 1651–1654.

18 S. J. Haswell and P. Watts, *Green Chem.*, 2003, **5**, 240–249.

19 D. Ott, S. Borukhova and V. Hessel, *Green Chem.*, 2016, **18**, 1096–1116.

20 S. Borukhova, T. Noël, B. Metten, E. de Vos and V. Hessel, *Green Chem.*, 2016, **18**, 4947–4953.

21 M. Escribà-Gelonch, T. Noël and V. Hessel, *Org. Process Res. Dev.*, 2018, 147–155.

22 M. Escribà-Gelonch, A. Halpin, T. Noël and V. Hessel, *ChemPhotoChem*, 2018, 1–10.

23 M. Escribà-Gelonch, V. Hessel, M. C. Maier, T. Noël, M. F. Neira d'Angelo and H. Gruber-Woelfler, *Org. Process Res. Dev.*, 2018, 178–189.

24 S. Fuse, N. Tanabe, M. Yoshida, H. Yoshida, T. Doi and T. Takahashi, *Chem. Commun.*, 2010, **46**, 8722.

25 T. Doi, M. Yoshida, I. Hijikuro and T. Takahashi, *Tetrahedron Lett.*, 2004, **45**, 5727–5729.

26 D. D. Bikle, *Chem. Biol.*, 2014, **21**, 319–329.

27 D. Cespi, E. S. Beach, T. E. Swarr, F. Passarini, I. Vassura, P. J. Dunn and P. T. Anastas, *Green Chem.*, 2015, **17**, 3390–3400.

28 C. Ponder and M. Overcash, *Sci. Total Environ.*, 2010, **408**, 1331–1337.

29 J. Guinée, in *Taking Stock of Industrial Ecology*, Springer, Cham, 2016, pp. 45–68.

30 R. U. Ayres, *Resour. Conserv. Recycl.*, 1995, **14**, 199–223.

31 M. Cellura, S. Longo and M. Mistretta, *Renew. Sustain. Energy Rev.*, 2011, **15**, 4697–4705.

32 A. E. Björklund, *Int. J. Life Cycle Assess.*, 2002, **7**, 64–72.

33 M. Guo and R. J. Murphy, *Sci. Total Environ.*, 2012, **435–436**, 230–243.

34 I. Aspen Technology, *Aspen Technol. Inc.*, 2000, 936.

35 S. Kim and P. L. Douglas, *Dev. Chem. Eng. Miner. Process.*, 2002, **10**, 89–103.

36 F. A. Mato and C. Berro, *J. Chem. Eng. Data*, 1991, **36**, 262–264.

37 A. Y. Sazonova and V. Raeva, *Int. J. Chem. Mol. Nucl. Mater. Metall. Eng.*, 2015, **9**, 288–

291.

38 B. P. Weidema and M. S. Wesnaes, *J. Clean. Prod.*, 1996, **4**, 167–174.

39 1971, 1–7.

40 3, 665,020, 2006, 2, 260–262.

41 3, 334, 118, 1967, 3–5.

42 R. Hischier, S. Hellweg, C. Capello and A. Primas, *Int. J. Life Cycle Assess.*, 2005, **10**, 59–67.

43 M. Goedkoop, R. Heijungs, M. Huijbregts, A. De Schryver, J. Struijs and R. Van Zelm, *ReCiPe 2008*, 2009.

44 C. K. Lee, H. H. Khoo and R. B. H. Tan, *Org. Process Res. Dev.*, 2016, **20**, 1937–1948.

45 US5081321A, 1992, 7.

46 A. Yardley–Jones, D. Anderson and D. V Parke, *Br. J. Ind. Med.*, 1991, **48**, 437–44.

47 Science Lab, *Sci. lab.com Chem. Lab. Equip.*, 2013, **4**, 4–9.

48 Thermo Fisher SCIENTIFIC, *Safety Data Sheet Diethyl Ether*, 2018, vol. 40.

49 R. K. Henderson, C. Jiménez–González, C. Preston, D. J. C. Constable and J. M. Woodley, *Ind. Biotechnol.*, 2008, 180–192.

50 D. Ott, D. Kralisch, I. Denčić, V. Hessel, Y. Laribi, P. D. Perrichon, C. Berguerand, L. Kiwi–Minsker and P. Loeb, *ChemSusChem*, 2014, **7**, 3521–3533.

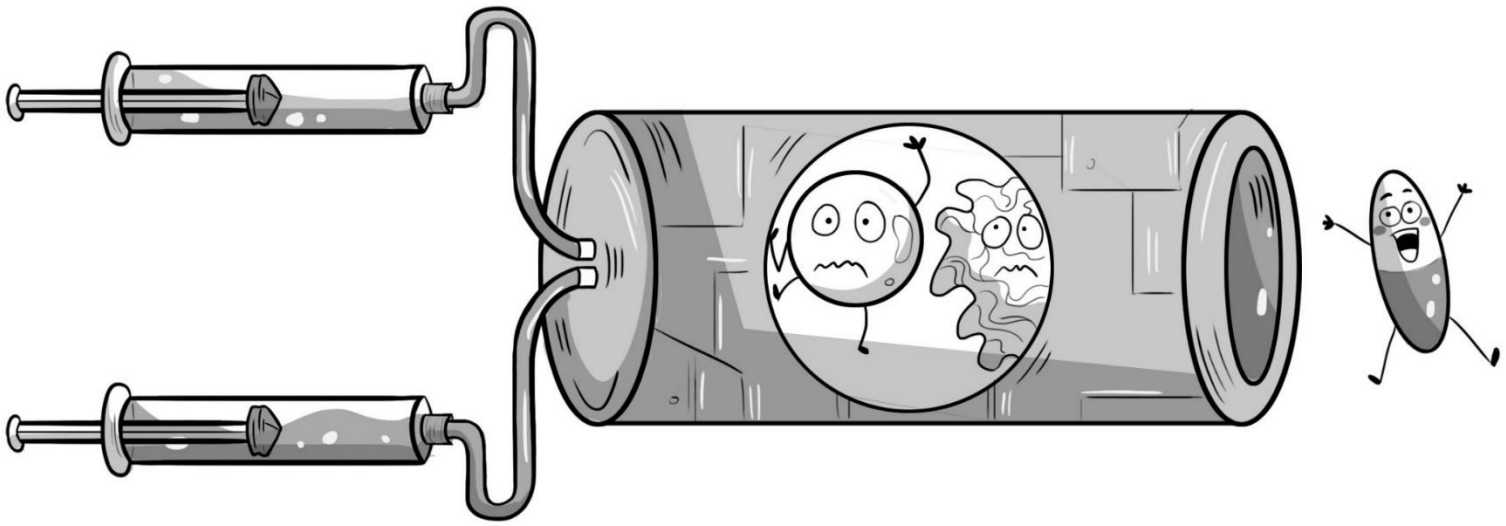
51 C. Jimenez–Gonzalez, C. S. Ponder, Q. B. Broxterman and J. B. Manley, *Org. Process Res. Dev.*, 2011, **15**, 912–917.

52 C. S. Slater, M. J. Savelski, W. A. Carole and D. J. C. Constable, in *Green Chemistry in the Pharmaceutical Industry : A Model for Sustainability*, 2008, pp. 49–81.

53 M. J. Raymond, C. S. Slater and M. J. Savelski, *Green Chem.*, 2010, **12**, 1826.

54 M. J. Savelski, C. S. Slater, P. V. Tozzi and C. M. Wisniewski, *Clean Technol. Environ. Policy*, 2017, **19**, 2467–2477.

55 D. M. Roberge, L. Ducry, N. Bieler, P. Cretton and B. Zimmermann, *Chem. Eng. Technol.*, 2005, **28**, 318–323.



# CHAPTER 3. TECHNO–ECONOMIC ANALYSIS OF COMPARTMENTALIZED CROSS–LINKED ENZYMATIC NANO–AGGREGATES (C–CLENA)

This chapter presents the results of the techno–economic analysis of a novel enzyme immobilization technique, Compartmentalized Cross–linked Enzyme nano–Aggregates (c–CLEnA), at a lab–scale. Immobilization of an enzyme can facilitate the recovery and recycling of it. Moreover, it can decrease the environmental impact of a process; however, the manufacturing costs increase. Production, hotspots, and potential areas for cost reduction are discussed in this chapter. Subsequently, the c–CLEnA costs were benchmarked against cross–linked support, and the use of loose enzymes to identify where this immobilization technique locates in comparison with other alternatives.

This chapter is based in the following paper:

O. M. Morales–Gonzalez, M. T. De Martino, J. C. M. van Hest, V. Hessel, F. Gallucci. Techno–economic Analysis of Compartmentalized Cross–linked Enzymatic nano–Aggregates (c–CLEnA). In preparation

## 3.1 INTRODUCTION

Catalysis is considered a crucial element for the sustainable production of chemicals[1–3]. The environmental performance of a catalytic system depends on the lifetime of the catalyst. Additionally, attention should be paid to the catalyst recovery operations and the preservation of its activity after multiple usages. In that respect, heterogeneous catalysis has advantages over homogeneous systems as it facilitates the separation of the catalyst from the reaction mixture[4]. For instance, a supported heterogeneous catalyst facilitates the use and reuse of the precious material multiple and longer times. However, quite often restrictions in terms of activity and mass transfer limitations of the reactants and/or products may be associated with heterogeneous catalysts, particularly with catalysts deposited in porous supports[5–7].

On the other side, homogenous catalysis is largely used in the chemical industry[4]. Particularly, biocatalysts are implemented due to their high product selectivity, and their milder operating conditions, which overall contribute to safer processes and a smaller environmental profile compared with traditional metal–catalysts[8]. Within the biotechnology field, enzymatic processing is considered one of the most promising and greener alternatives. In 2012, an environmental assessment was reported dealing with the industrial use of enzymes[9]. There, Jegennaathan and Nielsen (2013) showed that implementing enzymatic processes in place of thermochemical processes results in a reduced contribution to global warming, acidification, and photochemical ozone formation while saving energy and agricultural raw materials. Unfortunately, industrial use of enzymes is still limited by the low operational stability and by the difficult recovery–reuse process due to the excessive purification needed[10,11].

Isolation and purification processes of enzymes are more expensive than for heterogeneous catalysts. Before enzymes can be used, they must be purified. This purification process is complex as the enzymes can be easily denatured by foaming, drying, contact with solvents, or heating. The purification process also requires many steps, which increases their production cost[12,13].

Enzymes are also sensitive to process conditions, e.g., temperature, pH, or other substances that can act as inhibitors. To overcome these limitations diverse immobilization strategies have been explored over the years. Supported enzymes for industrial bio–catalysis are considered an attractive solution for a greener production[13,14].

Immobilization strategies are implemented to facilitate enzyme reuse and to make the entire process more efficient. The term immobilization is used when the enzyme is transformed from

a soluble (homogenous) species to a supported species. This is done by attaching the enzyme onto an insoluble carrier or by encapsulation[10,15–18]. The immobilization can increase the enzyme activity in organic solvents, facilitate product recovery, minimize contamination of the enzyme and enable an efficient recovery and re–use of the enzyme[11,16]. From the process perspective, benefits like enhanced performance and thermal stability of the enzyme and longer operation conditions are observed[10,15]. These advantages can be beneficial for the economics of production[16]. However, the main drawback of immobilization is that the activity of the enzyme is often lower compared to lose enzyme and substrate accessibility can be diminished[13]. In most cases, the support causes diffusional limitations that hamper the efficiency of the catalyst. Moreover, there is an additional cost associated with the support's production[16].

The most common immobilization strategies are chemical (or physical) binding of the enzyme to the carrier[18], physical entrapment[10], and formation of insoluble aggregates of enzymes via cross–linking[19]. However, the properties of the enzyme are modified due to the interaction between the enzyme and the support. These modifications depend on the support and the enzyme itself[10,11].

The binding strategy can be physical, e.g., using van der Waals interactions, but this binding is considered weak as the enzyme can get easily lost under normal operating conditions. Electrostatic interactions and covalent binding are used for a more stable immobilization. The main drawbacks of this kind of immobilization, are the enzyme deactivation and the that the support cannot be reused. A number of supports have been used, such as resins, biopolymers, or mesoporous solids[10,11].

In the second strategy, entrapment, enzymatic species are included in a polymer network or membrane. In some cases, the polymeric matrix is fabricated in the presence of the enzyme, *e.g.* sol–gel[20]. Porous nano–capsules or polymeric vesicles (so–called polymersomes)[21] have also been reported for enzyme entrapment[22]. Immobilization through polymeric vesicles helps to protect the enzymatic species and decreases the leakage during the reaction. The drawbacks of this strategy are the mass transfer limitations linked to the use of supports and the low capacity of enzyme loading[10,11].

A very interesting alternative for enzyme immobilization that is considered versatile and easy to achieve is the formation of micron–sized objects by crosslinking enzymes (without the introduction of supports). Drawbacks of crosslinked enzymes are the reduction of the activity attributed to the difficult accessibility of the substrate to the enzyme active site and restricted mobility upon protein folding[10,11]. Insoluble crosslinked enzymatic aggregates (CLEAs) without

any support might lead to inhomogeneity in the size distribution of the final aggregates due to limited capacity of adjustment in the size of the cross–linked proteins. CLEAs often lack mechanical stability which could be an issue in continuous operations. However, despite the drawbacks, their operational stability, high recycling potential, and applicability to several enzymes, make CLEAs suitable for industrial applications[13,23]. Consequently, there is a growing interest in implementing them at industrial scale.

Polymeric nanoreactors, an innovative and environmentally friendly tool for catalytic applications were developed in the last decade[24,25]. They enable reactions to proceed in water via compartmentalization[26] and they allow to perform sequential reactions in one pot[27].

Stomatocyte nanoreactors, are bowl–shaped polymersomes with an additional internal cavity, which have been found to be very suitable for bioconversions, and the inclusion of one or more enzymes has been demonstrated[28]. Moreover, enzymes are retained without posing additional barriers to substrate diffusion. Due to these reasons, stomatocyte nanoreactors are becoming an appealing class of nanoreactors to be explored for several applications[29].

Recently, **C***ompartmentalized*– **C**ross–linked **E**nzyme ***n****ano*–**A**ggregates (*c*–CLE*n*A), a novel and particularly interesting sub–class of nanoreactors were introduced. These nanoreactors can be derived from stomatocytes upon cross–linking the loaded enzymes (see Fig 3.1). The cross–linker normally is a small molecule, able to bridge together multiple enzymatic species. Crosslinking is performed in a nano–cavity, thus, generating in–situ *nano*–aggregates. These nano–aggregates limit the leaching of the enzyme, even for longer periods of time, enabling the use of *c*–CLE*n*A in continuous flow processing.

The introduction of *c*–CLE*n*As as an effective immobilization method could overcome the main drawbacks related to the traditional encapsulation and cross–linking methods. For instance, the polymeric membrane of the stomatocytes grants higher mechanical stability to the enzyme, while the inner cavity controls the size distribution of the *n*ano–aggregates in contrast with the direct CLEA cross–linking method. Besides, *c*–CLE*n*As have the capacity to encapsulate one or more enzymatic species with a high encapsulation efficiency, which can be easily tuned by varying the initial enzyme feed [24]. Their ability to be used and reused in–flow makes them interesting for industrial applications, and from a green chemistry perspective [30].

c–CLEnAs have shown advantages to improve synthetics processes, yet, until now they have only been studied from a technical viewpoint. To clearly establish how promising this sub–class of nanoreactors is, the process design and techno–economic of their applications should be

assessed as well.

In this chapter, a first look into the economics of the production of c–CLEnAs is presented. This will allow to identify area areas of opportunities at an early stage of development and evaluate where the production can be made more cost–effective before scaling up. Therefore, the aim is to provide recommendations that should be assessed experimentally in later stages. These recommendations will be regarding decreasing the cost.

It is known that the cost assessment of biocatalytic processes is rather complex due to the factors that contribute to the cost. Moreover, in literature, the focus is on large scale (e.g. tons based) production[8]. The approach taken here is different, based on lab–scale production. Scale–up is a complicated process, for which the lab scale process must be optimized, before upscaling[31]. Here it is aimed to determine the economic feasibility at lab scale (mg based). In this case study a commercial enzyme, Candida Antarctica Lipase B (CalB), is used and as a model reaction the hydrolysis of p–nitrophenyl acetate (p–NPA) will be studied.

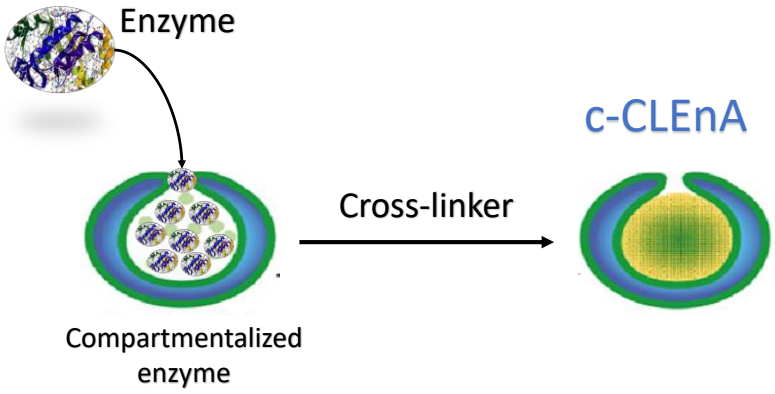



**Fig. 3.1** Schematic representation of the formation of Compartmentalized–Cross–linked Enzyme nano–Aggregates (c–CLEnA) via cross–linker addition (either glutaraldehyde or genipin) from a stomatocytes.

## 3.2 METHODOLOGY

The techno–economic assessment was conducted following the methodology reported in literature[24] for small scale processes. Below is described the synthesis procedure used for the techno–economic assessment.

### 3.2.1 Synthesis Procedure

#### Preparation of *c*–CLE*n*A with glutaraldehyde

The first step is the synthesis of the polymer poly(ethylene glycol)$_{44}$–polystyrene (PEG–b–PS)$_{140}$ (see Fig 3.2). This is synthesized through atom–transfer radical polymerization. The macro–

initiator, poly (ethylene glycol)$_{44}$ methyl ether 2–bromoisobutyrate, can be purchased or synthesized in the laboratory. The production process of the polymer starts with dissolving N–pentamethyl–diethylenetriamine (PMDETA) in toluene and mixing it with copper bromide under an argon atmosphere. The mixture is stirred and then a solution of the macro–initiator in toluene is added (Step 1– Fig. 3.2). The solution is degassed while cooling (Step 2– Fig. 3.2). Distilled styrene is added, and the mixture is heated to 70ºC overnight (Step 3– Fig. 3.2). Then dichloromethane is mixed, and the solution is filtered over an alumina column to remove the copper bromide (Step 4– Fig. 3.2). Finally, the solution is concentrated, and the polymer is precipitated in methanol. The product, PEG$_{44}$–*b*–PS$_{140,}$ is filtered and dried in vacuum overnight (Step 5– Fig. 3.2). Once the polymer is obtained, it is dissolved in a mixture of THF: dioxane (4:1 v/v) (Step 6– Fig. 3.3). Then MilliQ water was added, to form a cloudy solution. The solution is dialyzed against MilliQ water for 24h (Step 7– Fig. 3.3).

The following step is to obtain the open neck stomatocytes. The dialyzed product is mixed with a solution of THF: dioxane (4:1 v/v) (Step 8– Fig. 3.3). Then it is filtered and resuspended in MilliQ water (Step 9– Fig. 3.3).

The stomatocytes are loaded with the selected enzyme, e.g., CalB in phosphate buffer, and mixed. Then a solution of THF and dioxane (4:1 v/v) is added (Step 10– Fig. 3.4). The lose enzyme is removed using size exclusion chromatography (SEC) (Step 11– Fig. 3.4). Glutaraldehyde is added slowly while stirring. Then the reaction is quenched with sodium phosphate buffer (Step 12– Fig. 3.4). To purify them and obtain *c*–CLE*n*AS the excess buffer and glutaraldehyde are removed using spin filtration (Step 13– Fig. 3.4). Finally, the product is dispersed again in sodium phosphate buffer (Step 14– Fig. 3.4).

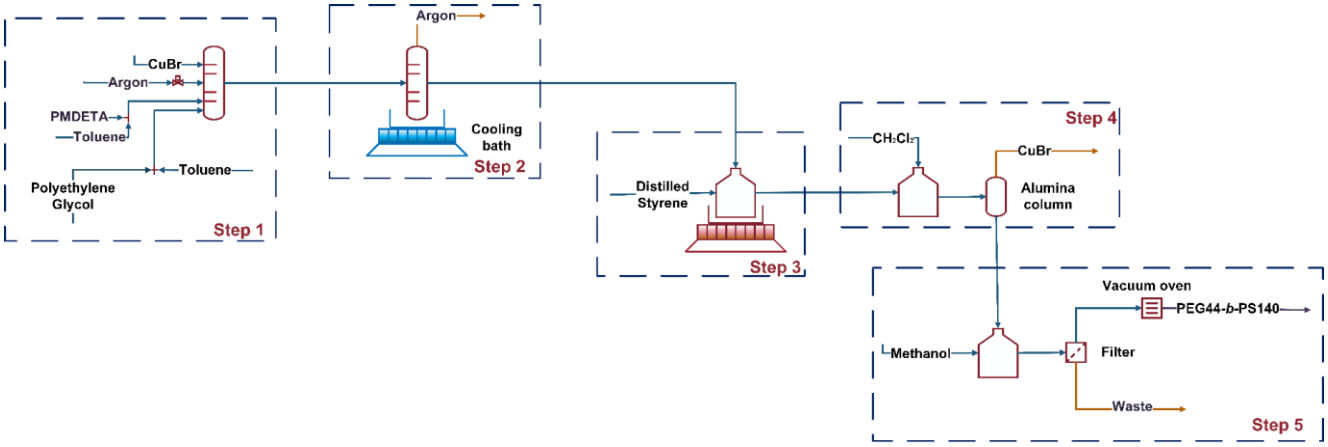



**Fig. 3.2** Process diagram of the synthetic procedure to obtain $PEG_{44}$–b–$PS_{140}$, polymer to synthetize the bowl-shape polymersomes. The steps correspond to the procedure explained in section 3.2.1.

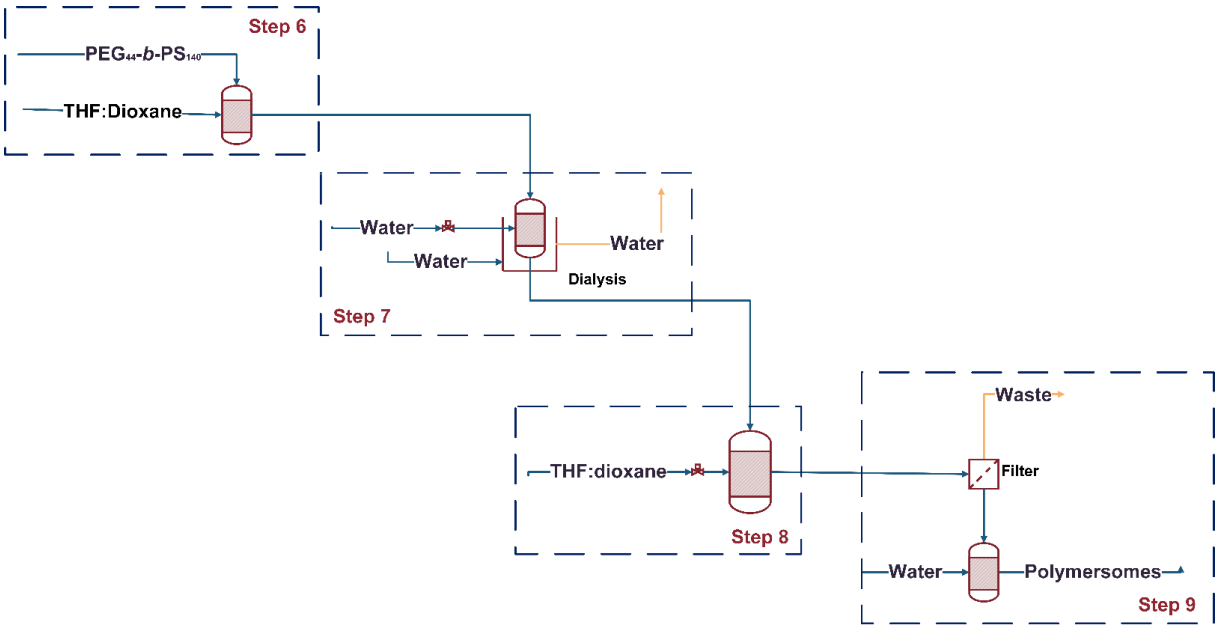



**Fig. 3.3** Process diagram of the synthetic procedure to obtain bowl-shaped polymersomes, or stomatocytes, starting from the polymer $PEG_{44}$–*b*–$PS_{140}$. This represents the steps after obtaining the polymer and before the enzyme is integrated in the matrix of the polymersome.

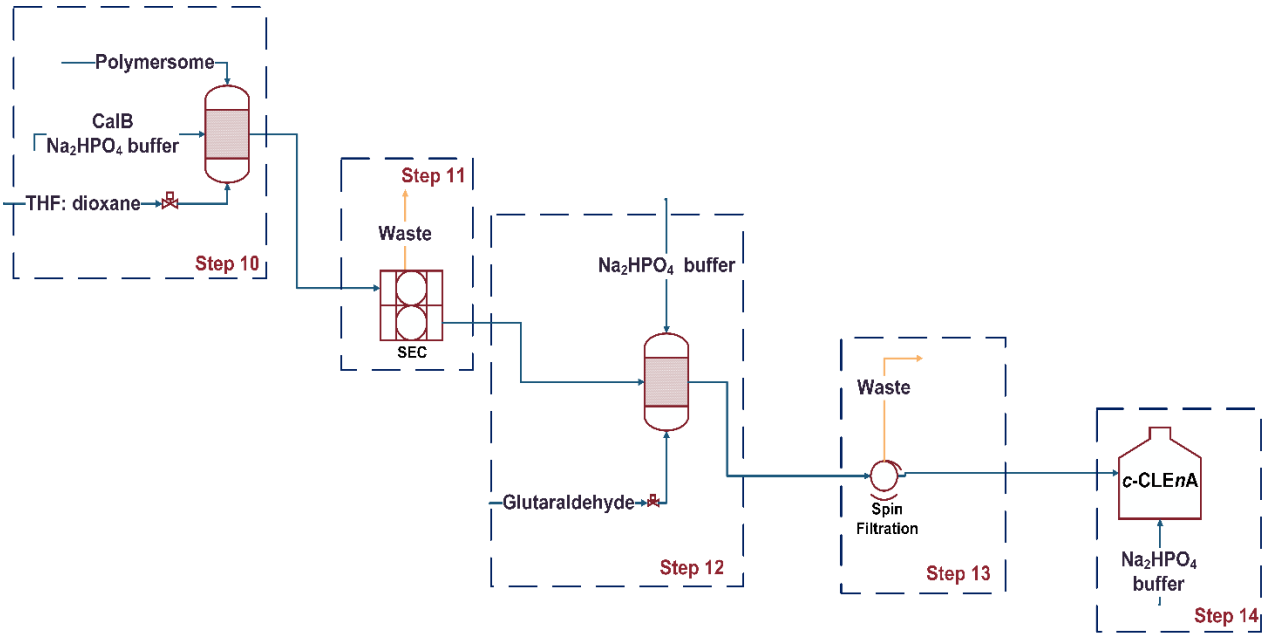



**Fig. 3.4** The process diagram shows the steps needed to obtain the c–CLEnA with CalB enzymes in buffer solution.

**Preparation of *CLEA with Glutaraldehyde***

To 100 µL of glutaraldehyde, 1 mL of commercial CalB (3 mg $mL^{-1}$) in sodium phosphate buffer was added at a constant rate of 100 µL $h^{-1}$ while stirring. This solution was kept for 8 h under incubation. After that, the excess buffer and glutaraldehyde were removed via spin filtration and concentrated CLEAs were obtained.

## 3.2.2 Benchmark Studies

To compare the performance of the CLEA and the *c*–CLE*n*A, the hydrolysis reaction of p–nitrophenyl acetate to nitrophenol was selected[24]. The performance in terms of recycling capacity and product yield was measured and compared between the lose enzyme, the CLEA and the *c*–CLE*n*A. The process of the hydrolysis reaction (benchmark study) is described below.

### 3.2.1 Experimental setup

The experiments were conducted in Spectrum Lab® tubular filters. These are equipped with a membrane–substrate inlet and a membrane–product outlet perpendicular to each other. A membrane, 10 kDa, was used to load the CLEA or *c*–CLE*n*A and collect them after the reaction. The substrate was loaded through the lateral inlet, and a tangential configuration was used to guarantee the interaction between the substrate and the CLEA or *c*–CLE*n*A.

#### 3.2.2 CalB *c*–CLE*n*A

CalB loaded *c*–CLE*n*A, 0.5 mL, were loaded through the 10 kDa membrane with a syringe pump. The loading process was conducted at 0.1 mL $min^{-1}$, to ensure homogenous distribution.

The reactor was fed with 3 mM of *p*–nitrophenyl acetate (*p*–NPA) mixed with 50 mM sodium phosphate buffer (pH 7.5) and 5% DMSO, at a flow rate of 0.6 mL $min^{-1}$. The product was collected at the end of the reactor and measured using HPLC.

#### 3.2.3 CalB CLEA

The same procedure as for CalB loaded *c*–CLE*n*A, both regarding the loading process and the reaction, was followed with CalB CLEA.

### 3.2.2 Cost analysis

One of the main purposes behind an economic evaluation is the assessment of the economic feasibility of a product compared with an existing one[32,33]. In this chapter, the production cost of *c*–CLE*n*A is assessed and compared to lose enzymes and CLEAs.

Here, the levelized cost associated with the production of one *c*–CLE*n*A unit, defined as 0.5 mL with 3 mg $mL^{-1}$ CalB, is calculated. This unit is based on the amount of *c*–CLE*n*A used in the test reaction, and therefore a point for comparison in terms of conversion and recyclability. The estimation of the cost was done following the methodology described in literature[8], where the total cost is obtained by estimating the capital investment (CAPEX) and the operation cost (OPEX) over the units produced within the plant's operational time. The units produced were calculated based on the production time at lab–scale within a year. For the case of the *c*–CLE*n*A the production rate over a year was 374 units, while for the CLEA it was 929 units.

CAPEX is the term used to refer to all the costs related to the purchase and installation of the process equipment. The list of equipment used was obtained from De Martino et al. (2020), and the cost used were based on average prices from market providers[34,35]. The equipment was separated into disposables and non–disposables, the latter are included in the CAPEX. Installation costs were estimated from multiplier factors[36,37] (cost factors are presented in Table s3.1). Finally, to estimate the cost per unit, the investment cost is converted to an equivalent annual cost using the annuity factor *k*. To obtain the annuity factor the interest rate factor, typically 6–7% and the equipment economic lifetime (t) are employed (see eq 1). For the base case an interest rate of 6% was chosen and a lifetime of 10 years[8].

$$k = \frac{i}{1-(1+i)^{-t}} \qquad [Equation\ 3.1]$$

The operating cost (OPEX) compromised both direct and indirect costs. The direct costs include the costs of the raw materials, disposables, utilities, and operating labor. Mass and energy balances were used to calculate the raw materials and utilities needed. For the base case, the cost of the raw materials was obtained from the average prices of market providers[34]. Utilities were calculated from energy balances and data from providers. Labor costs were excluded from the cost calculations, and all the costs were based on the situation that the plant is in western Europe.

Indirect cost comprises maintenance, depreciation, taxes, property rents, and insurance. Maintenance was calculated, including labor and material, as shown in the literature[8]. The cost of annual maintenance represents a value between 6 to 10% of the fixed capital investment. Here maintenance costs are calculated based on 8% of the annual capital investment. Depreciation can be calculated in different ways, e.g. straight line depreciation[36]. In Tufvesson et al. (2011) depreciation, taxes, property rent, insurance, and others are calculated as part of the fixed cost. These represent 12–17% of the annual capital investment. Here depreciation was calculated as part of the fixed cost considering 15% of the annual capital investment cost.

### 3.2.3 Benchmarking assumptions

As mentioned before the aim of this chapter is to have an estimation of the production cost of *c*-CLE*n*A to provide recommendations for scaling up. As well as benchmarking the cost of *c*-CLE*n*A against other biocatalyst immobilization techniques. In particular: CLEA and free enzymes. For each of the cases, the following assumptions were taken.

*Case study 1: Free enzyme*

To compare *c*-CLE*n*A with the free enzymes the following assumptions were taken. The reaction with the free enzyme would occur in the same experimental set-up. New lose enzymes are loaded after the reaction is completed, meaning no recovery of the free enzyme, and the amount used in every reaction was the same as the enzyme loaded in the stomatocytes (*c*-CLE*n*A).

*Case study 2: CLEA*

The cost of the production of CLEA was determined following the same methodology as for the *c*-CLE*n*A. The cost obtained was the levelized cost per unit, unit defined based on the amount used in the benchmark reaction.

### 3.2.4 Sensitivity analysis

Due to the early stage of development, the accuracy of the estimations may be offset due to the level of detail and the complexity. In literature, it is considered that at an early stage of development the accuracy is in the order of magnitude of ±30%[8,38,39]. Therefore, for the base cost analysis and the benchmark scenarios ±30% boundaries will be added.

Furthermore, two scenarios, detailed below, were developed with the purpose of evaluating the effect of modifications to the production process and evaluating the impact on the price.

*Sensitivity scenario 1: Purification using spin filtration*

As mentioned before, after narrowing the neck of the stomatocytes, these are purified using size exclusion chromatography (SEC). However, this purification process could be conducted using spin filtration. Therefore, in this scenario the impact on the cost is evaluated by substituting the SEC with spin filtration. It was considered that the filters can be cleaned and reused, for each filter is assumed that it can be reused 10 times before being disposed of.

*Sensitivity scenario 2: Enzyme recovery*

In the second scenario, the reuse of the enzymes will be evaluated. Enzymes represent a big part of the cost of bioprocesses[40]; therefore, their use for long periods of time and their efficient use should be considered. As mentioned in De Martino et al. (2020), the loading effectivity is not 100%. Increasing the loading capacity may require changing the process to an unknown extent, which cannot be evaluated here. However, in principle, the unloaded enzymes can be recovered and reused. In this scenario it is explored the retrievement of the enzymes from the solution using a filter, as in the previous sensitivity scenario. The enzymes recovered will be used later to produce more units of *c*-CLE*n*A.

## 3.3 RESULTS

### 3.3.2 Cost of *c*–CLE*n*A Production

Levelized production cost per unit was obtained for a plant (laboratory) with 10–year life span. The results of this assessment are presented in Table 3.1. A total cost of €139 per unit of c–CLEnA was obtained.

**Table 3.1** Estimated CAPEX and OPEX to produce a unit of c–CLEnA. Costs are based on the production of 374 units per year for a ten–year lifetime plant

| Concept | | Cost[1] |
|---|---|---|
| **CAPEX** | Equipment | € 97,857 |
| | Installation | € 116,449 |
| | Equivalent cost | € 291,173 |
| **OPEX** | Maintenance | € 23,294 |
| | Utilities | € 13,953 |
| | Fixed cost | € 43,676 |
| | Disposables | € 69,732 |
| | Raw materials | € 79,602 |
| **Total per unit** | | **€ 139** |

[1] Cost was consulted in November 2019.

The distribution of the cost, between CAPEX and OPEX is presented in Fig. 3.5. There, it can be observed that the CAPEX comprises the largest percentage of the cost with 56%. The CAPEX as mentioned before is determined by the equipment cost and the installation. The most expensive equipment is the HPLC system. It is a piece of complex and advanced equipment, that is only used for a couple of minutes per batch. Therefore, the HPLC investment can be made more profitable if the equipment is used more intensively, *i.e.* by increasing production, or the HPLC can be replaced by a filter technique that can perform the task with the same efficiency at a lower cost.

A major cost–sensitive parameter is the raw materials. They depend on the provider, the market, and the availability of bulk quantities. Since 2007 the volatility of chemicals has affected both producers and consumers[41]. Dealing with price volatility is very complex and there is no straightforward solution. While some companies may opt for broadening their portfolio[42], other authors suggest allocating the risk to the consumer or maximizing flexibility (i.e. fleximizing)[43]. Fleximizing refers to a general improvement, not only operational–wise but also being able to identify multiple feedstocks that can be used to substitute a raw material given the opportunity[43]. Limited market suppliers were consulted. Therefore, expanding the

search to other suppliers can change the market quotations. However, it is suggested to explore fleximizing to minimize the impact of cost–sensitive parameters, particularly for the $PEG_{44}$–*b*–$PS_{140.}$ For example, commercial polymers could be investigated. This suggestion needs to be addressed first in the lab and prove the effectivitiviness of multiple commercial polymers, before addressing the cost impact.

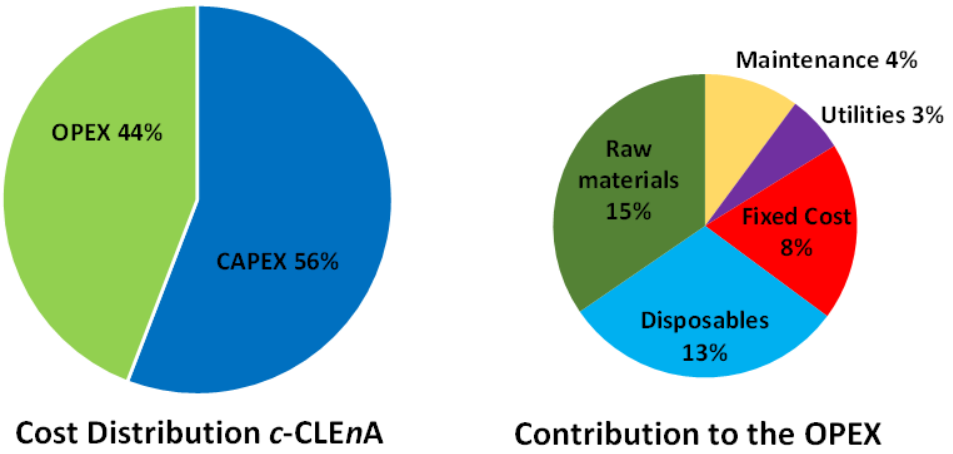



**Fig. 3.5** The right plot presents the distribution of cost (CAPEX and OPEX) in the base case of c–CLEnA production. The left presents the insights into the OPEX cost and the distribution within the OPEX.

In general, the process comprises some steps that are completed considerably fast, within one hour. However, the synthesis of the polymer, particularly the dialysis is lengthy (24 h) compared with the rest of the steps. This can be considered the bottleneck of the process[44]. It is an option to have multiple dialysis systems running in parallel when increasing the production scale. A second possible alternative to improve the continuity of the process is to explore the use of continuous dialysis, also known as diafiltration[45]. It is commonly used for the purifications of protein solutions, and thus it may be feasible to produce open neck stomatocytes. In this concept different membrane loops will be connected in series, wherein it is necessary to identify and select the correct membrane. Compared to the batch system, this continuous system will require more space, components such as pumps will increase the energy consumption, and to minimize the risk of contamination a control system is needed. On the other side, the amount of water and time will be reduced and the waste product, which will bring economic benefits[46].

### 3.3.3 Benchmarking

Despite the cost of this technology, benchmarking with other technologies, especially in the early stages of development, is necessary. Benchmarking has multiple purposes such as analysis of direct competitors, finding drawbacks and advantages, and finally finding potential areas for improvement.

The results of the first comparison are presented in Fig 3.6. Here free CalB enzyme is compared with the c–CLEnA in terms of the number of recycling needed (key parameter). As can be observed in the plot, c–CLEnA needs to be able to be reused 41 times (average) while keeping constant activity. In the cases of the upper and lower 30% boundaries, that is 53 and 28 times respectively. In the experimental results, it was proven that the c–CLEnA can be reused 10 times with constant activity. Therefore, it is considered promising that c–CLEnA can be used more times. However, it is necessary to ensure that the activity is maintained even after 53 uses (worst case scenario).

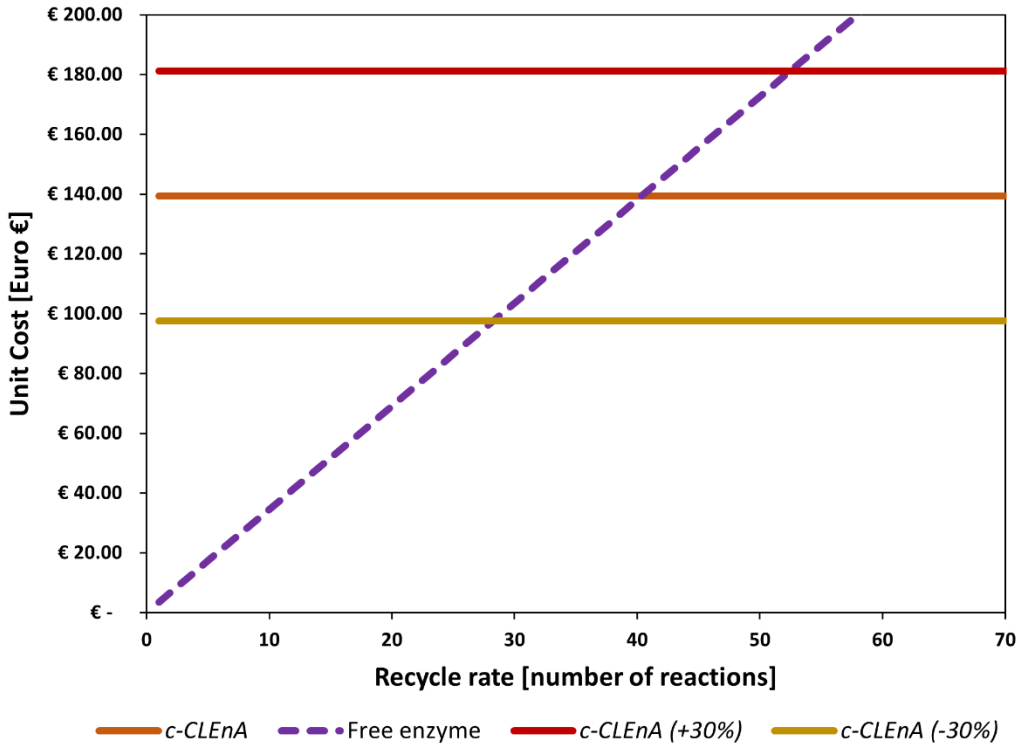



**Fig. 3.6** Benchmark with free CalB enzyme. Upper and lower boundaries (±30%) are added due to the accuracy estimated at low stage of development for c–CLEnA.

The second benchmark was conducted versus CLEA. CLEAs are a type of immobilization based on cross–linked enzyme aggregates. Their synthetic process is considered relatively simple, and they can be recycled[47].

The cost assessment was conducted following the same methodology as with the *c*–CLE*n*A. The results of this assessment are presented in Table 3.2, where the levelized cost obtained is €27. This cost will be used for the benchmark versus *c*–CLE*n*A.

**Table 3.2** Estimated CAPEX and OPEX to produce a unit of CLEA. Costs are based on the production of 929 units per year for a ten–year lifetime plant

| | Concept | Cost[1] |
|---|---|---|
| **CAPEX** | Equipment | € 37,357 |
| | Installation | € 44,454 |
| | Equivalent cost | € 111,155 |
| **OPEX** | Maintenance | € 29,885 |
| | Utilities | € 12,370 |
| | Fixed cost | € 16,673 |
| | Disposables | € 46,528 |
| | Raw materials | € 38,088 |
| **Total cost per unit** | | **€ 27** |

[1] Cost was consulted in November 2019.

The results of the comparison can be observed in Fig. 3.7. The shape of the curve observed for the cost of the CLEA is due to its 4–fold recycling, i.e. CLEA can be recycled 4 times before the activities decrease drastically[24] and discarded. The number of recycle times needed for the base *c*–CLE*n*A scenario is 21, which is equivalent to loading 5 times new CLEA units. For the top scenario (+30%) 21 *c*–CLE*n*A recycle times are required, equivalent to loading new CLEA 7 times. Finally, the lowest cost scenario (–30%) needs that *c*–CLE*n*A can run for 13 uses, equivalent to loading new the CLEA units 4 times. The lowest cost scenario (–30%) was almost close to the proven recycled times of *c*–CLE*n*A (10 times) [24].

Besides, with the *c*–CLE*n*A 10 times more product was obtained every time the benchmark reaction was conducted. Considering the amount of product produced, the investment is returned just after the catalytic process is conducted once, with a net return of around €135, which is almost equivalent to the production cost of one *c*–CLEnA unit (base scenario).

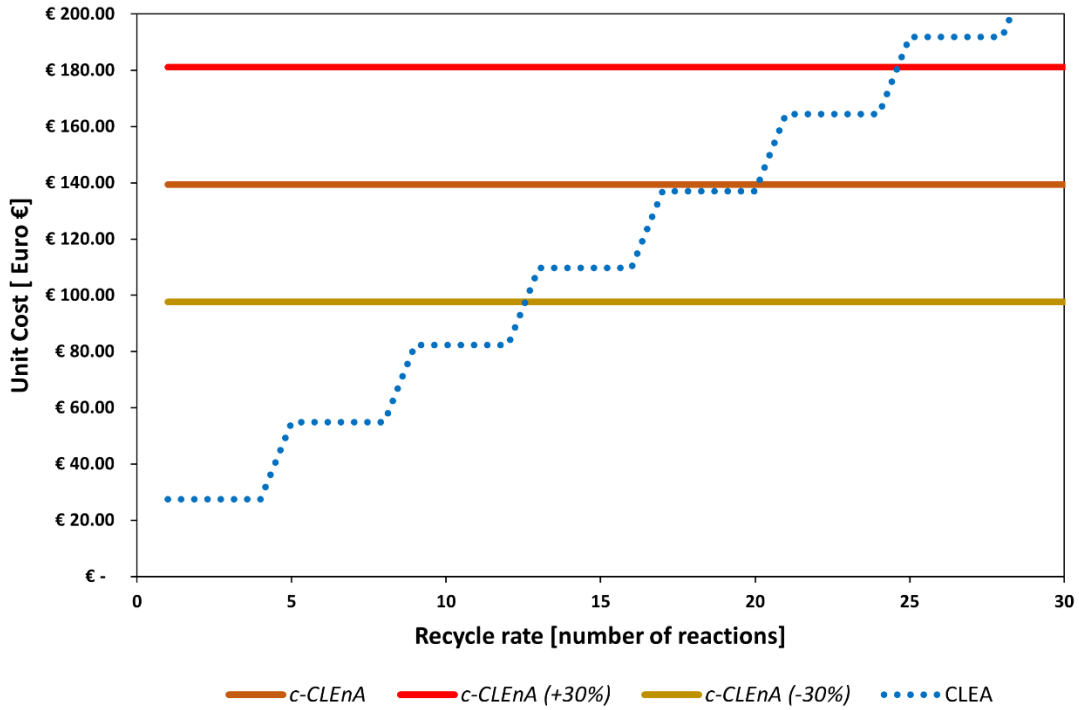



**Fig. 3.7** Benchmark with CLEA. Upper and lower boundaries (±30 %) are added due to the accuracy estimated at low stage of development for c–CLEnA. The accuracy for CLEA was not considered.

### 3.3.4 Sensitivity analysis

To address some of the uncertainties a sensitivity analysis was conducted. The aim is to visualize the impact that a change in the process would have and use this as guidance for future process design. The analysis was conducted by developing two scenarios where a specific part of the process was changed.

#### 3.3.4.1 Sensitivity scenario 1: Purification using spin filtration

With this scenario, the replacement of the HPLC system is evaluated. As shown in Table 3.3, replacing the HPLC system will have large benefits. Overall, a reduction of 51% of the CAPEX is observed CAPEX, due to the lower equipment cost, and therefore installation cost. An impact on the OPEX is also observed, as this equipment requires maintenance and other costs that are reflected as part of the fixed costs, which includes the depreciation. On the other side, the substitution with disposable equipment increases the costs of the utilities and disposables. Thus, recycling of the filters was implemented, and a small reduction in the cost of the disposables was observed. Finally, no change in the costs of the raw materials is observed, as efficiency and production capacity were kept constant.

**Table 3.3** Estimated CAPEX and OPEX to produce a unit of *c*–CLE*n*A following changes described in Scenario 1[1]

| Concept | | Cost | Difference* |
|---|---|---|---|
| **CAPEX** | Equipment | € 47,857 | 51% |
| | Installation | € 56,949 | 51% |
| | Equivalent cost | € 142,397 | 51% |
| **OPEX** | Maintenance | € 11,392 | 40% |
| | Utilities | € 13,951 | 18% |
| | Fixed cost | € 21,360 | 51% |
| | Disposables | € 55,771 | 20% |
| | Raw materials | € 79,602 | 0% |
| **Total cost per unit** | | **€ 87** | **69%** |

*Colour code used to indicate if the difference is positive (red) or negative (blue)
[1]No changes to the production and life span of the plant were applied

On the other side, more solid waste is produced, which has a negative environmental impact and repercussions for waste management.

#### 3.3.4.2 Sensitivity scenario 2: Enzyme recovery

In the second scenario an optimization of the raw materials, particularly the enzymes, is evaluated. In the base scenario, the enzyme represents 93% of the cost of the raw materials. Therefore, optimizing the enzyme use can be beneficial, especially moving to a larger production scale. The results of this analysis are presented in table 3.4.

**Table 3.4** Estimated CAPEX and OPEX to produce c–CLEnA following changes described in Scenario 2[1]

| Concept | | Cost | Difference |
|---|---|---|---|
| **CAPEX** | Equipment | € 97,857 | 0% |
| | Installation | € 116,449 | 0% |
| | Equivalent cost | € 291,173 | 0% |
| **OPEX** | Maintenance | € 23,294 | 0% |
| | Utilities | € 14,265 | 2% |
| | Fixed cost | € 43,676 | 0% |
| | Disposables | € 69,732 | 0% |
| | Raw materials | € 34,870 | 56% |
| **Total cost per unit** | | **€ 128** | **9%** |

*Colour code used to indicate if the difference is positive(red) or negative (blue)
[1]No changes to the production and life spam of the plant were applied

The optimization with the enzyme recovery has a low impact on the cost. The total cost per unit, with the optimization, was reduced by 9% with respect to the base case. This optimization has no impact on the CAPEX, and even increased the OPEX by 2% (utilities). To avoid the increase in costs of the disposables, the same reuse strategies as applied to the filters. Yet, the only benefit was observed in the raw materials, with a 56% cost reduction.

Besides analyzing the change in the process equipment and change in raw materials, the scenarios allowed to identify process sensitive parameters. Capex has a larger influence on the cost over the OPEX. Therefore, increasing production is considered the best strategy to lower the costs. Yet, changes in the process, such as process equipment need to be addressed before scaling up, e.g. it is important to be able to recycle the filters as much as possible, and avoiding fouling or clogging is essential to reduce costs. Then optimize the enzyme use. Finally, the dialysis step requires a large investment and in–depth design, such as the correct membrane loop. After that, scaling the production can be considered.

## 3.4 CONCLUSIONS

In this chapter the cost of producing a unit of c–CLEnA was estimated given the actual procedure followed at lab–scale, with the aim of guiding future scale–up and reducing cost at the early stages of development.

It was found that the costs are highly driven by the CAPEX, i.e. the equipment used and the requirements for the use of these. Therefore, changes in the process equipment should be considered the first step towards cost reduction. Some alternatives were suggested and evaluated. Using disposable equipment lowers the cost, yet this must be reused for as long as possible. Then, it is suggested to increase production capacity, while keeping the number of equipment constant.

Besides that, two strategies that can affect the production cost were suggested that require further lab investigation. The first one is fleximizing, an option that can allow to reduce costs and address the volatility in the cost of raw materials. The polymer used to produce the stomatocytes was not addressed in detail. This polymer is prepared in the laboratory, which makes it expensive[48]. The polymer, PEG–PS, is acknowledged for its variety of applications, and its potential in the pharmaceutical and biomedical field[49]. Optimizing and increasing its production could be of general interest and would make the *c*–CLE*n*A preparation more advantageous. This is considering that it is well known that economy of scale can lower production costs, making a business more attractive to the consumer[50]. Alternatively,

changing the polymer and the block co–polymer is suggested. This change could not be explored as the effect of a different starting material in the fabrication *of c*–CLE*n*A has not been reported yet, nor its impact when applied in a reaction. Future studies could be performed in this direction. As well it is suggested the implementation of continuous dialysis. As in the case of the polymer, this requires careful design, especially towards the selection of the membranes loop and its capacity. Continuous dialysis can increase the production capacity, yet the size of the membrane loop and the complexity need to balance the drawbacks of higher energy demand and complex equipment.

Besides looking at c–CLEnA's production cost, it is necessary to consider how their use affects the downstream process, i.e. accounting for the wider process. c–CLEnA's production steps are more complex and energy demanding compared with other immobilization techniques. Thus, a comparison with the cross–linked enzyme aggregates strategy and lose enzyme was done. In the case of the benchmark reaction selected, and to have higher benefits, it is necessary to ensure that the c–CLEnA can be recycled many times, over 15 depending on the benchmark. Other benchmark options were not assessed, as its experimental comparison was not conducted. For example, a potential comparison is Novozymes 435, a commercial immobilized preparation of CalB[51]. This has shown good enzymatic activity and it is commercially available[52]. Thus, it will be possible to compare its market price (around 13 €/gr), with the cost of the c–CLEnA and the process benefits and drawbacks.

Among the advantages of the c–CLEnA technique is the possibility to immobilize more than one kind of enzyme at a time. Multiple enzyme immobilization was not studied here, yet in the case that the recyclability is lower than expected, multiple enzyme immobilization could still favor its application in the market. Thus, complex cascades can be benefited economically by using c–CLEnA, instead of combining different immobilization techniques. Within a complex cascade, a cost–effective solution can be achieved. In this case, the product from the model reaction is inexpensive, around €40 per gram. Other production pathways would be more economical. Further studies should address the comparison of the c–CLEnA costs to the price of commercial "cascade".

## REFERENCES


1 P. L. Heider, S. C. Born, S. Basak, B. Benyahia, R. Lakerveld, H. Zhang, R. Hogan, L. Buchbinder, A. Wolfe, S. Mascia, J. M. B. Evans, T. F. Jamison and K. F. Jensen, *Org. Process Res. Dev.*, 2014, **18**, 402–409.

2 P. T. Anastas, M. M. Kirchhoff and T. C. Williamson, *Appl. Catal. A Gen.*, 2001, **221**, 3–13.

3 V. Polshettiwar and R. S. Varma, *Green Chem.*, 2010, **12**, 743.

4 X. S. Zhao, X. Y. Bao, W. Guo and F. Y. Lee, *Mater. Today*, 2006, **9**, 32–39.

5 I. Denčić, S. De Vaan, T. Noël, J. Meuldijk, M. De Croon and V. Hessel, *Ind. Eng. Chem. Res.*, 2013, **52**, 10951–10960.

6 F. H. M. Dekker, A. Bliek, F. Kapteijn and J. a. Moulijn, *Chem. Eng. Sci.*, 1995, **50**, 3573–3580.

7 D. Rotticci, T. Norin and K. Hult, *Org. Lett.*, 2000, **2**, 1373–1376.

8 P. Tufvesson, J. Lima-Ramos, M. Nordblad and J. M. Woodley, *Org. Process Res. Dev.*, 2011, **15**, 266–274.

9 K. R. Jegannathan and P. H. Nielsen, *J. Clean. Prod.*, 2013, **42**, 228–240.

10 R. A. Sheldon and S. van Pelt, *Chem. Soc. Rev.*, 2013, **42**, 6223–6235.

11 N. Miletić, A. Nastasović and K. Loos, *Bioresour. Technol.*, 2012, **115**, 126–135.

12 P. Vijayaraghavan, S. R. F. Raj and S. G. P. Vincent, eds. G. S. Dhillon and S. B. T.-A.-I. W. as F. for E. P. Kaur, Academic Press, San Diego, 2016, pp. 95–110.

13 A. A. Homaei, R. Sariri, F. Vianello and R. Stevanato, *J. Chem. Biol.*, 2013, **6**, 185–205.

14 L. Cao, *Immobilized Enzymes*, Elsevier B.V., Second Edi., 2011, vol. 2.

15 P. Grunwald, *Catalysts*, 2018, 396.

16 I. Eş, J. D. G. Vieira and A. C. Amaral, *Appl. Microbiol. Biotechnol.*, 2015, **99**, 2065–2082.

17 F. Cozzi, *Adv. Synth. Catal.*, 2006, **348**, 1367–1390.

18 S. Datta, L. R. Christena and Y. R. S. Rajaram, *3 Biotech*, 2013, **3**, 1–9.

19 R. A. Sheldon, *Catalysts*, 2019, **9**, 1–31.

20 D. Weiser, F. Nagy, G. Bánóczi, M. Oláh, A. Farkas, A. Szilágyi, K. László, Á. Gellért, G. Marosi, S. Kemény and L. Poppe, *Green Chem.*, 2017, **19**, 3927–3937.

21 F. Golombek and K. Castiglione, *Biotechnol. J.*, 2020, **15**, 1–10.

22 M. V. Dinu, I. A. Dinu, S. S. Saxer, W. Meier, U. Pieles and N. Bruns, *Biomacromolecules*, 2021, **22**, 134–145.

23 B. H. Lipshutz, N. A. Isley, J. C. Fennewald and E. D. Slack, *Angew. Chemie Int. Ed.*, 2013, **52**, 10952–10958.

24 M. T. De Martino, F. Tonin, N. A. Yewdall, M. Abdelghani, D. S. Williams, U. Hanefeld, F. P. J. T. Rutjes, L. K. E. A. Abdelmohsen and J. C. M. Van Hest, *Chem. Sci.*, 2020, **11**, 2765–2769.

25 M. C. M. van Oers, W. S. Veldmate, J. C. M. van Hest and F. P. J. T. Rutjes, *Polym. Chem.*, 2015, **6**, 5358–5361.

26 M. C. M. van Oers, L. K. E. A. Abdelmohsen, F. P. J. T. Rutjes and J. C. M. van Hest, *Chem. Commun.*, 2014, **50**, 4040–4043.

27 S. F. M. Van Dongen, M. Nallani, J. J. L. M. Cornelissen, R. J. M. Nolte and J. C. M. Van Hest, *Chem. – A Eur. J.*, 2009, **15**, 1107–1114.

28 L. K. E. A. Abdelmohsen, M. Nijemeisland, G. M. Pawar, G. J. A. Janssen, R. J. M. Nolte, J. C. M. Van Hest and D. A. Wilson, *ACS Nano*, 2016, **10**, 2652–2660.

29 M. Nijemeisland, L. K. E. A. Abdelmohsen, W. T. S. Huck, D. A. Wilson and J. C. M. Van Hest, *ACS Cent. Sci.*, 2016, **2**, 843–849.

30 S. V. Ley, *Chem. Rec.*, 2012, **12**, 378–390.

31 F. Piccinno, R. Hischier, S. Seeger and C. Som, *J. Clean. Prod.*, 2016, **135**, 1085–1097.

32 R. Davis, L. Tao, C. Scarlata, E. C. D. Tan, J. Ross, J. Lukas and D. Sexton, *Process Design and Economics for the Conversion of Lignocellulosic Biomass to Hydrocarbons: Dilute-Acid and Enzymatic Deconstruction of Biomass to Sugars and Catalytic Conversion of Sugars to Hydrocarbons*, 2015.

33 L. K. Kaushik and P. Muthukumar, *Appl. Therm. Eng.*, 2018, **133**, 316–326.

34 Merck, https://www.sigmaaldrich.com/nederland.html.

35 Avantor ®, VWR International, https://nl.vwr.com/store/.

36 D. E. Garrett, *Chemical Engineering Economics*, 1989, vol. 5.

37 D. J. Brennan and K. A. Golonka, *Chem. Eng. Res. Des.*, 2002, **80**, 579–586.

38 M. Doble, *Chem. Eng. Prog.*, 2006, **102**, 34–41.

39 C. Fernandez-Dacosta, P. N. H. Wassenaar, I. Dencic, M. C. Zijp, A. Morao, E. H. W. Heugens and L. Shen, *J. Clean. Prod.*, 2019, **230**, 137–149.

40 S. Budžaki, S. Sundaram, M. Tišma and V. Hessel, *J. Biosci. Bioeng.*, 2019, **128**, 98–102.

41 W. Beacham, *Chem. Mark. Report.*, 2011, **280**, 30–31.

42 ICIS Chemical Business, *ICIS Chem. Bus.*, 2011, **280**, 15.

43 S. Andre and S. Sanghvi, in *Value Creation*, John Wiley & Sons, Ltd, 2005, pp. 201–214.

44 D. McCarthy and N. Rich, *Process Stabilisation*, 2015.

45 S. W. Harcum, *Purification of protein solutions*, Woodhead Publishing Limited, 2008.

46 F. Lipnizki, *Membrane Processes for the Production of Bulk Fermentation Products*, Elsevier Ltd, First Edition., 2010.

47 R. A. Sheldon, *Appl. Microbiol. Biotechnol.*, 2011, **92**, 467–477.

48 S. Sievers, T. Seifert, G. Schembecker and C. Bramsiepe, *Chem. Eng. Sci.*, 2016, **155**, 153–166.

49 A. A. D'souza and R. Shegokar, *Expert Opin. Drug Deliv.*, 2016, **13**, 1257–1275.

50 R. Gupta and M. Gregg, *Modeling and Mapping Domestic Energy Refurbishment Measures on a Community Scale*, Elsevier Ltd., 2nd edn., 2018.

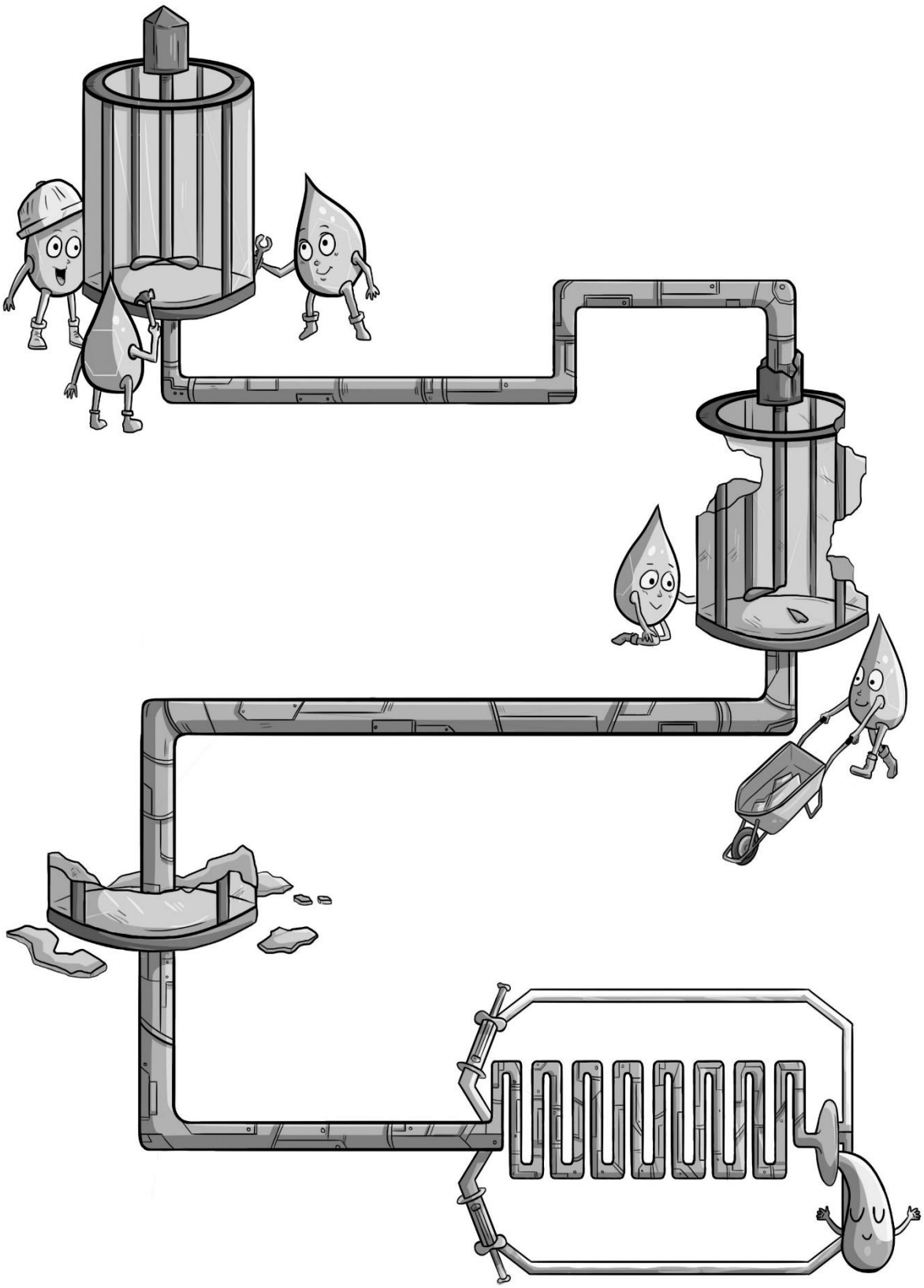
51 C. Ortiz, M. L. Ferreira, O. Barbosa, J. C. S. Dos Santos, R. C. Rodrigues, Á. Berenguer-Murcia, L. E. Briand and R. Fernandez-Lafuente, *Catal. Sci. Technol.*, 2019, **9**, 2380–2420.

52 N. Miletić, V. Abetz, K. Ebert and K. Loos, *Macromol. Rapid Commun.*, 2010, **31**, 71–74.

## Appendix A

**Table s3.1** Cost factors

| Concept | Cost Factor |
|---|---|
| Piping | 0.15 |
| Electrical | 0.1 |
| Instrumentation | 0.1 |
| Safety | 0.02 |
| Budlings | 0.05 |
| Environmental | 0.1 |
| Plant start–up | 0.05 |



# CHAPTER 4. ONE–FLOW FUNCTIONAL SOLVENT FACTORY: THE SOLVENT SELECTION METHODOLOGY

This chapter presents the concept of the Functional Solvent Factory, based on the key principle of automated separation, due to tailored and maximized solubility. A holistic methodology for the selection of the solvent for the FSF is developed here, based on its physicochemical properties, cost, safety, and environmental impact. It was shown how this methodology can aid in the selection of solvents that are not conventional, yet present the functionalities needed for the FSF. Then, a second case study was developed to model the FSF and obtain a first glance at the advantages and possible drawbacks that can be faced during the experimental development.

This chapter is based in the following papers:

Morales-Gonzalez, O. M., Zhang, C., Li, S., Hessel, V. Solvent impact assessment for the "One-Flow Functional Solvent Factory". Chemical Engineering Science: X. 3, 10 p., 100024.

Morales Gonzalez, O. M., Medrano, J. A., Gallucci, F. Hessel, V. Ecological assessment as balancing act between disruptive innovation and industrial implementation: Designer–solvent processes with automatic product purification and recycling. Journal of Cleaner Production. 318, 14 p., 128456.

## 4.1 INTRODUCTION

The ACS GCI Pharmaceutical Roundtable pursues the development of a greener pharmaceutical industry. The industrial mouthpiece encompassed, classified, and ranked green areas that have been pursued for some time in an isolated fashion. These key areas of focus have been continuous processing, separation and reaction technologies, etc.[1]. Particular emphasis has been given to solvent–related research like solvent selection[2].

The combination of an environmental assessment together with the physicochemical properties opens a vast solvent design space but increases the complexity of the solvent selection. Consequently, the use of computational methods has been suggested[3,4]. These computational tools can open new windows of opportunities for solvents that otherwise would have never been considered[5]. Moreover, these tools can support the search for substitutes to replace hazardous solvents, and evaluate the use of solvents produced with renewable resources (bio–solvents) and neoteric solvents[6].

Different approaches have been taken to minimize the use of solvents. Starting from the complete elimination of the solvent, i.e. solvent–free synthesis. This is considered a plausible solution as it reduces the amount of waste produced, it is low cost, and its relative simplicity for industrial implementation[7]. Solvent–free systems are also considered one of the most sustainable options[8], with the capacity to address key environmental issues of the pharma industry. These systems have been used successfully in the high–volume chemical industry. However, not all organic reactions can be conducted under solvent–free conditions[9].

The second approach is to identify better solvents. A better solvent can be defined as a solvent that avoids the environmental impact of common solvents, such as VOCs emissions[10]. It would also have low flammability, low toxicity, and would be not carcinogenic[8]. Water is considered an example of a better solvent. It has the potential to substitute many organic solvents and has been applied in many processes[10].

Neoteric solvents, such as supercritical carbon dioxide ($scCO_2$), and ionic liquids (ILs), have also been proposed to replace organic solvents. They are believed to be greener due to their low vapor pressure[11] and the added benefits, e.g. reactions' optimization[12]. An ionic liquid is a compound formed by anions and cations[13], considered with an environmental benign nature[12], and with high economic potential[14]. Ionic liquids are known as designer solvents, i.e. they can be tailored. A great number of ionic liquids can be prepared in the laboratory because of their Lego–like assembly of anions and cations. Moreover, cations can be

modified by a simple substitution, e.g. of alkyl chains. However, their commercial availability is limited to a few hundred.

In many laboratory scale cases ionic liquids could increase selectivity, act as catalysts, facilitate product purification, and aid in the recovery process of a solvent[15,16]. ILs present interesting features for extraction or purification processes. Solubility can be tuned to enable the formation of multiphase systems, which can be used for purification purposes. For example, biphasic systems have been observed when they are mixed with water. Furthermore, polarity, viscosity, density, and surface tension of the IL can also be tuned to create multiphase systems[11].

On the other side, ILs can be toxic, non–biodegradable, unstable, and under high temperature and low pressure they can evaporate[15]. Because of the previous reasons, it is necessary to account for their environmental impact during its production and in the process where the IL is used, before considering them greener than conventional solvents[17]. Phaseout of conventional solvents with IL is enforced by the EU REACH, yet in some cases, it was found that replacing a conventional solvent with an IL gave counterproductive results[16].

There are industrial processes that use ionic liquids[15]. Up to 2021, 57 industrial IL–base processes have been reported. Some industrial applications are examples of cases where the use of an IL developed a biphasic phase that facilitated the product or catalyst recovery as well the improvement in the performance parameters of the reaction such as yield or conversion. In the BASF BASIL process, 1–methylimidazolim chloride is used to create a biphasic mixture [16] and at the same time increases the yield by 30%[15]. These industrial processes show ways of recycling the catalyst or reducing the need for a purification train. However, full separation of the products and catalyst recovery via ionic liquids in continuous systems is still infrequent.

In Situ Product Removal (ISPR) has been proposed to increase the yield and productivity of bioprocesses[18]. It leads to a two–phase system in which the product and enzyme are separated based on their solubility[19]. ISPR was used in several microflow systems without the use of membrane separators. In this chapter, it is presented an alternative method to the downstream reactors–separators following ISPR, as well as multiphase extraction approaches[20] as a generalized concept. It goes beyond those concepts by considering a holistic separation and purification of reactants, catalysts, and products, designed for cascade reactions. The new concept presented here aims to mimic nature's catalytic cascades processing and prevent intermediate purification steps. This new process concept utilizes periodic (segmented) multi–phase flows as compartments for the desired set of reactants, catalysts, and products. These compartments can be combined on demand with other compartments.

By preferential solubility each reaction partner finds its right place, to facilitate further (down)processing. This can be done by modelling the solubility of a vast number of solvents, e.g. breaking 7665 solvents down to 1 candidate solvent, which then needs to be tested[21]. In the ideal case of exclusive solubility, a molecular species would be completely located in a single phase, and potentially eliminate the need for further separation and purification processes[22]. Multiphase technologies with designer solvents, particularly biphasic systems of fluorous solvents with organic solvents, ionic liquids with water, or ionic liquids with supercritical carbon dioxide are known[23]. Ionic liquids are not the only switchable solvents[24]; however, their tailoring capacity is very important for fitting cascade reactions[25]. This integrated reaction–separation performance of ionic liquids has been reported before[26].

Based on these previous concepts, this new process pathway has been named "Functional Solvent Factory (FSF)", due to the usage of carefully selected multi–phase liquids as integrated reactor–separator[27]. Figure 1 presents a simplified diagram of this system. Incorporation of supramolecular entities within this flow, such as Pickering emulsions [28], polymersomes [29] immobilization [30], or a combination thereof [31] can add further to reaction–separation performance. Altogether it provides a vision for conducting multiple reactions, such as catalytic cascades, just within one continuous–flow stream. This one continuous flow stream has been termed "One–Flow"[32].

To develop this concept, it is necessary to investigate the automated purification with ionic liquid functional solvents. Thus, the ILs need to be multifunctional: used as carriers, enablers of the reaction, and as a separation medium that facilitates recycling and product purification. These ILs need to be "multifunctional", meaning be actively involved in the reaction and purification steps. The use of ionic liquids as designer solvents can add to enhance simultaneous product separation[33]. That active solvent role will ideally eliminate the need for separation equipment. The reaction would be preferably conducted in a single phase. Once finalized, a multiphase system should be formed, in a compartment fashion. Each compartment will contain a component and therefore could be separated and recycled easily[34]. In this way, the process could be simplified and could potentially be greener[35].

These advanced separation functions are a central part of the ONE–FLOW approach. Therefore, it is necessary to design a solvent selection methodology that proposes solvents that create up to three fluidic phases, each solvent tailored to trap the reactants, the product, and the catalyst[36,37]. That would allow an advanced and simplified purification and recycling while achieving multi–step processing[32,36,37].

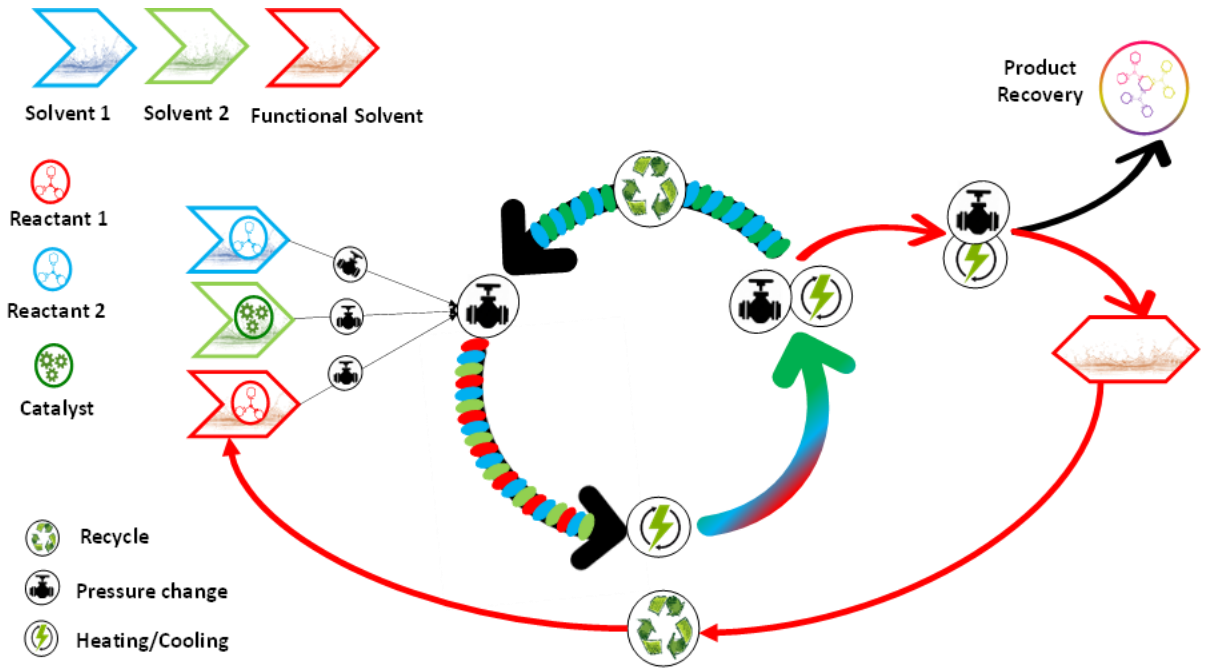



**Fig 4.1.** ONE–FLOW Functional Solvent Factory outline. IL stands for ionic liquid and CS for common solvent. This is the most general and ideal scheme. The real flow scheme might be more complex, depending on the number of solvents and additional workup steps needed.

In this chapter the conceptualization of the Functional Solvent Factory is presented. Due to the important role of the solvent, the first part introduces a methodology tailored for the selection of a solvent for the Functional Solvent Factory. The focus of this methodology is the selection of a solvent that will aid in the recovery of the product. The solvents used for the recovery of the catalyst and reactants will be presented elsewhere [22,38]. The second part of this chapter presents the design concept of a model solvent factory, where the product recovery will be investigated. It is considered that not every reaction system may be suitable for the Solvent Factory, and additional separation equipment may be needed [39]. It was decoded to start from the simplest case, to focus only on the extraction and purification of the product. Moreover, the concept of the Functional Solvent Factory is assessed considering possible constraints, which include recycling, shortcomings such as the degradation and contamination of ionic liquids, as well as the insufficient product purification, and requiring a separation train unlike the demands of the ideal factory concept (automated product purification). The study will focus on the synthesis of organic azides, particularly benzyl azide following a "Functional Solvent Factory" approach.

Organic azides are useful organic intermediates for the preparation of various nitrogen containing functional groups[40]. They are used in click chemistry to synthetize amines and other functional molecules[41]. Particularly of great interest are the heterocycles containing 1,2,3–triazoles ring. These triazoles have many applications, among them their use as a precursor for the synthesis of Rufinamide[42]. This drug is used as an anticonvulsant and in the treatment of Lenox–Gastaut syndrome[43]. However, its synthesis needs to be carefully controlled due to its explosive potential. Its hazardous nature is enhanced and expected for azido compounds with a (C+O)/N ratio under three, which is the case for the molecule of interest benzyl azide[44]. Therefore, the possibility of synthesizing azides and avoiding the use of high temperatures in the separation train could minimize the risks.

## 4.2 METHODOLOGY

### 4.2.1 Solvent selection methodology

Due to the importance of solvents in the FSF a cascade methodology was developed to select the solvent. To have a holistic selection, it is necessary to add to the physicochemical properties an economic, environmental, and safety considerations[37,38]. Below the methodology for the solvent selection is elaborated (see Fig. 4.2), focusing on sustainability.

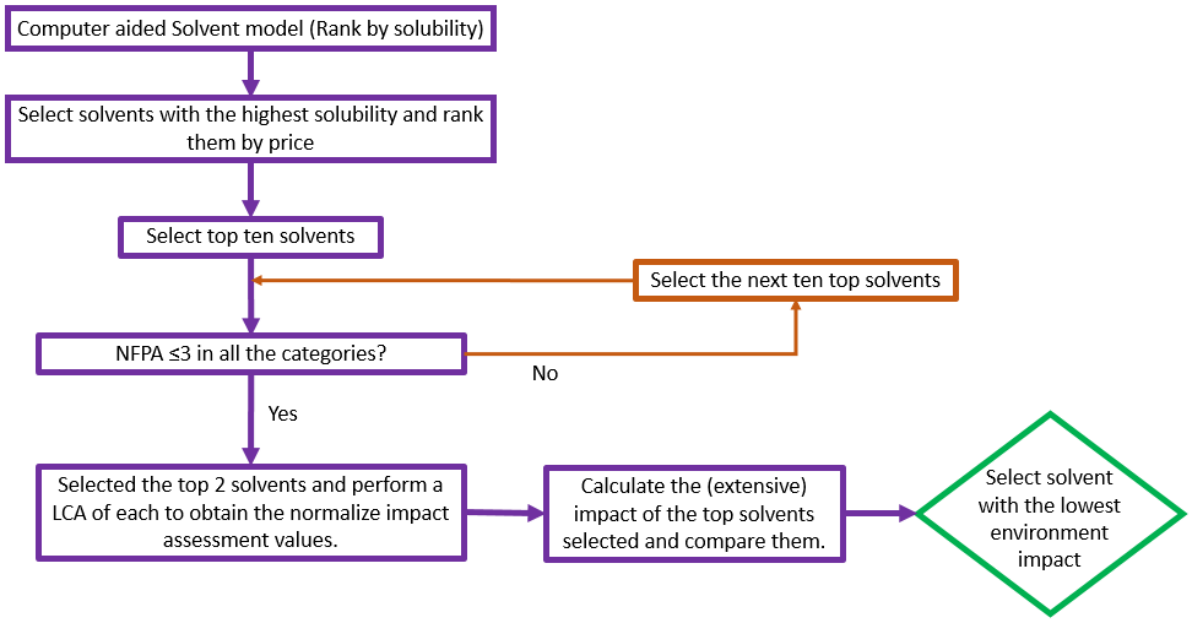



**Fig. 4.2.** Functional Solvent Factory Solvent Selection Methodology

**Step 1. Solvent selection**

The first step consists of the selection of the cascade. For this case study a bio–chemo cascade reaction for the production of 1–(3(chlorophenyl)butan–1,3–diol (see Fig. 4.3)[45,46] was selected.

As explained before, to achieve automatic separation the solvent selected should extract the product from the reaction media as pure as possible, meaning that the product should have high solubility in that solvent. Thus, solubility is used as a key parameter for the selection of the solvent. Product–Solvent interaction, i.e. solubility, was modeled in COSMO–RS, detailed methodology is presented elsewhere[36]. The prediction of the solubility was based on thermodynamical models. As a result of this modeling process a list of solvents was obtained, from which they were then ranked based on the solubility of the product.

**Step 2. Price Ranking**

From the list of solvents ranked by solubility, the first 50 were selected. These 50 solvents were ranked by the price, obtained from providers[47]. The economic constraints were aimed at future economic assessments to the FSF, rather than aimed at making a hard cut. The top 10 solvents are selected for the next step.

**Step 3. Safety Ranking**

The top 10 solvents undergo a safety ranking, in which the NFPA rating is used. The NFPA rating aims to advise on the potential hazards that may be encountered due to the use of a certain chemical. In the NFPA rating, chemicals are rated on a numeric scale from zero to four, with zero being the lowest (no hazard) and four the highest level of risk (severe hazard) [48]. Only the solvents with a score below or equal to three in all the categories will be considered for the next step. Moreover, if the solvents are peroxidizable or polymerizable will be discarded well to avoid the possibility of side reactions. Solvents without NFPA data will not be considered due to safety reasons.

**Step 4. Environmental Assessment**

The top four solvents from the safety rank were selected. For each solvent the amount of solvent needed to solubilize one mol of product is calculated. The top two solvents undergo a Simplified Life Cycle Assessment (SLCA). SLCA was conducted to identify ecological hotspots when data gaps and uncertainties are unavoidable. Furthermore, this assessment allows the opportunity of assessing and quantifying the potential environmental impact of the solvents,

i.e. rank the impact on a quantitative scale. However, as mentioned before this step can be very time consuming. Accordingly, it was limited to only two solvents.

For the SLCA the solvents were assessed from a cradle–to–gate approach, which means the assessment was conducted starting from the raw materials until obtaining the solvent. The functional unit selected for the SLCA is 1 kg of solvent.

The inventory for the conventional solvents was constructed from the LCI database Ecoinvent 2.2. This database is incorporated in the Umberto NXT LCA software used for the SLCA. In the case that the solvent was not found in the database, a retrosynthesis was conducted until the starting bulk materials were found. Information regarding the manufacturing process for the retrosynthesis was obtained from SciFinder® and relevant literature[49–52].

If a component needed for the synthesis of a solvent was not present in the database a proxy was used. For example, 2–Octanol, the precursor of 2–Octanone was not found in the database; thus the proxy "fatty alcohols" was used instead[53].

The fourteen ReCiPe Midpoint impact factors were used to evaluate the solvents, namely: Urban Land Occupation [ULOP $m^2$/yr], Natural Land Transformation [NLTP $m^2$], Climate change [GWP 100 kg $CO^2_{Eq}$], Ozone Depletion [ODP kg CFC–$11_{Eq}$], Particulate Matter Formation [PMFP kg $PM_{10-Eq}$], Photochemical Oxidant Formation [POFP $kg_{NMVOC}$], Marine Eutrophication [MEP kg $N_{Eq}$], Marine Ecotoxicity [METP kg 1,4–$DCB_{Eq}$], Freshwater Eutrophication [FEP kg $P_{Eq}$], Freshwater Ecotoxicity [FETP kg 1,4–$DBC_{Eq}$], Cumulative Energy Demand [CED Folsil Fuels $MJ_{Eq}$], Water Depletion [WDP $m^3$], Fossil depletion [FDP kg $oil_{Eq}$]), and Human Health (Human Toxicity [HTP kg 1,4–$DCB_{Eq}$]). All impact factors were considered with the same weighting factor. The total impact of the solvent was obtained by multiplying the impact factor (per kilogram of solvent) times the amount of solvent needed to dissolve one mol of product. Afterward, the total impact factor was normalized with respect to a solvent, in this case, acetic acid, to obtain dimensionless impacts. Consequently, each category can be added to obtain the overall impact of the solvent. The solvent with the lowest value will correspond to the lowest environmental impact. This solvent can be rated as the best solvent.

A sensitivity assessment was conducted by analyzing possible synthetic routes present in the market. Two scenarios were developed for the solvents for which a retrosynthesis was conducted. These scenarios consisted of two different production routes, to assess how these routes can change the environmental impact of the solvent.

### 4.2.2. Functional Solvent Factory Process design

The second part of this chapter presents the process conceptualization of a Functional Solvent Factory. As mentioned before a second reaction for this case study was selected, whereby the synthesis of benzyl azide via FSF will be initially assessed. Currently, this new process concept, the "Functional Solvent Factory" is at a technology readiness level (TRL) below 3[54], which indicates that it needs the analytical and experimental demonstration of the proof–of–concept[55]. This stage of development comes with many obstacles, such as the lack of data, to perform assessments. To manage this obstacle predictive scenarios were developed for the foreground systems. These foreground systems will be used to build on learning curves for the development of the technology[56].

Two types of FSF were developed based on literature data. Reported experimental data was selected to obtain insights into the events that might be faced at the early stages of development. These two scenarios were designed trying to maintain the innovative, disruptive idea of the functional solvent factory, yet compromising, mirroring, and adapting that to real industrial life due to the use of reported experimental data. Thus, this mirroring lacks some of the aspects of the "ideal" functional solvent factory as these processes were modified from batch to flow to adapt them better to the FSF concept. Table 1 reports the assets identified in the proposed functional solvent factories (Type 1 and Type 2) with respect to the ideal.

**Table 1.** Functional solvent factory assets

| Process | Automated Purification of product | Recycling Catalyst | Recycling Reactant |
|---|---|---|---|
| Type 1– Solvent Factory | Possible (need of extra solvent to extract) | No catalyst | Traces are recovered but not in the IL compartment |
| Type 2– Solvent Factory | Yes – in first step<br>Possible – in second step | No catalyst | Traces are recovered but not in the IL compartment |

#### Type 1– Solvent Factory

Type 1, interchangeably one–step process, refers to the synthesis of benzyl azide directly from benzyl alcohol, i.e. in *one–step*. The reaction pathway is present in Fig. 4.3. As it can be

observed in one–step the product of interest is achieved, without the need to conduct a second reaction.

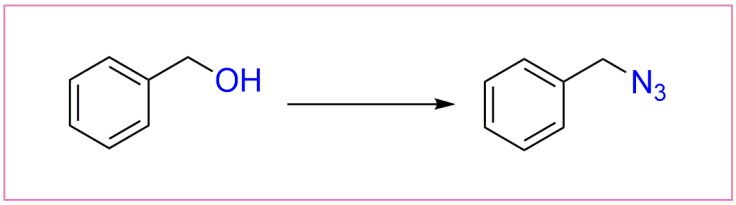



**Fig. 4.3.** Reaction schema for the type one (one–step) Functional solvent factory

This synthesis has been reported in literature using different acidic ILs such as 1–Hexyl–3–methyl–imidazolium–tetrafluoroborate[57] or N–methyl–2–pyrrolidone hydrogen sulphate[58]. These ILs fulfill multiple functions in the process, being both solvents and catalysts, and in this way, they enable the reaction to proceed without an intermediate, such as benzyl chloride.

The one–step process was based on the work described in Garg and Ling (2014)[57], detailed information on this procedure can be found in Appendix B (Fig s4.1). The adaptation to the FSF approach is presented in Fig. 4.4 and proceeds as follows: 1–methylimidazolium tetrafluoroborate (Hmim $BF_4$), benzyl alcohol and sodium azide are mixed. The reaction is conducted at 100 °C. After the completion of the reaction, the stream is cool down to ambient temperature, and it is washed twice with a solution of hexane–ethyl acetate (9:1 v/v). The inorganic phase (IL) is separated and washed with acetonitrile and filtered to remove the sodium hydroxide (NaOH) and sodium azide ($NaN_3$). Then the acetonitrile and remaining organic compounds are distilled and the IL is recovered. The organic phase is filtered to remove the sodium hydroxide (NaOH) and sodium azide ($NaN_3$), washed with water, and dried over magnesium sulfate ($MgSO_4$). The solvents are removed by distillation and the product is obtained.

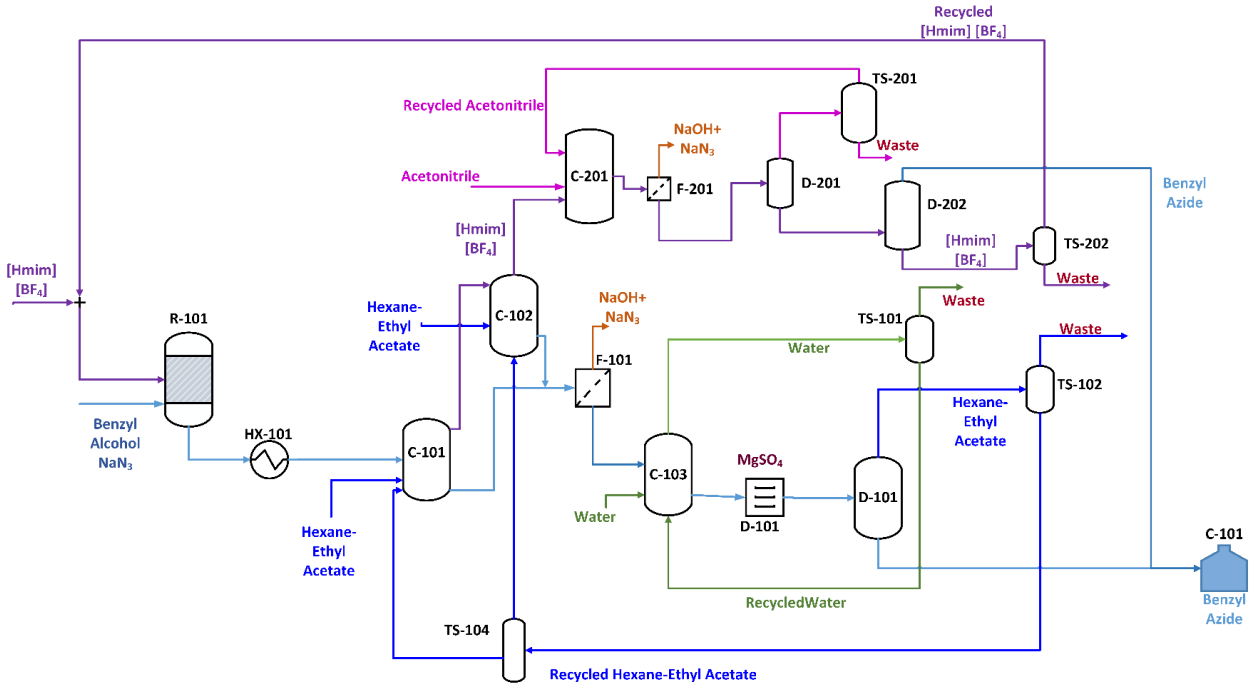



**Fig. 4.4**. Process diagram of the Type one Functional Solvent Factory (One-step process).

### Type 2– Solvent Factory

Type 2, interchangeably two-step process, consists of the following steps: benzyl alcohol is first reacted to form benzyl chloride, which is then reacted to form benzyl azide. Therefore, the reaction is carried out in *two steps* (see Fig. 4.5).

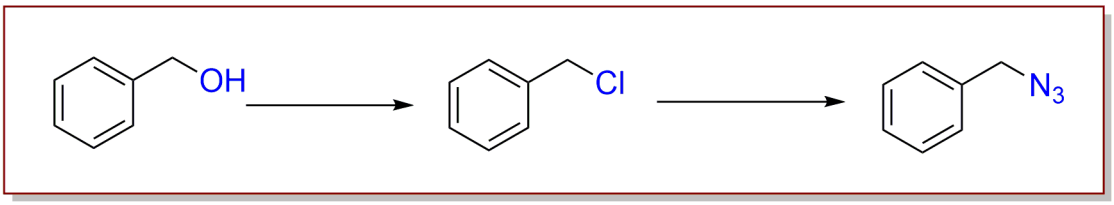



**Fig. 4.5.** Reaction schema for the type two (two-step) Functional Solvent Factory

Conversion of alcohols to the corresponding halide has been reported before[59]. This synthesis needs a Brønsted acid to catalyze the reaction, which converts the IL [Bmim] [X] into [Bmim] $HSO_4$ or [Bmim] $CH_3SO_3$. However, any of these ILs, [Bmim] $HSO_4$ or [Bmim] $CH_3SO_3$, are difficult to regenerate. Thus, it was decided to follow the reaction pathway presented in Wu et al. (2004) to minimize the potential loss of the IL[60].

The two-step process diagram adapted from Wu et al. (2004) and Zhong and Guo (2004)[61] is presented in Fig. 4.6, the batch process is presented in Appendix B (Fig s4.2). The process starts by mixing the IL 1-methylimidazolium chloride (Hmim Cl) with benzyl alcohol (B-OH). The reaction is conducted at 120°C. The alcohol dissolves easily in the IL while the product does not solubilize. Therefore, a second phase is automatically obtained. However, the IL decomposes and forms an organic product in which the product is soluble. Consequently, it is necessary to regenerate the IL to be able to remove the product easily. To regenerate the IL hydrogen chloride (HCl) is added. The mixture is stirred and the product, benzyl chloride, can be easily decanted. To recycle the IL, the water formed during the regeneration must be removed. The benzyl chloride obtained is then mixed with 1-butyl-3-methylimidazolium tetrafluoroborate (Bmim $BF_4$) and sodium azide, then heated to 60 °C. After completion, the mixture is washed with diethyl ether ($Et_2O$), and the IL (Bmim $BF_4$) is recovered. The organic fraction is then distilled to remove the solvent and obtain the product.

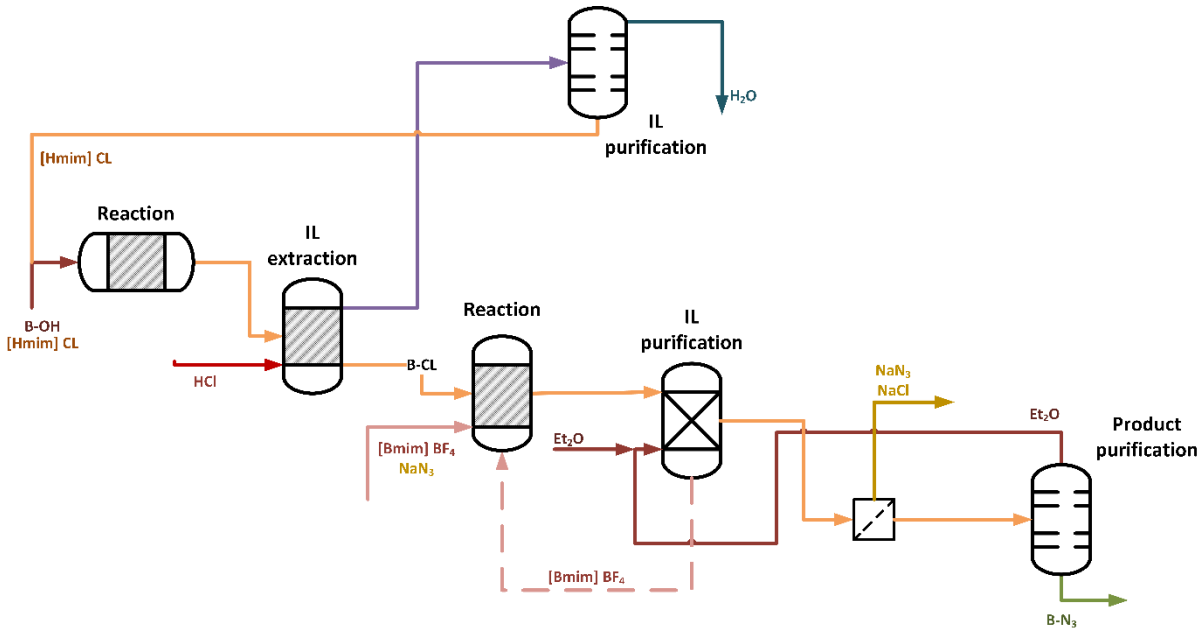



***Fig. 4.6**. Process diagram of One Flow Type Two (two-step) Functional Solvent Factory.*

## 4.3 RESULTS

### 4.3.1 Solubility Solvent selection

Solubility data of pharmaceuticals is rarely available. Selecting the best solvents requires experience and experimental testing, which may lead to a poor solvent selection, especially when time and economic constraints obstruct the possibility of trying an extensive number of solvents. Yet, solubility is the key parameter for the FSF concept, and selective solubility in a

multiphase system is the prerequisite for the functioning of the whole concept. Therefore, this parameter was used to determine possible solvents and as well consider the environmental implications of the use of that solvent. Therefore, solubility not only aids in the solvent election but also to determine the solvent with the potentially lowest environmental impact.

The methodology was applied for the first case study, a reaction to synthesize 1–(3(chlorophenyl)butan–1,3–diol. An extensive list of solvents was obtained from COSMO–RS and ranked by solubility to obtain the solvents with the highest values. The top 50 were selected and ranked by price, the top ten solvents are presented in Table 4.2.

It is important to note that the solvents given here are not "common", i.e., not in the group of bulk solvents such as ethanol or methanol. For comparison purposes, a common solvent, acetic acid, was included in the environmental assessment section.

**Table 4.2.** Top ten common solvents after price rank.

| Solvent | Solubility Rate | Rank |
|---|---|---|
| 2,2–Diethoxypropane | Maximum | 1 |
| 1–Propanol | Maximum | 2 |
| Decan–1–oic acid | Maximum | 3 |
| Lactic acid | Maximum | 4 |
| Propanal | Maximum | 5 |
| 4–Methyl–2–Pentanone | Maximum | 6 |
| Isophorone | Maximum | 7 |
| 2–Methyl–2,4–Pentanediol | Maximum | 8 |
| 2–Octanone | Maximum | 9 |
| Formic acid | Maximum | 10 |

After the price ranking, solvents were ranked based on safety consideration. The safety assessment considered first the flammability, followed by instability and finally health. Less importance was given to the health score considering that it is also evaluated in the environmental assessment (HTP category). Decan–1–oic acid scored the highest due to its low flammability; however, it ranks level 2 in the health category because it can cause incapacitation after continuous or intense exposure of the operators to it[48]. Following decan–1–oic acid, the next solvent with the highest rating was 2–ocatanone.

Afterward, a SLCA of the top–2 solvents and acetic acid was conducted. The impact factors were obtained as extensive properties, dependent on the mass. These impacts were adjusted to the mass of the solvent needed to extract one mole of product, which was calculated from the solubility results.

A retrosynthesis was conducted for 2–octanone. Two synthetic routes were studied to analyze different pathways and reduce uncertainties. These routes or scenarios are named "a" and "b" respectively (see Fig. 4.7). For example, 2–Octanone is obtained through the oxidation of secondary alcohols. Most frequently such kinds of reactions are performed using inorganic oxidants, particularly chromium, which cause great environmental damage[62]. Consequently, alternatives for this synthesis have been proposed[52,62–64]. The second route assessed used manganese as an oxidation agent. In Fig. 4.3 it is shown that the manganese–based process "a" is indeed greener than the state–of–the–art process. However, the remarkable difference is caused by the large amounts of diethyl ether used in the synthesis and in the separation stage.

The two scenarios modelled for the synthesis of decan–1–oic acid exhibit less discrepancy in the impact, with most of it attributed to the use of fatty acids as starting material in both cases.

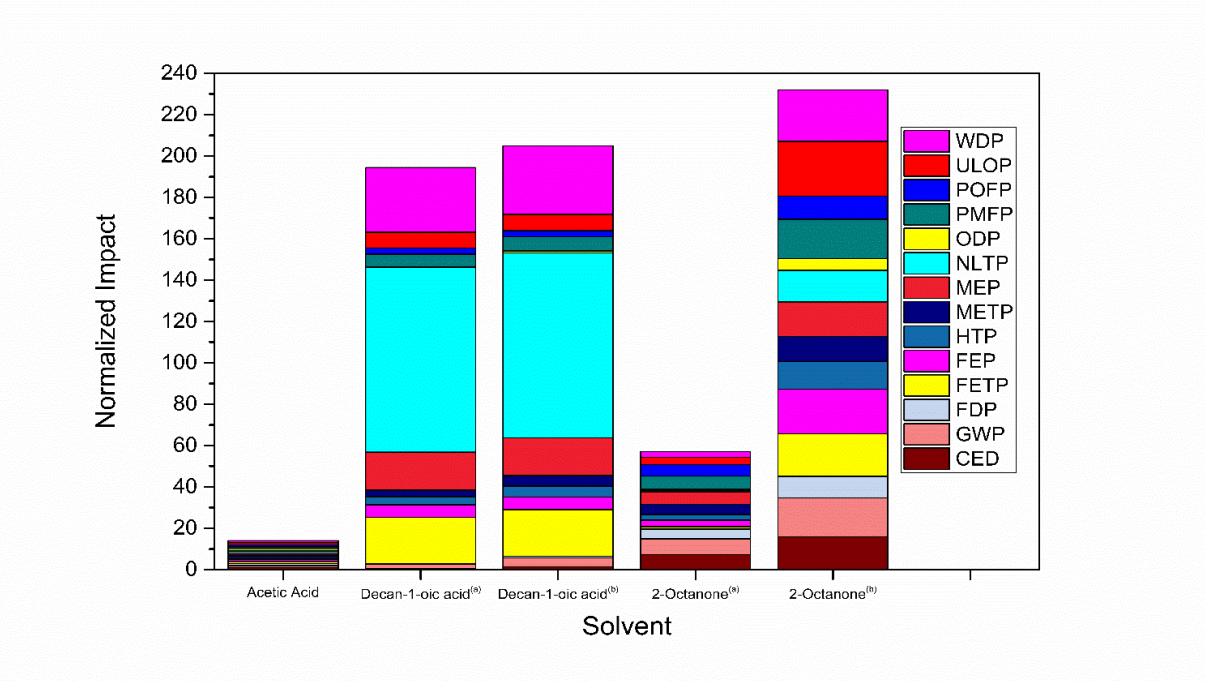



**Figure 4.7** Decan–1–oic acid and 2–octanone environmental impact results normalize with respect to the impact of acetic acid.

After the assessment, it can be concluded that unless 2–octanone is synthesized with a greener procedure, the best solvent is decan–1–oic acid. However, compatibility issues must be checked. Decan–1–oic acid is incompatible with the temperature at which the reaction is conducted due to its high melting point of it; therefore, it must be discarded. Other compatibility matters need to be addressed during the solvent selection process.

Compared with acetic acid, a common solvent, the impact of decan–1–oic acid is much larger. This was expected as the solvents needed for the FSF, are specialty solvents, that require many synthetic steps. However, it is considered that the impacts of the non–common solvents can be minimized through the elimination of purification equipment and high recyclability rates. Moreover, they are chosen due to their selectiveness for a reactant or product. In the case of the conventional solvent, acetic acid, its selectiveness was very low with respect to the other compounds in the reaction. Thus, despite the high solubility and low environmental impact, it is not a good candidate for the reaction.

There is a great interest in ionic liquids (ILs) for pharmaceutical applications[65,66]. In the particular case of the Functional Solvent Factory, ILs can be functional solvents; i.e. in combination with other(s) solvent(s) they can develop a multiphase system that can be switched to a single phase system by changing the conditions (e.g. temperature)[67]. Ionic liquids are commonly perceived as more environmentally friendly with respect to conventional organic solvents. Due to their low vapor pressure, and near zero flammability[68]. However, the synthesis of ILs requires extensive amounts of reagents, energy and solvents, and generates large amounts of waste [69]. Therefore, if it is desired to use them in the Functional Solvent Factory, it is imperative to select the best IL with the lowest environmental impact. However, their assessment and selection pose a great challenge. It has been reported that there are over $10^{18}$ ILs as a result of the possible cation–anion combinations[70]. The cascade methodology developed here for conventional solvents can be applied to ILs. Nonetheless, despite the extensive amounts of ILs not all of them are commercially available. In 2018, Merkc had available just over 200 ILs in its portfolio[71]. For the non–commercially available ILs, it is possible to get an estimation of the cost based on a laboratory scale production. However, using laboratory data may lead to inaccurate cost ranking; moreover, it will be time–consuming. Safety assessment will also need to be tuned for ILs, as it is possible that most of them do not count NFPA classification due to their non–commercial status.

### 4.3.2 Functional Solvent Factory Modelling

Due to the challenges to implement the solvent selection methodology for an IL, and the need for data to aid in the modelling process, the FSF cases developed below were based on literature. Furthermore, with this data, it was possible to consider the interaction between the solvents and reactants, and possible drawbacks. Information that is essential to further develop the FSF.

#### Type 1 (One–Step) Factory

The modeling process was carried out in Aspen Plus V9. All the compounds were present in the database. Yet, to model the interactions with the IL was necessary to add more parameters, which are dependent on the model. Different models can be applied to model the interaction with IL, e.g. COSMOS–RS, QSPR, and UNIFAC[72]. In this case the UNIFAC model was selected, which requires the group parameters of volume $R_k$ and surface area $Q_k$. These group contribution parameters are, as their name explains, given for groups. The groups are the different possibilities in which a molecule can be decomposed[73]. For the one–step process approach, it was decided to separate the molecule into the main skeleton and the structural variations, i.e. separate it into imidazolium tetrafluoroborate (main skeleton) and the methyl group (structural variation) (see Fig s4.3). The group–group interaction parameters $R_k$ [74] and $Q_k$[75] were obtained from literature (see Table 4.3). Besides the UNIFAC method, the solid method was selected for the solid components.

**Table 4.3.** UNIFAC group parameters for the One flow One–step (Type 1) process

| Parament | Group [Mim $BF_4$] |
|---|---|
| $R_k$ | 4.005 |
| $Q_k$ | 6.5669 |

The process starts with the reaction conducted in an RStoic reactor at 100 °C and 1 bar, where 99% conversion is achieved under these conditions. Once completion of the reaction, the mixture is cooled down to room temperature in a heat exchanger at ambient pressure. Then it is mixed with a solution of hexane–ethyl acetate (9:1v/v). Two extractions were conducted in a decanter with a 70% recovery of the product. The organic fraction was

separated, mixed, and filtered. The addition of the organic solvents causes the precipitation of salts, and any trace of them needs to be removed. A vacuum filter is used for a continuous process and is assumed that 100% of the solid is removed. After the filtration, water at room temperature is added to further wash the organic phase in a decanter, with this all traces of inorganic components are removed (see Table S4.1). A purge is added for the aqueous phase before being recycled, and 10% of freshwater is added. For the purge a splitter was used where the amount of water to be discarded was indicated. Then, the organic phase is dried over magnesium sulfate in an RStoic reactor, and a splitter is used to remove the solids formed. Finally, the product is purified in a flash column at 30 °C and 0.2 bar. The excess solvent is cooled down, and before recycling a fraction is purged and the same amount of fresh solvent is added.

On the other side, the IL phase is purified. After the wash with the hexane–ethyl acetate the IL is washed again with acetonitrile and filtered to precipitate any traces of sodium hydroxide. The acetonitrile and remaining organic compounds that were in the IL phase are dried under vacuum. A vacuum filter is used for a continuous process and is assumed that 100% of the solids are removed. Then it is necessary to remove the organic solvents, for that the Winn–Underwood–Gilliland method was used for shortcut design. A DSTWU column with 10 stages with a total condenser was selected. The pressure of the reboiler and condenser is 0.01 bar.

The authors mention that the IL can be recycled, but the yield is affected after two recycling cycles. This may be due to the compounds that cannot be removed with just one distillation. Thus, it was decided to model an extra column to recover the remaining product in the IL and assess its impact on the process. The Winn–Underwood–Gilliland method was used again for shortcut design of this new column. A DSTWU column with 20 stages and a total condenser was used. The pressure of the reboiler and condenser is 0.001 bar. Traces of the product are collected, and the IL is recycled (99% purity). Before being recycled a fraction of the IL is purged and the same amount of fresh IL is added. Although, this can guarantee that the yield remains constant, great losses of IL are caused. Table 4.4 presents the inventory for this process.

Despite the double functionalities of the IL, solvent and reaction enabler, the process modelled here was still complex and required many purification steps. These are all undesired aspects. In literature it is shown that these steps could be minimized due to the low solubility of the product in the IL. Yet this was not considered in the reported data. Therefore, the process requires large amounts of materials. Solubility of the product in the IL needs to be explored to eliminate or reduce the purification steps.

A key highlight is the large energy requirements needed to conduct this process due to the use of large amounts of IL and its heat capacity.

**Table 4.4**. Data inventory for the one–flow one–step process approach (Type 1).

| Component | Input[1] | Output[1] |
|---|---|---|
| Electricity (kW) | 11 | |
| Cooling (MJ) | 7191 | |
| Heating (MJ) | 7176 | |
| HCl (kg) | 5 | 0 |
| Benzyl alcohol (kg) | 8 | |
| Benzyl alcohol (waste) (kg) | | $6x10^{-3}$ |
| Benzyl azide (kg) | | 10 |
| Sodium azide(kg) | 5 | |
| Hexane (kg) | 94 | |
| Hexane (emissions) (kg) | | 0.2 |
| Hmim $BF_4$ (kg) | 110 | |
| Ethyl acetate (kg) | 42 | |
| Ethyl acetate (emissions) (kg) | | 0.1 |
| Magnesium sulphate (kg) | 0.9 | |
| Water (kg) | 39 | |

[1]Amounts are rounded up.

## Type 2 (Two–Step) Factory

To model this process Aspen Plus V9 was used. The UNIFAC method was selected again to predict the interaction between components. Group parameters for the ionic liquids were obtained from literature[76] (see Table 4.5).

**Table 4.5.** UNIFAC group parameters for the ILs in the One flow Two–step (Type 2) process.

| Parament | Group [Mim] | Group [Mim Cl] | Group [Cl] | Group [Mim $BF_4$] |
|---|---|---|---|---|
| $Q_k$ | 0.868 | 4.9741 | 0.673 | 4.005 |
| $R_k$ | 2.026 | 5.7073 | 0.65 | 6.5669 |

The components were charged into an RStoic reactor at 120°C and 1 bar. The IL decomposes during the reaction, and imidazole and chlorine are obtained. A regeneration step is necessary to recover the IL and the product. The product, benzyl chloride, is soluble in imidazole, while it is insoluble in the IL. The regeneration is conducted in an RStoic reactor under the same conditions as the reaction. The out stream is cooled down to room temperature in a heat exchanger. Then the mixture is split into the organic phase and the IL–phase in a separator component, where the fraction was specified based on the solubility of the components in water. The organic phase, i.e. the product, goes to the azidation step, while the IL is purified before recycling.

Water is formed as a byproduct of the regeneration of the IL and needs to be removed to avoid the risk of hydrolysis. It is not specified how the water was removed and there are many alternatives, but the most common is distillation. The shortcut design was made with the Winn–Underwood–Gilliland method. A DSTWU column with 10 stages and a total condenser was used. After the purification a fraction of 10% of the IL is purged, and the same amount of new IL is added and recycled.

In the next stage, the product is mixed with Bmim $BF_4$ and sodium azide ($NaN_3$). The reaction takes place in a RStoic reactor at 60 °C and 1 bar achieving 65% conversion. The out stream is cooled to room temperature with a heater. Then it is washed with diethyl ether, which will cause the salts to precipitate. The salts are removed in a continuous rotary vacuum filter. After a two–phase system will be formed. The IL–phase is washed again with diethyl ether and extracted. The organic phases are combined and distilled to remove the excess solvent. Due to the large amount of solvent used, the distillation was done in three steps. The first distillation is a flash column at 35 °C and 0.5 bar, where 87% of the solvent is removed. The second distillation was done again in a flash column at 40 °C and 0.5 bar, 22% of the remaining solvent

was removed. Finally, the third distillation is conducted at 80 °C and 0.5 bar where 99% of the remaining solvent is removed, and the product can be recovered.

The solvent, diethyl ether is collected from the distillations and cooled down to room temperature. Before recycling it, a fraction of 10% of the solvent is purged, and the same amount of new solvent is added. The same is done to the IL, after separating it from the organic phase. Table 4.6 presents the inventory for this process.

In this second case, some features of the FSF were observed, such as automated separation. Yet as mentioned before, the regeneration of the IL causes some drawbacks such as the additional purification stage needed. This can affect the number of recycling times of IL, which will need to be verified experimentally. In the second step of this process, a possible automated separation can be achieved due to the solubility. However, this was not considered in the reported data, and larger amounts of diethyl ether were used for the extraction. Automated separation would reduce the need for many purification stages, which would reduce the cost and the environmental impact. Hitherto the degree of automated separation needs to be assessed and balanced against the need for a solvent extraction process.

**Table 4.6.** Data inventory for the One–flow two–step process approach (Type 2).

| Component | Input[1] | Output[1] |
|---|---|---|
| Electricity (kW) | 4 | |
| Cooling (MJ) | 8262 | |
| Heating (MJ) | 15575 | |
| HCl (kg) | 5 | |
| Benzyl alcohol (kg) | 16 | |
| Benzyl azide(kg) | | 10 |
| Diethyl ether (kg) | 33 | |
| Diethyl ether (emissions) (kg) | | 1.5 |
| Sodium azide (kg) | 11 | |
| Hmim Cl (kg) | 2 | |
| Bmin $BF_4$ (kg) | 4.5 | |
| Wastewater (kg) | | 0.2 |

[1]Amounts are rounded up.

## 4.4 CONCLUSIONS

A comprehensive solvent assessment methodology for the Functional Solvent Factory was designed with solubility as a key selection parameter. It integrates a series of screenings (the environmental impact, the economic and the safety) together with the physical property of interest. It was demonstrated how this methodology can aid in the selection of solvents. For purposes of comparison, the conventional solvents also were assessed and compared against a common solvent. As was observed for the first cascade it can be concluded that decan–1–oic acid is potentially the greenest alternative. Especially, if the synthesis pathway of 2–octanone is unknown. However, when compatibility in the reaction is added, then the best solvent is 2–octanone. Moreover, it was observed that the environmental impact of these solvents is many times larger compared to conventional ones. Therefore, its use and recycling are key to the development of the Functional solvent Factory.

This methodology is the first step towards a green design of the Functional Solvent Factory, where the aim was to select and assess the solvents. As an outlook it is aimed to improve the methodology with a multicriteria perspective that includes the process and compatibility issues in detail. Evaluating how the solvent impacts the process and recyclability options are necessary for the green design of the Functional Solvent Factory.

The second part of this chapter presents a second case study, where the FSF was modelled to evaluate the potential advantages and drawbacks of this new concept. This was presented as a balancing act between innovation and real–life commercialization potential of automated separation via IL. Two scenarios were developed to give insights into the development of disruptive process technologies from the generic process concept of the "functional solvent factory", which utilizes ionic liquids (IL) as integrated reactor–separators. ILs are unique solvents in many aspects and can intensify chemical processes. As was observed, due to the use of foreground data the concept of the FSF could not achieve its expected potential. Accordingly, it is necessary to bare these drawbacks in mind in early stages of development, moreover, couple them with an environmental assessment which will be conducted in the following chapter.

## REFERENCES


1 C. Jiménez-González, P. Poechlauer, Q. B. Broxterman, B. S. Yang, D. Am Ende, J. Baird, C. Bertsch, R. E. Hannah, P. Dell'Orco, H. Noorman, S. Yee, R. Reintjens, A. Wells, V. Massonneau and J. Manley, *Org. Process Res. Dev.*, 2011, **15**, 900–911.

2 C. Jimenez-Gonzalez, C. S. Ponder, Q. B. Broxterman and J. B. Manley, *Org. Process Res. Dev.*, 2011, **15**, 912–917.

3 R. Gani, C. Jimenez-Gonzalez, A. ten Kate, P. A. Crafts, M. Jones, L. Powell, J. H. Atherton and J. L. Cordiner, *Chem. Eng. J.*, 2006, 30–43.

4 C. S. Slater and M. Savelski, *J. Environ. Sci. Heal. Part A*, 2007, **42**, 1595–1605.

5 D. J. C. Constable, C. Jimenez-Gonzalez and R. K. Henderson, *Org. Process Res. Dev.*, 2007, **11**, 133–137.

6 C. Capello, U. Fischer and K. Hungerbühler, *Green Chem.*, 2007, **9**, 927.

7 M. Lancaster, in *Green Chemistry: An Introductory Text*, RSC Paperbacks, 2002, pp. 130–165.

8 C. Jimenez-Gonzalez, *Curr. Opin. Green Sustain. Chem.*, 2019, **18**, 66–71.

9 K. Tanaka and F. Toda, *Chem. Rev.*, 2000, **100**, 1025–1074.

10 J. H. Clark and S. J. Tavener, *Org. Process Res. Dev.*, 2007, **11**, 149–155.

11 S. K. Shukla, S. Pandey and S. Pandey, *J. Chromatogr. A*, 2018, **1559**, 44–61.

12 P. G. Jessop, R. R. Stanley, R. A. Brown, C. A. Eckert, C. L. Liotta, T. T. Ngo and P. Pollet, *Green Chem.*, 2003, **5**, 123–128.

13 F. Bellina and C. Chiappe, *Molecules*, 2010, **15**, 2211–2245.

14 J. S. Wilkes, P. Wasserscheid and T. Welton, in *Ionic Liquids in Synthesis*, eds. P. Wasserscheid and T. Welton, Wiley-VCH Verlag GmbH & Co. KGaA., 2007, pp. 1–6.

15 N. V. Plechkova and K. R. Seddon, *Chem. Soc. Rev.*, 2008, **37**, 123–150.

16 A. J. Greer, J. Jacquemin and C. Hardacre, *Industrial Applications of Ionic Liquids*, 2020, vol. 25.

17 Y. Zhang, B. R. Bakshi and E. S. Demessie, *Environ. Sci. Technol.*, 2008, **42**, 1724–1730.

18 A. Freeman, J. M. Woodley and M. D. Lilly, *Bio/Technology*, 1993, **11**, 1007–1012.

19 A. Pohar, I. Plazl and P. Žnidaršič-Plazl, *Lab Chip*, 2009, **9**, 3385–3390.

20 A. Stankiewicz and J. A. Moulijn, *Re-Engineering the Chemical Processing Plant Process Intensification*, 1st edn., 2018.

21 C. Zhang, Z. Song, C. Jin, J. Nijhuis, T. Zhou, T. Noël, H. Gröger, K. Sundmacher, J. van Hest and V. Hessel, *Chem. Eng. J.*, 2020, **385**, 123399.

22 C. Zhang, Z. Song, C. Jin, J. Nijhuis, T. Zhou, T. Noël, H. Gröger, K. Sundmacher, J. van Hest and V. Hessel, *Chem. Eng. J.*, 2019, **385**, 123399.

23 B. Subramaniam, *Ind. Eng. Chem. Res.*, 2010, **49**, 10218–10229.

24 P. Pollet, C. A. Eckertabc and C. L. Liotta, *Chem. Sci.*, 2011, **2**, 609–614.

25 S. B. Jones, B. Simmons, A. Mastracchio and D. W. C. MacMillan, *Nature*, 2011, **23**, 1–7.

26 R. Villa, E. Alvarez, R. Porcar, E. Garcia-Verdugo, S. V. Luis and P. Lozano, *Green Chem.*, 2019, **21**, 6527–6544.

27 V. Hessel, D. Kralisch and U. Krtschil, *Energy Environ. Sci.*, 2008, **1**, 467.

28 B. P. Binks and J. H. Clint, *Langmuir*, 2002, **18**, 1270–1273.

29 H. Che and J. C. M. van Hest, *J. Mater. Chem. B*, 2016, **4**, 4632–4647.

30 F. Cozzi, *Adv. Synth. Catal.*, 2006, **348**, 1367–1390.

31 M. Wang, M. Wang, S. Zhang and J. Chen, *React. Chem. Eng.*, 2019, **4**, 1459–1465.

32 ONE-FLOW Research Project, https://one-flow.org/vision.

33 U. Novak and P. Žnidaršič-Plazl, *Green Process. Synth.*, **2**, 561–568.

34 E. Ayan, N. Baylan and S. Çehreli, *Chem. Eng. Res. Des.*, 2020, **153**, 666–676.

35 O. M. Morales-Gonzalez, C. Zhang, S. Li and V. Hessel, *Chem. Eng. Sci. X*, , DOI:10.1016/j.cesx.2019.100024.

36 C. Zhang, Z. Song, C. Jin, J. Nijhuis, T. Zhou, T. Noel, H. Gröger, K. Sundmacher, J. van Hest and V. Hessel, *Screening of functional solvent system for automatic aldehyde and ketone separation in aldol reaction: a COSMO-RS and experimental combined approach*, 2018.

37 V. Hessel, *Chem. Int.*, 2018, **40**, 12–16.

38 C. Zhang, T. Noel, S. Li, Z. Song, K. Sundmacher, H. Gröger and V. Hessel, *Spaciant Solvent Factory towards End-to-End Green Process Design for Pharmaceuticals in ONE-FLOW*, 2018.

39 I. Vural Gürsel, S. K. Kurt, J. Aalders, Q. Wang, T. Noël, K. D. P. Nigam, N. Kockmann and V. Hessel, *Chem. Eng. J.*, 2016, **283**, 855–868.

40 S. G. Alvarez and M. T. Alvarez, *Synthesis (Stuttg).*, 1997, **4**, 413–414.

41 A. Nemes, J. Rábai, M. Berta, D. Szabó, A. Dancsó and Z. Pathó, *J. Fluor. Chem.*, 2016, **196**, 57–62.

42 P. Zhang, M. G. Russell and T. F. Jamison, *Org. Process Res. Dev.*, 2014, **18**, 1567–1570.

43 S. Arroyo, *Neurotherapeutics*, 2007, **4**, 155–162.

44 S. Bräse and K. Banert, *Organic Azides*, 2009.

45 G. Rulli, N. Duangdee, K. Baer, W. Hummel, A. Berkessel and H. Gröger, *Angew. Chemie – Int. Ed.*, 2011, **50**, 7944–7947.

46 G. Rulli, N. Duangdee, W. Hummel, A. Berkessel and H. Gröger, *European J. Org. Chem.*, 2017, **2017**, 812–817.

47 Merck, https://www.sigmaaldrich.com/nederland.html.

48 J. Melorose, R. Perroy and S. Careas, *Statew. Agric. L. Use Baseline 2015*, 2015, **1**, 1–7.

49 J. E. Girard, *Nature*, 1980, **284**, 83.

50 US2964546A, 1964, 1–3.

51 S. Righi, V. Bandini, D. Marazza, F. Baioli, C. Torri and A. Contin, *Bioresour. Technol.*, 2016, **212**, 245–253.

52 A. Shaabani, Z. Hezarkhani and S. Shaabani, *RSC Adv.*, 2014, **4**, 64419–64428.

53 USDA and A. A. D. for the U. N. O. P. Agricultural Marketing Service, *Fatty Alcohols ( Octanol and Decanol )*, 2016.

54 Q. Deng, N. N. Tran, M. Razi Asrami, L. Schober, H. Gröger and V. Hessel, *Ind. Eng. Chem. Res.*, 2020, **59**, 21001–21011.

55 S. Gavankar, S. Suh and A. A. Keller, *J. Ind. Ecol.*, 2015, **19**, 51–60.

56 N. Thonemann, A. Schulte and D. Maga, *Sustainability*, 2020, **12**, 1192.

57 B. Garg and Y. C. Ling, *J. Chinese Chem. Soc.*, 2014, **61**, 737–742.

58 A. R. Hajipour, A. Rajaei and A. E. Ruoho, *Tetrahedron Lett.*, 2009, **50**, 708–711.

59 R. X. Ren and J. X. Wu, *Org. Lett.*, 2001, **3**, 3727–3728.

60 H.–H. Wu, J. Sun, F. Yang, J. Tang and M.–Y. He, *Chinese J. Chem.*, 2004, 319–621.

61 P. Zhong and S.–R. Guo, *Chinese J. Chem.*, 2004, **22**, 12–15.

62 R. A. Sheldon, I. W. C. E. Arends, G. J. Ten Brink and A. Dijksman, *Acc. Chem. Res.*, 2002, **35**, 774–781.

63 B. Ballarin, D. Barreca, E. Boanini, M. C. Cassani, P. Dambruoso, A. Massi, A. Mignani, D. Nanni, C. Parise and A. Zaghi, *ACS Sustain. Chem. Eng.*, 2017, **5**, 4746–4756.

64 M. Pagliaro, S. Campestrini and R. Ciriminna, *Chem. Soc. Rev.*, 2005, **34**, 837.

65 J. F. Brennecke and E. JMaginn, *AIChE J.*, 2004, **47**, 2384–2389.

66 K. B. Smith, R. H. Bridson and G. A. Leeke, *J. Chem. Eng. Data*, 2011, **56**, 2039–2043.

67 S. Liu, T. Fukuyama, M. Sato and I. Ryu, *Org. Process Res. Dev.*, 2004, **8**, 477–481.

68 M. Petkovic, K. R. Seddon, L. P. N. Rebelo and C. Silva Pereira, *Chem. Soc. Rev.*, 2011, **40**, 1383–1403.

69 S. P. F. Costa, S. A. P. Pereira, P. C. A. G. Pinto, A. R. T. S. Araujo, M. L. C. Passos and M. L. M. F. S. Saraiva, *ChemPhysChem*, 2017, **18**, 1351–1357.

70 J. Sangoro, T. Cosby and F. Kremer, in *Dielectric Properties of Ionic Liquids*, 2016, pp. 29–51.

71 Merck, Ionic Liquids, https://www.sigmaaldrich.com/chemistry/chemistry-products.html?TablePage=16255866, (accessed 27 September 2017).

72 Z. Lei, J. Zhang, Q. Li and B. Chen, *Ind. Eng. Chem. Res.*, 2009, **48**, 2697–2704.

73 Y. S. Kim, W. Y. Choi, J. H. Jang, K. P. Yoo and C. S. Lee, *Fluid Phase Equilib.*, 2005, **228–229**, 439–445.

74 P. Kolář, J. W. Shen, A. Tsuboi and T. Ishikawa, *Fluid Phase Equilib.*, 2002, **194–197**, 771–782.

75 Z. Lei, C. Dai, X. Liu, L. Xiao and B. Chen, *Ind. Eng. Chem. Res.*, 2012, **51**, 12135–12144.

76 P. Nancarrow, M. Lewis and L. Abouchacra, *Chem. Eng. Technol.*, 2015, **38**, 632–644.

## Appendix B

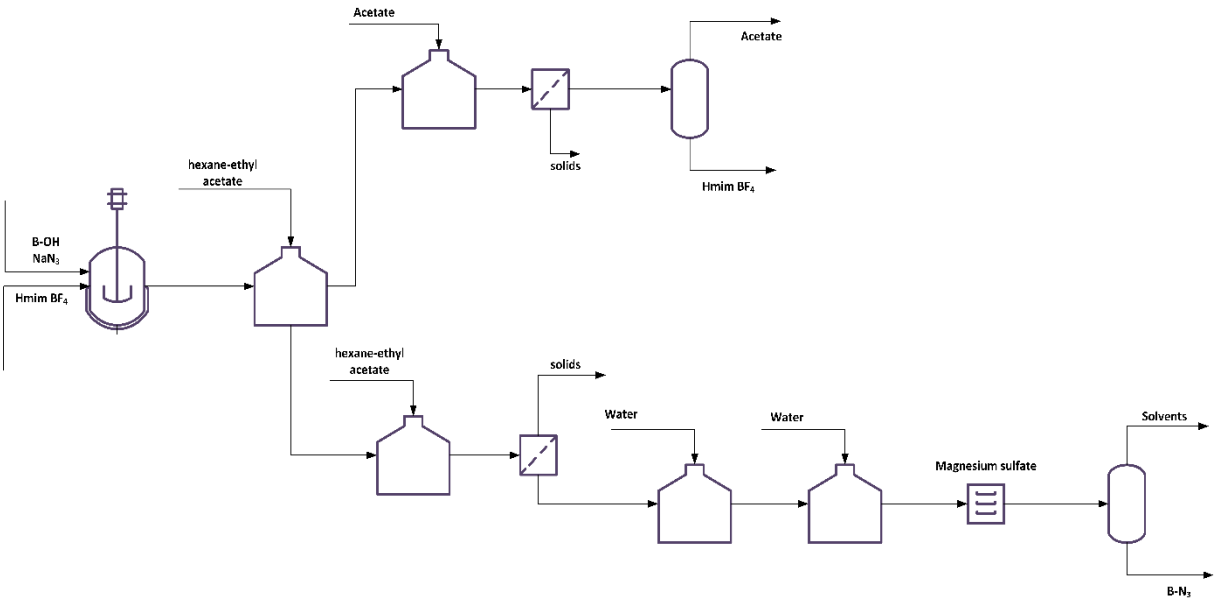



**Fig s4.1** Process diagram of the one–pot synthesis of azides from which the Type 1 (One–step) was adapted. A mixture of benzyl alcohol [B–OH] (2 mmol) and sodium azide [$NaN_3$] (2.1 mmol), is added to 5 mL of Hmim $BF_4$. Then the reaction is conducted at 100 ºC. After completion, a mixture of hexane–ethyl acetate (2 X 10 mL 9:1, v/v) is used to extract the organic phase and filter the solids. The organic phase is washed with water two times (10 mL) and dried over magnesium sulfate. Finally, the solvent is evaporated at low pressure. On the other side, the IL is washed with acetate and filtered. Then the solvent is evaporated under vacuum.

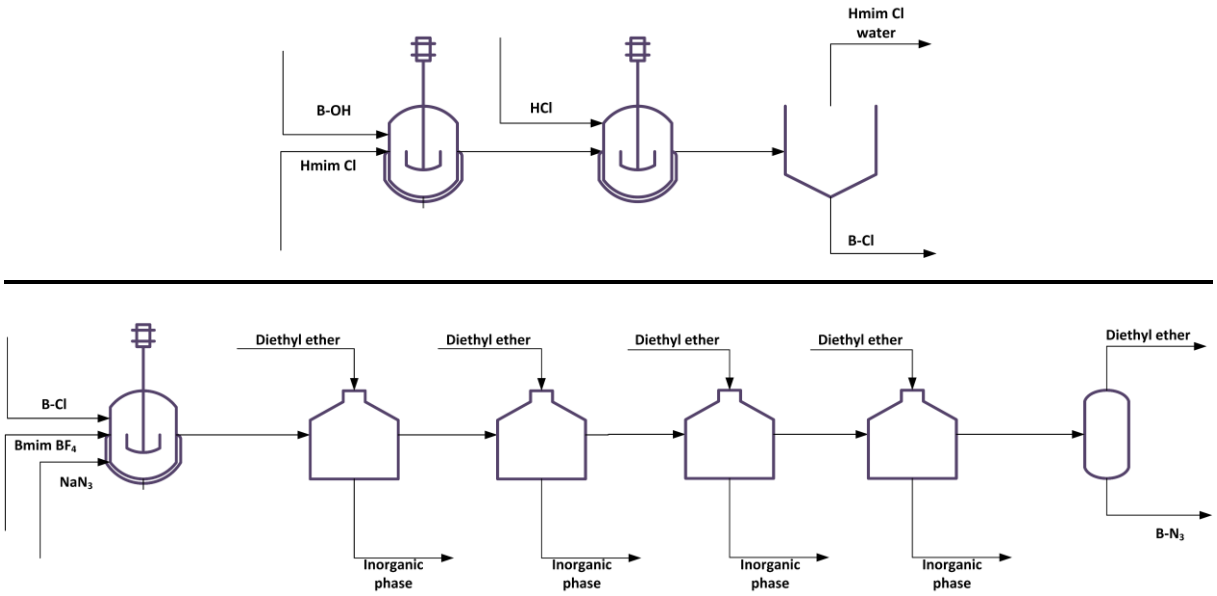



**Fig s4.2** Process diagram of the synthesis of benzyl chloride (Top) and benzyl azide (Bottom) in batch. In a flask 10 ml of 1–methylimidazolium chloride (Hmim Cl) were mixed with 10 mmol of benzyl alcohol (B–OH). Then the reaction was conducted at 120ºC for 12 h. Once the reaction is finalized HCl is added to regenerate the IL. The mixture was then stirred and decanted to extract the product (B–Cl). For the synthesis of benzyl azide 1mmol of B–Cl, 1 mmol of $NaN_3$ and 3 mL of Bmim $BF_4$ were mixed. Then the mixture was heated to 60ºC and stirred for 2 hr. After completion the mixture was washed with diethyl ether (4 x 20 mL). The organic phase was recovered, and the solvent was removed under vacuum. Finally, benzyl azide is obtained (B–$N_3$)

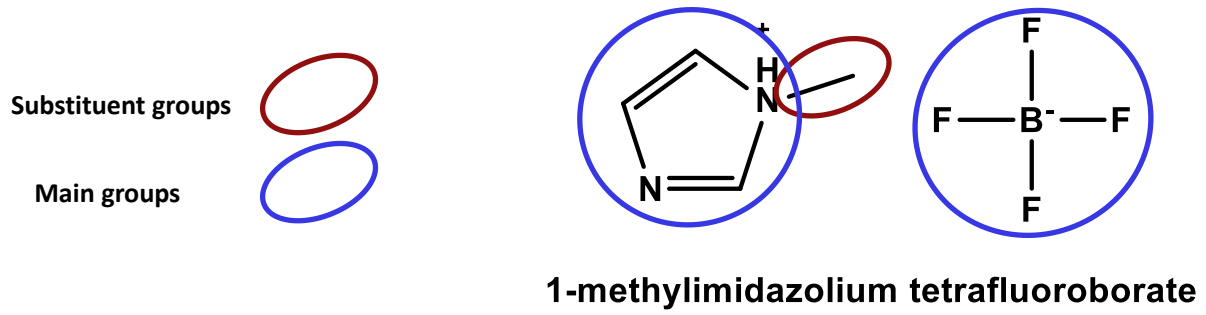



**Fig s4.3** IL group separation example case for Hmim $BF_4$

**Table s4.1** Mass balance of extraction with water sample case.

| | | 1 Extraction | |
|---|---|---|---|
| **Component** | **Initial [g/h]** | **Organic [g/h]** | **Aqueous [g/h]** |
| Hexane | 10.8 | 10.8 | 0.0043 |
| Ethyl acetate | 0.84 | 0.75 | 0.092 |
| Hmin $BF_4$ | 0.013 | 2.40E–09 | 0.013 |
| Benzyl alcohol | 1.56E–04 | 1.37E–04 | 1.91E–05 |
| Benzyl azide | 0.16 | 1.5 | 0.01296 |
| Water | 10 | 0.0085 | 9.99 |

# CHAPTER 5. LIFE CYCLE ASSESSMENT OF DESIGNER–SOLVENT PROCESSES WITH AUTOMATIC PRODUCT PURIFICATION AND RECYCLING

In this chapter, the use of ionic liquids to conduct in–situ purification is assessed by means of a Life Cycle Assessment. Ionic liquids have unique properties that can be exploited in the separation and recycling steps, which can minimize the need for a complex purification process and bring environmental benefits (i.e. lower the environmental impact). However, ionic liquids likewise shift the impact towards the early stages of production. Therefore, its use and implementation in a process need to be carefully evaluated and balance the advantages and disadvantages that they can bring. The processes developed in chapter 4 are hereby assessed to evaluate their environmental impact and identify hot spots before the experimental stages. These scenarios are benchmarked against a batch process and solvent–less process. The scenarios were then optimized to have 100% automated phase separation and reduce the purification needed. This optimization shows that under these conditions comparable systems to the performance of benchmark technologies are obtained. Moreover, it is possible that further optimization can lead to a greener process.

This chapter is based in the following paper:

Morales Gonzalez, O. M., Medrano, J. A., Gallucci, F. Hessel, V. Ecological assessment as balancing act between disruptive innovation and industrial implementation: Designer–solvent processes with automatic product purification and recycling. Journal of Cleaner Production. 318, 14 p., 128456.

## 5.1 INTRODUCTION

The pharmaceutical industry has determined specific key research areas to focus on and address the environmental challenges that this industry phases. Among the key areas are continuous processing, separation and reaction technologies, and the integration of environmental assessment[1]. Processes in the pharmaceutical industry are generally conducted in batch[2]. A change towards continuous production can lower operational costs and the environmental impact[1].

Purification processes are a major challenge due to the complexity and high use of resources. Solvents compromise the majority of these resources[3]. Around 80–90% of the total mass used during the production of an active pharmaceutical ingredient (API) can be attributed to solvent use[4]. Furthermore, some of these solvents can be hazardous, flammable, toxic, or carcinogenic[5]. Environmentally speaking, one of the mayor challenges is the volatile organic compounds (VOCs) emitted[6]. Thus, many approaches have been developed to minimize solvent use, from the complete elimination of solvent, i.e. solvent–free synthesis, to solvent substitution. Solvent–free synthesis can be applied in the industry relatively easily, reducing considerable waste production, yet its application is limited, especially in organic reactions[5,7,8]. Solvent–free synthesis is a major processing scheme in flow chemistry and can be considered within the 'novel process windows' (NPW)[9]. In the case of solvent substitution water, renewable solvents (bio–solvents) and neoteric solvents have been contempleted[6,10].

These problems have been carefully assessed within the European H2020 project One–Flow, and a novel process pathway has been proposed to tackle them. This new pathway, as mentioned in chapter 4, has been named "Functional Solvent Factory (FSF)". Now, this chapter moves one step further, from conceptualization to benchmarking. Some LCA studies of applications of ILs have been reported, but there are none reported using ILs for automated purification. In this chapter the processes modeled in chapter 4 are assessed in terms of their environmental impact. In the processes previously described, the ILs are multifunctional: used as carriers, enablers of the reaction, and as a separation medium that facilitates recycling and product purification. Multifunctional ILs are needed to conduct both the reaction and the purification steps. Moreover, ionic liquids are known as designer solvents, their capacity to be tailored can be used to facilitate simultaneous product separation[11]. Therefore, the active solvent role can eliminate the need for separation equipment. In the ideal FSF system the reaction will be conducted in a single phase. After the reaction, a multiphase system will be formed, in a compartment fashion where each compartment will contain a component and

therefore could be separated and recycled easily[12]. Thereby, the process could be simplified and potentially be more sustainable[13].

As in the case of solvent–free systems, it is considered that not every reaction system may be suitable for the Solvent Factory, and additional separation equipment may be needed[14]. Thus, it is started from the simplest case, to focus only on the extraction and purification of the product. This chapter makes the next step after the ideal model–case study of Deng et al. (2020) and the real–case study of Zhang et al. (2020), investigating the concept of the functional solvent factory under the known capping of real–life commercial constraints. Those results present the concept of the FSF in TRL 1–2. The study presented here includes recycling, shortcomings such as the degradation and contamination of ionic liquids, as well as the insufficient product purity which will require a separation train deviating from the ideal factory concept (automated product purification). The study is in line with the purpose of an ex–ante LCA, to identify the hot spots before moving to a lab production[15], and obtain a sustainable design and development. Ex–ante LCA studies of ionic liquids[16–18] point about the weakness of ILs concerning their environmental backpack (due to their synthesis). Yet, it remains unclear how that impacts when scaled up to industrial scale (e.g. at TRL 8), and when it is being used for automated purification.

The study will focus on the synthesis of organic azides, particularly benzyl azide following a "Functional Solvent Factory" approach (see figure 5.1), processes described in detail in chapter 4. Similar to what has been reported[19], and following substantial flow chemistry exploration[20] and LCA investigation[21]. There are many ways to synthesize this component, but the pathway selected follows the stages of the pharmaceutical industry. A state–of–the–art process will be used to benchmark the new functional–solvent–factory approach. As a second benchmark case, this chapter will consider the most innovative and environmentally assessed process approach, acknowledged by the author. There the authors reported there a solvent–free system that uses novel process windows and has been thoroughly assessed for its environmental impact[22].

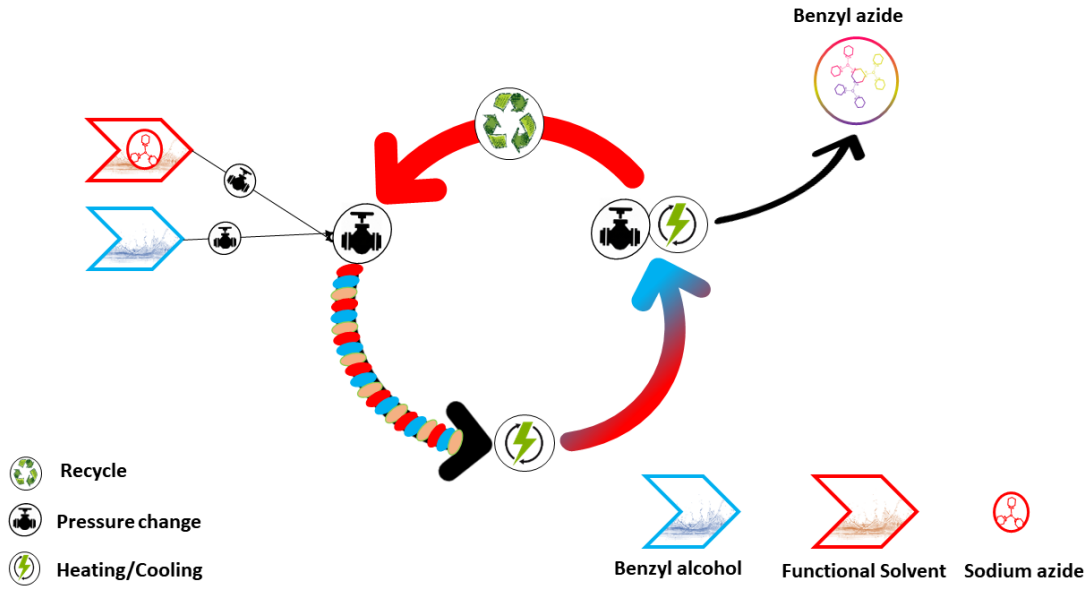



**Fig 5.1.** ONE-FLOW Functional Solvent Factory concept for the synthesis of benzyl azide. The functional solvent for the case study will be ionic liquid (e.g. Hmim $BF_4$). After the reaction is finalized a phase change due to solubility will enable the recovery of the product and the Il will be recycled.

## 5.2 METHODOLOGY

The evaluation of the FSF concept, as emerging technology, will be through an ex-ante Life Cycle Assessment (LCA). LCA is used to assess technology systems that are framed within a network of interlinked processes, where enough background and foreground data is available. This kind of LCA is known as ex-post. They can provide valuable insights into the areas of opportunity. However, applying changes to a technology that is at a late stage of development can be cumbersome[23]. Ex-ante LCA focus on assessing technologies before their (large-scale) implementation. This kind of LCA has the advantage of being able to guide the design and suggest improvements that can be implemented at an early stage of development. Moreover, ex-ante LCA needs to define the operation range of the new technology and be able to compare it with the incumbent technologies [24].

LCA systematic methodology was used to assess the environmental impact of the FSF. In this way the effects of obtaining the raw materials and their processing can be comprehensively studied much ahead of their real-life implementation[25], and the key enablers, in a kind of hot-spot analysis, can be identified[26]. The validity of the methodological approach for conducting an LCA for emerging technologies has to be adapted from an ex-post LCA, which is mostly applied for mature technologies[15].

Currently, the new process concept, the "Functional Solvent Factory" is at a technology readiness level (TRL) below 3[19], which indicates that it needs the analytical and experimental demonstration of the proof–of–concept[27]. This stage of development comes with many obstacles to performing the assessment. One of those obstacles is the lack of data; thus, to manage this obstacle predictive scenarios were selected for the foreground systems. These foreground systems will be used to build on learning curves for the development of the technology[28].

### 5.2.1 Goal, scope, and functional unit

The purpose of this study is twofold. Firstly, to obtain environmental information on the use of reactive extraction with IL for pharmaceutical applications in the lieu of the ambitious circular concept of a function solvent factory. Secondary, to compare the environmental performance with other process alternatives, i.e. the state–of–the–art (batch) and novel process windows approach, the latter leveraging intensification of flow chemistry.

Comparability aspects have been highlighted in the literature as a challenge[15]. In cases like this, the temporal correlation must be considered, i.e. selecting benchmark cases relevant to the timeline of the development of the FSF. It was decided in this work to carry out the comparison between two different strategies. On the one side, the pharmaceutical industry aims for continuous production, i.e. move from batch to flow processes[29]. Thus, flow technologies must outperform batch technologies. On the other side, this change is underway, and although the first industrial continuous–flow production plants have been installed in the industry in the last years, continuous production is not yet state–of–the–art in the pharmaceutical industry. Therefore, a batch production will be considered state–of–the–art for benchmarking. For the flow case, a solvent–free system will be used as a benchmark. Within the temporal correlation factor, it is also needed to consider possible future improvements, since emerging technologies are expected in a near future. For both benchmark cases no future improvements are foreseen.

The comparability also affects the selection of the functional unit. For both purposes the functional unit is defined as *10 kg of benzyl azide*. Scalability was addressed in a linear way, yet real–world systems are more complex and do not follow such a linear trend[30,31]. For all the cases, data from laboratory processes is used to design the scale up processes. Lab–scale data was used because the data present in patents is only for a small amount of product (at a g scale). Although, it is possible that the patents present a level of optimization that is not achieved in papers that present a lab scale process.

### 5.2.2 Definition of the systems and boundaries

The process is assessed from a cradle–to–gate approach, which encompasses all processes from the extraction of the raw materials up to the production of the benzyl azide, including the purification train to obtain the pure product. Pollution control measures, transportation, and the impacts associated with the manufacturing of the operational units (e.g. reactor) are out of the scope of this study.

### 5.2.3 Inventory analysis

Foreground data were used to develop the scenarios, which were later modeled in Aspen Plus to obtain the mass and energy balances for the functional unit selected. Below is presented a description of each of the processes to be analyzed, and detailed information on how these processes were implemented in Aspen Plus and Aspen Batch Modeler.

The benchmark cases are for the synthesis of difluorobenzyl azide in their process, but due to the lack of data in the solvent factory cases, it was assumed that the production of benzyl azide would occur under the same process conditions.

***Benchmark process 1: State–of–the–art***

For the industrial batch approach, the process was modelled following the conditions described in Wang et al. (2004)[32] and De Leon Martin et al. (2013)[33]. Figure 5.2 presents the process diagram of the batch approach. These patents describe a process that proceeds as follows (a description of the simulation can be found in Annex C): benzyl alcohol (B–OH) is mixed with diethyl ether ($Et_2O$) at 0ºC. In the same vessel thionyl chloride ($SOCl_2$) is added slowly. The reaction is conducted for 7 h while stirring. The mixture is transferred to remove the diethyl ether by evaporation. Then the mixture is washed with water followed by diethyl ether. Then organic fraction is extracted and washed with water. After that, it is dried over magnesium sulfate ($MgSO_4$), and the excess solvent ($Et_2O$) is removed by evaporation to obtain benzyl chloride (B–Cl).

Benzyl chloride (B–Cl) is dissolved in dimethyl sulfoxide (DMSO) and added slowly to a solution of sodium azide ($NaN_3$) in dimethyl sulfoxide. Then the mixture is left stirring at room temperature for 4 h. Once the reaction is finalized, the mixture is washed 2x with water and cyclohexane (Cy). Finally, the organic phase is recovered, and the solvent is vacuum distilled to obtain benzyl azide (B–$N_3$).

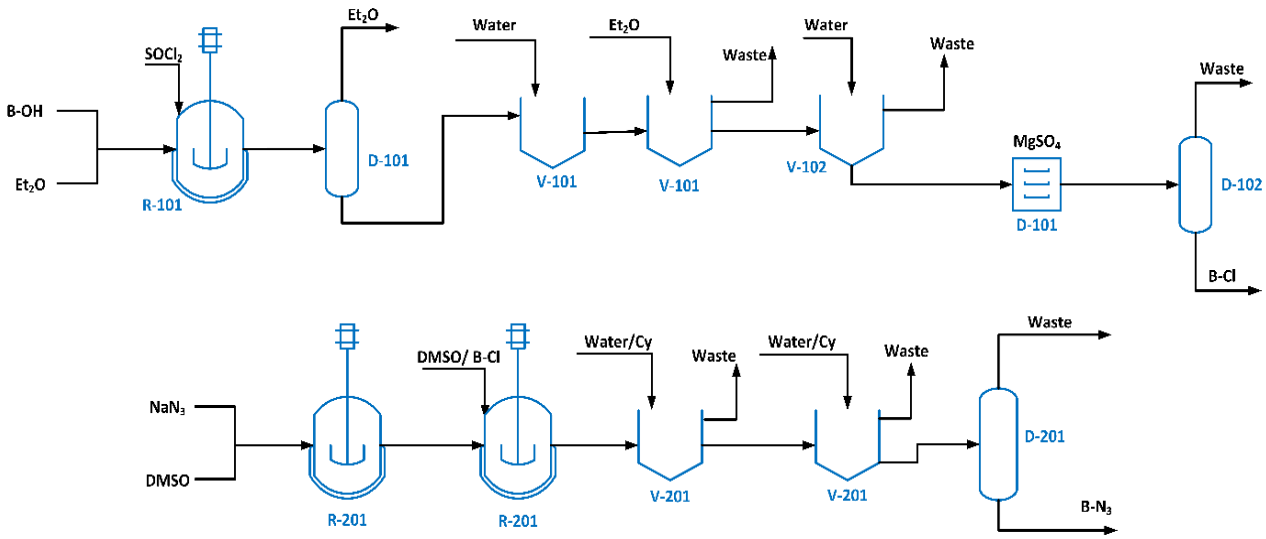



**Figure 5.2.** Process diagram of State–of–the–art process

***Benchmark process 2: Solvent–less process***

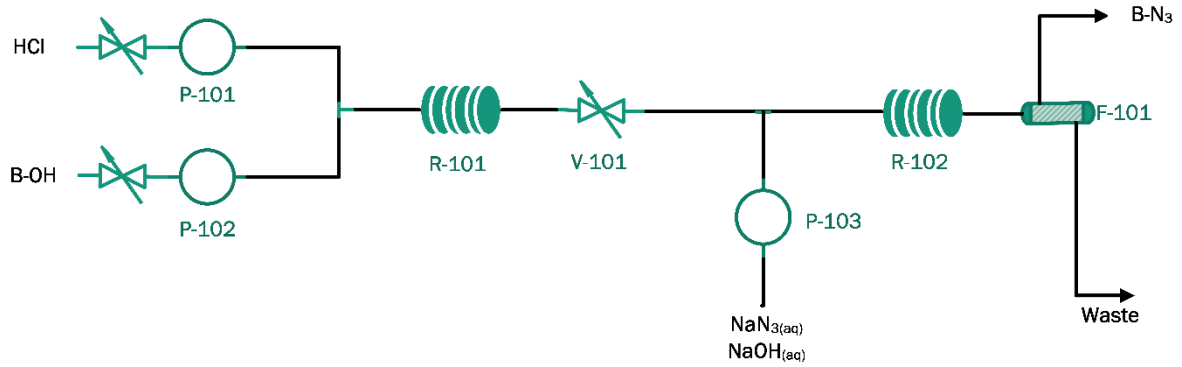



**Figure 5.3.** Process diagram of the Solvent–less process

The data for this scenario was obtained from literature[20]. The process is part of a multi–step synthesis[22], which is conducted without interruption in micro–flow. The first step consists of the hydrochlorination of the benzyl alcohol to benzyl chloride with hydrogen chloride (HCl) at 120°C and 12 bar. The second step is the synthesis of the azide from the organohalide with a solution of sodium azide ($NaN_{3(aq)}$) at 140°C. A solution of sodium hydroxide ($NaOH_{(aq)}$) is added together to force the equilibrium to the reactant side and to prevent the formation of the highly toxic and explosive hydrazonic acid. The product is filtrated in a Teflon®

membrane, which allows to remove the organic phase and retrieves the product as permeate (see Fig. 5.3, a description of the simulation can be found in Annex C).

***Functional Solvent Factory***

A functional solvent factory system for this reaction has not been developed. The two scenarios that will be used here have been constructed and developed based on literature data, in chapter 4 details of the simulation and conceptualization can be found. Real–life data was selected to obtain insights into the possibilities and problems that can be faced in an early–stage development process. The same chemical route was followed for all the process options considered to obtain the environmental impact for the same molecules and eliminate possible discrepancies.

In an ideal case for this multi–step process, the reactants are dissolved in the IL and the reaction is conducted preferably in one phase. Once the reaction is finished, a second phase is formed that allows the recovery of the product, and the remaining reactant can be easily recycled. Then this product would be mixed with the reactants for the second reaction, reacted in one phase, and after completion, a multiphase system will be obtained again. The product would be in one phase (or compartment), and the other compartments would be recycled or separated in case a purification is needed. As well, the product would be easily separated from the solvent under these circumstances. Yet, the scenarios evaluated, represent a non–ideal situation, giving the possibility to estimate some of the constraints that might be faced during experimental development.

As mentioned before, the first scenario, or one–step process, refers to the synthesis of benzyl azide directly from benzyl alcohol, i.e. in one–step. The second scenario, or two–step process, consists of the synthesis of benzyl in two steps.

### 5.2.4. Life Cycle Impact assessment (LCIA)

While the Life Cycle Assessment is a multi–step procedure for calculating the lifetime environmental impact of a specific, given product or service, LCIA uses such analysis to compare different products or services and/or optimize them. The focus is on the product and its development. This is particularly valuable when a product or service does not exist, at least in a mature format, as given for disruptive technologies. Rather a scenario analysis is made, comparing different chemical processes. LCIA is also particularly valuable in the sense that experimental investigations, for development or optimization, would cost much time and financial effort.

The mass and energy balances obtained from Aspen Plus (see Table 4.4 and 4.6) were processed with Umberto LCA+10.0.3 to obtain the corresponding environmental impacts. Background data was available in the Ecoinvent 3 database (v3.5). Due to the general perspective desired from the study (no geographical delimitation), the background data selected was [ROW] (i.e. rest of the world), and the effect of geographical consistency was underestimated. In the case that a component was not found in the database, a proxy was used. For the sodium azide and the ILs a retrosynthesis was conducted (routes followed are described in Annex C). This retrosynthesis considered only the stoichiometry of the reaction, and it was conducted following the guidelines described in literature[34]. The same guidelines were used to calculate the emissions to the atmosphere. For the case of the waste streams, the software allows changing the material into a material loss instead of waste. This option was selected since the treatment of those waste stream are out of the scope of the boundaries determined. Transportation, cleaning procedures and recyclability processes of the solvents for the state–of–the–art process were excluded from the assessment.

The impact categories selected from the ReCiPe Midpoint 2008 method[35] were: climate change potential (GWP), fossil depletion potential (FDP), human toxicity potential (HTPinf), ozone depletion potential (ODPinf), photochemical oxidant formation (POFP), and water depletion (WDP). Midpoint methods are selected based on recommendations[15].

## 5.3 RESULTS

In this section, the results of the assessment are presented. First, it is elaborated on the new technology, i.e. the "Functional Solvent Factory", and how the scenarios developed to give an insight into the possible advantages and shortcomings of this technology. Then, the Functional Solvent Factory is compared with the two different benchmark processes.

### 5.3.1 Functional Solvent Factory

Table 5.1 presents the LCIA results from the functional solvent factories presented. As can be observed from the table the one–step has a larger impact in all the categories compared to the two–step. It is important to analyze why the process simplification achieved in the one–step factory results in a larger impact. In Fig. 5.4 and Fig. 5.5 it is displayed the contribution of the components to the overall environmental impact of the one–step and two–step respectively.

**Table 5.1.** LCIA Results from the Functional Solvent Factory scenarios.

| Impact category | One–step | Two–step |
|---|---|---|
| Climate change (kg $CO_2$ to air) [GWP] | 15183 | 3655 |
| Fossil depletion (kg oil) [FDP] | 9181 | 1343 |
| Human toxicity (1,4–DCB to urban air) [HTP] | 5392 | 298 |
| Ozone depletion (kg CFC–11 to air) [ODP] | $6.5x10^{-03}$ | $4.8x10^{-04}$ |
| Photochemical oxidant formation (kg [NMVOC to urban air]) [POFP] | 85 | 8 |
| Water depletion ($m^3$ water) [WDP] | 87 | 18 |

In Fig. 5.4, it can be observed that the major cause of the impact in the Type 1 FSF (One–step) is associated with the materials used, particularly the IL. This is similar to processes that use common solvents, where approximately 80% of the impact is caused by the materials used[36]. The IL causes 84% to 96% of the impact in the categories considered, which share is similarly extensive to that of the common solvents in the pharmaceutical industry[36]. The rest is due to the utilities. That kind of dominant material fingerprint is seen for virtually all reactions in the chemical industry; yet, new in these cases is the relevance and dominance of the solvent, which is much higher. This is caused by the losses of IL during the purification stages, which impact was tried to minimize by implementing a small purge of 10%[37]. Increasing the recovery would minimize the impact. However, based on the high degree of dilution we can assume that the use of a concentrated system would have a larger positive impact, compared to focusing only on increasing the recovery. The high degree of dilution comes with many disadvantages, resulting in a large amount of IL needed.

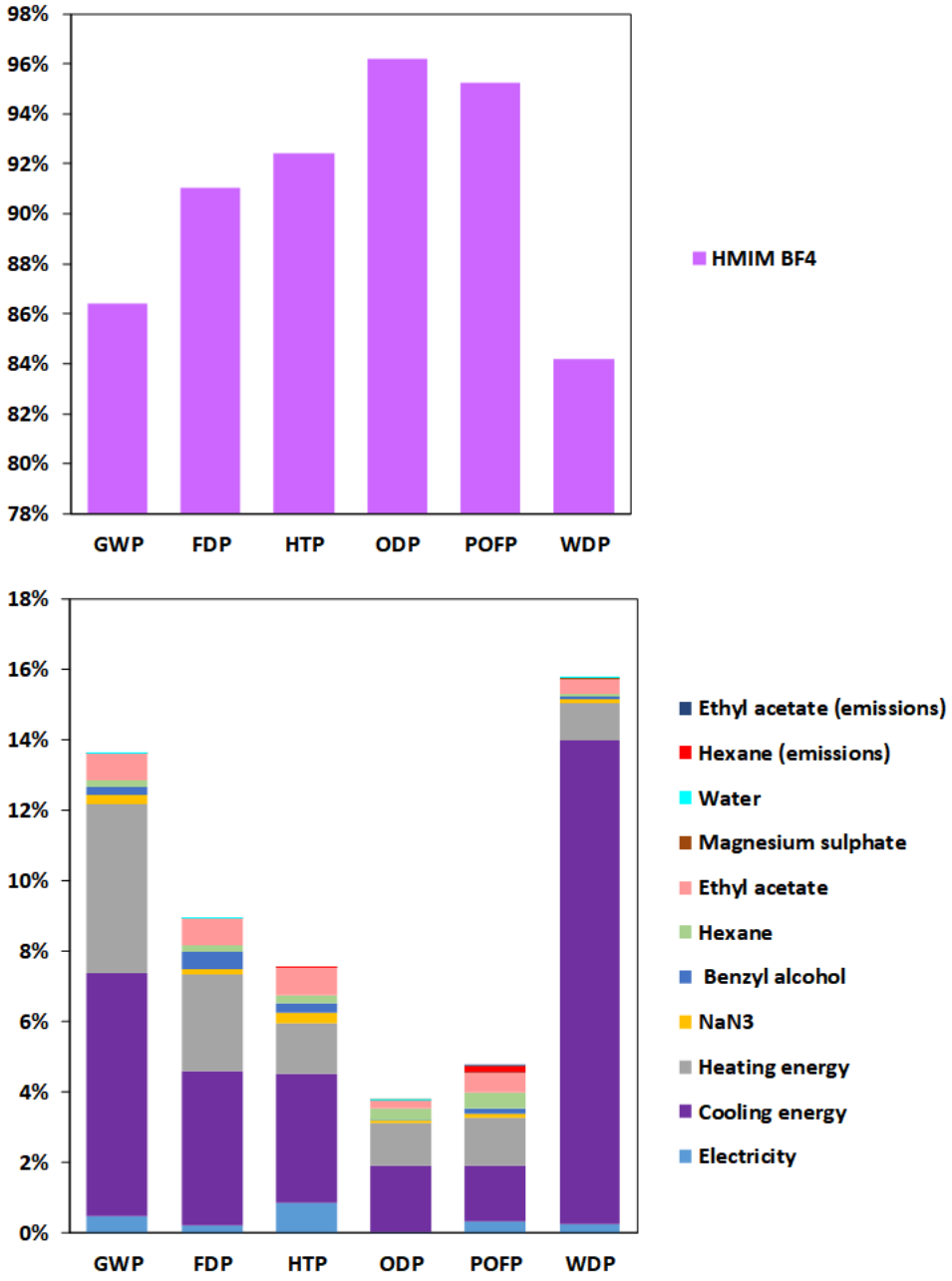



**Figure 5.4.** LCIA results for the One-Step (functional solvent factory) scenario. Top: presents the impact caused by the IL. Bottom: presents the impact caused by for the rest of the inputs.

Besides the reduction of the amount of IL, it is also necessary to eliminate the workup procedure. The concept behind the functional solvent factory system is to minimize or even eliminate the workup procedure, meaning to avoid the system complexity presented in the foreground data. This reaction is enabled by a Brønsted acidic IL, which works as a proton donor and solvent media[38]. This IL, Hmim $BF_4$, has been reported before as a recyclable catalyst and solvent achieving high yields[39]. The authors concluded in their results that the organic product obtained could be separated without the need for extra organic solvents.

Meaning an automatic separation in line with the solvent factory concept, that facilitates the recovery of the product and the IL. Yet this was not implemented in the original process. Thus, high recovery of this IL is needed due to its high cost[40].

The two-step process represents another scenario of the functional solvent factory. It is important to consider this due to the designer capacity of the ILs. This second scenario presents a more similar approach to what the ideal functional solvent factory is aiming for (see Fig. 5.5).

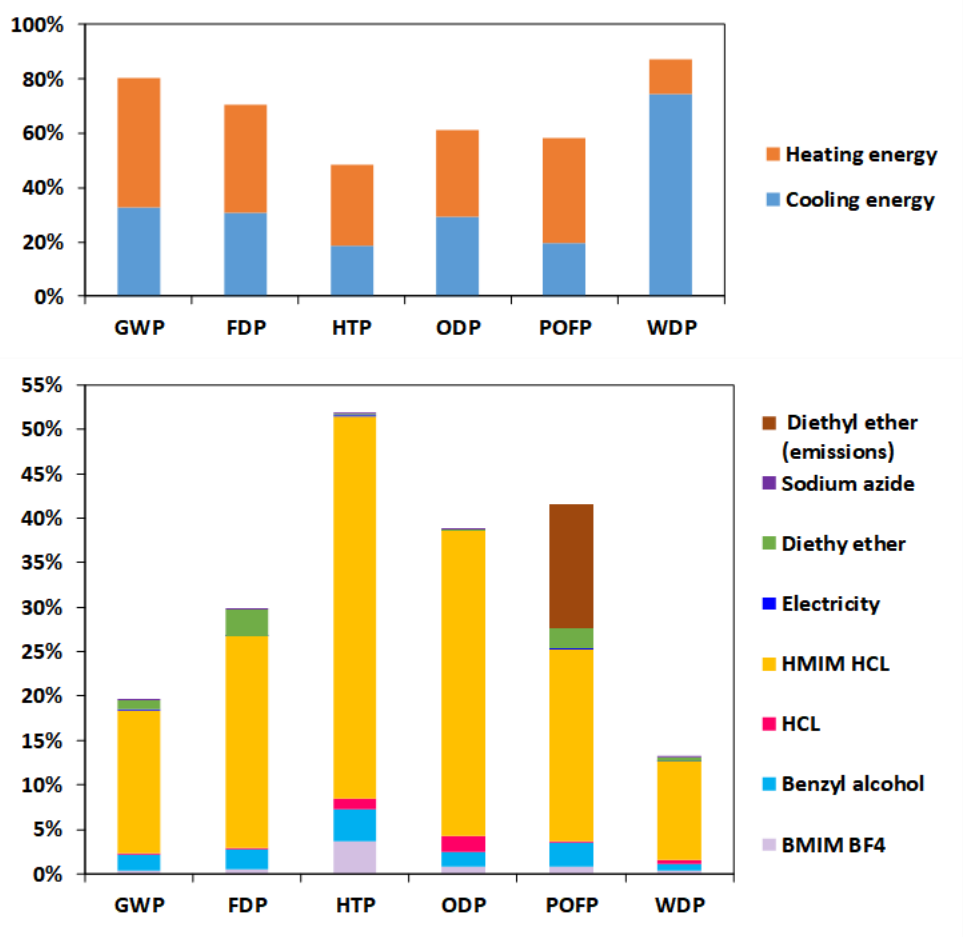



**Figure 5.5.** LCIA results for the Two-Step (functional solvent factory) scenario. Top: presents the impact caused by the materials. Bottom: presents the impact caused by the consumed utilities.

The profile of the second functional solvent factory's scenario is largely different from the first scenario proposed. Here it is observed how the impact of both ILs is minimized by using a lower amount of ILs. In the case of the Bmim $BF_4$, the impact is even comparable to that of the reactant, benzyl alcohol. The overall IL impact is also smaller than in the one-step, even though two ILs (Hmim Cl and Bmim $BF_4$) are employed. Around 40–80% of the impact in every

category is caused by the utilities. The reaction is conducted at high T, and compared with traditional organic solvents, the heat capacities of ILs are generally higher[41], which increases the demand for the utilities. Also, a great part of the utilities is consumed in the separation train. This also holds true for the one–step process. In the two–step scenario, the excess solvent is used to extract the product, and then it is removed by distillation, an operation that consumes high amounts of energy.

It is also evident the high human toxicity potential of the ILs. This is in agreement with what it is commonly found for ILs[42].

The scenarios were developed to serve as a guide to what could be the environmental challenges of the functional solvent factory. These scenarios present opposite poles with advantages and disadvantages. In both scenarios imidazolium ILs were used due to their Brønsted acid properties. However, the use of imidazolium ILs comes with additional challenges added to the life cycle impact. Firstly, in literature, it has been observed that imidazolium ILs can degrade upon heating. The processes, particularly the one–step separation train, were modeled considering temperatures below 150°C. These conditions need to be tested experimentally to guarantee a safe operation. Microflow intensification can be used in these cases, to allow concentrated solutions and improve the heating transfer[43]. Imidazolium ILs are also toxic and non–biodegradable[44]. Under certain conditions hydrolysis may occur and the ion $BF_4$ could react[42], releasing HF[42]. Therefore, the selection of the IL is of high importance, as each IL has different impacts.

The synthesis of ILs is complex and requires many steps and materials, which shifts the impact to earlier stages of the life cycle[45]. The synthetic routes are very important, e.g. quaternization has higher atom efficiency than metathesis. Moreover, the energy consumption during their preparation is also considerable[46]. The impact of ILs could be ameliorated in the future, as nowadays ILs are mostly produced on a lab–scale, production which is tailored towards quality. An improvement in the production, i.e. an overall optimization, and economy of scale could minimize the impact of the IL[6]. The lack of industrial production data has been identified as one of the major challenges for LCA studies on ILs[47]. Different methods have been proposed to address the emergent technology nature of ILs[48]. Among these methods a complex sensitivity analysis is highly recommended[47].

Compared to other systems where automatic separation with ionic liquids is achieved, similarities are observed. High conversion, high yields, and enabled reaction–separation are known factors[49]. However, most of them show limited recyclability (e.g. 5 times)[50]. The large impact of ILs in both scenarios proposed here highlights the need for continuous and long–

term recyclability of ILs, which is in agreement with other IL–based processes[51]. Without the guarantee of long–term use, archiving sustainable processing with low environmental impacts remains a challenge.

Other aspects of the ILs were not addressed here, and those must be considered for the correct management of the IL. The recyclability of the IL is sometimes limited to the concentration of contaminants in it. These aspects need to be addressed to ensure that the IL can be recycled, and for how many times. Here it is expected that the IL can be recycled up to 10 times, but if the IL is too sensitive to the presence of contaminants in the system (e.g. water can cause hydrolysis), the recyclability can be greatly affected. Recovery and purification are key. In literature, many options for recovery and purification have been researched[52] as this is considered one of the highest obstacles for large–scale implementation[53]. The optimal and most effective option or combination of processes needs to be assessed in future research.

Other aspects such as the degree of degradation, absorption on soil in case of spillage or accidents need to be investigated[47]. In that sense, it is possible to try ILs with groups that present fewer threats to the environment, such as morpholium, or pyridinium, and avoid the use of fluoride–containing anions[54].

### 5.3.2 Benchmark of the Functional Solvent Factory– Case Benzyl azide

As mentioned in section 5.2, comparability needs to be addressed for emerging technologies. The results of these comparisons are given in Fig. 5.6. The solvent–less process has the lowest impact of the four processes. This is due to the lack of solvents in the reaction, and the simple separation train, being only a Teflon membrane in a membrane module[20]. The first lesson learned from this comparison is that a concentrated system, such as in the solvent–less process, could minimize the complexity of the separation train.

Highly concentrated systems have been reported for ILs, yet being limited mostly to biomolecules such as cellulose, carbohydrates[55], and proteins[56]. To the knowledge of the author, high–c (high concentration), as proposed to explore novel process windows in micro–flow[9], has hardly been advocated for the ionic liquid processing, and awaits to be demonstrated.

Compared with the state–of–the–art process, the Solvent Factory scenarios have still a large environmental impact, around 4–7–fold higher than the standard (batch–technology). In these cases, it is observed how the separation train influences the impacts, as the demand for

energy and materials increases, and the benefits of the ILs are overpowered by the separation train.

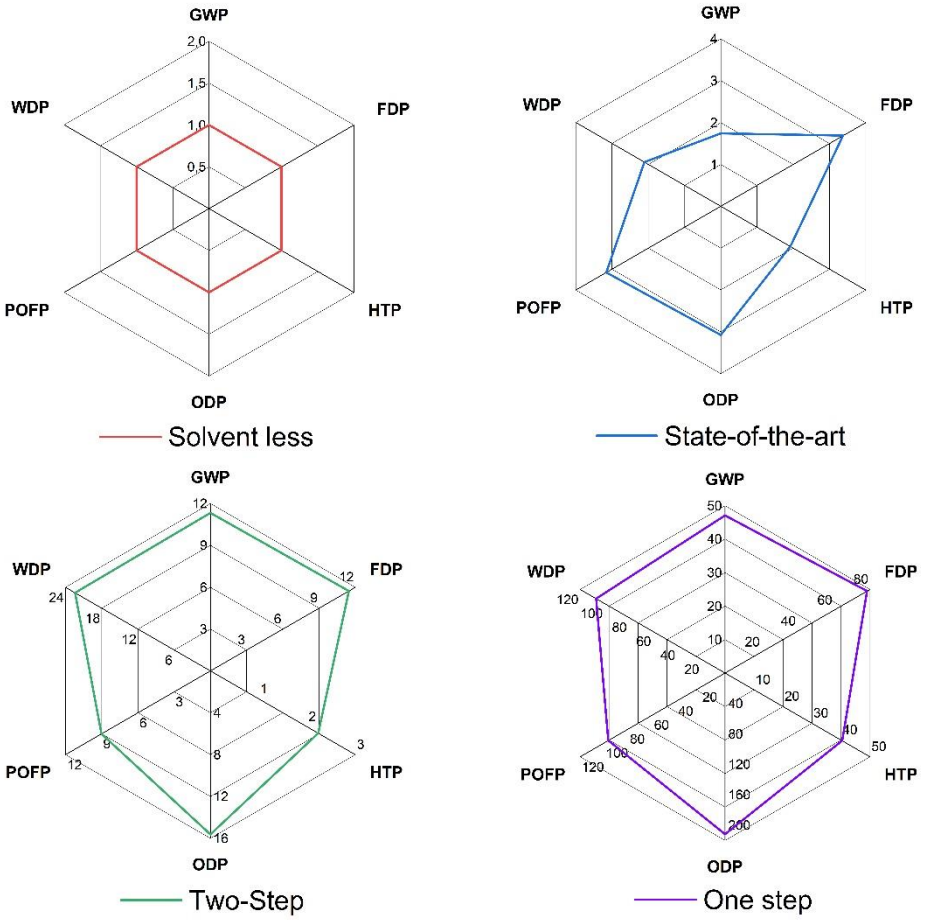



**Figure 5.6.** Environmental impact of the functional solvent factories compared with the state–of–the–art and solvent–less process technology. The results are normalized to the impact of the solvent less process

In Fig. 5.6 it is shown that the one–step process, although it simplifies the reaction, it is the worst alternative. Consequently, it was decided to assess how these scenarios would be impacted if they were optimized with an automated separation in line with the functional solvent factory concept. This concept, as per its definition given at the beginning before, would not require extra separation stages or equipment. Ideal case scenarios were considered assuming no separation train, where only the reaction was considered. Based on the solubility of organic compounds in these ILs from literature[39], automated separation could possibly be attained. For each case, it was created an "ideal scenario". The results of this final case are presented in Fig. 5.7, where the original scenario is compared to its ideal version respectively to observe the impact of eliminating the separation train. Moreover, it is possible to compare where this improvement sits with respect to the state–of–the–art benchmark case.

Under more "ideal conditions" the improvement of the one–step process is only 10% below respect to the original. It is a scenario where lowering the amount of IL would benefit more than achieving an automatic separation, which is clearly observed in the minimal improvements obtained. Without the separation train, the ideal two–step process presents great improvements in terms of the environmental impact. In this case, the impacts are minimized from 40 to 80% with respect to the original two–step process, depending on the category. These notorious improvements led to the comparison with the batch case (bottom plot). It is observed that the impact is 1 to 2–fold larger in all categories, except for the human toxicity potential, where the impact was lower than the benchmark case.

These ideal scenarios overlooked some challenges, such as the separation of the byproduct sodium chloride. Yet it can be observed that under the appropriate conditions (such as a simple separation train) and the fine tuning of the system (such as eliminating the disruption factors e.g. IL degradation) the functional solvent factory could provide a potential environmental solution to the need of achieving a more sustainable production the pharmaceutical industry.

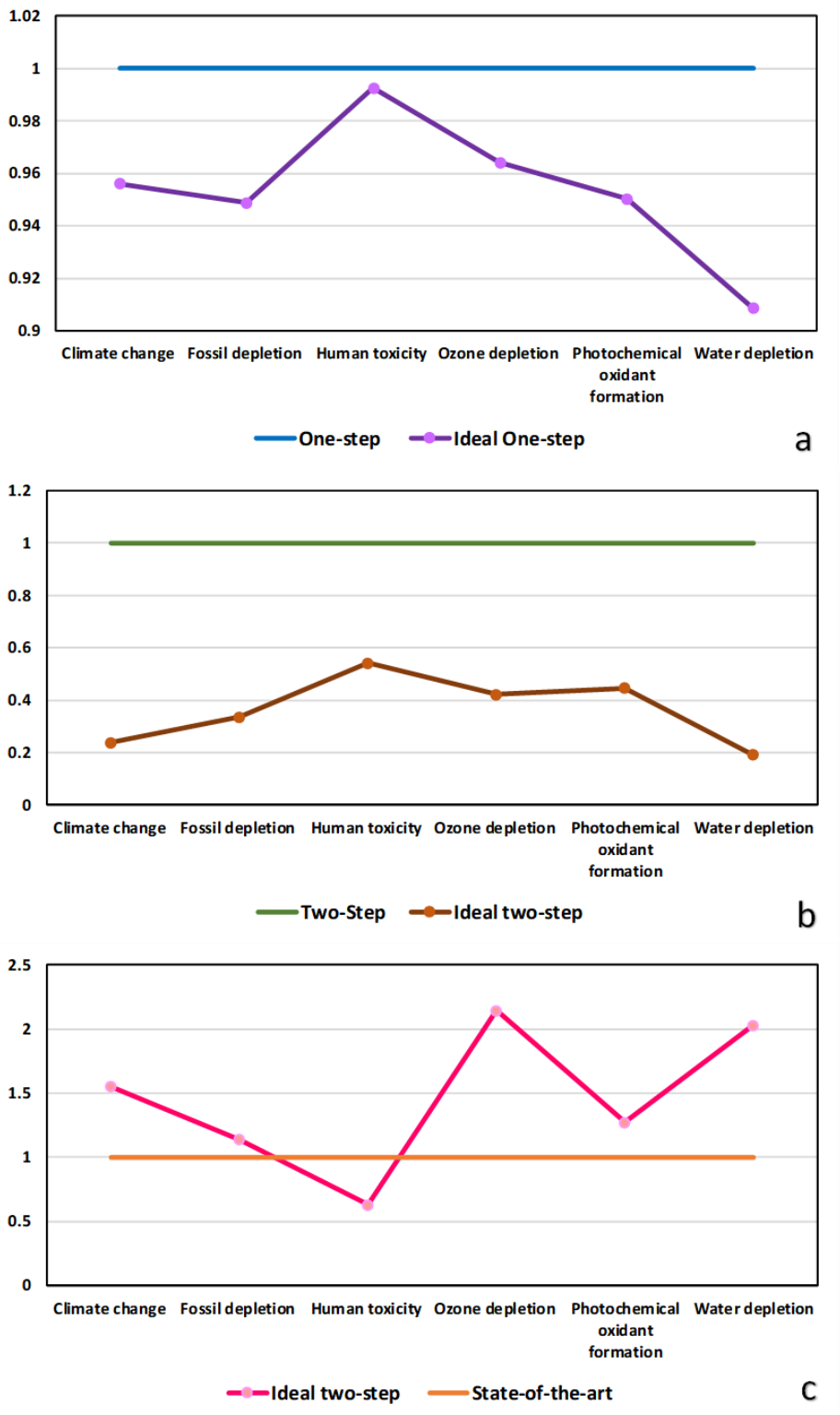



**Figure 5.7.** Change in the environmental impact of the functional solvent factory scenarios under the "ideal conditions", i.e. without separation train (automated product purification). Top(a): one–step versus the ideal one–step, the result has been normalized with respect to the corresponding original scenario. Centre (b): two–step versus the ideal two–step, the result has been normalized with respect to the corresponding original scenario. Bottom (c): ideal two–step versus the state–of–the–art, the result has been normalized with respect to the state–of–the–art scenario.

## 5.4 CONCLUSIONS

This chapter tries to make the balancing act between innovation and real–life commercialization potential of automated separation via IL from an environmental perspective. The scenarios developed give insights into the development of disruptive process technologies from the generic process concept of the "functional solvent factory", which utilizes ionic liquids (ILs) as integrated reactor–separators. ILs are unique solvents in many aspects (e.g. can intensify chemical processes), but their environmental impacts are worse than that of conventional solvents. This is mainly because they are not produced on an industrial scale and robust industrial recycling technologies are not hand. However, if they bring higher benefits to the process, then their implementation in the process must also be assessed for a better comparison. Here an LCA was conducted to evaluate the potential of separation via ILs and identify the hotspots for later improvement. Few LCAs are reported where ILs are implemented in pharmaceutical processes[51]. Thus, this chapter brings a contribution to the limited literature present in the area; especially on the use of ILs for automated purification with its own constraints.

The results obtained in both scenarios agree on the expected large impacts that the ILs have, where the amount of IL and the conditions play a very important role in the environmental impact. Yet, the main value is that smart, but influential differences are shown among the scenarios investigated and that learnings for the use of ILs and beyond (whole process) are drawn. In the latter sense, key parameters for further research and experimenting were obtained. The first key parameter for their sustainable implementation is the use of ILs in low amounts. The large amount of IL in the one–step process caused over 80% of the impacts. Even when the separation train was eliminated, the impacts only decreased by 10%. Secondly, recyclability is the key to their implementation. It is necessary to ensure that more than 90% of the IL can be recovered. As observed, the recyclability in the second scenario was close to 90% and the impacts obtained were higher than the benchmark cases. To ensure high recyclability rates it is also needed to avoid the degradation and contamination of the IL, which can become the road blocker to apply this technology in certain cases. Moreover, it is considered that conducting the reaction in an intensified micro–flow system, would deliver a higher yield and boosted reaction speed[43].

The study overlooked aspects that these scenarios did not allow to evaluate and could have a positive impact. The reaction here proceeds without a catalyst. Catalyst and unreacted compounds' recyclability can boost the environmental benefits. Attending this with ILs can shift the balance of the impact when a rare catalyst or certain reactants are used. In this

reaction, it was not possible to identify a solvent or process condition that allowed the recovery of the reactants as it was decided to start from the simplest case to obtain the first guidance for the design. Comparison with cases where a more integral separation, including the separation of byproducts and the recyclability of the catalyst, can help to answer the question of when the use of automated separation with ILs has ecological advantages. As it is considered that this is not an environmental plausible solution in all cases, which is very well exemplified in the first scenario (one–step synthesis).

The future of the functional solvent factory might depend on high–concentration processing. As an alternative, the mixing of ionic liquids at a low share with water creates an entirely new solvent class, the powerful catanionic hydrotropes, where both the cation and the anion synergistically contribute to increasing the solubility of biomolecules in water[57]. Mixtures of organic solvents and ionic liquids hardly have been utilized for chemical processing, but rather only investigated for their new physic–chemical properties[58].

Industrial cases show that it is possible to use ionic liquids at a large–scale production[59]. The lessons learned there are also key for the development of the function solvent factory and conduct multiple cascade reactions after each other, like in the two–step scenario. This two–step scenario showed that under optimization, the solvent factory can aid to solve some environmental problems.

Despite the different applications of ILs, the results obtained are alike results reported. The IL has a very large environmental impact in the process and strong optimizations are needed.

Finally, it is needed to complement this study with an uncertainty assessment, to increase the reliability and credibility of the LCA results for ex–ante technologies.

## REFERENCES


1 C. Jiménez-González, P. Poechlauer, Q. B. Broxterman, B. S. Yang, D. Am Ende, J. Baird, C. Bertsch, R. E. Hannah, P. Dell'Orco, H. Noorman, S. Yee, R. Reintjens, A. Wells, V. Massonneau and J. Manley, *Org. Process Res. Dev.*, 2011, **15**, 900–911.

2 C. Jimenez-Gonzalez, C. S. Ponder, Q. B. Broxterman and J. B. Manley, *Org. Process Res. Dev.*, 2011, **15**, 912–917.

3 C. Jimenez-Gonzalez, C. S. Ponder, Q. B. Broxterman and J. B. Manley, *Org. Process Res. Dev.*, 2011, **15**, 912–917.

4 P. L. Amado Alviz and A. J. Alvarez, *J. Clean. Prod.*, 2017, **168**, 1614–1624.

5 C. Jimenez-Gonzalez, *Curr. Opin. Green Sustain. Chem.*, 2019, **18**, 66–71.

6 J. H. Clark and S. J. Tavener, *Org. Process Res. Dev.*, 2007, **11**, 149–155.

7 M. Lancaster, in *Green Chemistry: An Introductory Text*, RSC Paperbacks, 2002, pp. 130–165.

8 K. Tanaka and F. Toda, *Chem. Rev.*, 2000, **100**, 1025–1074.

9 V. Hessel, D. Kralisch, N. Kockmann, T. Noël and Q. Wang, *Chem. Sustain. Energy Mater.*, 2013, **6**, 746–789.

10 C. Capello, U. Fischer and K. Hungerbühler, *Green Chem.*, 2007, **9**, 927.

11 U. Novak and P. Žnidaršič-Plazl, *Green Process. Synth.*, **2**, 561–568.

12 E. Ayan, N. Baylan and S. Çehreli, *Chem. Eng. Res. Des.*, 2020, **153**, 666–676.

13 O. M. Morales-Gonzalez, C. Zhang, S. Li and V. Hessel, *Chem. Eng. Sci. X*, , DOI:10.1016/j.cesx.2019.100024.

14 I. Vural Gürsel, S. K. Kurt, J. Aalders, Q. Wang, T. Noël, K. D. P. Nigam, N. Kockmann and V. Hessel, *Chem. Eng. J.*, 2016, **283**, 855–868.

15 S. M. Moni, R. Mahmud, K. High and M. Carbajales-Dale, *J. Ind. Ecol.*, 2019, 1–12.

16 D. Kralisch, D. Reinhardt and G. Kreisel, *Green Chem.*, 2007, **9**, 1308–1318.

17 D. Kralisch, A. Stark, S. Körsten, G. Kreisel and B. Ondruschka, *Green Chem.*, 2005, **7**, 301–309.

18 S. Kressirer, D. Kralisch, A. Stark, U. Krtschil and V. Hessel, *Environ. Sci. Technol.*, 2013, **47**, 5362–5371.

19 Q. Deng, N. N. Tran, M. Razi Asrami, L. Schober, H. Gröger and V. Hessel, *Ind. Eng. Chem. Res.*, 2020, **59**, 21001–21011.

20 S. Borukhova, T. Noël, B. Metten, E. de Vos and V. Hessel, *Green Chem.*, 2016, **18**, 4947–4953.

21 D. Ott, D. Kralisch, I. Denčić, V. Hessel, Y. Laribi, P. D. Perrichon, C. Berguerand, L. Kiwi-Minsker and P. Loeb, *ChemSusChem*, 2014, **7**, 3521–3533.

22 M. Escribà-Gelonch, G. A. de Leon Izeppi, D. Kirschneck and V. Hessel, *ACS Sustain. Chem. Eng.*, 2019, **7**, 17237–17251.

23 S. Cucurachi, C. van der Giesen and J. Guinée, *Procedia CIRP*, 2018, **69**, 463–468.

24 M. Villares, A. Işıldar, C. van der Giesen and J. Guinée, *Int. J. Life Cycle Assess.*, 2017, **22**, 1618–1633.

25 M. J. Raymond, C. S. Slater and M. J. Savelski, *Green Chem.*, 2010, **12**, 1826.

26 S. Righi, F. Baioli, A. Dal Pozzo and A. Tugnoli, *Energies*, , DOI:10.3390/en11040970.

27 S. Gavankar, S. Suh and A. A. Keller, *J. Ind. Ecol.*, 2015, **19**, 51–60.

28 N. Thonemann, A. Schulte and D. Maga, *Sustainability*, 2020, **12**, 1192.

29 I. Erdelmeier, *Sustain. Chem. Pharm.*, 2018, **10**, 79–83.

30 R. Heijungs, *Int. J. Life Cycle Assess.*, 2020, **25**, 1872–1882.

31 M. Pizzol, R. Sacchi, S. Köhler and A. Anderson Erjavec, *Front. Sustain.*, 2021, **1**, 1–16.

32 J. Wang, Z. Xie, L. Cui and Z. Quan, *J. Med. Sci. Yanbian Univ.*, 2004, 264–266.

33 2013.

34 R. Hischier, S. Hellweg, C. Capello and A. Primas, *Int. J. Life Cycle Assess.*, 2005, **10**, 59–67.

35 M. Goedkoop, R. Heijungs, M. Huijbregts, A. De Schryver, J. Struijs and R. Van Zelm, *ReCiPe 2008*, 2009.

36 W. De Soete, S. Debaveye, S. De Meester, G. Van Der Vorst, W. Aelterman, B. Heirman,

P. Cappuyns and J. Dewulf, *Environ. Sci. Technol.*, 2014, **48**, 12247–12255.

37 D. Ott, S. Borukhova and V. Hessel, *Green Chem.*, 2016, **18**, 1096–1116.

38 B. Garg and Y. C. Ling, *J. Chinese Chem. Soc.*, 2014, **61**, 737–742.

39 H. P. Zhu, F. Yang, J. Tang and M. Y. He, *Green Chem.*, 2003, **5**, 38–39.

40 H. Passos, M. G. Freire and J. A. P. Coutinho, *Green Chem.*, 2014, **16**, 4786–4815.

41 J. O. Valderrama, P. A. Robles and L. Serena, 2007, 1338–1344.

42 M. Cvjetko Bubalo, K. Radošević, I. Radojčić Redovniković, J. Halambek and V. Gaurina Srček, *Ecotoxicol. Environ. Saf.*, 2014, **99**, 1–12.

43 M. Escribà-Gelonch, T. Noël and V. Hessel, *Org. Process Res. Dev.*, 2018, 147–155.

44 S. K. Shukla, S. Pandey and S. Pandey, *J. Chromatogr. A*, 2018, **1559**, 44–61.

45 Y. Zhang, B. R. Bakshi and E. S. Demessie, *Environ. Sci. Technol.*, 2008, **42**, 1724–1730.

46 S. P. F. Costa, A. M. O. Azevedo, P. C. A. G. Pinto and M. L. M. F. S. Saraiva, *ChemSusChem*, 2017, **10**, 2321–2347.

47 V. G. Maciel, D. J. Wales, M. Seferin, C. M. L. Ugaya and V. Sans, *J. Clean. Prod.*, 2019, **217**, 844–858.

48 D. Kralisch, D. Ott and D. Gericke, *Green Chem.*, 2015, **17**, 123–145.

49 R. Villa, E. Alvarez, R. Porcar, E. Garcia-Verdugo, S. V. Luis and P. Lozano, *Green Chem.*, 2019, **21**, 6527–6544.

50 V. Gauchot, W. Kroutil and A. R. Schmitzer, *Chem. – A Eur. J.*, 2010, **16**, 6748–6751.

51 P. L. Amado Alviz and A. J. Alvarez, *J. Clean. Prod.*, , DOI:10.1016/j.jclepro.2017.02.107.

52 J. Zhou, H. Sui, Z. Jia, Z. Yang, L. He and X. Li, *RSC Adv.*, 2018, **8**, 32832–32864.

53 J. Bian and Q. Yang, *Advances in Synthesis and Purification Methods of Ionic Liquids*, Elsevier B.V., 2018, vol. 32.

54 N. L. Mai, K. Ahn and Y. M. Koo, *Process Biochem.*, 2014, **49**, 872–881.

55 L. Qingbin, M. H. A. Janssen, F. van Rantwijk and R. A. Sheldon, *R. Soc. Chem.*, 2005, **7**, 39–42.

56 N. Byrne, L. M. Wang, J. P. Belieres and C. A. Angell, *Chem. Commun.*, 2007, 2714–2716.

57 A. F. M. Cláudio, M. C. Neves, K. Shimizu, J. N. Canongia Lopes, M. G. Freire and J. A. P. Coutinho, *Green Chem.*, 2015, **17**, 3948–3963.

58 M. A. Iglesias-Otero, J. Troncoso, E. Carballo and L. Romaní, *J. Chem. Thermodyn.*, 2008, **40**, 949–956.

59 A. J. Greer, J. Jacquemin and C. Hardacre, *Industrial Applications of Ionic Liquids*, 2020, vol. 25.

60 I. Aspen Technology, *Aspen Technol. Inc.*, 2000, 936.

61 SciFinder®, scifinder.cas.org.

62 H. H. Jobelius and H.-D. Scharff, *Ullmann's Encycl. Ind. Chem.*, 2000.

## Appendix C

### State–of–the–art Process

The batch process is the result of the combination of two patents. The first patent (a)[32] was used to model the first step of the reaction (from benzyl alcohol to benzyl chloride). The second patent (b)[33] was used to model the second step of the reaction (from benzyl chloride to benzyl azide). The combination of these patents is shown in the schema present in Fig. s5.1.

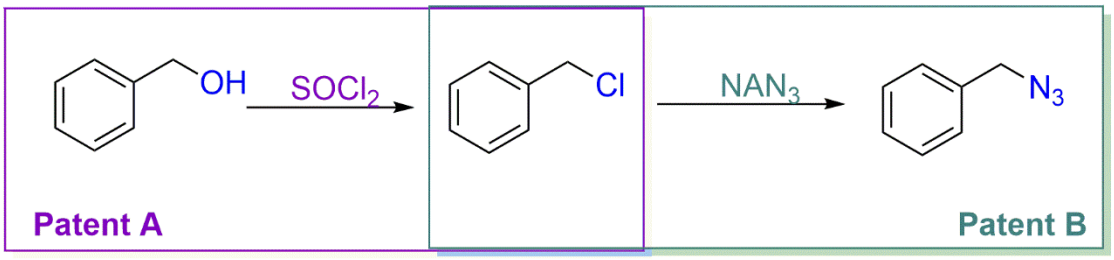



Fig s5.1 State–of–the–art reaction schema.

***Process description of state–of–the–art patents***

In a flask 7.1 g of benzyl alcohol are mixed with 12 mL of diethyl ether at 0ºC. In the same vessel 18 mL of thionyl chloride are added slowly. The reaction is conducted for 7 h while stirring. The mixture is transferred to remove the diethyl ether by evaporation. Then the mixture is washed with 30 mL of water followed by 30 mL of diethyl ether. Then the organic fraction is washed again with 30 mL of water again and recovered. The organic phase is extracted and washed with water. After that, the organic phase is dried over magnesium sulfate, and the excess solvent is removed by evaporation to obtain benzyl chloride.

Then 1.23 mmol of benzyl chloride is dissolved in 0.5 mL of dimethyl sulfoxide and added slowly to a solution of 1.23 mmol of sodium azide ($NaN_3$) in 2 mL dimethyl sulfoxide. The mixture is left stirring at room temperature for 4 h. The crude is washed with equal volumes of water and cyclohexane (1.6 mL). Finally, the organic phase is recovered, and the solvent is vacuum distilled to obtain benzyl azide.

***Process simulation***

Below is elaborated the implementation in the simulator Aspen Batch Developer V9. Aspen Batch Developer V9 was selected instead of Aspen Plus V9 due to the batch nature of the process. Besides the software is provided with a "Scale Up" feature, in which data from a

laboratory–scale process can be used to develop a pilot–scale plant. This feature is relevant since the patents describe a process on the g scale and the functional unit is on the kg scale.

The following assumptions were taken: 100% conversion in both reactions, based on the lack of data. Room temperature was established at 20 ºC.

All the components were present in Aspen's database, except for Benzyl azide which was inserted using the Pure Component Editor.

The reaction is conducted in a batch reactor. Once it is finished, the distillation occurs in the same unit. The conditions of the distillation were determined in a flash column in Aspen Plus V9. A flash column was used to represent a single stage distillation column. The conditions are 0.03 bar and 20 °C to obtain a composition at the bottom of 20.5% (w/w) thionyl chloride, 8.5% (w/w) diethyl ether and 1% (w/w) benzyl chloride. Then the mixture is moved to a decanter where the extraction of the product is conducted. The conditions of the extraction were determined in Aspen Plus V9 using a decanter, to simulate an extraction in one stage. The patent describes two extractions, and the process was modelled accordingly. The temperature and pressure in both extractions were 15 °C and 1 bar. The amount of water was constant in both extractions, only the amount of diethyl ether was varied. The final composition of the organic fraction after the extraction was 3% water, 1% thionyl chloride, 54% diethyl ether, and 42% benzyl chloride. Then the organic fraction was dried with magnesium sulfate and filtered using the filter–dry operation editor. Finally, the excess solvent was distilled using a batch unit. This distillation was modeled again in a flash column in Aspen Plus V9. The distillation is conducted at 24 °C and 0.03 bar.

The benzyl chloride obtained was charged into a batch reactor where the second reaction was conducted. Sodium azide and dimethyl sulfoxide were added, and the reaction was conducted at room temperature for 4 h. After the reaction was completed, a mixture of cyclohexane and water (1:1 w/w) was added to extract the product. Partition coefficients of the components in water were used to model the extraction. Finally, the excess solvent was removed by distillation at 113 °C and 0.1 bar. The conditions were determined as before using a flash column in Aspen Plus V9.

Final mass and energy balance are presented in Table s5.1.

**Table s5.1** Mass and Energy Balance of batch process for the syntheis of benzyl azide.

| Component | Input[1] | Output[1] |
|---|---|---|
| Cooling (MJ) | 7.05 | |
| Heating (MJ) | 40 | |
| Benzyl alcohol (kg) | 12 | |
| Diethyl ether (kg) | 30 | |
| Thionyl chloride | 50 | |
| HCl (emissions, kg) | | 4 |
| Sulfur dioxide (emissions, kg) | | 7 |
| Diethyl ether (emissions, kg) | | $3 \times 10^{-02}$ |
| Diethyl ether (waste, kg) | | 30 |
| Thionyl chloride (emissions, kg) | | 14 |
| Thionyl chloride (waste, kg) | | 36 |
| Water (kg) | 179 | |
| Wastewater (kg) | | 178 |
| Benzyl chloride (kg) | | 2 |
| Magnesium sulphate (kg) | 1 | |
| Magnesium sulphate heptahydrate (kg) | | 2 |
| Sodium azide (kg) | 5 | $1 \times 10^{-02}$ |
| DMSO (kg) | 133 | 133 |
| Sodium Chloride (kg) | | 4 |
| Cyclohexane (kg) | 60 | |
| Cyclohexane (emissions, kg) | | 0.1 |
| Cyclohexane (waste, kg) | | 60 |
| Benzyl azide (kg) | | 10 |
| Benzyl azide (waste, kg) | | 0.2 |

[1]Amounts are rounded up.

## Solvent free Process

The process was modelled according to the results obtained by Borukhova et al. (2016). The pathway followed is presented in Fig. s5.2, the same as in the state–of–the–art (i.e. from benzyl alcohol to benzyl chloride and finally benzyl azide).

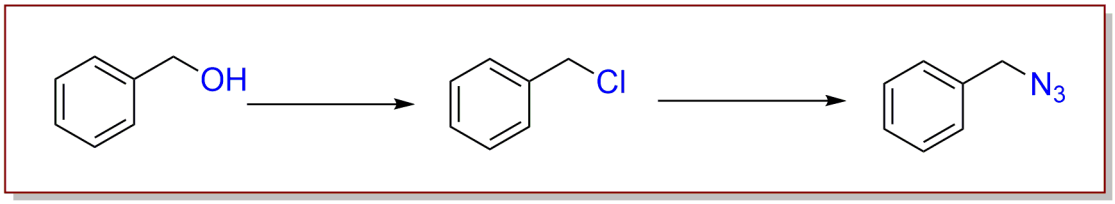



**Fig. s5.2** Reaction schema for solvent–less process.

The following assumptions were taken to model the process: room temperature was set to 20ºC and steady state.

This process was developed in continuous setup, therefore Aspen Plus V9 was selected to model the process. The UNIFAC (UNIversal Functional Activity Coefficient) method was employed based on its capacity to predict activity coefficients, calculate group contributions and estimate missing parameters[60]. This method as well as all the components used were already present in the libraries from Aspen Plus V9.

The process starts by mixing all the components with a stream mixer, then they are input into the reactor. An RStoic reactor was used due to the unknown kinetics. The stoichiometry, conversion, and reaction conditions (110 °C, 7 bar) were specified. The outlet stream of the reactor was mixed with a solution of sodium hydroxide and sodium azide in water. Then the last reaction was conducted in two steps. The first step was the neutralization followed by the formation of the azide. The addition of the sodium hydroxide hinders sodium azide's solvation and therefore the production of hydrazonic acid ($HN_3$). This step occurs faster than the synthesis of the azide, and therefore was conducted first. The reactions were conducted at 160 °C, 7 bar. Like the chlorination step, an RStoic reactor was used due to the lack of kinetic data. After the reaction, the product is removed using a membrane, which was modeled using the separator component.

Table s5.2 presents the final mass and energy balance.

**Table s5.2** Data inventory for the of Solvent–less process.

| Component | Input[1] | Output[1] |
|---|---|---|
| Electricity (kW) | 11 | |
| Cooling (MJ) | 5.3 | |
| Heating (MJ) | 3 | |
| Benzyl alcohol (kg) | 9 | |
| Benzyl chloride (waste, kg) | | 0.5 |
| Benzyl azide (kg) | | 10 |
| Sodium azide (kg) | 9 | |
| Sodium azide (waste) | | 3 |
| Sodium Hydroxide (kg) | 1 | |
| Sodium Hydroxide (waste, kg) | | 5 |
| HCl (kg) | 3 | |
| HCl waste (kg) | | 0.5 |
| Water (kg) | 23 | |
| Wastewater (kg) | | 24 |
| Sodium chloride (kg) | | 1 |

[1]Amounts are rounded up.

## Retrosynthesis[61]

| Compound | Route |
|---|---|
| Sodium Azide[62] | $N_2O + 2\ NaNH_2 \rightarrow NaN_3 + NaOH + NH_3$ |
| 1–methylimidazolium chloride | $C_4H_6N_2 + HCl \rightarrow C_4H_7ClN_2$ |
| 1–Methylimmidazole | (CHO)2 + CH2O + CH3NH2 + NH3 → H2C2N(NCH3)CH + 3 H2O |
| 1–Methylimidazolium tetrafluoroborate | $C_4H_7ClN_2 + NaBF_4 \rightarrow NaCl + C_4H_7BF_4N_2$ |
| 1–Butyl–3–methylimidazolium chloride | $C_4H_6N_2 + C_4H_9Cl \rightarrow C_8H_{15}N_2Cl$ |
| 1–Chlorobutane | $HCl + C_4H_9OH \rightarrow C_4H_9Cl + H2O$ |
| 1–Butyl–3–methylimidazolium tetrafluoroborate | $C_8H_{15}N_2Cl + NaBF_4 \rightarrow NaCl + C_8H_{15}BF_4N_2$ |

# CHAPTER 6. COMPARATIVE LIFE CYCLE ASSESSMENT OF THE USE OF AUTOMATED PURIFICATION WITH IONIC LIQUIDS IN THE CASE STUDY OF THE SYNTHESIS OF BENZYL AZIDE

To complement the study of chapter five, in this chapter a detailed comparative uncertainty assessment using the overlap area approach is implemented to assess the tradeoffs of the functional solvent factory pathways (Type 1 One-step and Type 2 Two-step) presented in chapter five. The emergent nature of the Functional Solvent Factory pathway comes with many uncertainties due to the unpredictable changes that the process can take from the lab to an industrial scale. Therefore, qualitative, and quantitative characterization of the uncertainties is needed. These results provide the key parameters for further development and the areas of environmental significance and help to bridge the technology readiness level (TRL) gap between laboratory and industry.

This chapter is based in the following papers:

Morales Gonzalez, O. M., Medrano, J. A., V. Hessel, F. Gallucci, Comparative uncertainty assessment of the use of automated purification with ionic liquids in the case study of the synthesis of benzyl azide. In Preparation

## 6.1 INTRODUCTION

The pharmaceutical industry is known to have a higher waste rate production compared to other sectors in the chemical industry[1]. Thus, changing the way of processing can open the windows for emergent technologies that can produce new products at a faster pace and address the waste production issues[2].

In chapter 4, the concept of Functional Solvent Factory (FSF) was introduced as an emergent technology that can potentially address many of the challenges of the pharmaceutical industry[3–6]. For this processing platform, designer solvents, such as ionic liquids, can aid the purification of a product of interest and recovery of catalyst and other reactants. It consists of the formation of multiple phases, in which the purification or reaction can be conducted selectively[3,4,7]. At the same time, this processing platform can address the key areas of continuous processing, separation and reaction technologies, and process intensification; which are of interest to the Pharmaceutical Roundtable on Green Chemistry[8].

In previous chapters, the automated purification with ionic liquids as multifunctional solvents was investigated, i.e. used as carriers, as enablers of the reaction and as a separation medium that facilitates recycling and product purification[3,9]. Solvent's multifunctionality is key to performing the process under the FSF production platform, meaning the solvents need to be actively involved to intensify the process. A life cycle assessment (LCA) was conducted on the two proposed types of FSF to evaluate the environmental impact of the production platform and identify hot spots for improvement and key parameters.

An LCA is a systematic method developed to identify the environmental trade–offs of existing technologies[10–13]. It considers the life cycle of a product from the extraction of resources to the disposal of waste. It is also a support tool that aids in the decision making process[14] for systems for which sufficient data is available, when cause–effect relationships are well identified[10], i.e. an ex–post system[15].

As a decision–making tool, LCA is also applied to processes with a future–oriented scope[16], that can guide policies, and support the improvements and designs at an early stage of development[15]. Particularly, for the development of new chemical processes it can aid in the selection of compounds, process parameters, and their (re)design[17]. Design stages are crucial, as the decisions made at this stage account for 70% of the final cost, functional requirements and environmental impacts[18]. Therefore, it is important to conduct an LCA in the early stages of development. On the other side, data collection and comprehension of the system

relationships at early stages is more challenging[10]. It is known that uncertainties arise in any kind of LCA. Yet for the case of emergent technologies the challenge is even greater due to the inherent variability of the input parameters and assumptions made due to data incompleteness[15,19]. Moreover, the lack of maturity combined with the forecast nature of emergent technologies has more and greater sources of uncertainty[10].

To assess emergent technologies, generally data from prototypes and research publications are used. These data reflect a technology with low maturity, thus it is important to evaluate the impact of this technology when a higher level of maturity or a larger scale of production is reached[20]. For example, consider the change of a lab scale batch production, which is less efficient and lower yields are obtained, versus continuous production, where higher production capacity is achieved with constant quality[18,21]. Furthermore, the use of lab scale data cannot be adequately translated directly to large scale productions. It is reported that the impact can be drastically reduced when increasing the technology readiness level of a process[22]. Scale–up of emerging technologies can be assessed with scenarios that represent the future performance, in a prospective fashion. These scenarios can be later compared with an incumbent technology[15].

Increasing the credibility and reliability of the LCA is necessary due to the hampering effect of the uncertainties[23]. Different types of uncertainties can be present such as parameter, scenario, and model uncertainties[24]. Common practices used to treat the uncertainties of deterministic LCA include the use of a probability distribution function, to obtain a probability of values, rather than a fixed impact score[10]. At the same time, the assessment of the different sources of uncertainties is conducted.

In previous chapters, a case study was reported for the assessment of the FSF, where two production pathways were analyzed following the FSF platform[5,6]. However, due to the use of scientific publications the high uncertainty that this assessment holds needs to be acknowledged. Therefore, in this chapter, it is deepened the results by using an uncertainty statistical method to increase the level of likelihood of the confidence in the conclusions previously drawn. At the same time, the study is aimed to get a visualization of the possible level of optimization that can be reached at a higher maturity level, as well as the tradeoffs that can question the sustainability of this new platform. A better understanding of the trade–off between the alternatives can help to identify the environmental implications, which cannot be observed based on a single mean value[25].

## 6.2 METHODOLOGY

### 6.2.1 Goal and Scope

The goal of this study is to conduct a comparative assessment of the two solvent factory scenarios presented in chapter 4, and to analyze the uncertainty of the scenarios proposed. For that, two methodologies are selected[23,26], which compromise the following steps: characterization, uncertainty analysis, and communication. With these it is aimed to look at the cause of the uncertainties and the impact they have on the results to have a more thorough understanding of the FSF concept. The second methodology particularly focuses on the uncertainty calculation and the comparison aspects, to focus on which environmental impact categories are mostly burdened.

The functional unit will be for both cases the production of 10 kg of benzyl azide, and the scope will be cradle–to–gate.

### 6.2.2 Life cycle inventory

The scenarios were modelled in Aspen Plus using foreground data from literature[27–30]. The process flow diagrams of these two types of FSF are presented in Fig. 4.4 and Fig. 4.6 (Chapter 4). To obtain the overall dispersion and probability distribution, changes to the processes were implemented and modelled in the software Aspen Plus, and with this assess multiple optimizations that were not considered in the original model. The optimizations and their descriptions are presented in Table 6.1 and Table s6.1, respectively. From the results of these models, means for the mass and energy balance were obtained. Then these means were implemented in the Activity Browser from the Brightway2, to calculate the environmental impacts using foreground data from Ecoinvent 3.7. The activity browser is part of Brightway2 LCA open–source framework, which allows for the implementation of new modelling strategies. In the activity browser a new activity is created, wherein the mass and energy balance to produce 10 kg of benzyl azide were input, accordingly to the FSF Type.

**Table 6.1.** Scenarios for the Functional Solvent Factory Type 1 and Type 2

| Scenarios FSF Type 1 | Scenarios FSF Type 2 |
|---|---|
| 1. Increase concentration of benzyl alcohol | 1. IL (Hmim Cl)– water purification |
| 2. Conversion | 2. Ideal case (no purification needed) |
| 3. Ideal case | 3. Ionic liquid recovery |
| 4. Use of solvent | 4. Increase concentration of benzyl chloride |
| | 5. Increase conversion |

### 6.2.3 Life cycle impact assessment

The same five impact categories implemented in the previous assessment were selected, namely: climate change potential (GWP), fossil depletion potential (FD), human toxicity potential (HT), ozone depletion potential (OD), photochemical oxidant formation (POF), and water depletion (WD). All of these correspond to the ReCiPe Midpoint method[31], which was selected based on recommendations[22], and no normalization or weighting was performed.

### 6.2.4 Uncertainty calculations

The first step consists of the qualitative characterization of the uncertainties, i.e. location and nature of the uncertainties, followed by their quantification. In many LCAs studies this is evaluated with scenario analysis; however, this approach is considered misleading when the probabilities of occurrence are not incorporated. Moreover, the number of scenarios generated can grow exponentially, and a one–by–one analysis can be extremely complicated[10].

To obtain the uncertainty parameters the background and foreground inventory data were propagated using a thousand Monte Carlo iterations. The number of iterations was decided based on literature[26,32] and convergence of the results. Uncertainty due to allocation, impact assessment methods and correlations were not considered. Dependent sampling was used in the calculation of the paired samples by using the same technology and environmental matrix. Dependent sampling is necessary to avoid an overestimation of the uncertainty[33].

The results were then compared using the overlap area of probability distributions. This is a statistical method used to interpret comparatives LCA with uncertainty[25,26].

The overlap area is defined as the area where two or more probability distribution functions

intersect and can be used as a tool to measure quantitatively the similarity or difference among samples. Due to its versatility it can be used in multiple applications[34]. The overlap area was measured in the software Minitab using a 0 to 1 scale, where 0 is low to no overlap and 1 is for complete overlap (e. g. identical distributions)[25,26].

## 6.3 Results

As an emergent technology, only limited data is available, especially for the FSF considered in this assessment. The two pathways (Type 1 and Type 2) were developed and modelled using background data from literature. These processes did not reflect 100% of the inherent potential of the FSF, due to the lack of automated purification (i.e. use of a purification train). But these processes were used to assess possible process limitations based on the level of purification obtained. Due to the use of lab–scale data to model a continuous large scale process, it is expected that the process could be more efficient compared to the modelled case[35]. On the other side, variation in data measurements such as by–products or waste can be uncovered when the process is scaled up[18]. This discrepancy observed during the scale up of the process can question the results. Therefore, an uncertainty assessment of this case study, synthesis of benzyl azide under the FSF platform, was conducted. The results are presented below to complement the results obtained and to go one step further in the analysis of the FSF.

Firstly, the sources of uncertainty are identified followed by the comparison of the two FSF types.

### 6.3.1 Qualitative Characterization

Uncertainty has been defined as a deviation from the ideal of a deterministic knowledge and is classified into three dimensions. It can be in the parameters, in the model, and in the scenarios. These relate to the inputs, through the mismatches selected to understand the system of study. It is also necessary to identify the nature of the uncertainty to characterize it. This nature can be epistemic or ontic. Epistemic uncertainty is due to the lack of knowledge, consistency, and representativeness, which can only be improved with more research. The ontic nature, on the other side, is due to the inherent variability of the system and cannot be reduced by any means[23].

Below the dimensions of uncertainty for this case study of the functional solvent factory are identified.

**Table 6.2.** Nature and localization of uncertainty in FSF case study

| LCA Stage | Case | Location | | | Nature | |
|---|---|---|---|---|---|---|
| | | Context | Model structure | Quantity | Epistemic | Ontic |
| Goal and scope | Technological representativeness | x | x | | x | |
| | Geographical representativeness | x | | | x | |
| Life cycle Inventory | Representativeness of the interactions | | x | | x | |
| | Representativeness of background process used | | x | | x | |
| | Representativeness of background data | | x | | x | |
| | Variability of flows | | x | x | x | |
| | Representativeness of materials used | | x | | x | |
| | Representativeness of model selected | | x | | x | |
| Life cycle impact assessment | Representativeness of characterization factors | | | x | x | |
| | Variability of characterization factors | | | x | | x |

From Table 6.2, it is clear that except for one, all the uncertainties are of an epistemic nature, which can be expected in ex–ante LCA, where the lack of data is a common obstacle. With respect to the location, the context uncertainties identified were due to the system's stochasticity. No specific geography was defined; thus, variations in locations can have an impact on different variables (e.g. the energy mix of different countries). On the other hand, due to the ambiguity of the location, unrepresentativeness was avoided by not using average data to represent a specific site [36]. As the technology progresses, the TRL level will increase, and a specific location(s) can be selected. Then geographical representativeness can be

addressed by increasing the resolution and attempting to include representative data from different areas within the vicinity[37].

Technological representativeness was also identified as a source of uncertainty both within the context and within the model structure. Technological representativeness has no specific criteria and there is no specific approach. In the previous studies benchmark data from other two technologies was used to address the technological representativeness[36]. These two benchmark cases have a higher TRL and are in the market. Those were a batch process (state–of–the–art) and a solvent–less process[38]. Due to the higher TRL, operating conditions and process scale were known; which allowed higher technological representativeness on the benchmark side[37]. However, technological representativeness was limited when modelling the functional solvent factory, particularly for the recovery technologies for ionic liquids. In literature a number of process options are presented that can be used for the purification of ILs[39], namely: distillations, extraction, adsorption, membranes, multiphase extraction, and crystallization. During the modelling process, distillation was selected[39,40]. Thus, testing and modelling other process options is necessary for technological representativeness. As an emergent technology, the technological pathway assessed here is still at low stages of development and there are areas that need to be further defined. The purification technology selected will in the end depend on the purity needed in the IL to conduct the reaction[41], and the tradeoffs between conversion and environmental impact.

The second area, where a lack of technological representativeness was identified is in the synthesis of ILs. ILs are also considered emerging materials, as result there are few inventory databases available[42]. They are mostly synthetized in the laboratory and there are many different routes that can be followed. These routes generally focus on quality rather than being an optimized pathway[39].

Finally, the last uncertainties were identified in the representativeness of the background data, the interactions, and the model. The data available do not allow the identification of possible side reactions or other process key performances that can affect the interactions of the materials and the process. Obtaining this data would require experimental testing and bringing the process pathway to a higher TRL.

### 6.3.2 Uncertainty analysis

The pathway from the laboratory to the market is unpredictable and many optimizations are expected before bringing a process to the industry[10]. To address these possible changes four and five extra scenarios were developed for the FSF type 1 and 2 respectively, which are

presented in Table 6.1. and Table s6.1. Moreover, considering these scenarios allowed the collection of the statistical data needed to quantify the uncertainties.

Then the uncertainty data was generated using the Pedigree Matrix. The Pedigree Matrix was developed as a data quality indicator[43], and provides an understanding of the kind of data used in the assessment[42]. These indicators of data quality can also be applied as estimates of data uncertainty[43], especially for processes at an early stage of development. The Pedigree Matrix generates a log–normal distribution for each impact category based on uncertainty coefficients[25] for indicators, namely: completeness, reliability of the source, temporal differences, geographical differences, and other technological differences. The former assesses the stage of development (e.g. lab scale).

There are different ways to estimate uncertainty. Often a combination of approaches, such as in the case considered in this chapter, are reported. For example, experimental data in combination with expert judgment has been used to estimate variations in emissions from a waste incineration plant[44]. These variations are used to propagate the uncertainties by random sampling and calculate the impacts using Monte Carlo simulations. The results of the uncertainty propagation for the FSF Type 1 and Type 2, are presented in Fig. 6.3.

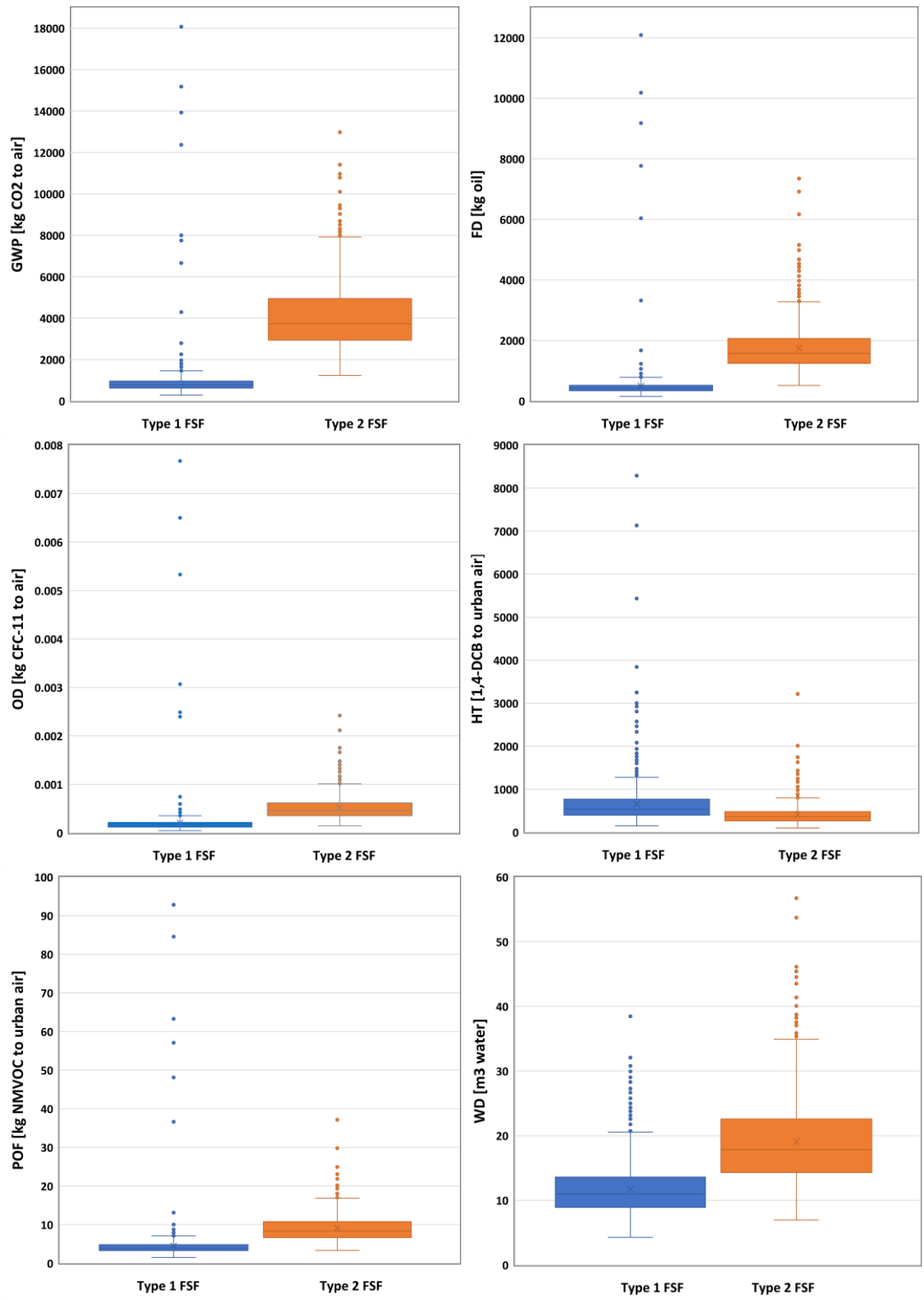



**Figure 6.1.** Distribution difference due to assumptions taken during modelling and data collection of Functional Solvent Factory Type 1 and Type 2. LCI uncertainty propagation was conducted for the impact categories: Global warming potential [GWP], Fossil depletion potential [FD], Ozone depletion potential [OD], Human toxicity potential [HT], Photochemical oxidant formation [POF], and Water depletion [WD].

The multiple scenarios presented in Table 6.1 were used to assess the uncertainty and get a better understanding of these FSFs. The mean environmental impact of the first FSF (Type 1) is considerably lower compared to the deterministic values obtained in all the categories. The deterministic values calculated can be observed as outliers in the box plots. As well it is possible to notice that the outlier tail is longer for the Type 1 FSF, in the box plot this is represented in the points outside the whiskers. This kind of behavior is observed due to the log–normal distribution selected for the uncertainty calculations. When the data is fitted to that log–normal distribution, the curve of the plot presents a positive skew with a long tail, in this case the mode is in the center of the highest point of the curve while the mean will be towards the right. In the box plot the mean is located in the upper quartile, and the mode in the bottom, as it is more sensitive towards extreme scores which are more present in the Type 1 FSF [45]. Type 2 also presents a plosive skew.

The uncertainty assessment also shows that the impact of the Type 1 FSF can be lower in most of the categories except for the category of human toxicity (HT) potential. This can be seen by comparing the mean of the box in each category for each FSF type. The same behavior is observed in all the categories when comparing the variability. The boxes of Type 2 tend to be larger in size compared with Type 1, particularly for the categories of GWP and WD. The variability observed here is larger than in the other categories and can be explained due to the variability in the purification of the IL used in the first stage of the Type 2 FSF. In this case the IL requires a high energy input to conduct the reaction and for the purification of it. On the other side, in the category of human toxicity potential the variability of the Type 2 FSF is smaller compared to Type 1. The change in this category can be attributed to the ILs used, and how the synthesis of these ILs was modelled. Type 1 uses a more complex IL, that requires more synthetic steps and more reactants that have a large contribution to this category. Despite the use of two ILs in the Type 2 FSF, it is observed that the HT is lower and less variable, which highlights the importance of selecting the IL based on a holistic assessment that includes environmental and technical concerns.

In comparative LCA, it is necessary to understand the environmental implication of each system. Particularly, the focus should be on the differences[25], and these differences cannot be completely assessed through the normalization of deterministic values, as this would focus on the hot spots rather than the trade–offs. To understand better the trade–off of these two FSF the overlap area was calculated (see Table 6.3). The intersected area is a simple way to quantify the trade–off based on the distributions of two samples[34].

The results of the overlap area are in line with the results obtained in the distribution difference. The Type 1 factory overlap with the Type two is very low in all the categories, below 30%, except for HT and water depletion (WD). This means that Type 1 presents lower values for the impact in most of the life cycle categories. However, in the case of the HT and WD, there is little difference in the two pathways proposed, especially in the HT category with an overlap of 66%. These two categories have a large impact contribution from the IL selected. Type 1 uses a complex IL that has a similar impact, in those categories, to the two ILs used in Type 2, which again addresses the need for a holistic selection of the IL.

**Table 6.3.** Relative trade–off significance of the FSFs according to the overlap area approach.

| Impact category | Average overlap area |
|---|---|
| Climate Change | 0.04 |
| Fossil depletion | 0.06 |
| Human Toxicity | 0.66 |
| Ozone Depletion | 0.21 |
| Photochemical oxidant formation | 0.24 |
| Water depletion | 0.45 |

## 6.4 CONCLUSIONS

This chapter presents the use of the overlap area method to calculate the trade–offs of two different FSF scenarios for the synthesis of benzyl azide. These scenarios were developed to assess the use of automated separation with ionic liquids in the synthesis of fine chemicals and pharmaceuticals. As the FSF is in an early stage of development with a low TRL, many uncertainties in the LCA are expected due to its ex–ante nature. An uncertainty assessment was conducted to assess in depth this new platform for the synthesis of fine chemicals and pharmaceuticals. Moreover, this assessment helped to understand better the tradeoffs of the scenarios proposed and the environmental implication that the FSF can have.

The nature and where these uncertainties originate were identified. These uncertainties were corresponding to a high overview assessment of technologies with low TRL, such as in the

representativeness within the international context due to undefined geography. Technological representativeness was also identified due to the also emergent characteristic of ionic liquids and the purification level needed in the process.

Then the uncertainties were quantified using the overlap area approach. This methodology allowed the comparison of the tradeoffs between processes and gives an understanding of the data uncertainty. As it was observed in the results Type 1 is the best alternative, with an overall lower impact. This highlights that the use of only one ionic liquid, that can simplify the process will yield better environmental results. However, in two categories, namely human toxicity and water depletion, the distinction was not very clear, despite the use of two ionic liquids in the FSF Type 2. It is important to take this into account in future designs, as one ionic liquid can simplify the reaction, but, on the other side taking a complex IL that requires multiple synthetic steps can have a negative effect on other areas. Therefore, the selection and the synthesis of the ionic liquids is a key parameter to consider as the FSF is brought to higher TRL.

On the other side, the overlap area approach has some limitations. This method can only be used if the probability distribution is lognormal. According to literature, the lognormal distribution can be a good fit for the emission factors in the Ecoinvent database. However, other types of distributions (e.g. uniform, normal) might be more representative for other inputs[46], such as fuel or chemical inputs. Yet, the use of a single probability distribution function for all inputs is considered the best approach when information or expert knowledge is missing[47]. Further models and research efforts, particularly for the steps prior to the FSF, i.e. the synthesis of the IL and the purification are needed.

## REFERENCES


1 R. A. Sheldon, *Green Chem.*, 2017, **19**, 18–43.

2 K. Plumb, *Chem. Eng. Res. Des.*, 2005, **83**, 730–738.

3 C. Zhang, T. Noel, S. Li, Z. Song, K. Sundmacher, H. Gröger and V. Hessel, *Spaciant Solvent Factory towards End-to-End Green Process Design for Pharmaceuticals in ONE-FLOW*, 2018.

4 O. M. Morales-Gonzalez, C. Zhang, S. Li and V. Hessel, *Chem. Eng. Sci. X*, , DOI:10.1016/j.cesx.2019.100024.

5 O. M. Morales-Gonzalez, J. A. Medrano-Jimenez, F. Gallucci and V. Hessel, *J. Clean. Prod.*, 2021, **318**, 128456.

6 F. Grimaldi, N. N. Tran, M. M. Sarafraz, P. Lettieri, O. M. Morales-Gonzalez and V. Hessel, *ACS Sustain. Chem. Eng.*, 2021, **9**, 13135–13150.

7 C. Zhang, Z. Song, C. Jin, J. Nijhuis, T. Zhou, T. Noël, H. Gröger, K. Sundmacher, J. van Hest and V. Hessel, *Chem. Eng. J.*, 2019, **385**, 123399.

8 C. Jiménez-González, P. Poechlauer, Q. B. Broxterman, B. S. Yang, D. Am Ende, J. Baird, C. Bertsch, R. E. Hannah, P. Dell'Orco, H. Noorman, S. Yee, R. Reintjens, A. Wells, V. Massonneau and J. Manley, *Org. Process Res. Dev.*, 2011, **15**, 900–911.

9 Q. Deng, N. N. Tran, M. Razi Asrami, L. Schober, H. Gröger and V. Hessel, *Ind. Eng. Chem. Res.*, 2020, **59**, 21001–21011.

10 C. F. Blanco, S. Cucurachi, J. B. Guinée, M. G. Vijver, W. J. G. M. Peijnenburg, R. Trattnig and R. Heijungs, *J. Clean. Prod.*, , DOI:10.1016/j.jclepro.2020.120968.

11 G. A. Keoleian, *J. Clean. Prod.*

12 C. Jiménez-González, A. D. Curzons, D. J. C. Constable and V. L. Cunningham, *Int. J. Life Cycle Assess.*, 2004, **9**, 114–121.

13 S. Editors, W. Klöpff and A. Curran, *Special Types of Life Cycle Assessment*, 2016.

14 R. Heijungs and M. a J. Huijbregts, *iEMSs 2004 Int. Congr.*, 2004, 8.

15 S. Cucurachi, C. van der Giesen and J. Guinée, *Procedia CIRP*, 2018, **69**, 463–468.

16 R. Arvidsson, A. M. Tillman, B. A. Sandén, M. Janssen, A. Nordelöf, D. Kushnir and S.

Molander, *J. Ind. Ecol.*, 2018, **22**, 1286–1294.

17 D. Kralisch, D. Ott and D. Gericke, *Green Chem.*, 2015, **17**, 123–145.

18 M. Villares, A. Işıldar, C. van der Giesen and J. Guinée, *Int. J. Life Cycle Assess.*, 2017, **22**, 1618–1633.

19 M. Lacirignola, P. Blanc, R. Girard, P. Pérez-López and I. Blanc, *Sci. Total Environ.*, 2017, **578**, 268–280.

20 S. Gavankar, S. Suh and A. A. Keller, *J. Ind. Ecol.*, 2015, **19**, 51–60.

21 H. Leuenberger, *Eur. J. Pharm. Biopharm.*, 2001, **52**, 289–296.

22 S. M. Moni, R. Mahmud, K. High and M. Carbajales-Dale, *J. Ind. Ecol.*, 2019, 1–12.

23 E. Igos, E. Benetto, R. Meyer, P. Baustert and B. Othoniel, *Int. J. Life Cycle Assess.*, 2019, **24**, 794–807.

24 M. A. J. Huijbregts, W. Gilijamse, A. M. J. Ragas and L. Reijnders, *Environ. Sci. Technol.*, 2003, **37**, 2600–2608.

25 V. Prado-Lopez, B. A. Wender, T. P. Seager, L. Laurin, M. Chester and E. Arslan, *J. Ind. Ecol.*, 2016, **20**, 710–718.

26 A. Mendoza Beltran, V. Prado, D. Font Vivanco, P. J. G. Henriksson, J. B. Guinée and R. Heijungs, *Environ. Sci. Technol.*, 2018, **52**, 2152–2161.

27 B. Garg and Y. C. Ling, *J. Chinese Chem. Soc.*, 2014, **61**, 737–742.

28 A. R. Hajipour, A. Rajaei and A. E. Ruoho, *Tetrahedron Lett.*, 2009, **50**, 708–711.

29 R. X. Ren and J. X. Wu, *Org. Lett.*, 2001, **3**, 3727–3728.

30 H.-H. Wu, J. Sun, F. Yang, J. Tang and M.-Y. He, *Chinese J. Chem.*, 2004, 319–621.

31 M. Goedkoop, R. Heijungs, M. Huijbregts, A. De Schryver, J. Struijs and R. Van Zelm, *ReCiPe 2008*, 2009.

32 R. Heijungs, *Int. J. Life Cycle Assess.*, 2020, **25**, 394–402.

33 R. Heijungs, P. J. G. Henriksson and J. B. Guinée, *Int. J. Life Cycle Assess.*, 2017, **22**, 461.

34 M. Pastore and A. Calcagnì, *Front. Psychol.*, 2019, **10**, 1–8.

35 R. Frischknecht, S. Büsser and W. Krewitt, *Int. J. Life Cycle Assess.*, 2009, **14**, 584–588.

36 T. Henriksen, T. F. Astrup and A. Damgaard, *J. Ind. Ecol.*, 2021, **25**, 51–66.

37 A. Edelen and W. Ingwersen, 2016, 47.

38 M. Escribà-Gelonch, G. A. de Leon Izeppi, D. Kirschneck and V. Hessel, *ACS Sustain. Chem. Eng.*, 2019, **7**, 17237–17251.

39 J. Zhou, H. Sui, Z. Jia, Z. Yang, L. He and X. Li, *RSC Adv.*, 2018, **8**, 32832–32864.

40 M. J. Earle, J. M. S. S. Esperança, M. A. Gilea, J. N. C. Lopes, L. P. N. Rebelo, J. W. Magee, K. R. Seddon and J. A. Widegren, *Nature*, 2006, **439**, 831–834.

41 A. J. S. McIntosh, J. Griffith and J. Gräsvik, eds. O. Kuzmina and J. P. B. T.-A. Hallett Purification, and Recovery of Ionic Liquids, Elsevier, Amsterdam, 2016, pp. 59–99.

42 V. G. Maciel, D. J. Wales, M. Seferin, C. M. L. Ugaya and V. Sans, *J. Clean. Prod.*, 2019, **217**, 844–858.

43 B. P. Weidema and M. S. Wesnaes, *J. Clean. Prod.*, 1996, **4**, 167–174.

44 S. M. Lloyd and R. Ries, *J. Ind. Ecol.*, 2007, **11**, 161–179.

45 J. Malça and F. Freire, *J. Ind. Ecol.*, 2010, **14**, 322–334.

46 O. Larsson Ivanov, D. Honfi, F. Santandrea and H. Stripple, *Struct. Infrastruct. Eng.*, 2019, **15**, 711–724.

47 J. Clavreul, D. Guyonnet, D. Tonini and T. H. Christensen, *Int. J. Life Cycle Assess.*, 2013, **18**, 1393–1403.

## Appendix D

**Table *s*6.1.** *Details on the s*cenarios *simulated* for the Functional Solvent Factory Type 1 and Type 2

| | Scenarios | Description |
|---|---|---|
| **FSF Type 1** | 1. Increase concentration of benzyl alcohol | Data measurements were obtained from the following changes:<br>a) Benzyl acohol 200% increase<br>b) Benzyl acohol 400% increase<br>c) Benzyl acohol 800% increase<br>d) Benzyl acohol 1600% increase<br>Sodium azide concentration was increased at the same time to adjust mass balance.<br>Solvent extraction was adjusted correspondingly to adjust mass balance. |
| | 2. Conversion | Original conversion was 99% thus it was decreased in intervals of 10% down to 60% conversion. Conditions described in Scenario 1, higher concentration of benzyl alcohol, were implemented. |
| | 3. Ideal case | No purification process, adapted to the ideal concept of the FSF.<br>Separation was conducted with purges in which the product was separated due to solubility. Product recovery rates were:<br>a) 50%<br>b) 60%<br>c) 70%<br>d) 80%<br>e) 90%<br>f) 100%<br>Purification was adjusted accordingly to the mass of product recovered. Conversion rages of scenario 2 were implemented. |
| | 4. Use of solvent | Solvents used for extraction processes: hexane, ethyl acetate and acetonitrile were decreased in the original scenario by:<br>a) 20%<br>b) 40%<br>c) 60%<br>d) 80%<br>Scenarios of case 3 were implemented.<br>Water mass balance was adjusted accordingly. |
| **FSF Type 2** | 1. IL (Hmim Cl)– water purification | Purification of IL (Hmim Cl) to remove excess water was varied in intervals of 2% from 99% to 91%.<br>Further decrease was not considered due to possible negative effects over conversion. |

| | |
|---|---|
| 2. Ideal case (no purification needed) | No purification process, adapted to the ideal concept of the FSF.<br><br>Separation was conducted with purges in which the product was separated due to solubility. Product recovery rates were:<br><br>a) 50%<br>b) 60%<br>c) 70%<br>d) 80%<br>e) 90%<br>f) 100%<br><br>IL regeneration was adjusted accordingly to the mass of product recovered.<br><br>Water removal rages of scenario 1 were implemented.<br><br>Solvent extraction with diethyl ether was adjusted accordingly. |
| 3. Ionic liquid recovery | Recovery of IL (Hmim Cl) was varied from 0% to 99% using the scenarios developed before (2. Ideal case) |
| 4. Increase concentration of benzyl chloride | a) Benzyl chloride 200% increase<br>b) Benzyl chloride 400% increase<br>c) Benzyl chloride 800% increase<br>d) Benzyl chloride 1600% increase<br><br>Sodium azide concentration was increased at the same time to adjust mass balance.<br><br>Previous scenarios were implemented |
| 5. Increase conversion | Conversion was increased in ranges of 10% up to 100% conversion, and the changes were done to the previous scenarios. |

# CHAPTER 7. CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

## 7.1 CONCLUSIONS

The development of new process technologies that allow continuous production of pharmaceuticals and fine chemicals is necessary to cope with the challenges and needs, in terms of cost and capacity, of the coming generations. Batch production will then not play the role that it has today. Yet new technologies must also meet the high environmental requirements that the future demands. Therefore, in this work new synthetic pathways for the continuous production of pharmaceuticals and fine chemicals have been assessed, with the aim to address the challenges and key areas of the pharmaceutical industry. To maximize the benefits of emergent technologies– particularly with respect to the environmental impact– hotspots need to be identified at early stages, where changes are easier to implement. The three different process technologies assessed in this work were Novel Process Windows, Compartmentalized– Cross–Linked Enzyme Nano–Aggregates, and the Functional Solvent Factory. The last two as part of the One–Flow strategy for compartmentalized cascade reactions.

First, in **Chapter 2** Novel Process Windows were applied to produce vitamin $D_3$, under continuous and intensified conditions. The process was assessed to evaluate its environmental impact and benchmarked against multiple batch process scenarios. Under continuous and intensified conditions, the production of vitamin $D_3$ presents a smaller environmental impact compared to the batch processes, due to the optimized use of resources.

Despite the conditions, high temperature, and high pressure, no degradation of vitamin D3 was observed. Conversely, it favoured conditions that enhanced the resistance of the components.

In addition, hotspots were identified, to improve the environmental performance of the process. The process should address the missing recycling loops, particularly for the solvents methyl tert–butyl ether and acetonitrile. Minimizing the use of solvent is a priority, and an issue for the pharmaceutical industry. Recovery and reuse are the first strategies to implement, as they avoid the use of new material, and thus, emissions. Yet, these steps should balance the use of energy for the recovery and purification of the solvents with the volumes and quality needed.

Next in **Chapter 3** the strategy of compartmentalization through cross–linked enzyme nanoaggregates was assessed. The foci were given to the cost, and how the production process could be optimized at lab scale, before moving to larger stages.

The costs of Compartmentalized cross–linked enzymatic nano –aggregates are highly driven by the CAPEX, i.e. the equipment used and the requirements for the use of these. Based on these, changes in the equipment were proposed and assessed. The assessment showed that disposables could be used, yet they must be recycled as much as possible to maintain the cost. It was also assessed the reuse of the enzyme that could not be trapped in the polymer, and although the overall cost did not reduce significantly, it should be further explored due to the environmental implications.

Other areas to further explore experimentally were proposed, one of them was the polymer used, poly(ethylene glycol)–polystyrene. The second was the use of continuous dialysis systems. As mentioned in the chapter, these changes require deeper changes and could not be elaborate further in this work.

The second compartmentalization strategy, the Functional Solvent Factory, was elaborated in **Chapter 4.** This process idea was inspired by nature, and the compartmentalization done in the cell structures that allow the continuous synthesis and purification of compounds.

It was started by developing a comprehensive solvent assessment methodology, with solubility as a key selection parameter. There are many examples of solvent selection methodologies in literature, yet, targeting the selection of a solvent using physicochemical properties with LCA is not common due to the time requirements of these assessments. Moreover, complex, especially since not common solvents are rarely assessed. However, as expected from previous studies, the environmental impact of these solvents is many times larger compared to conventional ones despite the high selectivity due to solubility. Therefore, its use and recycling are key for the development of the Functional Solvent Factory. Furthermore, it is necessary to weigh them against the benefits obtained in the whole process, and not a straightforward comparison against common solvents.

The second part of this chapter presents a second case study, where a concept case of the Functional Solvent Factory was modelled with the aim to evaluate potential advantages and drawbacks. Although this case study only emulates some of the principles of the Functional Solvent Factory, it was presented as a balancing act between innovation and real–life commercialization potential of automated separation via ionic liquids. The case study presents two scenarios with functional ionic liquids, developed from foreground data. Unfortunately, the performance behind those data was not enough to release the intrinsic potential of the functional solvent factory. Yet, many lessons can be learned from such, considering the early stage of development, that can bring valuable knowledge for experimental development. In **Chapter 5** an environmental assessment was conducted to evaluate the benefits and identify

hotspots. The key parameters recognized, for which further research and experimenting is necessary were a) the amount and type of ILs. The ILs are greatly responsible for the impact in all categories. Even without a separation train, the impacts were largely influenced by the ILs. Secondly, b) recyclability, it is necessary to ensure that more than 90% of the IL can be recovered and used many times. That also means prevents the degradation and contamination of the IL, which can become the road blocker to applying this technology in certain cases.

Finally, in **Chapter 6** the assessment conducted in Chapter 5 was complemented with an uncertainty assessment. This assessment is necessary for emergent technologies, as many uncertainties are expected due to the assumptions taken at early stages of development. Moreover, this works as a support to understand better the tradeoffs of the scenarios proposed and the environmental implication that the FSF can have. In the first place, the nature and the location of the uncertainties were identified. The different kinds of uncertainties observed were due to the undefined geography (geographical representativeness), and the emergent nature of the ILs, themselves also not in commercial production (technological representativeness).

Then the uncertainties were quantified using the overlap area approach. The overlap area approach helps to compare two or more technologies/processes when uncertainties are considered. The results showed that the Type 1 Functional Solvent Factory proposed has a smaller impact in most of the categories. Yet, in two categories, human toxicity and water depletion, the distinction was not very clear, which emphasized the key role of the selection of the ionic liquid.

The results concluded above show the common dilemma with almost all emerging technologies at an early stage. They comprise insufficient reaction performance and/or material or energy efficiencies, which prevent them to be as powerful as they might be. In this thesis, these shortcomings are mainly in the environmental profile of the solvents and the costs of the cross–linked polymers, both used for compartmentalization. As a second shortcoming, the new technologies have often not been tested in a comprehensive process. Here, this was observed in the lack of data bout recovering and recycling.

## 7.2 RECOMMENDATIONS

The use of novel process windows, compared to the other strategies analyzed in the work, has been developed and studied further, i.e. higher TRL. Further work should focus on

addressing recycling loops. Solvent recovery is key to a more sustainable pharmaceutical industry. In the vitamin $D_3$ process, two solvents, namely acetonitrile and methyl tert–butyl ether used in the solvent swap are not recycled. Thus, it is suggested to analyze the possibilities of recovering these solvents. Forming an azeotrope, distillation, a common technique for solvent recovery and purification is discarded and other alternatives should be investigated. One of those alternatives could be membrane–based pervaporation, which has been used to separate the azeotropic binary mixture of methyl tert–butyl ether and methanol.

Due to the emergent nature of the compartmentalized strategies assessed it is necessary to dive deeper. Firstly, the environmental impact of cross–linked enzyme nanoaggregates should also be addressed and conduct a life cycle assessment. This study could complement the technoeconomic assessment and guide future process design. Some of the changes suggested may have a large implication on the environmental impact, for which is necessary to complement the study with a life cycle assessment. Secondly, as suggested it would be beneficial to analyze the use of diverse– commercial– polymers to produce the stomatocytes. It is necessary to assess the capacity and interaction of different polymers, especially commercial ones, as this would reduce cost and risks. Then it is also proposed to analyze the options to run the process continuously, thus some steps like the dialysis would need to be changed. Continuous dialysis can be achieved through a series of membranes, these membranes would need to be carefully selected and tested to achieve the purity needed. Once the membranes have been corroborated, then the control system and the pump can be designed. The production cost is expected to go up, however, it is as well expected to be balanced by the improvement in the production capacity. Moreover, this would facilitate further scale up plans.

Finally, it is expected that most of the benefits are obtained in complex cascades, cascades that need two or more enzymes. Thus, it is recommended to evaluate the use of cross–linked enzyme nanoaggregates in a complex cascade, throughout the whole process and including the purification train. Then, it is necessary to compare it with other immobilization strategies, that can replace the same functions to position the cross–linked enzyme nanoaggregates in the market.

In the case of the Functional Solvent Factory, it is necessary to bring this platform to a higher TRL. It is necessary to develop multiple proofs of concept, i.e. cascade reactions, where this synthetic platform is evaluated and data can be collected. The first studies guided towards the low temperatures and high concentration when conducting the cascade reaction. Yet, developing multiple cascade reactions is necessary to fine tune the process guidelines.

These concept cases are needed to assess how the environmental impact changes when the recovery and recycling of the catalyst and reactants are achieved. This should be done particularly, from the solvent's perspective, as it was observed very high recoveries are needed. But the environmental load can be reduced when valuable products are recovered, i.e. would eliminate the need for purification processes for each of the reactants, products, and catalyst. Moreover, this can help to answer the question of when the use of automated separation with ILs has ecological advantages.

One of the most sensitive parameters is the long–term recycling of the ionic liquid, thus if the ILs are contaminated during the process it is necessary to consider and implement a purification strategy. Recovery and purification are key and considered one of the most important obstacles to large–scale implementation. The optimal and most effective option or combination of processes needs to be assessed in case of contamination.

Once this system has been designed and data has been collected, it is necessary to assess it again and compare it with other synthetic strategies. Moreover, it will be possible to reduce the uncertainty in some areas, for example by obtaining better data regarding conversion and purification. Yet other areas, like the ionic liquid production, are not going to be impacted, unless a commercial ionic liquid is selected. Furthermore, by having this data the best fitting probability distribution function can be implemented to calculate the uncertainty.

Then it is recommended to complement the studies with a technoeconomic assessment and optimize the processes from this perspective.

Finally, it is necessary to bear in mind the development of IL is the market. Although this was out of the scope of this thesis, it is evident that if this platform is desired to be implemented in the future more research and market development for ILs is necessary. As mentioned before, only a short number of ILs are available commercially. On the other side, the FSF approach relies on fine tuned ILs, of which data and commercial availability need to be developed as well. Therefore, synergies with the academy and industry are needed to make sure the resources will be available for its implementation.

# RESEARCH OUTPUT

## Journal publications

- O. M. Morales–Gonzalez, J. A. Medrano–Jimenez, F. Gallucci and V. Hessel (2021). Ecological assessment as balancing act between disruptive innovation and industrial implementation: Designer–solvent processes with automatic product purification and recycling. Journal of Cleaner Production, 318 (14), 128456.
- Morales–Gonzalez, O. M., Escribà–Gelonch, M. & Hessel, V. (2019). Life cycle assessment of vitamin D3 synthesis: from batch to photo–high p. International Journal of Life Cycle Assessment, 24 (12), 2111–2127.
- Morales–Gonzalez, O. M., Zhang, C., Li, S. & Hessel, V. (2019). Solvent impact assessment for the "One–Flow Functional Solvent Factory". Chemical Engineering Science: X. 3(10), 100024.

## In preparation

- O. M. Morales–Gonzalez, M. T. De Martino, J. C. M. van Hest, V. Hessel, F. Gallucci. Techno–economic Analysis of Compartmentalized Cross–linked Enzymatic nano–Aggregates (c–CLEnA). *In preparation*
- Morales Gonzalez, O. M., Medrano, J. A., V. Hessel, F. Gallucci, Comparative uncertainty assessment of the use of automated purification with ionic liquids in the case study of the synthesis of benzyl azide. *In Preparation*

## Collaborations during thesis

- Grimaldi, F., Tran, N. N., Sarafraz, M. M., Lettieri, P., Morales–Gonzalez, O. M. & Hessel, V. (2021). Life Cycle Assessment of an Enzymatic Ibuprofen Production Process with Automatic Recycling and Purification. ACS Sustainable Chemistry and Engineering, 9 (39), 13135–13150.
- Tran, N. N., Tišma, M., Budžaki, S., McMurchie, E. J., Ngothai, Y., Morales Gonzalez, O. M. & Hessel, V. (2021). Production of Biodiesel from Recycled Grease Trap Waste: A Review. Industrial and Engineering Chemistry Research, 60 (46), 16547–16560.
- Nghiep Tran, N., Tisma, M., Budzaki, S., McMurchie, E. J., Morales Gonzalez, O. M., Hessel, V. & Ngothai, Y. M. (2018). Scale–up and economic analysis of biodiesel production from recycled grease trap waste. Applied Energy, 229, 142–150.

## Oral presentations

- O.M. Morales Gonzalez, J. Medrano Jimenez, F. Gallucci, V. Hessel. LCA–Process Scenario Analysis for the Rufinamide Precursor Production (Benzyl azide) – is a 'Functional Solvent Factory' Achievable. APCBM 2019, 3rd August 2019, Chengdu, China.
- O.M. Morales Gonzalez, F. Gallucci, V. Hessel. Life–Cycle Thinking for the ONE–FLOW Solvent Factory. CHISA 2018, 28th August 2018, Prague, Czech Republic
- O.M. Morales Gonzalez, C. Zhang, S. Li, V. Hessel. Sustainability assessment of cutting edge microflow process technology: Functional Solvent Factory. CHAINS 2017, 6th December 2017, Veldhoven, The Netherlands.

# ACKNOWLEDGEMENT

*Promoveren doe je niet alleen*

I would like to take this opportunity to express my deepest gratitude to the people that have joined me along this exciting journey. Having this opportunity has taught me a lot, and these skills will come with me forever.

This journey was possible due to the person that decided to give me the opportunity to participate in the ONE–FLOW project, thank you very much Dr. Volker Hessel. As well to you Dr. Fausto Gallucci, for welcoming me into your group after knocking at your door under unexpected circumstances. Thank you for your support, valuable discussions, and teachings.

To the members of my committee prof. Adelio Mendes, prof. Edwin Zondervan, prof. Timothy Noël and prof. Jan van Hest, for taking the time to read my dissertation and providing me with your valuable feedback.

Thank you Sirui and Jose, for being my daily supervisors. Sirui, even though you were only my supervisor for a short time, I appreciate the time that you gave me and your guidance. Jose, muchas gracias! for becoming my scientific support and daily guidance, you always had some words to guide me, even when I came with lots of doubts. I am grateful for your time and input in my manuscripts.

This experience would have also not been the same without the people that surrounded me. To my office mates that were there to talk and listen. Jannelies, you were my first office mate. You were always helpful with all kinds of questions that I had, thanks for your advice, for practicing Dutch with me, for the coffees, and games you taught me. Luca, madono!, you make me laugh so much with all your occurrences and your unique style. You are so bold and relaxed, which made that year with you one of a kind. Camila, you are such a good college and friend. Thank you for listening, for all the coffees and lunch together, and for bringing balance to our office by being so calm and responsible. I wish you the best in your Ph.D.

I cannot forget my colleagues and former colleagues. My always cheerful guys, Serena2, Arash2 and Thijs. Every time I saw you put a smile on me, keep that energy and positive attitude. Arash1, thank you for your wise and thoughtful advice. Radka, I have never met someone with such a people personality, thank you for everything. Smitha and Katerina for

sharing your experience and knowledge with Aspen simulations and LCA models, your knowledge is very valuable and gave me great ideas. Carlos, you are such a dedicated and hardworking man. Mark, thank you for our great collaboration. Thank you: Rohit, Xintong and Liangliang, Aitor, Hamid, for all the good times we shared in the office. Although I did not have an experimental setup, Carlos, Marlies, Erick and Pieter, it was great to get to know you and interact with you. I wish you a lot of success in your carries and thank you for being part of my journey.

Of course, to the people that keep this department running. Many thanks to our secretaries Jose, Denise and Saskia. Jose, your sweetness, and kindness were contagious. Thank you for easing my way in, and always helping me with my questions and doubts. Denise, powerful and efficient, you took over us and continue helping us. Thank you! I hope you are enjoying your retirement. Saskia, thanks for helping me in this last sprint with the organization of my defense.

Thank you, ONE–FLOW team, it was such a pleasure to learn from such a brilliant consortium. Special thanks to Teresa and Chenyue for our collaborations.

To my friends in Eindhoven, Alexandra, Anita, Miguel, Olga, and Erdem. Your words of encouragement and having your here is something amazing. A mis amigos mexicanos, Karla, Ezequiel, Emilio, Rose, Arturo, Jesus, Stephanie muchas gracias por lo momentos, las risas y la rica comida que hemos compartido.

A mis las majores amigas, Andy y Ana Karen. Gracias Andy por ayudarme con el diseño de la portada. Desde pequeñas supe que era muy talentosa, y apesar de lo acupada que estas econtraste el tiempo para ayudarme. Gracias, por hacerme sentir en casa y como si el tiempo no pasara cada vez que podemos vernos.

To my wonderful new college and friend Peps, for your craziness and support. I am glad I have met you and had the pleasure to work with someone so dedicated, careful, and fun.

To the ones that are no longer with me, Abuelo and Mariano, I will always remember you.

Gracias a mi familia, estar lejos de ustedes no es algo fácil. Pero es su apoyo incondicional y el que crean en mi lo que me ha traido aqui. Mamita, muchas gracias por ser el ejemplo de fuerza mas grande que tengo. Eres una mujer sin igual. Tu fuiste mi mayor motivacion para estudiar fuera, y un gran apoyo en todo momento. Gracias por los consejos, por escucharme y por el amor incondicional que me das cada día. Papa, gracias por ayudarme, apollarme y creer en mi. Dario, gracias por se un gran hermano y ejemplo de fuerza y trabajo duro, sigue luchando por cumplir tus metas.

To the person that has been next not me all this time. You have listened to me, you have encouraged me, you have made me laugh, you have comforted me, and you have supported me in all my crazy ideas. Even when I had 8 cats in the house! You are my best friend and my better half. Gracias Kevin! It was you who help me to apply for this PhD, and now we are here together. In yaakumech. Muchas gracias también a tu familia, y a tu mama en especial por el apoyo.

Finally, and most important to the one that makes all things possible.

I thank and praise you, God of my ancestors: You have given me wisdom and power.

Daniel 2:23

# ABOUT THE AUTHOR

Olivia M. Morales Gonzalez was born on January 28, 1991 in Tehuacán, Mexico. She obtained Bachelor's in Environmental Engineering from the Benemerita Universidad Autonoma de Puebla in 2013. Then due to her passion for sustainability and drive to develop scientific and engineering skills she moved to the Netherlands to study her master in the University of Twente where she obtained the degree of MSc. in Environmental and Energy Management with a CONACYT scholarship. Her ambitions led her to the Eindhoven University of Technology, where she obtained her second MSc. in Sustainable Energy Technologies, on the subject of catalytic delignification of lignocellulosic biomass, with an ALSP scholarship.

In 2017, she joined the Micro Flow Chemistry and Process Technology group at the Eindhoven University of Technology, as a PhD candidate under the supervision of Prof. Volker Hessel and Prof. Fausto Gallucci. Her doctoral research was part of the ONE–FLOW project founded by the H2020 FET–OPEN program of the European Commission. Her research focused on the ex–ante assessment of novel compartmentalization strategies for the synthesis of pharmaceuticals and fine chemicals, with an environmental and economic perspective. The results are presented in this dissertation.

In 2021 she joined GoodFuels as Project Researcher, and currently she is working as EHS Expert Energy and Climate Action in ASML, where continues with her wishes to contribute to a sustainable world.