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Retrofit Design of a Pharmaceutical Batch Process Considering "Green Chemistry and Engineering" Principles

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Considering the capital intensive nature of the chemical industry, redesign of existing production plants is a strategic decision. In this study, retrofitting is performed using a systematic path flow decomposition method, enriching it with hazard assessment and life cycle analysis path flow indicators and proposing a classification scheme for coupling these new path flow indicators with relevant heuristics for process alternative generation. The developed methodology is applied in a batch production plant from the pharmaceutical industry. The method highlights solvent recovery or substitution as important retrofitting actions, generates diverse process layout structures to achieve this task and evaluates them from cost, hazard and life cycle assessment point of view. Extractive distillation using glycol as an entrainer is identified as the multiobjective optimal option for separating the THF/Water azeotrope with improvement up to 40% for the various objectives compared with a base case where the waste solvent is incinerated. © 2015 American Institute of Chemical Engineers *AIChE J*, 61: 3423–3440, 2015

Keywords: path flow decomposition, sustainable process design, inherent safety, waste solvent recovery, life cycle assessment

Introduction

The chemical industry is currently facing a rising concern about sustainability aspects of chemical production. This is mainly due to increasing regulatory efforts from governments to protect the environment as well as to decreasing social acceptability with respect to catastrophic events during the last decades. At the same time, considering sustainability in chemical process design is not a straightforward task, as sustainable development is a complex concept and there is still ongoing effort to find common terms for describing it. In this context, several paradigms of sustainability in chemical process design can be considered, including inherent safety, health and environmental hazard assessment, green chemistry, and green engineering principles. In fact, as discussed in several approaches, one should not focus only on a single aspect[1] without addressing aspects from all three main pillars of sustainability, that is, economic, environmental, and social ones.[2]

In this direction, a first step for pursuing sustainability in the chemical industry is to develop specific indicators for various sustainability aspects, in order to be included in a multicriteria analysis of chemical process design alternatives. Several studies have addressed the inherent safety perspective of process design[3–7] emphasizing on substance and process hazard assessment. Green chemistry[8–10] and green engineering[11–13] studies have mainly focused on environmental aspects, for instance, in the specific topics of pollution prevention and waste reduction.[14,15] An extensive taxonomy of sustainability indicators has been recently presented following the GREENSCOPE methodology[16] and the authors have further discussed the data needs[17] for the calculation of the respective indicators. A part of this taxonomy refers to economic performance indicators, highlighting the fact that profitability remains a very crucial aspect of any sustainable chemical process design.

In fact, considering the capital intensive nature of chemical production, the retrofitting of existing production plants is a key strategic decision for the chemical industry. However, most of the studies which refer to the above mentioned sustainability paradigms focus on grassroot and early process design stages.[18,19] On the other hand, retrofit design methods are typically classified by incentives like overall cost efficiency,[20,21] production capacity,[22] and process flexibility.[23,24] Retrofitting studies targeting at sustainability aspects such as process integration[25,26] and waste minimization[27,28] have also been presented but only few studies[29,30] have attempted to provide systematic frameworks for the retrofitting task that simultaneously address diverse sustainability aspects. The lack of such multicriteria studies is even more profound in the case of "low volume-high value" chemical products typically produced in batch plants.[31–33]

The current study aims at enriching a class of systematic, multicriteria, retrofit design frameworks which are based on the path flow decomposition (PFD) concept.[34] The PFD method is a "source-to-sink" graph based approach that transforms all mass and energy flows of the process into open and cycle path flows of the components involved in the process. The original method included a set of path flow indicators

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Additional Supporting Information may be found in the online version of this article.

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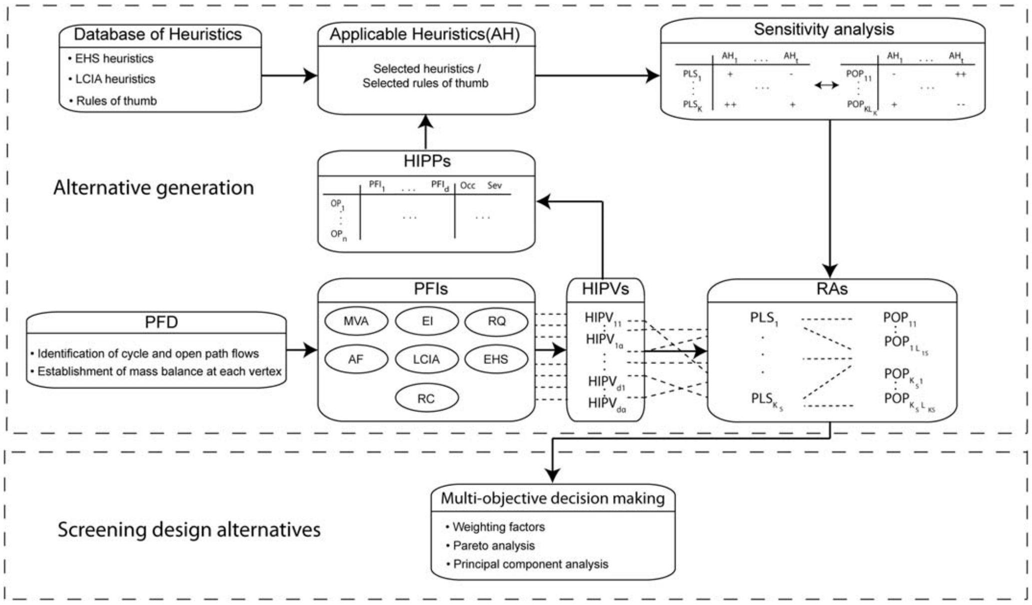

Figure 1. General retrofitting framework based on path flow decomposition, path flow indicators, heuristics, and sensitivity analysis for process alternative generation and multicriteria screening.

(PFIs) focusing on economic efficiency. A detailed description of these PFIs is provided as Supporting Information (Part A). A set of general heuristics has been associated with these PFIs to direct the search for retrofit design alternatives. More PFIs have also been added in other studies following this approach.[31–33] Moreover, a similar graph based approach using p-graphs[30] (i.e., directed bipartite graphs for representing process structures suitable for synthesis problems, where material streams are represented by circles, operating units by bars and connection between material streams and operating units by directed arcs) has been proposed for identifying retrofit alternatives (RAs).

In this study, new PFIs belonging to the categories of environmental, health, and safety (EHS) hazard assessment and life cycle impact assessment (LCIA) are introduced and added to the previously established PFIs to further facilitate green chemistry and engineering practices in the search and evaluation of RAs. Additionally, a set of relevant EHS and LCIA heuristics were collected from literature and adapted to the PFD based framework. A detailed list of these heuristics is available as Supporting Information (Part D). The applicability of the enriched overall framework is demonstrated in the retrofit of a batch process from the pharmaceutical industry, with special focus on alternatives for solvent substitution and recovery. The base case and all identified RAs have been rigorously modeled using commercial simulation software (Aspen Plus® from AspenTech) and available phase equilibrium data (Supporting Information, Part E). The results demonstrate the logic for selecting process layout settings (PLSs) and operating parameters with the help of the enriched PFD based framework, including the specific characteristics of the batch production mode. Moreover, the performance of the process alternatives is thoroughly discussed on the basis of a multicriteria assessment, considering instances of all three different pillars of sustainability, that is, economic, environmental, and social ones, expressed as operating costs, LCIA and EHS hazard assessment, respectively. Finally, the study concludes by highlighting some important next steps for further research within the PFD based retrofit design framework.

Methods

In the first part of this section the key concepts of the PFD based retrofit design framework are shortly described. Then, the second part comprises the main novel features of this study. In a first aspect these include the newly introduced EHS and LCIA relevant PFIs, which are defined in detail. Although a specific EHS method and LCIA metrics are proposed, the formulas for the respective PFIs are generic and substituting these with other methods and metrics is straightforward. A second novel aspect is a generic procedure for incorporating not only these newly introduced PFIs but also any other new indicators in the calculation of highest impact potential values (HIPVs) and paths. A third novel aspect is using known heuristics from the field of process design and inherent safety adjusted for the first time for the PFD framework. Although they are presented as Supporting Information (Part D) they are discussed in detail when the method is applied in the case study. Finally, a last novel aspect is the combination of these heuristics with sensitivity analysis for the generation of RAs.

It should be noted that although in several parts of the case study and the analysis of the results special reference is made to the particular features of the batch production, the proposed method is generic to any type of chemical production retrofitting.

PFD based retrofit design

After defining the process analysis boundary conditions, which are typically case study specific,[33] the PFD based retrofit design framework can be divided into two parts (Figure 1), namely the generation of RAs and the multiobjective screening of the generated alternatives. In the first part, cycle and open path flows (CP, OP) of all the substances in the process are identified and the mass and energy flows are allocated to the path flows by considering the respective balances at each vertex of the process graph and predefined mixing and allocation rules.[34] Then, PFIs are calculated for all path flows identified in the previous step and tabulated in a PFI matrix, where the rows represent the CP and OP flows and the columns represent the PFIs. The originally defined PFIs comprise the material value added (MVA), energy consumption (EC), reaction quality (RQ), accumulation factor (AF), and renting cost (RC), a detailed definition of which is provided as Supporting Information (Part A). In addition to these previously defined indicators, two new PFIs, namely the EHS hazard assessment and LCIA are newly introduced in this study. Each PFI is normalized according to the respective HIPV,[33] on the basis of which the highest impact potential paths (HIPPs) can be selected. The details on calculation of the newly defined PFIs as well as the selection of the corresponding HIPPs are given in the sections "New PFIs for Green Process Retrofut Design" and "From HIPVs to HIPPs" respectively.

After selecting the HIPPs, the next step is to generate RAs focusing on reduction of the negative impacts of these critical path flows. To this end, LCIA and EHS hazard assessment related heuristics were collected from scientific literature, adapted to the PFD based framework and added to those already existing in the framework. An extensive list of these newly added heuristics is available as Supporting Information (Tables S6 and S7 in Part D). The EHS relevant heuristics were classified into four classes, that is, general, reaction, separation, and storage specific heuristics, and also categorized according to four established inherent safety principles, that is, intensification, limitation of effect, substitution, and attenuation.[35] The LCIA relevant heuristics were also classified into three classes, that is, resource recovery, heat recovery, and waste treatment heuristics. Both types of heuristics were supported by rules of thumb for process design, safety, and green engineering (Supporting Information, Part D, Table S8). The combined use of heuristics and rules of thumb on HIPPs results in a set of applicable heuristics and rules of thumbs (AHs) targeting at the improvement of the HIPPs with respect to one or more HIPVs. The transformation of these general heuristics and rules of thumbs to specific PLSs and process operating parameters (POPs) requires engineering know-how assisted by sensitivity analysis. Moreover, for every selected PLS/POP combination there may be multiple set-values indicated by the sensitivity analysis. Hence, every PLS/POP/set-value combination denotes an RA. In summary, the essence of the PFD based retrofit design approach is to reduce the search space for the generation of RAs by exploiting the synergistic effects of PFD, PFIs, engineering knowledge based heuristics and local sensitivity analysis. In particular, the approach can be flexible depending on the scope of the retrofit design by focusing on those PFIs and heuristics which are more relevant to either economic performance, safety, green chemistry and engineering, or any combination of the above. It should also be mentioned that methodologies for grass-root design should always be a reference in retrofit design. Grass-root design methodologies are usually part of the retrofit design problem, as this often results in introducing a new subsystem in the process. Some examples of this kind refer to the change of the supply chain which can result to a totally new design of the upstream processes, the decision to increase the capacity and move from batch to continuous design, and the design of a new downstream material recovery system when the base case option is the disposal of the respective materials. The multicriteria analysis is intrinsic in the method, either directly due to the selection of the HIPPs on the basis of multiple PFI categories, or indirectly by monitoring the effect of the generated RAs in the overall PFI matrix.

In the second part of the method, a multiobjective screening of the selected RAs is proposed according to predefined objective functions calculated on the basis of the overall process (i.e., not of its decomposed counterpart like in the case of the PFIs). To this end, any objective functions representing the three main pillars of sustainability can be used in multiobjective decision making frameworks involving a priori weighting schemes, statistically derived ones (e.g., using principal component analysis) or Pareto front analysis. In this study, the operating costs are used as economic objective, the overall EHS indicator proposed by Sugiyama et al.[19] as hazard assessment objective for the social aspects and the cumulative energy demand (CED) as LCIA objective for the energy related environmental aspects.

New PFIs for green process retrofit design

Two types of new PFIs are introduced in the PFD based retrofit design framework, namely LCIA and EHS hazard assessment relevant ones. They are directly related to four out of the twelve principles of green chemistry,[10] that is, prevention of waste, design for energy efficiency, safer solvents and chemical auxiliaries, and inherently safer chemistry for accident prevention. They are also related to four principles of green engineering,[11] namely inherent rather than circumstantial, prevention instead of treatment, design for separation, and efficiency maximization.

PFI for EHS Hazard Assessment. Several inherent safety and EHS hazard assessments have been proposed and compared for chemical process design.[36,37] Actually, one of them, the inherent safety index (ISI),[18] has already been used in combination with PFD.[29] In this study, the definition of the hazard oriented PFI is based on the original EHS hazard assessment framework of Sugiyama et al.,[19] which captures in more detail the interaction between process inventories (i.e., expressed as stream flows) and inherent hazards of the respective components in these streams (i.e., expressed as dangerous properties such as mobility, fire and explosion, toxicity, degradation, etc.). This approach is more suitable than the ISI method for defining a new PFI, because it considers for each path flow both its extensive (i.e., mass flow) and intensive (i.e., dangerous properties of the substance referring to this path flow) information, rather than, for instance, considering only the maximum inventory in the process, as proposed in the ISI method. In order to provide a more versatile calculation of this new PFI, slight modifications were introduced with respect to the considered dangerous properties and their calculation. In this EHS framework a set of substance properties is the basis for an index calculation ranging between 0 (least hazardous) and 1 (most hazardous). For each substance property reliable data are selected from a variety of databases and estimation tools and priorities are set depending on the data availability. The detailed calculation procedure of the modified EHS framework is available as Supporting Information (Figures S1 to S3 in Part B). The EHS indicator calculated by this framework is incorporated in the PFD based retrofit design approach as a new PFI (EHS_P) according to Eq. 1

$$\mathrm{EHS}_P = m_p N_p \sum_{dp=1}^{DP} \max_u (\mathrm{Ind}_{p,dp,u}(T_u, P_u)) \tag{1}$$

where $\mathrm{Ind}_{p,dp,u}(T_u, P_u)$ is the index value derived by the EHS framework for path flow p and dangerous property (dp), (i.e., air effect, water effect, accumulation, irritation, acute toxicity, chronic toxicity, mobility, fire/explosion, reaction/decomposition) depending on temperature (T_u) and pressure (P_u) of the respective unit operation that the path flow passes through, N_p is the number of units the path flow passes through and m_p is the mass flow of the path flow. From the definition of EHS_P, it is obvious that this PFI penalizes flowsheet intensive path flows with respect to the number of unit operations the path flows are involved, and also incorporates the sense of a worst case scenario with respect to the conditions of the unit operations that the path flow passes through. EHS_P is applicable for both open and cycle path flows.

PFI for LCIA. Several LCIA indicators exist for the assessment of chemical products and processes and the following have been recently reported for fine chemical and pharmaceutical production[38]: the resource use oriented CED, the greenhouse gas emissions oriented Global Warming Potential (GWP), the damage oriented Eco-Indicator99 (EI99), IMPACT2002+ and ReCiPe, the "distance-to-political-target" oriented Ecological Scarcity 2006 and the North American perspective of environmental damages oriented Tool for the Reduction and Assessment of Chemical and Other Environmental Impacts. There is currently ongoing research about the use and correlations between these different methods.[39,40] Choosing an LCIA method might be dependent on the particular industrial sector as well as on company's interest. With energy related impacts gaining interest in nowadays economies, the CED is chosen here to demonstrate how such indicators can be incorporated in the PFD based retrofit design approach. This decision is also based on the industrial partner's interest that provided the case study for the application of the method and the fact that typically waste management systems need to satisfy legal emission limits, leaving EC as the most important degree of freedom for the process design from LCIA perspective. However, including other type of indicators in Eq. 2 should be straightforward with only minor adjustments. Hence, CED is incorporated in the PFD based retrofit design approach as a new PFI for open path flows ($\mathrm{LCIA}_{\mathrm{op,CED}}$) according to Eq. 2

$$\mathrm{LCIA}_{\mathrm{op,CED}} = m_{\mathrm{op}}(\mathrm{CED}_{\mathrm{op,pr}} + \mathrm{CED}_{\mathrm{op,tr}}) \tag{2}$$

where $\mathrm{CED}_{\mathrm{op,pr}}$ and $\mathrm{CED}_{\mathrm{op,tr}}$ are respectively CED values for production and treatment of the substance flowing in the respective open path (m_{op}), for example, by recovery, incineration, or waste water treatment (WWT). $\mathrm{CED}_{\mathrm{op,pr}}$ for reactants, auxiliaries, and process utilities can be calculated using available databases (e.g., EcoInvent[41]) or estimation tools,[42] while $\mathrm{CED}_{\mathrm{op,tr}}$ can be based on life cycle inventories for recovery and waste treatment technologies resulting from rigorous simulation or shortcut estimation methods based on industrial case studies.[43,44] $\mathrm{CED}_{\mathrm{op,tr}}$ is zero for open paths consumed by reaction, while $\mathrm{CED}_{\mathrm{op,pr}}$ for open paths originated by reaction follows a similar allocation pattern with the respective MVA calculation for the same paths.

From HIPVs to HIPPs

As depicted in Figure 1, after the calculation of all PFIs, the next step is to determine a set of HIPVs for each PFI. The original PFI matrix is normalized to a maximum value of 1 for each PFI according to the maximum negative impact potential expressed by the PFI definition. Then, a certain percentage of HIPVs per PFI is selected (e.g., in this study the top 10% HIPVs per PFI were used). After highlighting these HIPVs, the number of occurrences ($\mathrm{Ocr_p}$) of HIPVs within a path flow can be calculated. This should be done separately for the cycle and open paths, since some PFIs are applicable to only cycle or only open path flows. If two or more path flows have the same number of $\mathrm{Ocr_p}$, then a severity (Sev_p) measure is calculated based on all the PFI values of the respective path flow according to Eq. 3

$$\mathrm{Sev}_p = \sum_j \mathrm{PFI}_{p,j} \tag{3}$$

where $\mathrm{PFI}_{p,j}$ refers to the j-PFI of path flow p. Therefore, path flows are primarily ranked according to Ocr_p and secondarily according to Sev_p. The HIPPs are defined according to this ranking.

It should be mentioned that there are alternative approaches to identify HIPPs on the basis of HIPVs. For instance, the decision maker could prioritize the individual PFIs. Some examples in this direction is to follow a version of preemptive goal programming approach,[45] where the various PFIs are prioritized according to the decision maker preferences, and the optimal solutions identified in the most important PFI are further prioritized according to the next one until all PFIs are exhausted or only one solution is achieved. Alternatively, the decision maker can also empirically set weights for the various PFIs or follow a more consistent procedure according to the analytical hierarchy process[46] or a statistically driven principal component analysis.[47]

A different approach is to avoid an overall ranking of the paths, namely not to use a single metric that combines multiple criteria and characterizes the overall path profile. Instead, after the HIPVs are obtained for each PFI, the respective paths are analyzed according to applicable heuristics to derive a set of process alternatives resulting in potentially optimal solutions for each individual PFI. The next step would be to evaluate this significantly larger number of alternatives with respect to the overall objectives (i.e., process costs, LCIA and EHS hazard assessment). This approach would obviously generate more options and perhaps more tradeoffs, but it is also significantly more time-consuming. Therefore, the current approach can be considered as an efficient shortcut approach, where the promising paths are first identified based on their overall profile combining different criteria and then the process alternatives are generated by looking more carefully into this profile.

From HIPPs to AHs

Every HIPP defined by the procedure described above comprises two important features, a path flow profile defining the process sections crossed by the HIPP and a PFI profile defining the specific indicators that should be improved. These two features are used to guide the search for applicable path flow heuristics and rules of thumb from available databases, as depicted in Figure 2. In this study, the classification of the process flowsheet into reaction, separation and storage should be considered as a first generic classification with respect to the proposed heuristics and rules of thumb provided as Supporting Information (Tables S6–S8 in Part D). It should be noted that this first generic classification comprises neither an exhaustive list nor a specialized matching of heuristics and rules of

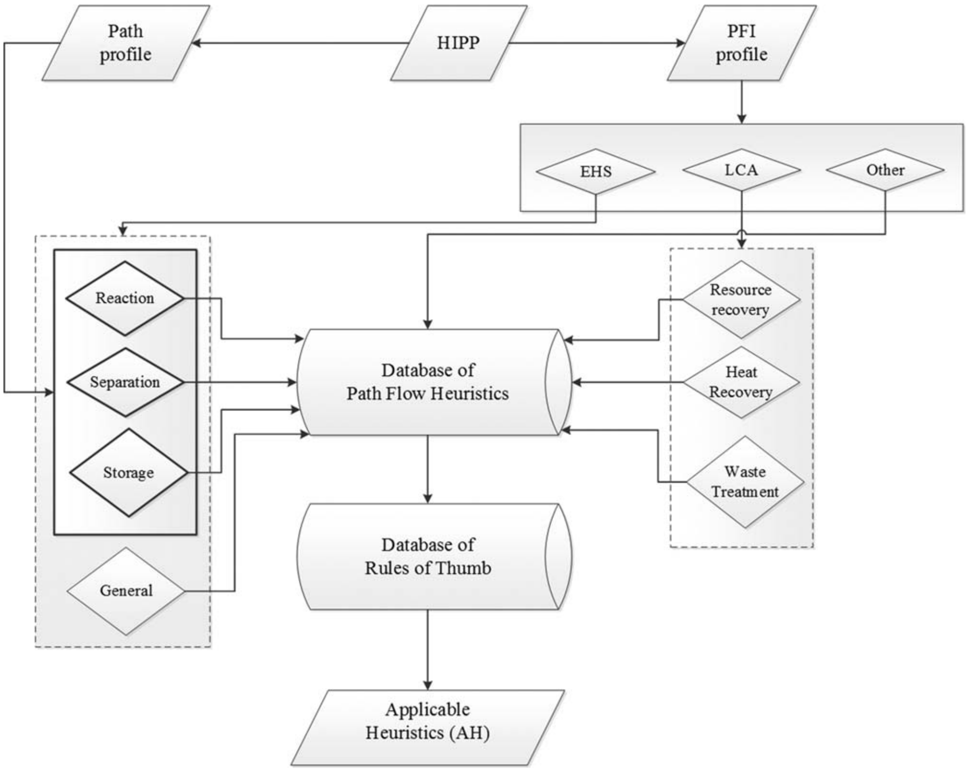

Figure 2. Flowchart for screening applicable heuristics (AHs) starting from higher impact potential paths (HIPPs).

thumbs to specific types of reactions (e.g., specific heuristics for gas phase reactions, fluidized beds, homogeneous or heterogeneous catalytic systems, etc.), separation processes (e.g., specific heuristics for distillation, extraction, adsorption, crystallization, membrane separation, etc.) and storage systems (e.g., specific heuristics for compressed gas, low temperature systems, etc.). It rather represents a top-level classification of heuristics in two dimensions, namely a generic unit operation dimension and a generic inherent safety principle dimension (Kletz's rules in Tables S6-S8 in Part D of the Supporting Information).

At the same time the PFI profile indicates whether priority should be given in the improvement of EHS, LCIA, or other (e.g., MVA, RQ, etc.) indicators. Being the primary focus of the current study, EHS and LCIA PFIs are further analyzed to search for improvement potential by matching with the classification of EHS and LCIA heuristics, that is, into general reaction, separation and storage specific heuristics for EHS, and resource recovery, heat recovery and waste treatment heuristics for LCIA. Therefore, for every HIPP a profile is created according to the criteria mentioned above that is supporting the search in the existing databases of path flow heuristics and rules of thumb. The result of this search is a set of applicable heuristics and rules of thumb (AHs) extracted from the original databases.

On the basis of these AHs, the process designer is motivated to propose new PLSs and their corresponding POPs, which should undergo a sensitivity analysis to quantify their impact on the improvement of the targeted HIPPs. This last step relies heavily on the modeling detail to which the process is described, is case study dependent and typically requires engineering know-how. Therefore, this last step will be best illustrated with the application of the updated PFD based framework in the industrial case study.

Case Study

A case study from the pharmaceutical industry was selected for the application of the PFD based retrofit design approach updated with the new PFIs and list of heuristics. Batch processes typically target dynamic markets of "high-value-low-volume" products. In this production sector minimizing the "lab-to-production" time can lead to suboptimal process design, which is later subjected to retrofitting. However, although the flexible nature of production allows changes from one production campaign to the next, good manufacturing practices and economic incentives still pose great challenges for application of green chemistry and engineering principles in retrofit designs. In fact, retrofitting batch processes in the pharmaceutical industry is even more challenging due to strict regulations when registering the production conditions and procedures. Therefore, this case study focuses on RAs not contradicting the industrial partner's common practices. A typical example refers to the material recovery section, where chemical reagents or auxiliaries are used either in the same process or in other processes of the plant, based on clearly defined purity specifications.

In the case study presented here, the boundary conditions of the batch production are the following: the batch size is 168 kg of an essential intermediate in pharmaceutical production (CarbamatB), 300 batches are produced per year in a non-overlapping mode (i.e., one major equipment is used for all the steps except for the centrifugation), and the reaction conditions (i.e., temperature and pressure) are strictly defined. Figure 3 presents the reaction scheme and the process flowsheet comprising the most important material flows, unit operations and their respective occupancy times. More specifically, dissolved SaltA in THF is charged in the reactor, the temperature is set at −5°C and a chloride solution in THF at 20°C is dosed for 0.5 h. The resulting reaction is exothermic with an

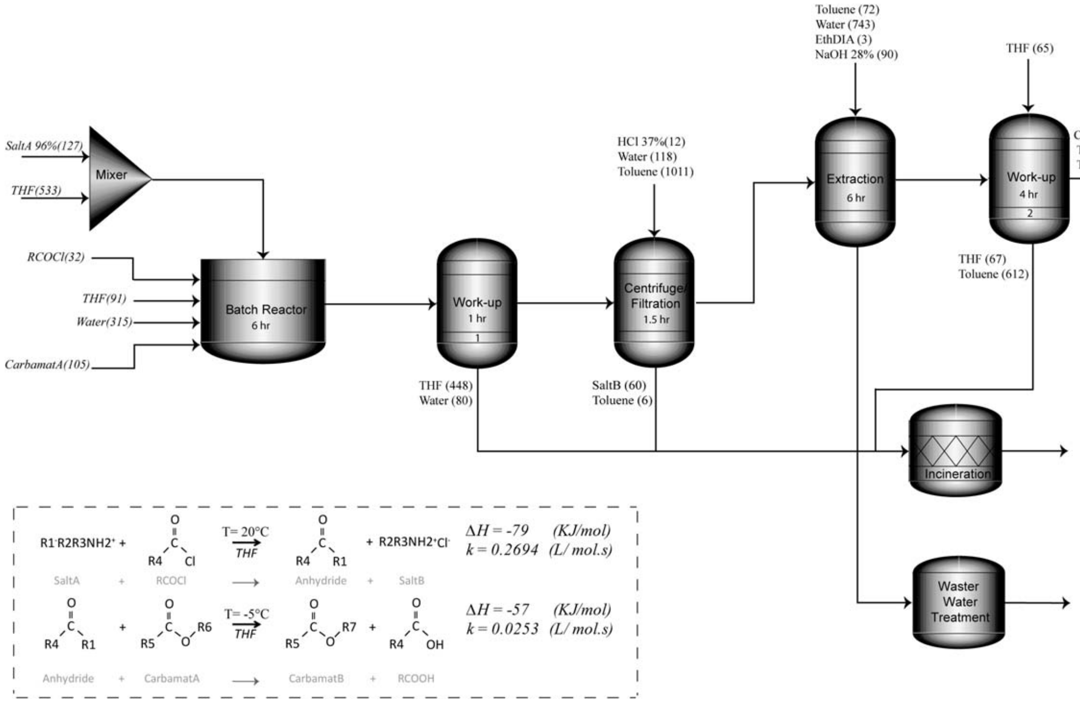

Figure 3. Reaction scheme and process layout for the base case of the production line of a pharmaceutical intermediate.

The main material flows of the process are indicated in parenthesis (kg/batch).

adiabatic temperature rise of 9°C and the semi-batch reactor is operated in a range of temperatures between −5 and 5°C. After the dosing, the mass is let to react for 1 hour before the subsequent dosing of CarbamatA for 0.5 h at 5°C. An amount of THF is used to facilitate the dosing of CarbamatA. After this dosing step the mixture is let to react for 4 h at a temperature between 20 and 25°C. This reaction is also exothermic with an adiabatic temperature rise of 6°C. Calorimetric data were available for the estimation of the reaction rate constants (L/[mol s]) and reaction enthalpies (KJ/mol) according to second order reaction kinetics. At the end of the reaction, water is added to wash the reactor in order to avoid product losses since the reacting system is rather a suspension than a solution. The reaction mixture undergoes a series of downstream workup stages. First, the reaction mass is concentrated by separating a mixture of THF and water, which is sent to the incinerator. Toluene, water and a solution of HCl are added and the mixture is sent to centrifugation to mainly separate SaltB, while the mother liquor is transferred with the help of some Toluene back to the reactor to undergo a series of liquid phase separation (extraction) stages. In every extraction stage water, solution of sodium hydroxide and ethylendiamine (EthDia) are added to remove remaining amounts of salts, anhydride, and acid (R_4COOH) in the water phase, which is sent to WWT. Therefore, after every extraction stage, the organic phase is gradually becoming richer in CarbamatB, THF and Toluene. After the series of extraction stages and washing with THF, the mixture is concentrated in a final downstream workup stage, after which a mixture of THF and mostly Toluene is sent to the incinerator, while the concentrated mixture containing CarbamatB is used in the next production stages.

Starting from the base case of the process described above, all alternatives generated by the PFD based retrofit design approach considered a maximum mass fraction of 0.2 for non-organic content as a constraint for the incineration of a waste stream. The positive energy gain from the incineration is calculated as a direct energy input to the system with efficiency of 75% (kg-steam equivalent). For the biological WWT a dilution factor is calculated for every treated waste stream based on its total organic carbon (TOC) content, the allowed toxicity levels for biological WWT (i.e., at maximum 20% of the LC50 values) and solubility parameters. The final dilution factor is considered to be the maximum of these three dilution factors. Detailed information about the calculation of the inventories for the incineration and WWT are provided as Supporting Information (Part C). With the exception of these end-of-pipe processes that are modeled using empirical correlations based on industrial data,[43,44] the modeling of all other unit operations for the base case and all RAs is performed using Aspen Plus® [48] with the help of industrial and experimental data (from DECHEMA[49]) for the selection of appropriate thermodynamic property estimation methods and estimation of separation efficiencies. More details are provided as Supporting Information, Part E.*

Results and Discussion

Retrofitting task and generation of alternatives

In order to highlight the potential for improvement in the base case presented above, the PFD based retrofit design approach was systematically implemented. The flowsheet decomposition resulted in a set of 25 open path flows using an equipment unit based representation (Table 1). To exemplify how these open paths are obtained, one can use the example of Toluene. Toluene has two sources in the flowsheet (i.e., centrifugation and the second work-up stage) and three sinks (i.e., the WWT and incineration facilities, as well as the next step

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*Due to confidentiality reasons, the respective flowsheets can not be readily available; the interested reader is, however, encouraged to contact the authors for further information.

Table 1. Identification of the Open Paths in the Case Study Process and their Description

Paths	Component	Equipment Units Crossed	Description
OP1	RCOCl	R	Consumption of reactant RCOCl in the first reaction
OP2	SaltA	M-R	Mixing of SaltA with THF and consumption in the first reaction
OP3	SaltA	M-R-W1-CF-E-WWT	Mixing of SaltA with THF, not converted in the first reaction, staying dissolved in the mother liquor during the first work-up and centrifugation stages, extracted in the water phase before discarded in the wastewater stream
OP4	CarbamatA	R	Consumption of Carbamat A in the second reaction
OP5	Anhydride	R-W1-CF-E-WWT	Remaining Anhydride after production in the first reaction and consumption in the second reaction, staying dissolved in the mother liquor during the first work-up and centrifugation stages, extracted in the water phase before discarded in the wastewater stream
OP6	CarbamatB	R-W1-CF-E-W2	Production of CarbamatB in the second reaction, staying dissolved in the mother liquor during the first work-up and centrifugation stages, extracted and concentrated in the last work-up stages and sent to the next production stages
OP7	RCOOH	R-W1-CF-E-WWT	Production of RCOOH in the second reaction, staying dissolved in the mother liquor during the first work-up and centrifugation stages, extracted in the water phase before discarded in the wastewater stream
OP8	SaltB	R-W1-CF-Inc	Production of SaltB in the second reaction, staying dissolved in the mother liquor during the first work-up stages, separated during the centrifugation stage and sent to the incineration plant
OP9	THF	M-R-W1-Inc	Mixing of THF with SaltA, acting as solvent in the first and second reaction, extracted during the first work-up stages and sent to the incineration plant
OP10	THF	M-R-W1-CF-E-WWT	Mixing of THF with SaltA, acting as solvent in the first and second reaction, staying dissolved in the mother liquor during the first work-up and centrifugation stages, extracted in the water phase before discarded in the wastewater stream
OP11	THF	R-W1-CF-E-WWT	THF addition to facilitate the dosing of CarbamatA for the second reaction, staying dissolved in the mother liquor during the first work-up and centrifugation stages, extracted in the water phase before discarded in the wastewater stream
OP12	THF	R-W1-CF-E-W2-Inc	THF addition to facilitate the dosing of CarbamatA for the second reaction, staying dissolved in the mother liquor during the first work-up, centrifugation and extraction stages, separated during the concentration of the mixture in the last work-up stages and sent to the incineration plant
OP13	THF	W2-Inc	Addition of THF in the last work-up stages, separated during the concentration of the mixture and sent to the incineration plant
OP14	THF	W2	Addition of THF in the last work-up stages, staying in the concentrated solution and sent to the next production stages
OP15	Water	R-W1-Inc	Addition of water after the end of the second reaction to wash the reactor, extracted during the first work-up stages and sent to the incineration plant together with THF
OP16	Water	R-W1-CF-E-WWT	Addition of water after the end of the second reaction to wash the reactor, staying dissolved in the mother liquor during the first work-up and centrifugation stages, extracted in the water phase before discarded in the wastewater stream
OP17	Water	CF-E-WWT	Addition of water for the centrifugation stage, extracted in the water phase before discarded in the wastewater stream
OP18	Water	E-WWT	Addition of water for the extraction, extracted in the water phase before discarded in the wastewater stream
OP19	Toluene	CF-E-WWT	Addition of toluene for the centrifugation stage, extracted in the water phase before discarded in the wastewater stream
OP20	Toluene	CF-E-W2-Inc	Addition of toluene for the centrifugation stage, extracted in the organic phase, separated during the concentration of the mixture and sent to the incineration plant
OP21	Toluene	CF-E-W2	Addition of toluene for the centrifugation stage, extracted in the organic phase, staying in the concentrated solution and sent to the next production stages
OP22	Toluene	E-W2	Addition of toluene in the extraction stage, extracted in the organic phase, staying in the concentrated solution and sent to the next production stages
OP23	HCl	CF-E-WWT	Addition of HCl in the centrifugation stage, extracted in the water phase before discarded in the wastewater stream
OP24	NaOH	E-WWT	Addition of NaOH in the extraction stage, extracted in the water phase before discarded in the wastewater stream
OP25	EthDIA	E-WWT	Addition of EthDIA in the extraction stage, extracted in the water phase before discarded in the wastewater stream

Table 2. Normalized Path Flow Indicator (PFI) Matrix for the Base Case According to the Higher Value Observed for Every Indicator

Paths	Mass (kg/batch)	MVA	EHS	LCIA	EC	RQ	RC	AF	Ocr	Sev	Rank
OP1	32	0	0.06	0.00	0.05	0.00	0.00	0	0	0.12	16
OP2	120	0	0.25	0.00	0.17	0.00	0.02	0	0	0.44	14
OP3	2	0.64	0.00	0.18	0.00	0.00	0.00	0	1	0.83	7
OP4	106	0	0.08	0.00	0.02	0.07	0.02	0	1	0.18	10
OP5	5	1.00	0.00	0.56	0.01	0.15	0.00	0	3	1.73	2
OP6	168	0.00	0.15	0.00	0.01	0.00	0.03	0	0	0.19	15
OP7	27	0.48	0.04	0.12	0.07	0.00	0.00	0	0	0.71	11
OP8	60	0.67	0.11	0.01	0.08	0.00	0.16	0	2	1.03	4
OP9	448	0.24	0.73	1.00	0.87	0	0.81	0	4	3.65	1
OP10	85	0.05	0.14	0.94	0.16	0	0.01	0	1	1.30	5
OP11	33	0.02	0.05	0.36	0.06	0	0.01	0	0	0.50	12
OP12	58	0.03	0.09	0.13	0.11	0	0.10	0	0	0.47	13
OP13	9	0.00	0.01	0.02	0.00	0	0.01	0	0	0.05	22
OP14	56	0.03	0.09	0.00	0.00	0	0.00	0	0	0.12	17
OP15	82	0.00	0.02	0.01	0.35	0	0.15	0	1	0.53	9
OP16	233	0.00	0.05	0.00	1.00	0	0.04	0	1	1.09	6
OP17	118	0.00	0.03	0.00	0.00	0	0.00	0	0	0.03	25
OP18	816	0.00	0.09	0.00	0.00	0	0.00	0	0	0.09	20
OP19	6	0.00	0.01	0.00	0.00	0	0.02	0	0	0.03	24
OP20	612	0.03	1.00	0.18	0.00	0	1.00	0	2	2.21	3
OP21	393	0.02	0.64	0.00	0.00	0	0.00	0	1	0.66	8
OP22	72	0.00	0.12	0.00	0.00	0	0.00	0	0	0.12	18
OP23	4	0.00	0.00	0.03	0.00	0	0.00	0	0	0.04	23
OP24	25	0.02	0.04	0.01	0.00	0	0.00	0	0	0.07	21
OP25	3	0.00	0.01	0.08	0.00	0	0.00	0	0	0.09	19

The underlined values are the top 10% higher impact potential values (HIPVs). Ocr (Occurrence) refers to the number of occurrences of HIPVs and Sev (Severity) to the sum of the values of all PFIs for each open path. If the PFI values are not zero by default, they are specified by two decimal points. Details about the path flow indicators and their calculation are provided in the text for LCIA and EHS, and as Supporting Information, Part A.

of the production process together with CarbamatB). The biggest amount is clearly introduced in the centrifugation step (Figure 3), while a significant amount is incinerated and most of the rest is going to the next process step. The PFD has followed this source-sink matching and identified four open paths for Toluene, namely OP19 to OP22 in Table 2. OP19 represents the small amount of Toluene leaving the centrifugation together with SaltB, mixed with waste water and treated in the WWT facilities. OP20 represents the part of Toluene that after the extraction, washing and concentration steps is incinerated. OP21 and OP22 represent the part of Toluene that goes together with CarbamatB in the next process step, the difference between the two paths being their source (centrifugation for OP21 and extraction for OP22).

No cycle path flows were identified, as there was no recovery and reuse of any substances in the process base case. More open paths could be identified using a unit operation representation; for example, an additional open path could be written for the anhydride considering that it is produced in a first reaction task and partially consumed in the second reaction task. Similarly, each one of the extraction and washing stages could be represented as a different unit operation increasing the number of open paths. However, the present study focuses mainly on the use of the newly proposed indicators within all stages of the framework and, therefore, for demonstration purposes the aggregation of different unit operations into an equipment unit based representation should be adequate. All mass and energy flows for the identified open paths are calculated with Aspen Plus®.[48]

Calculation of PFIs and Identification of HIPPs. The normalized PFI matrix is presented in Table 2 and includes the HIPVs, Ocr_p and Sev_p values as well as the respective ranking of the HIPPs. The open paths OP9, OP5, OP20, OP8, and OP10 are indicated as the top five HIPPs. Two of these (OP9 and OP10) refer to THF as a waste solvent with very high values for the new PFIs related to EHS and LCIA. Therefore, the management of THF as a waste solvent should be of interest for the pharmaceutical company in order to increase the "green-ness" of this production process.

The open path of anhydride (OP5) obtains a high ranking mainly due to its importance as valuable reactant indicated by the high MVA and RQ values designating a different path profile than OP9. RAs with respect to OP5 would first seek to increase the conversion of the anhydride in the second reaction so that less unreacted anhydride is lost in the waste water streams of the process. This would mean to decrease the excess of the anhydride to CarbamatA while keeping the same productivity levels for CarbamatB. To do this by providing an excess of CarbamatA to consume all the anhydride in the second reaction would be pointless, since CarbamatA is a "fresh" reactant (i.e., not an intermediate like the anhydride) and, therefore, this would only shift the problem to another open path (i.e., OP4), which after this RA would obtain high MVA and RQ scores in return. In this case a strategy for recovering CarbamatA would be required. If we aim to decrease the excess of the anhydride to CarbamatA by producing less anhydride in the first reaction (i.e., decreasing the amounts of RCOCl and SaltA and having also a positive impact to OP8 by decreasing the amount of SaltB), while still consuming all CarbamatA in the second reaction would mean different recipes for both reactions. This would affect reaction temperatures and durations and, perhaps, a strategy for recovering the unreacted raw material RCOCl and SaltA in the case of reduced time duration and lower conversions. This type of RAs are not further investigated in this study since the batch size, the number of batches, the nonoverlapping mode, and the reaction conditions are given as strict boundary conditions that should not be changed by process retrofitting. This is not an

Table 3. Applicable Heuristics and Rules of Thumb for OP9 Derived by the Respective Databases (Tables S6–S8 in Supporting Information, Part D)

	Heuristic	Class/Inherent Safety Rule	Relevant Rules of Thumb
1	Replace path flows with less hazardous ones.	General/Substitution	When possible, intensification is better than substitution
2	Substitute path flows of auxiliaries having low boiling point.	Reaction/Substitution	When possible, intensification is better than substitution
3	Optimize recovery of those path flows with RQ≥0 taking into account their AF.	Reaction/Limitation of effect-Attenuation	Be aware of trade-offs between attenuation and intensification. Continuous processes are usually safer than batch ones.
4	Use alternative recovery system to separate the path flow in case of inefficient separation.	Substitution	Consider liquid-liquid extraction and membrane based separations as alternatives to energy intensive distillation/evaporation.
5	Recover path flows of primary materials if direct recycling is not efficient.	Resource recovery	Consider poor selection of solvent and process inefficiencies as the main cause of solvent waste. Optimize entrainer to feed stage for extractive distillation.
6	Substitute path flows of traditional organic solvents, such as chlorinated and aromatic hydrocarbons, by more environmentally friendly alternatives.	Resource recovery	Consider material produced by biomass resources.
7	Increase the ratio of path flows of renewable feedstock to path flows of depleting sources sent to waste treatment units.	Waste treatment	

unusual case in pharmaceutical production, where the processes are registered in "test batches" decreasing the degrees of freedom for retrofitting. Of course, one could still test these cases for relatively mild "fine-tuning" of the processes or in a scenario based analysis. Such options have been adequately demonstrated in other PFD relevant publications.[29–34] Moreover, they seem to be independent from the solvent recovery RAs (i.e., there seem to be no common decision variables to lead to contradicting design alternatives and interesting trade-offs).

Another option would be to recover the anhydride from the waste water stream (i.e., the last unit operation in the path profile of OP5). However, this is not a promising RA since the amount of anhydride in this waste water stream is 5 kg/batch, which is less than 1 wt % considering the rest of the material for the work-up and washing stages described in the recipe.

For OP20, a reduction of the amount of Toluene mainly used for the separation of SaltB via centrifugation would be targeted, while for OP8 any mass reduction is related to the desired amount of anhydride as a coupled product. The rest of the study focuses on the generation and assessment of RAs based on OP9, the HIPP with the highest rank. In a complete retrofit study a similar analysis should be done for the rest of the HIPPs, but it is not presented here in order to illustrate in detail the use of heuristics, and in particular the newly introduced EHS and LCIA related heuristics, for the generation of RAs and their assessment.

Connecting HIPPs to Heuristics. Focusing on OP9, its path profile comprises four unit operations, including both reaction and separation sections. No specific storage section is considered, because the storage tanks associated with the end-of-pipe treatment (i.e., in this case the incineration) are not assigned to the process, as they are assumed to be plant operation dependent. However, storage tanks associated with solvent recovery (i.e., in retrofit actions) are assigned to the process, since they are assumed to be process operation dependent. Looking at the PFI profile of OP9, the RQ indicator is by default zero, since as a solvent THF is not considered to have a positive or negative effect in the reaction. The high value for the EC indicator is mainly influenced by the amount of THF, as no extreme conditions are used in the reactor or the workup process, and the high value for the RC indicator is influenced by both the mass of THF and the time that this path flow occupies the reactor (i.e., being present in both reaction steps). Reducing the mass of THF in the reactor with respect to the reactants is not possible due to solubility issues. Other more general volume-time debottlenecking policies for reducing the mass flows, which could also affect more open paths, for instance moving from a nonoverlapping to an overlapping mode using more equipment units or changing to a continuous system, are out of the scope of the retrofitting policies considered by the pharmaceutical company due to equipment availability and standard production policies, respectively.

Coming back to the newly introduced EHS and LCIA indicators, OP9 is the only path with very high values in both of them, as indicated in Table 2. In particular, OP9 has the first HIPV in the LCIA indicator and the second HIPV in the EHS indicator after OP20, an open path of Toluene. The big difference in LCIA between the values of OP9 and OP20 is mainly due to the $CED_{op,pr}$ values (i.e., 126.4 MJ-eq/kg for THF and 63.2 MJ-eq/kg for Toluene). On the other hand, THF and Toluene have similar overall EHS profiles (Table S2 in Supporting Information, Part B), and the difference in the EHS indicators of the open paths is mainly due to the respective mass flows. Compared with the open paths of THF sent to the WWT (OP10 and OP11), OP9 has a more severe LCIA impact again because of the relevant mass amounts. Obviously, a retrofit action would not be to shift even small amounts of THF waste streams from the incineration to the WWT, because the respective energy relevant environmental impacts for THF are −40.5 MJ-eq/kg, and 293.1 MJ-eq/kg respectively, without considering the required fresh solvent amounts.

With this analysis in mind for the path and PFI profile of OP9, the available path flow heuristics and rules of thumb in

Table 4. Important Properties of THF, MeTHF, and CPME in Standard Conditions

Property	THF	MeTHF	CPME
Density (g/cm^3)	0.89	0.85	0.86
Solubility in water (g/100g)	Infinite	14	1.1
Flash point (°C)	−14.5	−11.0	−1.0
Boiling point (°C)	65	80	106
Azeotropic temperature (with water) (°C)	64	71	83
Azeotropic composition (solvent, % w)	93.3	89.4	83.7
Peroxide formation	High	High	Low
Solubility of SaltA (g/L)	252	298	236
Solubility of CarbamatA (g/L)	68	15	3
Solubility of CarbamatB (g/L)	458	228	31

the database (Tables S6-S8 in Supporting Information, Part D) were screened resulting in a set of applicable heuristics reported in Table 3. To this end, the path profile of OP9 involves the operations of mixing (M), reaction (R), separation (W1) and finally incineration (Inc). Therefore, storage specific heuristics are not considered. Here, it should be mentioned that THF is actually stored before being fed to the incineration unit, since the operation of the incineration unit is managed dynamically considering all available effluents in the production plant and not only those produced by the investigated process. Therefore, it is obvious that the amount of THF in the storage tanks, that is the number of batches stored before the amount is fed to the incineration, does not depend only on the operation or retrofitting of the investigated process but mainly on the overall plant waste management. This case shows the importance of a clear definition of the system boundaries for the retrofitting task.

From the "general class" of heuristics, only heuristic-1 has been included in Table 3 referring to substitution of the path flow with a less hazardous solvent. Of course, the application of this heuristic would probably affect all open paths of THF passing through the reactor, that is OP10-OP12. If this other solvent is not compatible with THF because, for instance, of separation problems, then also OP13 and OP14 would be affected by this heuristic, since THF would also have to be replaced there. However, all these open paths of THF have much lower impacts in almost all indicator categories mainly because of their relatively small mass flows. Therefore, even if trade-offs exist, OP9 is expected to play a dominant role in the system performance. Moreover, the substitution of THF is also suggested by heuristic-6 in Table 3 that refers to the high environmental impact indicated by the LCIA profile of OP9 and supported by the directly affected open path, OP10. Clearly, in this case, there is a "win-win" situation for this heuristic indicated by both EHS and LCIA reasoning. On the other hand, a relevant rule of thumb indicates that, at least for cost reasons, intensification is usually prioritized to substitution. However, groundbreaking intensification solutions are outside the retrofitting scope for the specific production environment of the pharmaceutical company and, therefore, this rule of thumb is not considered to be decisive.

Other OP9 relevant heuristics from the general class of Table S6 (available as Supporting Information, Part D) are the reduction of the amount of the path flows to reduce inventories, rerouting of path flows with low boiling substances (e.g., 65°C for THF) or the use of excess of non-hazardous substances in the same path profiles. These are already satisfied in the base case scenario of the process, the first by solubility limitations and the other two by the water open paths OP15 and OP16. Other heuristics that are also satisfied by the base case are the operation close to ambient conditions, the avoidance of path flows with flammable material in low pressure systems, the avoidance of common paths with hazardous profiles (i.e., in this case the Toluene paths do not cross similar units as the OP9 path), the reduction of the number of process operations of the path flow profile and the depletion of a path flow as early as possible (i.e., OP9 is a rather short path). Finally, there are also OP9 irrelevant heuristics, at least with respect to the base case set-up. These include the elimination of impurity related path flows, the rerouting or removing of cycle path flows to avoid inventories, the reduction of the source of path flows that end-up to WWT (i.e., this would be relevant for OP10 and OP11 for THF) and the reduction of oxygen containing path flows. However, it should be noted that some of these heuristics may become relevant for alternative process layouts. This is true, for instance, for the cycle path flows relevant heuristics, if recovery of THF is suggested as a RA.

In a similar way EHS relevant heuristics for OP9 are selected by screening the reaction and separation specific classes (Table S6 in Supporting Information, Part D). Substitution of THF due to its relatively low boiling point and optimization of recovery of path flows with either neutral or positive RQ are the two OP9 relevant reaction specific heuristics. The option of parallel reactors or even continuous operation modes to intensify the process and reduce the inventories of hazardous path flows is restricted by the case study constraints about the accepted type of retrofit actions. On the other hand, suggested heuristics for rerouting of path flows to the reactor to further dilute the solution are not relevant here because of already low adiabatic temperature rise values (9°C and 6°C for the two reactions, respectively) and generally not severe hazards allocated to the reaction itself. Moreover, there are no path flows with boiling points below the reactor operating conditions. Although some of the rest of the reaction specific heuristics would be relevant for other HIPPs (e.g., for OP5 to alternate the reactor conditions of path flows with RQ>0), one would not identify them at this point of analysis because of their low EHS profile. However, these or similar heuristics may be applicable for improving the profitability or the LCIA impact, and, therefore, they could be identified for a path flow like OP5.

The separation specific heuristics, from EHS point of view, also identify the recovery of OP9 as an important retrofit action. Using an alternative recovery system for the work-up process (W1) that belongs to the path profile of OP9 is a second applicable heuristic. Since W1 is a simple evaporation, the distillation relevant heuristics (e.g., use of alternative entrainers) are not applicable for the base case scenario, although most of them would become relevant if reflux conditions are introduced in W1.

LCIA relevant heuristics from the resource recovery, heat recovery and waste treatment categories (Table S7 in Supporting Information, Part D) are also reported in Table 3. Substitution of traditional organic solvents by more environmentally benign ones is certainly applicable for a solvent such as THF with high $CED_{op,pr}$ value. The heuristic indicating recovery of path flows when direct recycling is not efficient is also applicable here because the first reaction step takes place in a water free reaction mass, which does not allow direct recycling of the THF/Water mixture. Other LCIA heuristics could become relevant after implementing some of the aforementioned ones. For instance, if THF is recovered, then minimization of the

EC PFI for the cycle paths of the recovery system could be targeted and heat integration of path flows could be possible. Typically, some LCIA heuristics from the database are not applicable in this case study. For instance, the heurisitc referring to the right vertex for recycling OP9 is not of particular interest, since this is not a very complicated flowsheet with many recycling options for THF. Other LCIA heuristics could be again applicable for the rest of the open paths (e.g., for OP5 and OP10 to prevent the formation of path flows which end-up in WWT), while some other heuristics lie outside the system boundaries (e.g., those referring to optimization of mixing/splitting of path flows before assignment to waste treatment, because such a decision would be made centrally at the plant waste management level).

On the basis of this screening of heuristics for OP9, a first obvious strategy is to recover the respective amount of THF. As OP9 has to be separated from water path flows (OP15) forming azeotropic mixtures with THF, continuous pressure swing distillation (PS_c) is considered and compared to the alternative technology of continuous and batch extractive distillation (ED_c and ED_b) with respect to the recovery efficiency. In this case, a careful selection of entrainers is suggested by the rules of thumb (Table S8 in Supporting Information, Part D), to avoid inefficiencies and solvent waste.

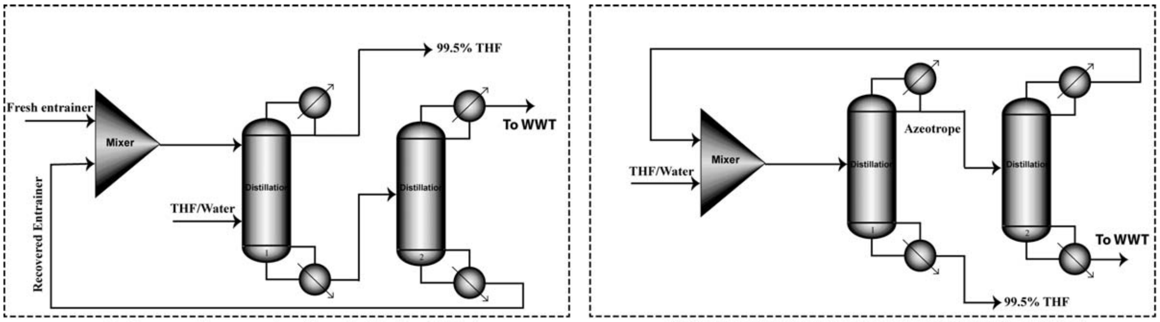
Moreover, alternative recovery systems in case of inefficient or energy intensive distillations are proposed in Table 3 by the heuristics and rules of thumb. For the THF-Water system, industry heuristics[50] mention that addition of certain water immiscible solvents can effectively dry THF to the required purity. Therefore, in this study a continuous liquid-liquid extraction (EX_c) with pentane is also considered as a structural alternative. Here, it should be mentioned that the rules of thumb generally favor continuous over batch processes. Batch distillation is included in this study because it offers more flexibility and is more easily accepted as a retrofitting option in a batch operating production environment.

It should also be mentioned that other separation techniques of recovering THF from water are also effective in industrial practice. These include mainly brine extraction, liquid phase adsorption with molecular sieves, and dehydration with caustic soda or calcium chloride in liquid-solid contact columns. The brine extraction method can be applied in batch or continuous operation and is generally preferred for large quantities of THF provided a high degree of dryness is not required (e.g., not more than 99.5%wt.). Both conditions do not hold in the case of the present case study (i.e., relatively small quantities and high degree of purity required). Pressure swing and extractive distillation can reach purities of at least 99.5 wt %. On the other hand, the same purity can be achieved by the aforementioned methods employing solids.[50] However, rigorous process simulation of these systems is more demanding with respect to experimental data. Since this kind of data was not available, a comparison of solid/liquid based THF recovery systems to the vapor/liquid based ones would not be done on a similar basis. Moreover, the main focus of this work is not to exhaust the potential separation possibilities. This has been demonstrated elsewhere for the case of the PFD framework in continuous[29] and batch systems.[32]

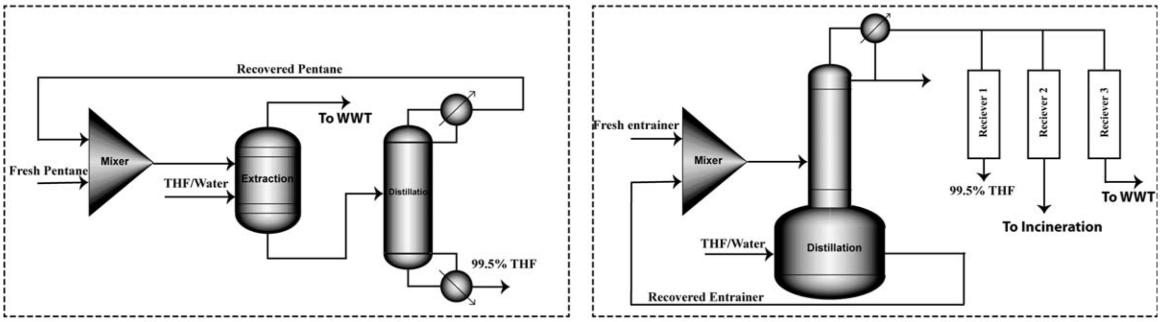
The second strategy investigated in this study is to substitute THF, possibly with methyl-THF (MeTHF) or cyclopentyl methylether (CPME), which are both compatible with the process chemistry of the case study and are often referred to as "greener" solvents than THF.[51,52] For instance, MeTHF can be produced from agricultural feedstocks having therefore a much lower $CED_{op,pr}$ (36.7 MJ-eq/kg), while CPME has some more favorable EHS hazard related properties (e.g., higher boiling point, low peroxide formation, see also Table 4), and both MeTHF and CPME have a lower EHS hazard profile than THF (Table S3 in Supporting Information, Part B). However, it should be kept in mind that according to the available rules of thumb (Table S8 in Supporting Information, Part D), intensification is preferable to substitution, and therefore substitution of THF with MeTHF or CPME would also have to be investigated under the scope of recovery of these solvents. Table 4 illustrates some of the important properties of THF, MeTHF, and CPME which affected the results and decisions

Table 5. Process Layout Settings Derived by Heuristics and Rules of Thumb

PLS	Abbreviation	Entrainer	Settings
Continuous pressure swing distillation	PS_c	–	A two-column system is used, the first column operating at low and the second column at high pressure. For the THF-water minimum boiling azeotrope, the pure THF is collected at the bottom of the first column and the water at the bottom of the second column.
Continuous extractive distillation	ED_c	Glycerol, ethylene glycol, propanediol, hexanediol	A two-column system is used, the component with higher volatility (THF) being collected at the top of the first column and the entrainer/water mixture at the bottom of the first column. The entrainer is recovered in the second column.
Batch extractive distillation	ED_b	Glycerol, ethylene glycol, propanediol, and hexanediol	The entrainer is fed in a semi-continuous mode at a particular column stage. The detailed steps of conducting batch extractive distillation using Aspen Plus ® are provided as Supporting Information, Part F).
Continuous liquid-liquid extraction	EX_c	Pentane	Adding pentane to the THF/Water mixture causes formation of two phases, an organic phase containing pentane, most of the THF and a small amount of Water, and an aqueous phase containing some THF and traces of pentane. Pure THF is obtained from the organic layer by distilling off pentane and water. Pure pentane is recovered from the top of the column and recycled back to the extraction unit.



Option continous extractive distillation (ED_c)   Option continous pressure swing distillation (PS_c)



Option continous extraction (EX_c)   Option batch extractive distillation (ED_b)

Figure 4. Different process layout settings for THF recovery from a THF/Water waste stream.

in this case study. Because of the low solubility of reactant (CarbamatA) and product (CarbamatB), CPME was not further investigated in this study. The basic PLSs, for which the operating parameters were thoroughly investigated with sensitivity analysis, are described in Table 5 and schematically presented in Figure 4.

Regarding pharmaceutical case studies facing similar solvent recovery issues, other structural alternatives could also be considered such as pervaporation[53] to avoid energy intensive distillation. Moreover, in the case of using MeTHF and recovering it from a mixture with water, the option of conventional batch azeotropic distillation with a decanter after the overhead condenser has been reported to give 50% to 85% cost savings (i.e., for MeTHF recoveries between 70% and 95%, respectively) compared to the case that THF is not recovered.[54] Although this option is not rigorously modeled in the present study, the results of the identified process alternatives are also put into perspective with respect to this reported performance.

Sensitivity Analysis for POPs/PLSs and Generation of RAs. The heuristics listed in Table 3 are formulated in a generic way and have to be associated with specific POPs to result in clearly stated RAs. To this end, besides engineering knowledge, a sensitivity analysis is also necessary to comprehend the process behavior and assess the relevance of the RAs. Here we applied a local, first order sensitivity analysis, namely for every POP (e.g., entrainer to feed stage ratio [E/F]) dependent variables (e.g., reflux ratio, distillate rate) were identified so that the design specification (e.g., purity of recovered solvent) was always satisfied and the solvent recovery was maximized, while the rest of the variables remained at their base case values. These fixed base case values were atmospheric pressure for all the column systems (i.e., with the exception of the high pressure column in pressure swing distillation which was set to 10 bar), an E/F ratio of 2, and five theoretical stages.

It is important to keep in mind that the sensitivity analysis in the PFD method is not necessarily meant to produce optimal RAs; it is rather meant to create a reasonable set of "well-performing" alternatives based on PFIs and/or local process parameters and after screening the most promising ones to assess them from a multicriteria point of view based on generic objectives (e.g., cost, LCA, hazard analysis). Of course, when more RAs are generated and/or screened according to higher order sensitivity analysis, then the resulting multicriteria assessment can even claim global optimality. However, this was outside the scope of this study, whose main goal was to demonstrate how to use the newly introduced notions in PFD.

Table 6 illustrates a small part of this sensitivity analysis for recovery scenarios for the THF-water mixture, considering batch and continuous extractive distillation (ED_b, ED_c, respectively). The actual numerical values behind the "+/−" notation in Table 6 can be found in Part G of the Supporting Information (Table S11). The entrainer to feed stage ratio (E/F) was indicated as an important POP by the heuristics. Generally, the positive effect of increased E/F values compared to the base case ($E/F = 2$) is demonstrated for all entrainers, expressed as higher THF recovery, lower amount of entrainer and lower reboiler and condenser duties. In this case, there is no trade-off between the LCIA and EHS related PFIs. However, the optimum value of this ratio is clearly case dependent, comparing the behavior of different entrainers. For glycerol and glycol one could go higher than the indicated values to reach an optimum, while for hexanediol and propanediol the respective optimum has already been reached. This ratio is equally important for both batch and continuous distillation and deriving an optimum value resulted in an improvement of more than 10% in the column performance. A detailed analysis of the E/F impact is provided as Supporting Information (Figures S4a and S4b in Part G). Another example of a

Table 6. Sensitivity Analysis Results for the Original Process Layout Using THF as Solvent

POP	Value	PLS	Reboiler Duty	Condenser Duty	Entrainer Mass	Recovery	LCIAop	EHSop	EHScp
$A1_{E/F}$	2.5	$ED_{b,Glycerol}$	–	0	–	+	–	–	–
$A2_{E/F}$	5	$ED_{b,Glycerol}$	–	0	–	+	–	–	–
$A3_{E/F}$	3.5	$ED_{b,Glycol}$	–	0	–	+	–	0	0
$A4_{E/F}$	10	$ED_{b,Glycol}$	–	0	–	++	–	–	–
$A5_{E/F}$	10	$ED_{b,Hex}$	0	0	0	++	–	–	–
$A6_{E/F}$	13	$ED_{b,Hex}$	0	0	–	+	0	–	–
$A7_{E/F}$	6.5	$ED_{b,Prop}$	0	0	–	++	–	–	–
$A8_{E/F}$	10	$ED_{b,Prop}$	0	0	–	+	–	0	0
$A9_{E/F}$	3	$ED_{c,Glycerol}$	–	–	–	++	–	–	–
$A10_{E/F}$	4	$ED_{c,Glycerol}$	–	–	–	++	–	–	–
$A11_{E/F}$	2.5	$ED_{c,Glycol}$	–	–	–	+	–	0	–
$A12_{E/F}$	3.5	$ED_{c,Glycol}$	–	–	–	++	–	–	–
$A13_{E/F}$	6	$ED_{c,Hex}$	–	–	0	++	–	–	–
$A14_{E/F}$	9	$ED_{c,Hex}$	–	–	0	+	0	–	–
$A15_{E/F}$	4.5	$ED_{c,Prop}$	–	–	0	++	–	–	–
$A16_{E/F}$	6	$ED_{c,Prop}$	–	–	0	+	–	0	–

In this example, the process layout setting of the generated alternative is the extractive distillation in continuous and batch operating mode ($ED_{c,}$ ED_b) and the process operating parameter is the entrainer to feed stage ratio (E/F). Various alternatives ($A_{E/F}$) are checked and the values are compared to a base case where E/F=2. Along with the change in the indicated POP other POPs may also be changed (e.g., reflux ratio) to satisfy the purity of the recovered solvent (0.995 mass fraction). The symbols have the following meaning: 0: change in the values of the respective parameter less than 2%, +/−: increasing/decreasing values of the respective parameter up to 10%, ++/−−: increasing/decreasing values of the respective parameter more than 10%.

sensitivity analysis procedure for the extractive distillation system refers to the number of stages in the distillation column for recovery of the entrainer. Further details on these sensitivity scenarios are also provided as Supporting Information (Figures S5a and S5b, in Part G).

Similar sensitivity analysis scenarios have been performed for other PLSs, such as the continuous pressure swing distillation and the liquid-liquid extraction systems. All the aforementioned scenarios have been repeated for exchanging THF with MeTHF in the process, with the exception of liquid-liquid extraction, where no suitable solvent was found in literature. Figure 5 summarizes the gate to gate EC of the various systems for THF and MeTHF. It can be seen that in this case study some vapor-liquid separation options (ED_c with Glycol, Glycerol, Propanediol, and PS_c) are competitive from EC point of view with the tested liquid-liquid extraction system, obviously due to increased EC for the recovery of pentane. Moreover, comparing the THF and MeTHF systems, similar trends for different entrainers are observed, while THF was favored by the pressure swing distillation system. These results show that based on the specific settings of a case study, local sensitivity analysis plays an indispensable role to validate and improve the generic heuristics and suggest meaningful RAs.

Screening design alternatives

All generated RAs were compared in order to identify the best options in a multicriteria assessment. Here, one has to

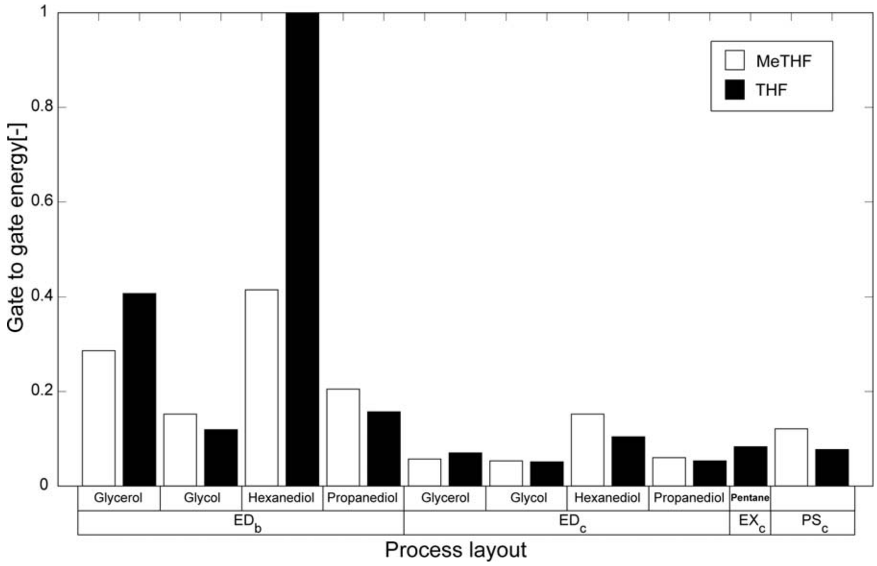


Figure 5. Gate to gate energy consumption of the various process alternatives for recovering THF from a THF/Water waste stream and MeTHF from a MeTHF/Water waste stream, when MeTHF substitutes THF in the production process.

The values of gate to gate energy consumption are normalized according to the highest observed value. The solvents used for the extractive distillation and extraction are provided for every case (ED_b: extractive distillation in batch mode, ED_c: extractive distillation in continuous mode, EX_b: extraction in continuous mode, PS_c: pressure swing distillation in continuous mode).

Table 7. Number of Solutions in Pareto Fronts for Different Number of Objectives

Number of Objectives	Type of Objectives	Pareto Front-I	Pareto Front-II	Pareto Front-III
7	EHS production, EHS storage, EHS recovery, Gate to gate energy, Cradle to gate energy, Capital Cost, Operating Cost	36	–	–
5	EHS production, EHS storage, EHS recovery, Cradle to gate energy, Cost	18 (18)	7 (15)	8 (23)
3	EHS, Cradle to gate energy, Cost	5 (5)	9 (10)	10 (13)

The numbers without parentheses show how many of the 36 solutions of the 7-objective problem belong to the respective Pareto fronts, while the number in parentheses refer to the total number of solutions in the respective Pareto fronts. (Pareto front-I: the Pareto front consisting of those solutions dominating all other solutions, Pareto front-II: the Pareto front consisting of those solutions dominating all other solutions, without considering the Pareto front-I solutions, Pareto front-III: the Pareto front consisting of those solutions dominating all other solutions, without considering the Pareto front-I and Pareto front-II solutions).

remember that the generated RAs in this study are by no means exhausting the design space, since they result from a first order, local sensitivity approach. The RAs here are meant to illustrate the proposed approach. It is, therefore, possible that a more thorough screening of the design options can generate more promising alternatives for the multicriteria assessment.

Several different approaches that formulate multiobjective optimization of monetary and nonmonetary objectives are available in literature.[2,19,55] In this work, a Pareto front approach has been applied consisting of seven objectives. It has also been investigated in what extent all the objectives were necessary for deriving the Pareto front solutions. Table 7 demonstrates the corresponding objectives and the number of Pareto front solutions starting from the case of seven objectives where 36 alternatives have been identified in the first Pareto front (Pareto front-I). It also shows how these Pareto optimal alternatives are reduced and distributed into the subsequent Pareto fronts (Pareto front-II and III) as the number of objectives is reduced by merging some of the original seven objectives. For instance, by merging annualized capital and operating cost into a single cost category and similarly cradle to gate and gate to gate energy in another single category, only 50% of the previous Pareto optimal alternatives remain in Pareto front-I. Their performance in all five objectives is presented and compared with the base case in Figure 6, where there is an obvious tradeoff between EHS recovery and EHS storage and a clear cutoff in terms of cost compared to the base case. On the other hand, the LCIA effect expressed by the cradle to gate EC is significantly lower. A further reduction of the number of objectives to three reduces predominantly the Pareto front-I objectives, although it can also be observed that approximately 70% of the seven objective Pareto front-I solutions are also maintained in the first three Pareto fronts of the three objective solutions. Therefore, for simplification purposes, it was considered reasonable to proceed into screening of the design alternatives based only on three objectives and their first three Pareto fronts without significant loss of multicriteria optimality.

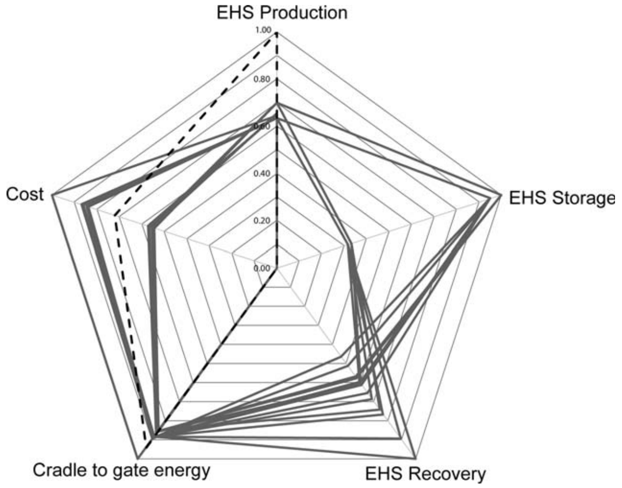


Figure 6. Multiobjective performance of process alternatives for solvent recovery belonging to Pareto front-I (the case of five objectives, see also Table 7).

The performance of the base case (waste solvent incineration) is presented in dashed line. The objective values are normalized according to the highest observed values.

This procedure was applied separately to every PLS and Figures 7 and 8 illustrate the overall performance of the RAs belonging to the first three Pareto fronts. The base case refers to the incineration of THF and MeTHF, respectively, with no solvent recovery. As it can be seen from Figure 7, substituting THF with MeTHF leads to higher costs because of the higher amounts of MeTHF required (i.e., due to the lower solubility of CarbamatA and B in MeTHF, as reported in Table 4) and its higher price, while the hazard performance is similar. Comparing Figure 7 and Figure 5, we can infer that the gate-to-gate EC of the recovery process is not the main factor in this case, neither for THF nor for MeTHF. For instance, the batch extractive distillation using hexanediol is approximately 10 and 4 times more energy intensive than the pressure swing distillation for the recovery of THF and MeTHF, respectively (Figure 5). However, from the overall cost perspective, this accounts for an improvement of less than 30% and 10% for THF and MeTHF, respectively. Therefore, the reported 85% cost savings in the recovery of MeTHF through conventional batch distillation[55] would not significantly cover the cost gap between THF and MeTHF in this case study.

For both solvents four clusters are identified, the batch distillation systems (ED_b) demonstrating the lowest hazard mainly because of lack of excessive storage in buffer tanks connecting the batch production with the continuously operated systems. For THF, the EX_c and PS_c alternatives are in the same cluster with ED_c, the PSc alternatives demonstrating slightly higher hazards because of higher operating pressures. On the other hand, Figure 8 shows that the base case for incineration of MeTHF was preferable from energy point of view compared to THF. This was due to the lower CED values for production of MeTHF originating from renewable feedstock. However, in contrast to the THF alternatives, the recovery systems for MeTHF are more energy intensive compared to the base case of incineration. In addition, the EX_c alternative for THF is now in the same cluster as ED_c and PS_c alternatives for

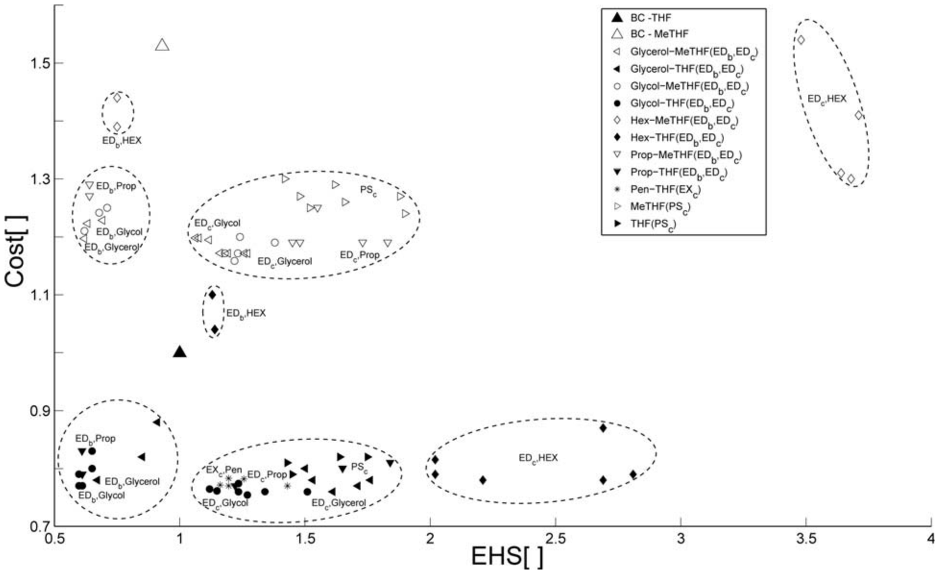


Figure 7. Cost (operational and annualized capital cost) versus EHS hazard assessment for the generated process alternatives.

The base case (BC) represents the incineration of the waste solvent stream containing THF or MeTHF, respectively. The circled areas depict clusters with similar performance. The objective values are normalized according to the performance of the base case. (ED$_b$: extractive distillation in batch mode, ED$_c$: extractive distillation in continuous mode, EX$_b$: extraction in continuous mode, PS$_c$: pressure swing distillation in continuous mode, Hex: hexanediol as solvent for extractive distillation, Prop: propanediol as solvent for extractive distillation, Pen: pentane as solvent for extraction).

MeTHF with higher cradle to gate EC than the respective recovery systems for MeTHF. This shows that the cost assessment for this liquid-liquid extraction system is not dominated by the energy related LCIA.

As mentioned in Table 7, the three objective system had five alternatives in Pareto front-I which can also be recognized by the two dimensional projections in Figures 7 and 8. These belong predominantly to THF recovery via extractive distillation using glycol as an entrainer either in batch or continuous operating mode. Compared with the base case for THF, an overall improvement of 10–20% is observed in cost units and up to 40% in EHS units. The improvement in LCIA units is lower than 10%. On the other hand, focusing only on MeTHF, extractive distillation using glycol or glycerol either in batch

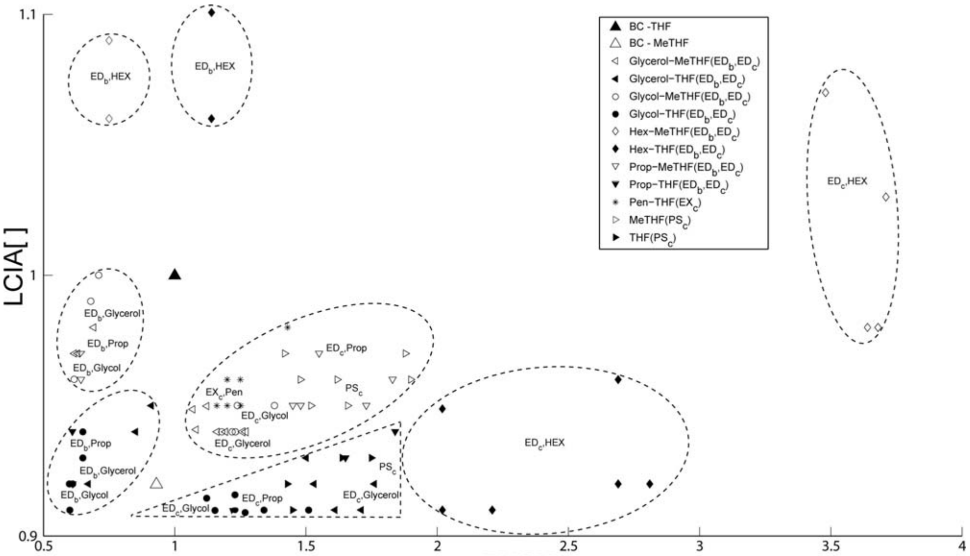


Figure 8. Life cycle impact assessment versus EHS hazard assessment for the generated process alternatives.

The base case (BC) represents the incineration of the waste solvent stream containing THF or MeTHF, respectively. The circled areas depict clusters with similar performance. The objective values are normalized according to the performance of the base case. (ED$_b$: extractive distillation in batch mode, ED$_c$: extractive distillation in continuous mode, EX$_b$: extraction in continuous mode, PS$_c$: pressure swing distillation in continuous mode, Hex: hexanediol as solvent for extractive distillation, Prop: propanediol as solvent for extractive distillation, Pen: pentane as solvent for extraction).

or continuous operating mode are cost effective solution with an improvement of approximately 15% and up to 40% in EHS units. However, it should be noted that the base case of incineration belongs to the Pareto front of the MeTHF solutions, since it outperforms all other alternatives from LCIA point of view.

Conclusion and Outlook

The modern chemical industry is firmly dependent on remarkable achievements of process synthesis over the last century. In some sections, such as in the pharmaceutical industry, rarely a new plant is built to accommodate a new process or product and therefore, the role of retrofit design is more crucial. Moreover, the high amount of solvents per mass of final pharmaceutical product has recently raised questions about sustainability issues of pharmaceutical production. So far in the literature, studies refer to the retrofitting task from various perspectives, however only few of them systematically consider green chemistry and engineering principles.

To this end, this study proposes a highly systematic PFD methodology coupled to heuristics highlighting EHS and LCIA metrics in search for “greener” process retrofitting alternatives. After integrating into this established methodology two new PFIs capturing the EHS and LCIA process performance, the corresponding higher impact potential values and paths were identified and analyzed using generic heuristics and sensitivity analysis. The recovery of a THF path flow from a common path flow of water has been indicated as the most promising retrofitting action for process improvement. The suggested structural alternatives representing diverse recovery systems were screened in a multiobjective way. The results have indicated extractive distillation as the best solvent recovery strategy, the selection of the entrainer being of great importance, (glycol demonstrated the best performance) along with column operating parameters (e.g., entrainer to feed stage ratio).

The same scenarios were tested for substituting THF with MeTHF, which has been recently indicated as a “greener” solvent mainly because it is produced from renewable feedstock. The multicriteria results of this case study do not generally support such a decision not only because of the higher price of MeTHF compared with THF but also from the higher quantities required by the process due to solubility issues. This makes a good example for differentiating between “green” substances and substances that make a specific process “greener” or more sustainable. However, it should be noted that a more thorough screening of the design space for the POPs of the recovery systems could further enhance the generated RAs and, therefore, the multicriteria assessment.

Regarding pharmaceutical case studies facing similar solvent recovery issues, other structural alternatives could also be considered such as pervaporation[53] as an alternative to energy intensive distillation. Moreover, in the case of using MeTHF and recovering it from a mixture with water, the option of conventional batch azeotropic distillation with a decanter after the overhead condenser can also be examined.[51]

In conclusion, this work has not only demonstrated but also enriched the PFD framework for process retrofitting with green chemistry and engineering principles. It is of course desirable to further apply the proposed approach to more case studies. This may lead to refinement of the proposed metrics and certainly to enriching the database of heuristics and their generic classification proposed herein. This was outside the scope of the current paper, which focused on the combination of elements that have been developed, demonstrated and validated in other studies in the framework of PFD to further enrich its mutlicriteria performance in terms of green chemistry and engineering principles.

Future work should also focus on enhancement of the PFIs to also capture other sustainability relevant issues, such as emission, supply chain, product quality, and social factor related effects of process design. For this, not only a proper definition of PFIs will be necessary but also a continuous enrichment of the database of heuristics and rules of thumb facilitating systematic generation of process alternatives and minimizing human interaction. It is important to move from the current generic to a more specialized classification of heuristics, considering specific reaction, separation and storage systems. This becomes particularly relevant for the application of the method for a large number of identified HIPPs as well as for complicated processes where the path flow profiles contain a large number of unit operations.

Finally, the method should also be compared with established heat and mass integration frameworks to look for synergies between these system-oriented approaches and a system-decomposition approach that is the PFD. To this end, advanced simulation/optimization frameworks can be applied[56] that take full advantage of rigorous process flowsheeting (such as Aspen Plus®) coupled with MINLP optimization solvers. Finally, for multiobjective optimization and dimensionality reduction, principal component analysis could be compared against or combined with traditional Pareto-fronts analysis.

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Notations

AF = accumulation factor
AH = applicable heuristic
CED = cumulative energy demand
CP = cycle path
CPME = cyclopentyl methyl ether
DP = dangerous properties
EHS = environmental, health, and safety
EC = energy consumption
EI99 = eco-indicator 99
EDb = batch extractive distillation
EDc = continuous extractive distillation
EXc = continuous extraction
GWP = global warming potential
HIPV = highest impact potential value
HIPP = highest impact potential path
ISI = inherent safety index
LCIA = life cycle impact assessment
MSDS = material safety datasheets statements
MVA = material value added
MeTHF = methyltetrahydrofuran
Ocr = occurence
OP = open path
PFD = path flow decomposition
PFI = path flow indicator
PLS = process layout setting
POP = process operating parameter
PSc = continuous pressure swing distillation
RA = retrofit alternative
RC = renting cost
RQ = reaction quality
Sev = severity

THF = tetrahydrofuran
TOC = total organic carbon
WWT = waste water treatment

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