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Intensified downstream processing for bioenzymatic HMF valorization: Design, simulation, and techno-economic feasibility

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ABSTRACT

The industrial viability of bioenzymatic production pathways for value-added chemicals relies on the development of energy-efficient and economically feasible downstream processes. This study presents the design, simulation, and techno-economic assessment of a novel downstream separation and purification process for the bioenzymatic conversion of 5-hydroxymethylfurfural (HMF) into four value-added products, namely: 2,5-bis(hydroxymethyl)furan (BHMF), 5-(aminomethyl)-2-furanmethanol (AMFM), R-1-phenylethylamine (R-PEAM), and S-1-phenylethylalcohol (S-PEA). The newly proposed process integrates a heat pump-assisted vacuum distillation column (supplying 5.38 MW_{th} to drive water evaporation) with pinch-optimized heat exchanger networks, reducing the heat pump system's total cost of ownership by 3% relative to a classic 10 °C minimum temperature approach design (44.31 vs. 45.67 M\$). Alternative separation routes for the amine products and their process intensification via dividing wall column (DWC) were systematically evaluated against the base case across economic and environmental metrics. The DWC implementation of Route 2 (Case c) achieved high amine recovery (>99.88%) at the production cost of 42.94 \$/kg of pure product and lowest pollutant and toxic materials emissions of 0.469 kg_{pt}/kg_{product}, although at a marginal increase in material intensity (0.0425 vs. 0.0420 kg_{waste}/kg_{product}) relative to the base case. All four products were obtained at purities exceeding 98%wt for BHMF and 99.9%wt for the remaining products. Economic feasibility is primarily determined by the price ratio of AMFM to phenylsilane feedstock, with AMFM currently priced significantly above the estimated production cost. This work demonstrates that heat pump integration and process intensification via DWCs offer measurable (but system-specific) advantages for bioenzymatic downstream processes, providing a quantitative basis for industrial scale-up decisions.

1. Introduction

Around 10% of the oil and gas resources are directly consumed in the production of chemicals. This is expected to rise to 20% by 2040 since the chemical industry's demands are foreseen to rise faster than those of any other sector [1]. At the same time, industrial processes are the third biggest source of greenhouse gas (GHG) emissions with a contribution of 6.5% [2]. The transition of the chemical industry toward sustainable practices, reducing its reliance on fossil-based raw materials, is therefore of global importance. Chemical synthesis from biomass is becoming a more preferred option representing this transition due to the renewable nature and abundance of biomass [3]. The most promising bio-based chemicals in this sense were identified by the U.S. Department of Energy and their industrial implementation is considered of key

importance toward a circular economy [4]. Two of these chemicals, i.e., 2,5 furandicarboxylic acid and levulinic acid, can be produced from 5-hydroxymethylfurfural (HMF), and it is the main route of production for 2,5 furandicarboxylic acid [5].

As a consequence, HMF is also considered a bio-based platform chemical [6], which can be transformed into a range of derivatives with utilizations as plastic materials [7], pharmaceuticals [8], food products [9], or fuels [10]. The transition toward bio-based chemical production has intensified interest in HMF as a versatile platform molecule derivable from biomass [11], especially lignocellulosic biomass due to its low cost, minimal impact on the food supply chain, and carbon-neutrality [12]. Its enzymatic and biocatalytic conversion into high-value derivatives (including chiral amines, amino alcohols, and diol compounds) offers a sustainable route to specialty chemicals [13] that are otherwise synthesized through multi-step, solvent-intensive chemical pathways

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Nomenclature

AMFM	5-(aminomethyl)-2-furanmethanol
BHMF	2,5-bis(hydroxymethyl)furan
BMED	Bipolar membrane electrodialysis
CAPEX	Capital expenses
CCC	Cold composite curve
CEPCI	Chemical engineering plant index
COP	Coefficient of performance
CH	Cyclohexane
DSP	Downstream process
DWC	Dividing wall column
GCC	Grand composite curve
GHG	Greenhouse gas
HCC	Hot composite curve
HEN	Heat exchanger network

HEX	Heat exchanger
HMF	5-hydroxymethylfurfural
IEC	Installed equipment cost
IEX	Ion exchange
LLX	Liquid-liquid extraction
MT	Metric ton
NF	Nanofiltration
OPEX	Operational expenses
PC	Production cost
PEA	1-phenylethylalcohol (reactant)
R-PEAM	R-1-phenylethylamine
RO	Reverse osmosis
S-PEA	S-1-phenylethylalcohol (product)
TCO	Total cost of ownership
TEA	Techno-economic assessment
TOL	Toluene

[14]. Among these derivatives, 2,5-bis(hydroxymethyl)furan (BHMF) is a promising bio-based diol for polymer applications [15], while R-1-phenylethylamine (R-PEAM) and S-1-phenylethylalcohol (S-PEA) are enantiomerically pure building blocks of considerable pharmaceutical [16] and agrochemical value [17]. 5-(Aminomethyl)-2-furanmethanol (AMFM), a bifunctional amine-alcohol is an emerging specialty chemical with limited commercial availability and thus high market value [18]. The simultaneous production of all four compounds via a single bio-enzymatic cascade reaction is an industrially attractive opportunity, provided that efficient downstream separation can be achieved.

Despite growing research on HMF valorization, downstream processing (DSP) remains one of the principal bottlenecks limiting the industrial deployment of bioenzymatic production routes, as these can contribute up to 90% to the overall production costs [19]. Bioreactor effluents are characteristically dilute aqueous streams, with target compound concentrations often in the low millimolar range necessitating the removal of large water quantities prior to product recovery [20]. Conventional distillation-based separation of thermally labile furan derivatives such as BHMF is further complicated by low degradation temperatures [15], requiring operation under vacuum conditions that substantially increase associated costs [21]. Previous work on the separation of HMF and its derivatives has demonstrated the technical feasibility of distillation-based routes, but has identified high energy consumption as a critical barrier to economic viability [22,23]. Heat integration strategies (especially heat pump-assisted distillation and pinch analysis-guided heat exchanger network design) have been shown to reduce utility requirements in analogous separation systems with high water content [24,25], yet their application to multi-product bio-enzymatic DSP has not been systematically investigated.

Process intensification through dividing wall columns (DWCs) offers a new way for improving the efficiency of multi-component separation. DWCs integrate thermally coupled distillation into a single vessel, reducing both capital expenditure and energy use compared to conventional column sequences [26,27]. Their application to pharmaceutical and fine chemical separations has expanded considerably in recent years [28], though implementation in bioenzymatic downstream processes (where product streams are dilute, thermally sensitive, and chemically diverse) face design challenges that remain largely unexplored in the open literature.

Several studies demonstrated the applicability of DWCs for intensified bio-based separations, such as the downstream processing of enzymatic systems [29] and dilute fermentation-derived products [30,31]. However, the separation of bio-derived compounds remains particularly challenging when products are present at low concentrations and exhibit limited thermal stability. The low concentration of the bio-derived products increases the importance of the liquid and vapor

flows distribution within the DWC, as separation efficiency and energy performance are highly dependent on the selected split ratios [32]. The selection of an appropriate DWC configuration is therefore critical, as the location of side-stream withdrawals and split ratios strongly influence the separation performance and controllability [33]. For such systems, fully thermally-coupled DWC configurations represent an attractive choice, as the side-stream withdrawal geometry and dividing-wall location can be tailored to accommodate intermediate boiling compounds while maintaining favorable internal vapor and liquid distribution [33]. Consequently, fully thermally coupled DWC configurations equipped with structured packing are particularly attractive due to the enhanced separation efficiency while minimizing pressure drop and liquid holdup, as such reducing the thermal exposure of temperature-sensitive products and preserving the benefits of process intensification.

Techno-economic assessment (TEA) is a key tool for evaluating the industrial readiness of emerging separation processes and identifying the cost drivers that must be addressed to enable scale-up [34]. Combined TEA and environmental impact assessments, applying established cost estimation frameworks [35,36] alongside green chemistry performance metrics [37], provide the quantitative basis needed for technology development decisions.

This original study – invited for the Special Issue (Separation and Purification Technology) on Recent Developments in Bioseparation Science and Technology – addresses these research gaps by developing and assessing a fully integrated downstream separation process for the simultaneous recovery and purification of BHMF, AMFM, R-PEAM, and S-PEA from a bioenzymatic reaction mixture at a production scale of about 1000 MT per year per product. The process combines vacuum distillation, liquid-liquid extraction, ion exchange, nanofiltration, and bipolar membrane electrodialysis, unified through a pinch-optimized heat pump system. Two alternative amine separation routes and their DWC implementations are evaluated comparatively on economic and environmental grounds. This work provides the first integrated TEA of a heat pump-assisted, DWC-intensified downstream process for this bio-enzymatic product system, offering a quantitative basis for assessing industrial feasibility and guiding future process development.

2. Methodology

2.1. Plant configuration and design specifications

The bioenzymatic synthesis of 5-hydroxymethylfurfural (HMF) to value-added derivatives was based on another study (n.b. the experimental data are part of another scientific paper currently under evaluation for publication), taking into consideration the reaction between racemic 1-phenylethylalcohol (PEA) and HMF. The maximal suggested

reactant concentration of 30 mM was taken into account with total conversion of HMF into an equimolar mixture of R-1-phenylethylamine (R-PEAM), 2,5-bis(hydroxymethyl)furan (BHMF), S-1-phenylethylalcohol (S-PEA), and 5-(aminomethyl)-2-furanmethanol (AMFM). The implications of sub-complete conversion for the downstream process are discussed in Section 4. The current study focused on the separation and purification of these high-value compounds for a scaled-up system with a productivity of ~1000 metric tons (MT) per year for all four value-added derivatives. The base case of the proposed DSP is presented in Fig. 1.

The detailed description of the filtration of solids (i.e., cells and phenylsilane derivatives) from the bioreactor's product stream was not the scope of the study, as solids removal from an aqueous stream is well described in the literature. Consequently, the rigorous simulation in Aspen Plus V11 software environment was aimed at the separation and purification of the resulting aqueous stream which was assumed to contain only the four value-added HMF derivatives. The ELECNRTL property method was employed to capture the non-ideal behavior of the multi-component system, addressing the chemical speciation of amines and the impact of ionic strength on the activity coefficients of polar organic solutes. The selected method can handle both dilute and concentrated aqueous and mixed solvent systems. The separation of the mentioned products was previously studied [38], however, the present study focused on enhancing the reported energy intensive system with the main scope of integrating low-enthalpy processes, the possibilities of process intensification, as well as the economic assessment of the proposed DSP cases. Since distillation is a well-established separation technology that is employed on an industrial scale, it was considered as the primary recovery method. All distillation columns (C1–C4, DWC) were simulated in Aspen Plus V11 using the RadFrac equilibrium-stage (MESH) model with 100% stage efficiency. Pressure drop was neglected for C1–C4 (design-stage approximation) and set to 0.3 mbar/theoretical stage for the DWC's Mellapak structured packing [39]. Due to the lack of experimentally validated mass-transfer data, a rigorous rate-based model was not applied. As such, the results should be regarded as appropriate for conceptual process design and comparative techno-economic assessment. Furthermore, owing to the limited literature information available for the purification of several compounds, parts of the proposed process were modeled based on the assumptions presented in Table 1.

Table 1

Main design assumptions of the proposed DSP.

Process	Assumptions
Pre-filter system	Consists of disk stack centrifuge, bag filters, and cartridge filters. Solids are fully separated from the aqueous stream.
Reverse osmosis	RO separates 50% of water from the incoming stream, while 99% of organic compounds are retained in the original stream.
Nanofiltration	Nanofiltration (NF) reduces the water and acid/base content of the inflow stream by 80%. A 1% loss of organics was assumed.
Bipolar membrane electro dialysis	Acid/base recovery of 99% is assumed in R1 and R2 streams. All organics remain in the outgoing streams, i. e., S9 and S32. A 1% loss of organics was assumed.

The first step of the separation, was the removal of half of the water content from the bioreactor stream through reverse osmosis (RO). This was followed by reduction of the stream's pH to a value of around 2, in which case the AMFM and R-PEAM products would be in the form of protonated amines. As such, the amine and alcohol compounds are separated through an ion-exchange process considered to be ideal in terms of separation of these two types of products. Before the separation of the alcohol products, the water and acid content reduction of the stream take place employing a nanofiltration (NF) and a bipolar membrane electro dialysis (BMED) process, respectively. Following these processes, the resulting stream (S9) is neutralized in consideration of supplementary equipment costs due to the material selection that would be otherwise necessary for the dilute HCl stream. The alcohol products are then separated by vacuum distillation, which is necessary due to the reported low degradation temperature of BHMF of above 120 °C [15]. The distillation process is to be performed at 0.1 bar absolute at the top of the column (C1), in order to obtain the bottom product (i.e., BHMF) under 120 °C. Due to the lack of experimental data, the UNIFAC estimates of the BHMF-water NRTL parameters were utilized in the Aspen simulation. The sensitivity study presented in the Supplementary Material (Fig. S1) showed that the same quantity and quality of the BHMF product can be obtained with the different binary parameters by correspondingly adjusting the reboiler duty of C1. The significant quantity of vapors obtained as the distillate (S13) is further utilized in a heat pump system for heat integration purposes, i.e., the preheating of

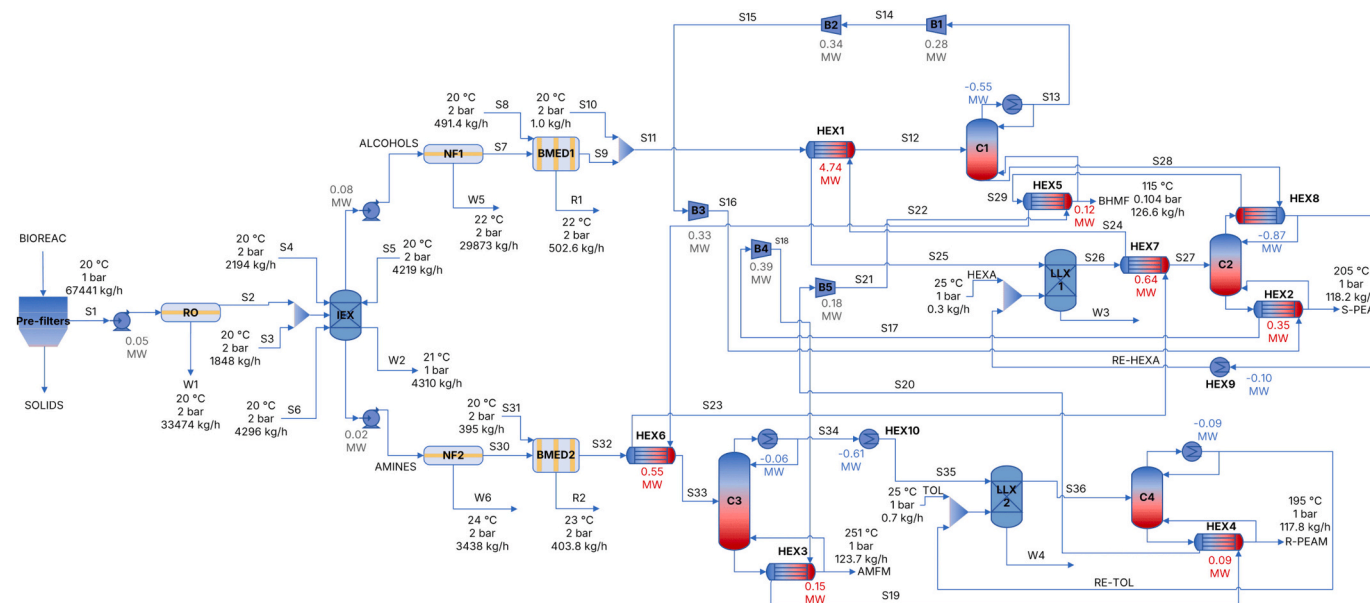


Fig. 1. Scheme of the heat integrated downstream process for the separation and purification of BHMF, S-PEA, R-PEAM and AMFM. Detailed stream information is provided in Table S2.

feed and heat pump assisted distillation. The liquid-liquid extraction process of S-PEA was performed with hexane as solvent based on its reported best recovery performance of 2-phenylethylalcohol from a dilute aqueous stream compared to other solvents [40].

This system was modeled considering the UNIFAC estimates of the temperature dependent binary parameters of S-PEA–hexane, for which a sensitivity analysis is presented in the Supplementary Material (Fig. S2). In the worst-case scenario ($b_{ji} = 1104$, i.e. +20% from the estimated value), the hexane recycle requirement almost doubles to ~9000 kg/h and S-PEA loss increases to 0.524 kg/h. However, the LLX1 separation remains technically feasible at this condition. To quantify the economic impact, the production cost was re-evaluated under the worst-case hexane recycle. The increased utility demand and solvent make-up cost raises the overall production cost by about 0.4 \$/kg (~1% relative increase from the base case of 42.94 \$/kg). This confirms that the process remains economically viable even under maximum NRTL parameter uncertainty for this binary pair.

This is followed by distillation column C2 where S-PEA can be obtained as the bottom product while the distilled hexane is recycled, greatly reducing the necessary hexane make-up (HEXA) for the LLX1 process. In terms of the amine products, the stream (AMINES) undergoes similar water and base content reduction, through NF and BMED processes. Afterwards, the preheated S33 stream is fed to column C3 responsible for the separation of AMFM from the aqueous feed as the bottom product. The AMFM–water binary parameters were UNIFAC estimated. A sensitivity study is presented in the Supplementary Material (Fig. S3) for the effect of the binary parameters' values on the C3 distillation process. Similarly to the C1 unit, the analysis showed that by adjusting the reboiler duty of column C3, the same quantity and quality of AMFM can be obtained. R-PEAM is separated and purified based on reported industrial processes of liquid-liquid extraction (in LLX2), and distillation (in C4) [41]. The base scenario was modeled considering toluene (TOL) as the extractant for LLX2. The NRTL parameters of the R-PEAM–toluene system from relevant scientific literature were utilized [41]. In this manner all four products are obtained at commercial purities of above 0.98 and 0.99 mass fractions.

The heat pump system utilizes the vapor distillate of C1 (i.e., stream S13), and is employed in the preheating of the feed streams and heat pump assisted distillation for the other three columns (i.e., C2 to C4). As the greatest challenge is the evaporation of the large water quantities present in S11 and S32 streams, the majority of the thermal energy is utilized for preheating (i.e., HEX 1 and HEX 6), obtaining partially vaporized feeds for columns C1 and C3. As all four products have higher boiling points than water, this heating requirement is at a lower temperature than those of the column reboilers. As such, the compressed streams (i.e., S16, S18 and S21) are firstly employed for heat pump assisted distillation. The main design specifications of the above-mentioned DSP are presented in Table 2. The unusual value of >1.0 for C1 bottoms-to-feed ratio (calculated relative to the feed components listed in Table 2's feed basis) was necessary to maintain the BHMF product stream's temperature under 120 °C, even at the considered operation under vacuum of the column (i.e., 0.1 bar at the top). The distillation columns were first designed with the presented specifications, afterwards their condenser and/or reboiler were replaced with heat exchangers in a manner that respected the initial design. It should also be noted that the number of stages reflect the whole initial column including the first and last stages that, in Aspen Plus, represent the condenser and the reboiler.

The process presented in Fig. 1 is the result of an in-depth energy utilization assessment regarding the heat integration. Pinch methodology was utilized in scope of the processes' thermal integration. Pinch analysis employs overall system energy balances to identify available heat sources (hot streams) and heat sinks (cold streams). Within each temperature interval, hot process streams are aggregated to construct the hot composite curve (HCC), while an analogous procedure is applied to generate the cold composite curve (CCC). The net energy flows,

Table 2

Design specifications of the separation and purification units.

Design spec	Process unit					
	C1	C2	C3	C4	LLX1	LLX2
Number of stages	20	10	11	10	15	7
Feed stage	2	4	3	5	–	–
Top pressure (bar)	0.1	1	1	1	1	1
Reflux ratio (mole)	0.1099	1	0.1	0.5	–	–
Bottoms-to-feed ratio	0.0165	0.0256	0.1133	0.2278	–	–
Bottoms-to-feed ratio considering feed basis*	1.0150	0.99875	1	1.0005	–	–
Feed basis	BHMF and NaCl	S-PEA	AMFM and NaOH	R-PEAM	–	–

* Ratio calculated considering only the feed components mentioned in the feed basis row.

defined as the differences between the hot and cold composite curves across temperature intervals, are subsequently used to develop the grand composite curve (GCC). These graphical tools collectively enable the determination of overall energy targets for the plant and facilitate the evaluation of utility consumption [42]. The hot and cold composites curves for the heat exchanger network (HEN), i.e., HEX 1 to HEX 8, as well as the grand composite curve are presented in Fig. 2. The ideal integration of the heat upgraded through the heat pump system can be noticed in the same figure. The usage of the S13 stream in the heat pump system is crucial for providing heat to the most energy intensive step of the process, i.e., evaporation of water. As shown in Fig. 2 a), the water evaporation from the alcohol and amine product streams (about 5.4 MW_{th}) illustrated by the horizontal segments of the CCC at 47 °C and 100 °C, represents 71.7% of the downstream process' heating requirement. The COP for the heat pump system is of ~4.3, illustrating its viability. The boundary flows of the base case and their composition are presented in Table 3, while an equipment list for the HEN is provided in Supplementary Material (Table S1) to assist in navigating the compression train. At the same time, a summary of all streams is available in Supplementary Material (Table S2).

Other than the evaluation of the base case design presented previously in Fig. 1, alternative separation routes of the amine products, as well as process intensification possibilities were considered, presented in Fig. 3. The two solvents considered (i.e., toluene (TOL) and cyclohexane (CH)) were utilized as a pseudo-entrainer in C3 in case of separation route b), followed by simple decanting instead of the LLX2. In case of separation routes a) and b) both solvents were utilized, whereas Case c) was modeled only for the superior solvent choice. Process intensification (Case c)) was considered by employing a dividing wall column (DWC) as the integrated configuration was shown to not only reduce equipment costs and energy requirements, but also enhance separation processes [43]. Including the base case, two configurations with two possible solvents for the separation and purification of R-PEAM and AMFM were investigated along with the possible implementation of the best alternative scenario as DWC, as shown in Fig. 3 a) to c). For a fair comparison, all investigated configurations were kept to the same minimal standards: 99.5% recovery (in the desired outlet stream) of the amine products from the feed stream (S33); 0.995 weight fraction purity for both amine products. The performance of the proposed configurations was assessed in terms of economic and environmental impact.

2.2. Methodology of performance assessment

The economic evaluation was conducted based on validated and commonly utilized methodologies described in relevant literature

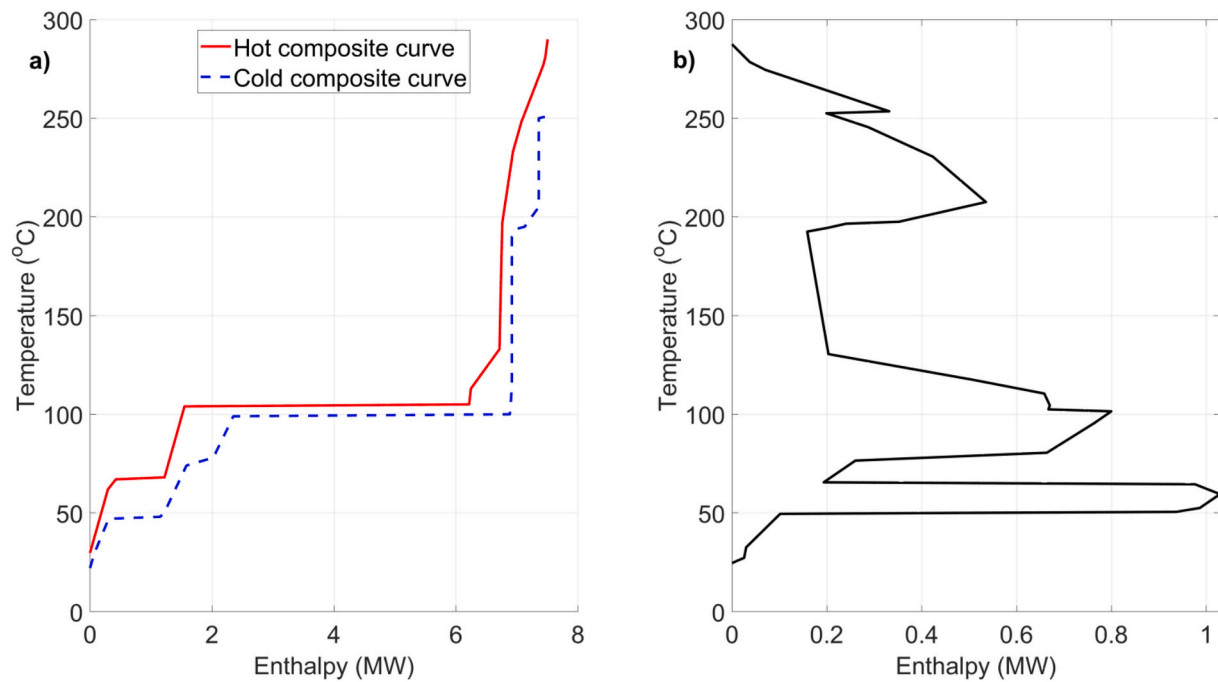


Fig. 2. Heat integration results for the HEN of the downstream process: a) hot and cold composite curves; b) grand composite curve.

Table 3

Boundary stream properties for the base case of the proposed DSP.

[illegible]

0* – mass fraction value lower than 1E-03.

[35,36]. The capital cost calculations of various equipment were performed following the methodologies presented in the above literature, based on the calculation of purchased equipment cost (C_p) with either eq. (1) or (2).

$$C_p = a + b \bullet S^n \quad (1)$$

$$\log_{10} C_p = K_1 + K_2 \bullet \log_{10} S + K_3 \bullet (\log_{10} S)^2 \quad (2)$$

where, a , b , n , K_1 , K_2 , K_3 are cost constants described in Turton et al. [35] and Towler and Sinnott [36] for each equipment type, while S is the sizing parameter of the equipment. In both cases, the material, pressure,

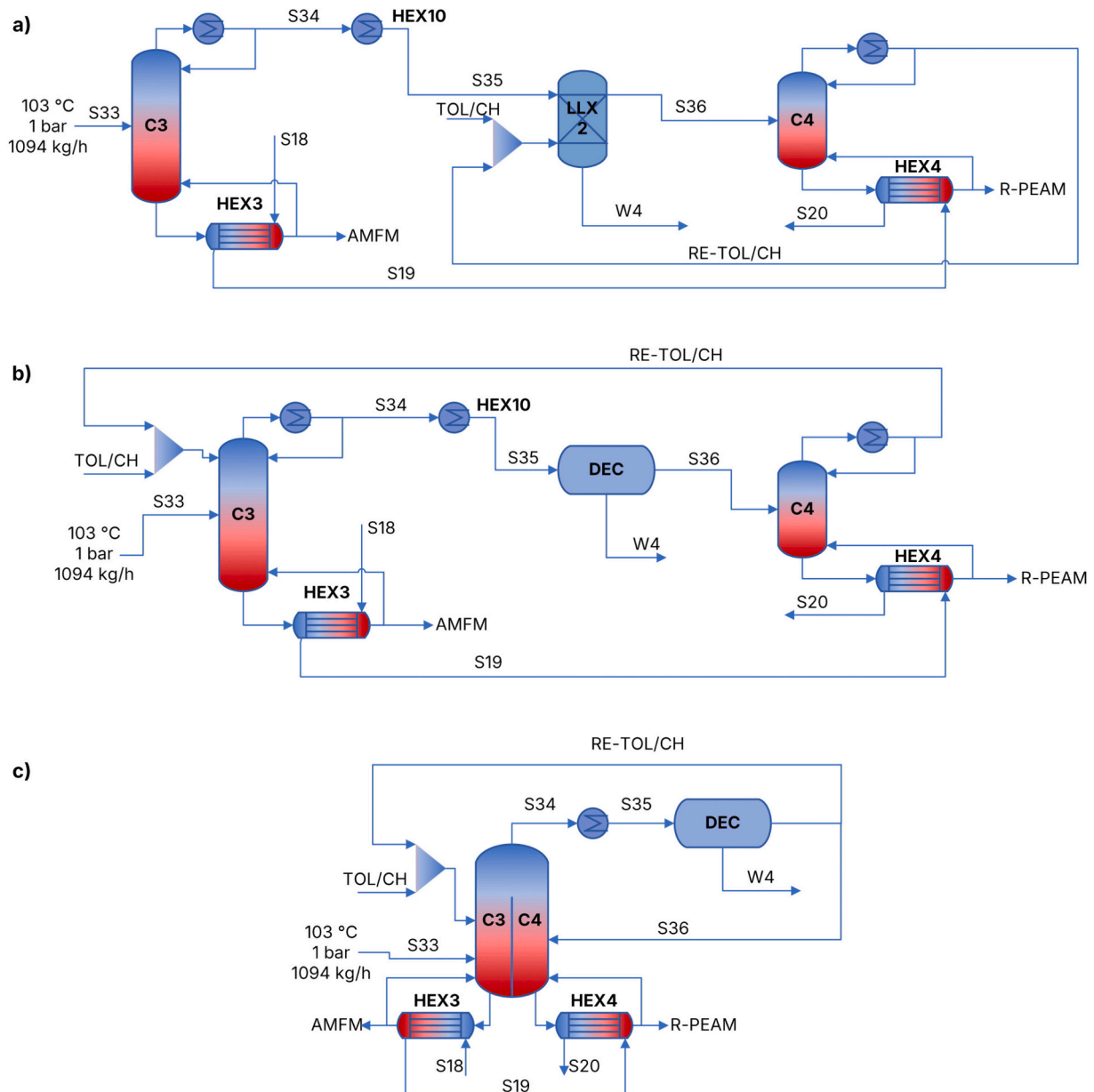


Fig. 3. Scheme of investigated amine products separation and purification cases: a) amine products separated by distillation, extraction and distillation; b) amine products separated by distillation, decanting and distillation; c) DWC implementation of b).

and other relevant cost factors were taken into account as described in the referenced literature. All equipment costs were estimated for U.S. Gulf Coast basis and were correlated with present costs by employing the value of the Chemical Engineering Plant Index (CEPCI) of 842.1 for July 2025 as described in eq. (3).

$$\frac{C_{p, \text{year1}}}{C_{p, \text{year2}}} = \frac{CEPCI_{\text{year1}}}{CEPCI_{\text{year2}}} \quad (3)$$

The heat pump system was assessed based on the total cost of ownership (TCO) and coefficient of performance (COP) which were calculated as described in eqs. (4) and (5).

$$TCO = IEC_{HP} + \sum_{t=1}^{20} C_{elec} \cdot W_{comp,t} \quad (4)$$

where IEC_{HP} is the installed equipment cost (IEC) of blowers B1–B5 and heat exchangers HEX1–HEX8, C_{elec} is the electricity price, $W_{comp,t}$ is the annual compressor power consumption. A plant operational life t of 20

years was used (distinct from investment payback time).

$$COP = \frac{Q_{\text{useful}}}{W_{\text{comp, total}}} \quad (5)$$

where Q_{useful} is the net upgraded heat delivered to the process (after accounting for the S25 cooling penalty as negative performance) and $W_{\text{comp, total}}$ is the total compressor electric input.

In case of equipment cost estimated based on Turton et al., CEPCI of 397 was considered (year 2001), whereas for calculations according to Towler and Sinnott CEPCI value of 532.9 was utilized (year 2010). The main economic considerations and assumptions for capital and operational expense calculations are presented in Table 4. Other than the equipment purchase and installation costs, the capital expenses (CAPEX) comprise of field expenses, site development, construction of homes and offices, project contingency, additional piping, warehouse, working capital, proratable expenses, and initial water and chemicals. The operational expenses (OPEX) take into account raw materials, utilities,

Table 4
Main economic considerations and assumptions for CAPEX and OPEX calculation.

System component/economic consideration				Notes
Pre-filters				
Disk stack centrifuge	Calculation based on:	Towler-Sinnott	S - diameter	[36]
Cartridge filter	Calculation based on:	Turton et al.	S - area	[35]
	Filter:	Pall profile II		[44]
	Replacement interval:	1 month		
Cartridge absolute filter	Calculation based on:	Turton et al.	S - area	[35]
	Filter:	Supor EX ECV		[45]
	Replacement interval:	3 months		
Reverse osmosis	Calculation based on:	Turton et al. (horizontal vessel)	S - volume	[35]
	Filter:	FilmTec BW30 PRO-400		[46]
	Replacement interval:	2 years		
Ion-exchange	Calculation based on:	Turton et al. (vertical vessel)	S - volume	[35]
	Resin:	DuPont AmberLite HPR 1200H		[47]
	Replacement interval:	5 years		
Nanofiltration	Calculation based on:	Towler-Sinnott (horizontal vessel)	S - mass	[36]
	Filter alcohol stream:	AMS A-3011		
	Filter amine stream:	AMS B-4021		[48]
	Replacement interval:	2 years		
Bipolar membrane electrodialysis	Calculation based on:	Virruso et al.	S - area	[49]
	Replacement interval:	3 years		
Heat exchangers	Calculation based on:	Turton et al.	S - area	[35]
Distillation columns	Calculation based on:	Towler-Sinnott		[36]
	Equipment considered:	Vessel (vertical), internals, reflux drum, storage tank (where relevant), reboilers and condensers calculated as heat exchangers		
Liquid-liquid extraction	Calculation based on:	Towler-Sinnott (vertical vessel)	S - mass	[36]
Pumps	Calculation based on:	Turton et al.	S - power	[35]
Blowers	Calculation based on:	Towler-Sinnott (compressor)	S - power	[36]
	Assumption:	Blower price is half the price of the corresponding compressor		[50]
Cooling water		0.07 (\$/MT)		
	Assumption:	Make-up is 2%		
Wastewater treatment		2 (\$/m ³)		
Cooling water treatment		0.003 (\$/m ³)		[51]
Personnel expenses	Number of personnel:	50		
	Annual pay:	50,000 (\$/year)		
Interest during construction	Interest rate:	8%		
	Build time:	2 years		
	Investment over build time:	50%, 50%		
Plant operation time		20 years		
Administrative costs	Assumption:	30% of personnel expenses		
Annual maintenance	Assumption:	4% of CAPEX		
Annual production time		8000 h		
Cost of electricity		0.0832 \$/kWh		[52]
Deionized water cost		0.83 (\$/MT)		[53]
Chemicals cost				
HCl 35%		250.67 \$/MT		[54]
NaOH		0.36 \$/kg		[55]
Phenylsilane		25 \$/kg		[56]
HMF		3\$/kg		Alibaba
PEA		5\$/kg		Alibaba
Hexane		1.68 \$/kg		[57]
Toluene		0.94 \$/kg		[58]
Cyclohexane		0.96 \$/kg		[59]

labor, solvent makeup, maintenance, wastewater treatment and membranes/filters replacement costs. It was assumed that utilities are purchased and wastewater is processed by a third party at a fixed price per unit volume rather than explicitly modeling utilities and wastewater treatment plants.

The sustainability assessment was carried out utilizing performance metrics from published procedures [37,60]. Energy intensity, water consumption, greenhouse gas (GHG) emissions, material intensity, wastewater intensity and pollutant and toxic materials indices were considered. These metrics were calculated for a functional unit of 1 kg of pure product.

3. Results and discussion

In terms of the thermal integration of the proposed downstream process, an initial minimum temperature approach of 10 °C was considered. However, as a large water quantity is present that has to be evaporated in this process, which is achieved with the use of mostly water vapors, a pressure difference between the two streams is necessary to maintain the desired temperature approach. The required pressure difference can be obtained through the compression of the vapor stream through B1 to B5, and it is closely related to both the capital and operational expenses of these equipment as both calculations relate to the equipment's power. On the other hand, the decrease in the minimum temperature approach determines larger required heat exchanger areas that directly relate to the cost of these equipment. As such, an in-depth investigation was performed on the trade-off between TCO regarding the heat pump system (i.e., B1 to B5 and HEX1 to HEX8) and minimum temperature approach. The TCO only included the same initial installed equipment costs and electricity costs tied to the operation of the blowers. Other trade-offs such as equipment space requirement or weight were not considered as the process is in the design phase, however, these should also be taken into account in a retrofitting scenario. Other than the capital expenses, the heat pump system's COP was also calculated at the different minimum temperature approach values, these results are presented in Fig. 4.

It can be observed that both the TCO and COP are more advantageous at smaller minimum temperature approach values. In case of TCO, this can be attributed to the electrical costs over the 20-year period (that is the assumed plant operational life used for OPEX annualization in the TCO comparison which is distinct from the investment payback time) of continuous utilization of the equipment that is not offset by the increased cost of heat exchangers even at a temperature difference value

of 5 degrees. To reach temperature differences above 5 °C, the heat transferred through compression to the S13-S21 streams will be larger than the heating need of the process. As such, an additional heat exchanger and cooling utility have to be employed to remove the excess heat from S25 before the LLX1. The temperature of this stream influences the performance of the separation in terms of S-PEA and hexane that are lost in the W3 stream, as shown in Fig. S4 of the Supplementary Material. The COP calculation was performed by taking into account the heat removal necessary for stream S25 to be at 29.6 °C (baseline taken from the heat integrated process at 5 °C temperature difference) as negative performance. Considering the mentioned results regarding COP and TCO, the minimum temperature approach value of 5 °C was selected as optimal for the heat pump system, which is still in the range of typical values utilized [35]. Although greater financial and performance-wise benefits could probably be obtained employing a lower temperature difference, it was considered that the control and robustness of the process would be put to risk at a minimum temperature approach below 5 °C [61]. In comparison to the commonly used temperature difference value of 10 °C, the TCO of the heat pump system decreases by 3%, whereas the COP increases by 0.44, i.e., a surplus heat of 137 kW is avoided in stream S25 at the temperature difference of 5 °C. The economic viability of the heat pump system was confirmed by a discounted payback period of 8 years relative to the non-integrated base case, calculated based on the annual utility cost savings achieved, considering a discount rate of 8% and steam price of 34 \$/MT [62].

The economic evaluation performed for this scenario (Case a) TOL) resulted in a production cost over the assumed 20-year plant operational life of 42.94 \$/kg (averaged over the four products). Although the production costs are significant, the market price of the products are in the range of 1 \$/kg to over 1000 \$/kg. BHMF is on the lower end of the price range (i.e., 1 to 5 \$/kg), followed by R-PEAM (1 \$/kg to 10 \$/kg), S-PEA (5 to 20 \$/kg), and AMFM currently at the higher end with market prices of over 1 \$/g. As such, the viability of the designed process is closely tied to the market price of AMFM. The economic analysis results are presented in Fig. 5. In terms of IEC, the largest contributors are the filtration systems and the pumps/blowers making up more than 70% of the IEC. These equipment are all tied to the major drawback of the bioenzymatic processes, i.e., a very dilute inflow stream. The majority of the water from S1 was considered to be removed through low-enthalpy processes, however, the necessary equipment (specific membranes) and pumps (e.g., 50 bar for NF) contribute significantly to the IEC. Moreover, five blowers were considered for a heat pump system that was primarily employed in order to evaporate the water from the feed streams. As

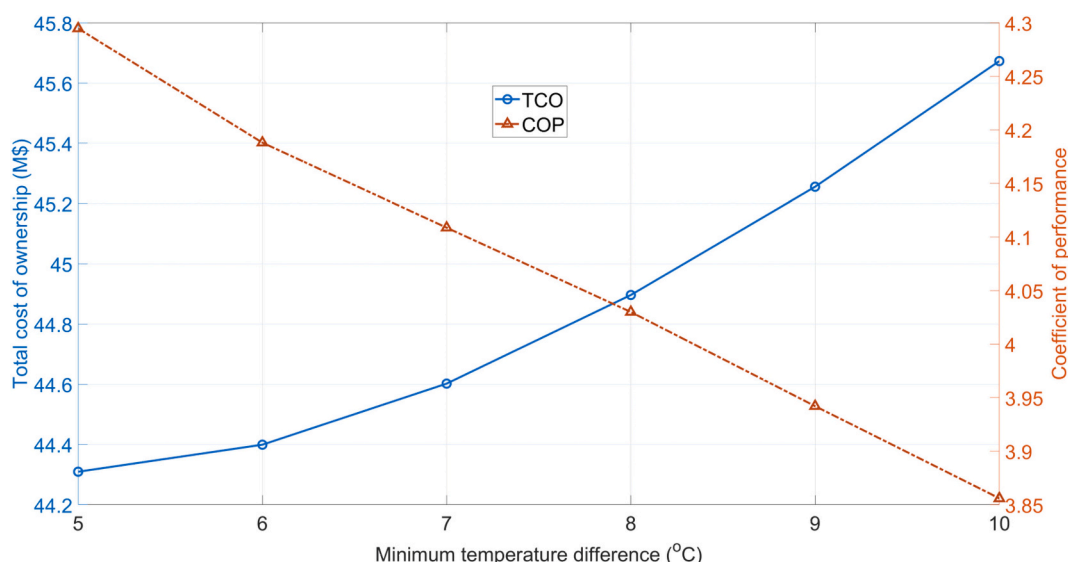


Fig. 4. Total cost of ownership (left) and coefficient of performance (right) of the heat pump system in function of minimum temperature approach.

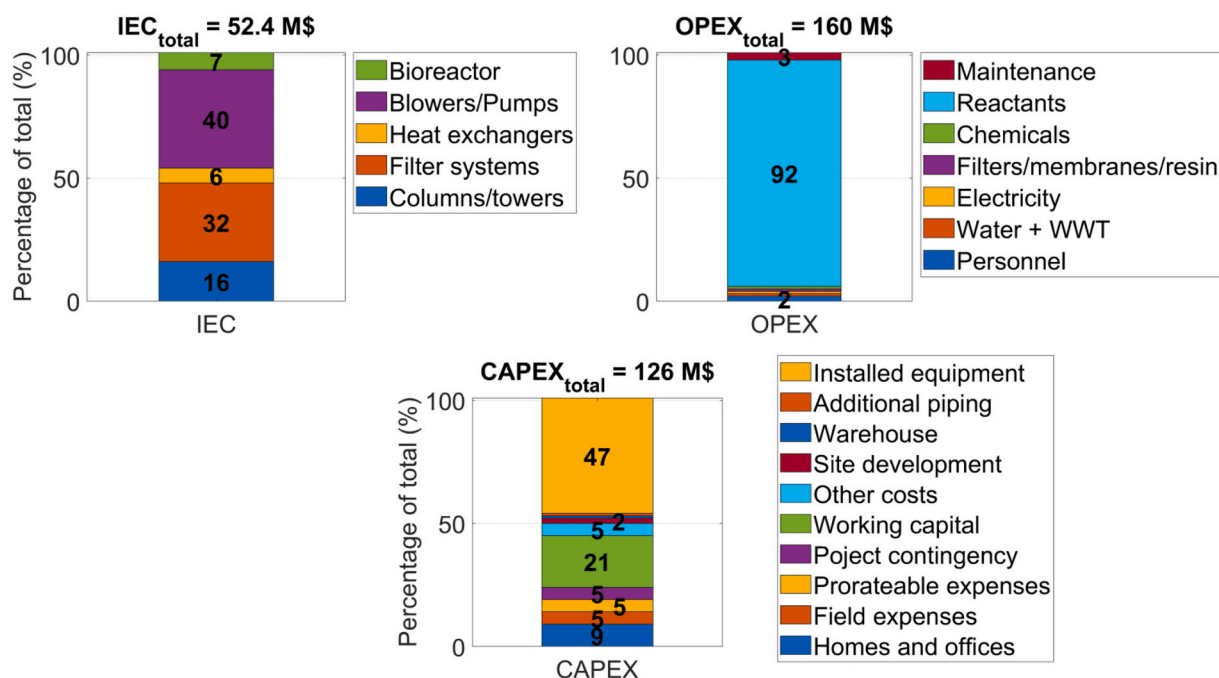


Fig. 5. Economic analysis results for Case a) TOL of the downstream process.

such, ~72% of the IEC can be tied to the removal of water from S1.

In regards to the CAPEX and OPEX, it is apparent that the yearly operation of the proposed DSP (~160 M\$/y) is considerably larger than the capital investment of the plant (~116 M\$). As such, the feasibility of the process hinges on the OPEX to which the reactants are by far the greatest contributor with a share of ~92%. Out of the reactants (i.e., HMF, PEA and phenylsilane), phenylsilane is the most expensive and largest contributor toward the OPEX. In consequence, the economic viability of the studied bioenzymatic process largely depends on the price ratio between AMFM and phenylsilane.

Sensitivity analysis of the production cost (PC) was performed for various scenarios encompassing varying feedstock prices, electricity

cost, and CEPCL. The sensitivity analysis results on the production cost are presented in Fig. 6. The PC of the four products linearly increases with the parameters considered for the sensitivity analysis. The amplification of the varied parameters over the PC was calculated as the slope of the linear functions. In this sense, the electricity cost has the greatest escalation over the PC, any change in this parameter results in a close to 4 times more pronounced change in the PC value. However, the changes in the price of electricity are expected to remain below one unit (in \$/kWh), thus the smaller overall influence on the PC. The second largest growth over the PC was obtained at the variation of the phenylsilane cost. The change in this feedstock's price causes a change amplified by 1.37 times in the PC. The largest relative variation was considered for

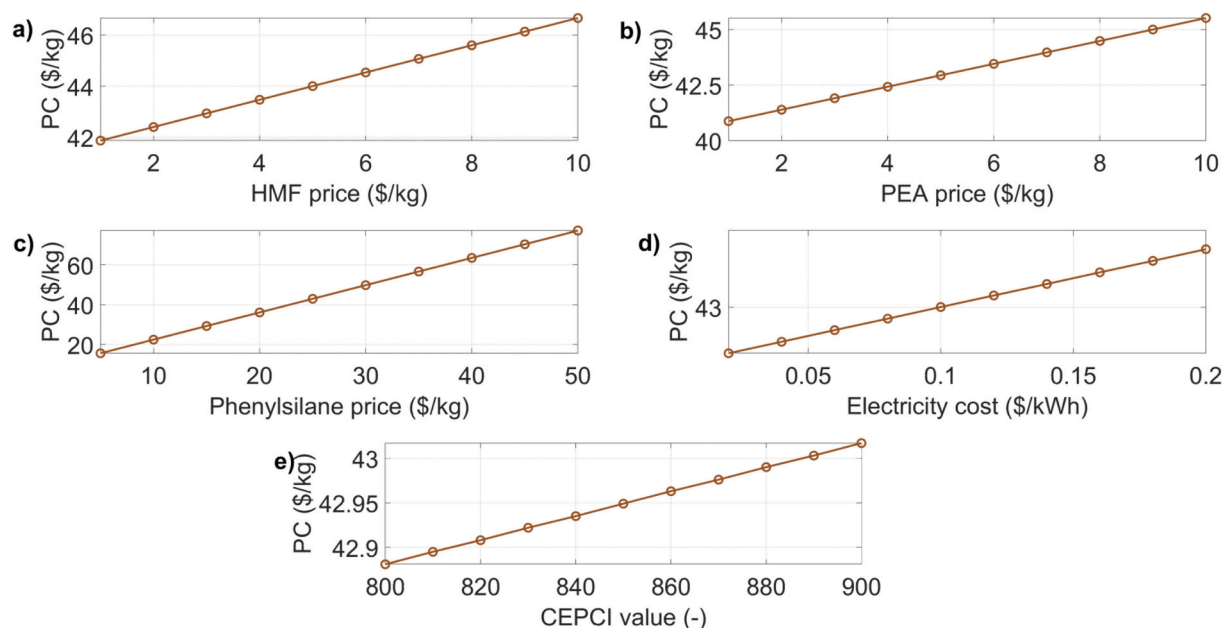


Fig. 6. Sensitivity study for the PC of the proposed DSP considering: a) price of HMF; b) price of PEA; c) price of phenylsilane; d) cost of electricity; and e) CEPCL value.

this parameter due to the uncertain estimated bulk price of this compound. At the upper end of the range (i.e., PC of 50+ \$/kg), the economic feasibility of the process relies on the selling price of AMFM. Assuming that the bulk price ratios of AMFM to phenylsilane would adhere to the small-scale price ratio of ~ 28.3 to 1 [63,64], the investigated process has considerable economic potential. The reactants, i.e., HMF and PEA also have considerable influence over the PC, with amplification factors of 0.53 and 0.52, respectively. The variation of CEPIC had close to no influence over the PC, which can be attributed to the fact that the yearly OPEX is almost 1.3 times larger than the CAPEX of the plant. To assess the economic impact of product purity requirements, a sensitivity analysis was performed by relaxing the purity specifications of the non-AMFM products as far as 0.95 wt. fraction, revealing only a marginal reduction of less than 4% in product cost and confirming that reactant costs remain the dominant economic driver of the process. These results are presented in **Table S10** of the Supplementary Material.

Currently, the IEX process is modeled as an ideal separation with no crossover losses between amines and alcohols. However, in a dilute, multi-component system containing structurally similar compounds (i. e., R-PEAM, AMFM, S-PEA, and BHMF) achieving perfect separation is unlikely. A sensitivity analysis on partial amine/alcohol crossover was carried out to quantify its specific impact on final product purity and production cost. The sensitivity analysis results are presented in **Table S8** of the Supplementary Material. Due to the similar compound pairs, all of the product streams are affected by the crossover at the IEX as BHMF and AMFM, respectively S-PEA and R-PEAM will leave the DSP together. As less product is recovered in the desired product streams, the purity of all products decreases while the production cost linearly

increases with the crossover percentage due to the PC being calculated per mass of pure product. It is important to note that a 2% crossover reduces product purity to a weight fraction of ≤ 0.98 , most product streams falling below the standard threshold for high-purity specialty chemicals, directly reducing the market value of the products.

Other than the base case of the heat integrated DSP presented in **Fig. 1**, a second amine product recovery route and the process intensification possibility by DWC (**Fig. 3**) were investigated. The DWC was simulated in Aspen Plus as its two-column thermodynamic equivalent [26]. The design specifications (e.g., specifications mentioned in **Table 2**) of the DWC were varied with the aim of minimizing energy requirements while complying with the minimal product recovery and purity standards mentioned previously. All of the columns were operated at atmospheric pressure, and structured packing type Mellapak was considered due its low pressure drop (i.e., 0.3 mbar per theoretical stage) [39]. The two sides of the DWC were designed considering Mellapak 250 $\times$ at 80% flooding, while Mellapak 500 $\times$ was used for the common overhead resulting in 79.96% approach to flooding. The flowsheets of the separation and purification scenarios implemented in Aspen Plus are presented in **Fig. 7**. The results of the processes are summarized in **Table 5**, while the stream properties, compositions, and design specifications of the DWC can be found in **Table S3** to **Table S7** of the Supplementary Material.

It is important to note the purity of the obtained products, an important parameter for possible utilization in the pharmaceutical industry. It can be observed that pure products were obtained for all investigated scenarios, however, Case a) showed better performance for both solvents in terms of product recovery compared to their respective alternative Case b). The differences in product recovery are of 0.4% and

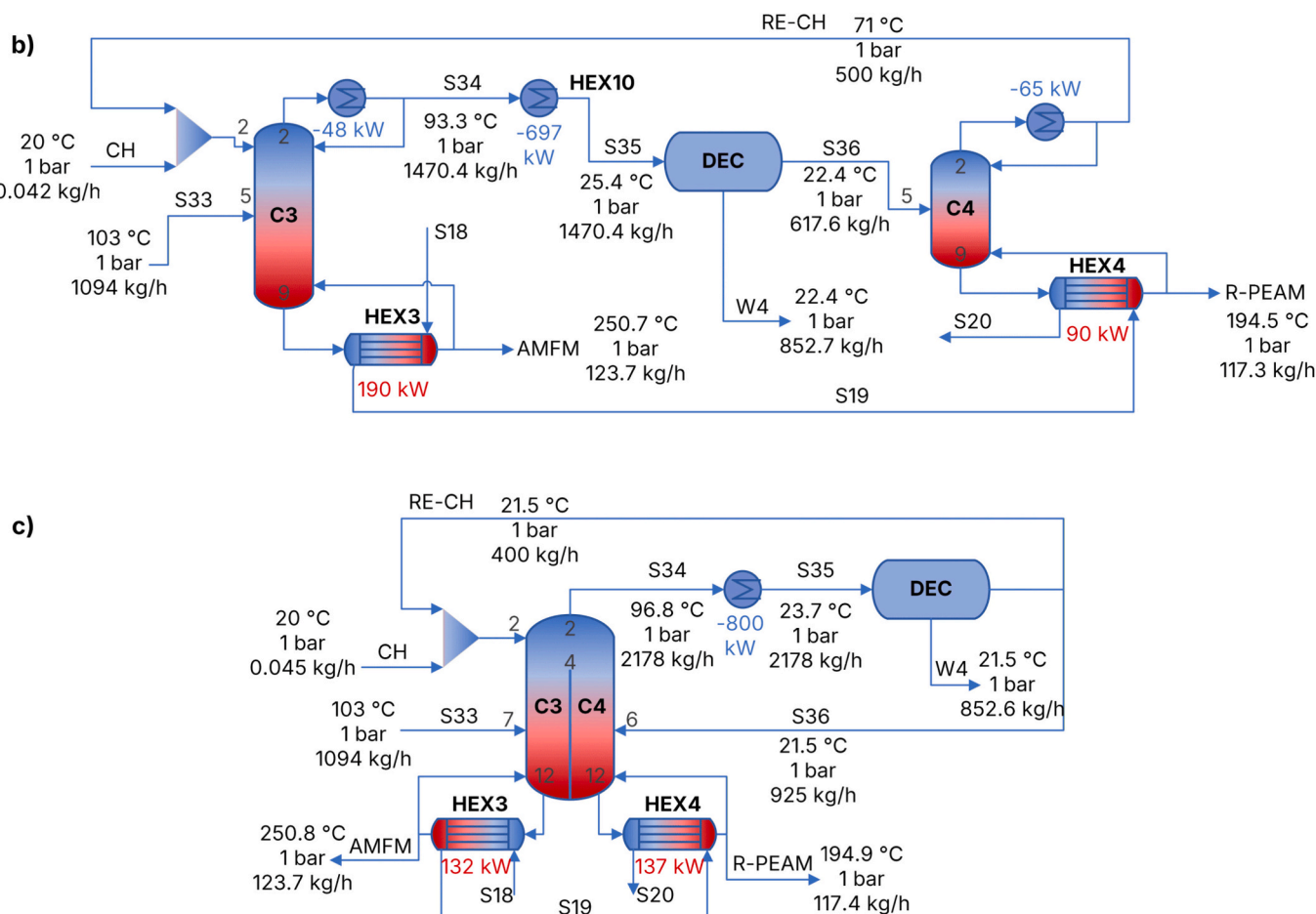


Fig. 7. Design of the investigated alternative separation route (Case b) CH and its DWC equivalent (Case c) CH.

Table 5

Results of the four investigated amine recovery and purification cases.

	Heating (kW)	Cooling (kW)	Products recovery (%)	R-PEAM purity (wt. frac.)	AMFM purity (wt. frac.)	Installed equipment cost (M\$)
Case a) TOL	238	750	99.99	0.999	0.999	1.66
Case a) CH	234	740	99.99	0.999	0.999	1.58
Case b) TOL	282	793	99.59	0.999	0.999	1.42
Case b) CH	280	810	99.81	0.999	0.999	1.41
Case c) CH	269	800	99.88	0.999	0.999	1.01

0.18%, a slight overall advantage of Case a) over the alternative Case b) considering the production costs. However, it is important to recover as much as possible from the products and solvents for the sustainability of the process as all products and solvents are toxic for aquatic life. The energy necessities of Case a) are lower by 18.5% and 5.7% (for TOL), 19.7% and 9.5% (for CH) in terms of heating and cooling, respectively. In contrast, the installed equipment cost is reduced by 14.5% and 10.8% compared to Case a) for TOL and CH, respectively. In terms of solvent selection, the separation with CH resulted in higher product recovery with smaller equipment than the same scenario with TOL (i.e., LLX2 with 5 stages compared to 7 stages). As such, the IEC is reduced when CH is employed both in Case a) by 4.8% and marginally in Case b). At the same time, the make-up of solvent is reduced when utilizing CH as less is lost in stream W4. Consequently, CH was considered as the superior solvent choice and Case c) was implemented with CH as solvent.

The intensification of the best alternative route (i.e., Case b) CH) was successfully performed by utilization of DWC. The intensified scenario (i.e., Case c) led to improvements in all investigated indicators. The product recovery was slightly enhanced by 0.07% while energy requirements were reduced by 3.9% and 1.2% compared to Case b) CH in terms of heating and cooling, respectively. The largest improvement was obtained for the IEC which was reduced by 28.4% compared to Case b) CH and by almost 40% compared to the base case (Case a) TOL). These results were achieved by considering a DWC with 13 stages (when stage 1 is the condenser and stage 13 represents the reboiler), which is divided from the bottom till stage 4. The amine products are obtained as the bottom products of the DWC's two sides with close to ideal mass purities of 0.999. Although the energy requirements are larger when compared to the base case, the necessity at HEX 3 was reduced by 58 kW compared to Case b) CH, and by around 10% compared to the base case. Taking into account strictly the part of the DSP responsible for the recovery of the amine products, of the investigated alternative cases, the separation route performed with DWC and CH as solvent (i.e., Case c) CH) showed the best overall results. Compared to the base case, the energy requirements increased the least (out of scenarios b) and c)) by 13% and 6.6% in terms of heating and cooling, while the product recovery reached 99.88%. At the same time, both products were obtained at near ideal purity, and the IEC (for the amine separation part of the DSP) was reduced by 39%. The implementation of Case c) CH in the full DSP also showed advantages for the heat integration. Although the overall heating energy requirement of Case c) CH is higher, the temperature at which the heat has to be provided also shifted. Compared to Case a) TOL, the heat required at ~250 °C was reduced (i.e., from 145 kW in Case a) TOL to 132 kW in Case c) CH). As it can be observed from Fig. 2, the heat pump covers all the heating required in the DSP, however, some of the upgraded heat is retained in S25 which, in turn, affects the extraction in LLX1. The pressure of the heat pump system was designed to avoid the surplus heat in S25, this could not be completely avoided as a pressure difference has to be maintained between the hot and cold aqueous streams for the 5 °C temperature difference between boiling points to exist. Thus, the heat upgraded through the heat pump system can still account for additional heating requirement if the heat pump works at the same pressure. At higher energy demand of the process, other than the increased COP (i.e., due to the larger heating covered by the heat pump), the temperature of stream S25 is lowered for the system to cover the additional 31 kW necessary while maintaining a 5 °C temperature

approach. An alternative is to employ high-pressure steam for the heating beyond what the heat pump can handle, but another two heat exchangers would be necessary in this case. The first exchanger for the heating with the high-pressure steam, while the second is necessary to provide cooling before the LLX1 process to the S25 stream. In regards to the separation and purification of the amine products, Case a) CH showed the best results. Although Case c) CH exhibited higher energy requirements, the associated benefits in terms of improved heat integration and reduced IEC for amine separation were evaluated and compared with the base case (Case a) TOL). Consequently, the influence over the economic and separation performance of the whole designed process was investigated.

It should be noted that the design choices adopted for the heat pump and the DWC were guided by different optimization objectives and therefore do not represent contradictory process development strategies. The heat pump configuration was optimized based on the minimization of the overall TCO, where the reduction in long-term utility consumption justifies the additional investment associated with larger heat-exchange areas and compressor requirements. In contrast, the implementation of the DWC was specifically targeted at reducing the installed equipment cost within the amine-separation sub-section by consolidating separation tasks into a single intensified unit. Consequently, a small increase in the local heating and cooling requirements was considered acceptable in exchange for the substantial reduction in IEC and equipment number of the amine recovery sub-section. Furthermore, the amine-separation sub-section contributes only a fraction of the total IEC, while the alcohol recovery section, processing a significantly larger mass flowrate, remains the dominant contributor to the overall energy demand of the process. As such, the different trade-offs adopted for the heat pump and DWC reflect the local economic characteristics of each unit operation and are consistent with the objective of improving the overall process performance.

The idealized assumption of perfect amine/alcohol separation at the ion-exchange (IEX) step was evaluated through a dedicated crossover sensitivity analysis, the results of which are presented in Table S8 of the Supplementary Material. The analysis examined amine/alcohol crossover fractions of 0–2%, where crossover is defined as the fraction of amine (or alcohol) product that exits in the undesired product stream. The results show that the process remains commercially viable at crossover levels up to about 0.5%, at which point all four product purities remain at or above their respective commercial thresholds (≥ 0.983 wt for BHMF, ≥ 0.995 wt for the remaining three products) and the production cost increases by only 0.24 \$/kg relative to the ideal case (42.94 to 43.18 \$/kg). Beyond 1% crossover, BHMF purity falls to 0.973 (approaching the lower limit of commercial acceptance) and the production cost increases to 43.42 \$/kg. At 2% crossover, the BHMF purity threshold of 0.98 wt is breached (0.963 wt), indicating that the process design is sensitive to IEX performance and that maintaining crossover below 1% is critical to meeting product specifications. The selected resin, DuPont AmberLite HPR1200 H, is a strong acid cation exchange resin (SAC) with uniform particle size that operates via proton-exchange, retaining protonated amines (present at pH ~2) while allowing neutral alcohol species to pass through. Literature reports on analogous amine/alcohol separations with SAC resins indicate that strong cation exchangers can achieve high amine selectivity for protonated aliphatic and aromatic amines relative to neutral organic

species, with crossover values well below 1% under optimized pH and flow conditions. While experimental validation for the specific AMFM-R-PEAM-BHMF-S-PEA system is not available, the pH-driven charge difference between the protonated amines and the neutral alcohol products provides a basis for expecting crossover below the 0.5% viability threshold under controlled IEX operation.

It should be noted that the cost estimation methodology employed is classified as a study-level estimate with an inherent accuracy of $\pm 30\%$, meaning that the absolute production cost values have an uncertainty range of roughly ± 13 \$/kg. Consequently, the observed differences between cases (which are below 1% across nearly all economic and environmental metrics) fall well within this methodological uncertainty band and cannot be considered statistically distinguishable on a deterministic basis.

The economic and sustainability evaluation results are presented in Table 6 while the summary of process streams for Case c) CH is shown in Table S9 of the Supplementary Material. The overall thermal energy requirements were calculated by considering a 2.5 factor for electric to thermal energy. It can be observed that in Case c) CH the energy intensity of the whole downstream process marginally increased. As the pressure of the heat pump system had to be modified to cover the additional heating (i.e., output pressure of B5 to 1.25 bar from 1.21 bar) and that the presented metrics are calculated per kg of pure product, the larger energy requirement is attributed to this modification and the reduced product recovery of about 0.05% (i.e., 483.67 kg/h compared to 483.91 kg/h) for the overall process relative to Case a) TOL. The largest percentual increase (i.e., $\sim 3.6\%$) was noticed at the water consumption of the process due to the additional cooling necessity (i.e., 135 kW). Another disadvantage in terms of sustainability of Case c) CH was observed at the material intensity metric which can be traced to the lower product recovery. However, the pollutant and toxic material emissions were lowered, owing to the lower temperature of stream S25 (i.e., 27.8 °C compared to 29.6 °C) which, in turn, reduced the loss of hexane and S-PEA in W3 by $\sim 3.3\%$ (i.e., 0.619 kg/h compared to 0.641 kg/h) relative to the base case. Another factor in the reduction of pollutants and toxic material emissions was the solvent choice, i.e., the usage of CH over TOL resulted in a reduction of solvent loss in W4 (0.045 vs. 0.576 kg/h) compared to the base case. As all waste streams of the process are aqueous, the pollutant and toxic materials metric took into account pollution and toxicity for aquatic life. Only a marginal decrease of $\sim 0.3\%$ was obtained as the greatest contributor to this metric are the acid, base and salt compounds remaining in W2, W5, and W6, i.e., HCl, NaOH and NaCl. As these compounds have a contribution of $\sim 93\%$ while W2 represents more than 40% of this metric, for an overall more sustainable process, these streams (prioritizing W2) ought to be neutralized, desalinated and recycled, or acid and base recovery through BMED should be implemented. The marginal change in the wastewater intensity of the process is due to the difference in product recovery between the two DSP cases. As there are no direct emissions from the proposed process, the GHG emissions result from indirect emissions,

represented solely by the specific emission of electricity generation. This was calculated by considering a factor of 0.3674 kg CO_{2eq}/kWh for electricity production, based on the U.S. national average total output emission rate reported by the U.S. Energy Information Administration for 2023 [65]. The emission factor averaged over all energy sources for the U.S. was utilized as the plant location considered was the U.S. Gulf Coast. The increase in GHG emissions clearly results from the increase of electric energy requirement of 21 kW compared to the base case. An overall slight increase in the sustainability metrics can be attributed to the difference in efficiency of the separation between Case a) TOL and Case c) CH, as all metrics were reported for a unit of pure product.

Similarly to the sustainability metrics, the economic metrics show almost negligible differences between the two investigated cases. The enhanced product recovery observed in Case a) TOL is offset by the lower IEC of Case c) CH, resulting in an identical PC of 42.94 \$/kg for both configurations. Although a substantial reduction of almost 40% in the IEC was observed for the amine separation section of the DSP in Case c) CH, this did not provide a significant economic advantage on the overall process as the columns/towers account for only 16% of the total IEC. The total investment remains dominated by the alcohol separation section, as the mass flowrate of alcohol (S11) stream is approximately 7 times that of the amine stream (S32). Consequently, as the two investigated scenarios demonstrate comparable performance across both sustainability and economic metrics, the selection between enhanced product recovery and reduced initial investment remains a strategic decision of stakeholders. Nevertheless, the implementation of DWC holds the potential for significant economic benefits in similar processes where the intensified process section accounts for a more substantial share of the capital expenditure.

4. Limitations and future directions

While the proposed process provides a foundational framework for the separation of high value-added HMF derivatives, several technical assumptions and uncertainties warrant further investigation. A primary source of uncertainty lies in the performance of the reverse osmosis (RO) stage. The model currently assumes a 50% water recovery rate with a 99% retention of organic species. The selection of the FilmTec BW30 PRO-400 membrane (a brackish water module) is based on a general molecular weight cut-off (MWCO) of ~ 100 Da of the RO process [66], also mentioned in the FilmTec RO membrane's technical manual [67]. While literature for aromatic compounds of similar molecular weights shows that the assumed high rejection rate can be reached [68], the lack of experimental data for furanic derivatives at the proposed operating conditions is a major source of uncertainty that should be addressed through empirical testing.

Quantification of the impact of non-ideal IEX performance is provided in Table S8 (Supplementary Material). The analysis establishes that a crossover fraction below $\sim 0.5\%$ is required to maintain all product purities above commercial thresholds and limit the production cost penalty to less than 0.25 \$/kg. Crossover above 1% causes BHMF purity to fall below 0.98 wt, which constitutes the binding constraint. Experimental characterization of the IEX step using the selected resin and actual bioreactor effluent composition should be a priority for future experimental validation work.

Should crossover exceed 0.5% in practice, mitigation could include a polishing IEX guard bed, tighter pre-IEX pH control, a second cation-exchange stage, or increased resin regeneration frequency, at an estimated marginal OPEX addition of around 0.62% when doubling the regeneration frequency.

Additionally, the solids removal by the pre-filter system is considered to achieve "full separation", yet this step was not explicitly modeled. In a real application, any phenylsilane residues entering the aqueous stream could interact significantly with downstream membrane and ion-exchange steps, potentially leading to fouling or reduced efficiency.

While waste stream W2 was identified as the key contributor to the

Table 6

Economic and sustainability performance indicators for the proposed downstream process base case (Case a) TOL) and alternate scenario (Case c) CH).

Performance metrics	Case a) TOL	Case c) CH
Sustainability		
Energy requirements (kW _{th} /kg)	9.22	9.33
Water consumption (m ³ /kg)	0.0050	0.0052
GHG emissions (kg CO _{2eq} /kg)	1.355	1.371
Material intensity (kg _{waste} /kg)	0.0420	0.0425
Wastewater intensity (m ³ _{ww} /kg)	0.1642	0.1643
Pollutant and toxic materials (kg _{pt} /kg)	0.470	0.469
Economic		
IEC (M\$)	52.44	51.68
OPEX (M\$)	159.92	159.92
Production cost (\$/kg)	42.94	42.94

pollutant and toxic emissions metric (>40%), the proposal to implement bipolar membrane electrodialysis (BMED) for its treatment was not fully developed or quantified in this study. Future work should focus on integrating BMED into the process model and experimentally verifying membrane rejection coefficients to refine the accuracy of the mass balance and environmental impact assessments.

Finally, the present study assumes complete (100%) conversion of HMF and racemic PEA in the bioenzymatic cascade reaction, as reported under optimal laboratory conditions. In practice, enzymatic cascade reactions of this complexity rarely achieve complete conversion under industrially relevant conditions, with yields typically limited by substrate inhibition and enzyme stability. At sub-complete conversion, unconverted HMF and residual racemic PEA would remain in the bioreactor effluent fed to the DSP, introducing additional components that are not accounted for in the current simulation. HMF in particular (being a furan aldehyde with moderate water solubility and a boiling point of 291 °C) would co-elute with the heavier alcohol products in column C1, potentially compromising BHMF purity. Residual PEA would enter the alcohol stream and require additional separation. The quantitative impact of realistic conversion rates on product purity, recovery, and production cost is outside the scope of the present work but is an important subject for future process development, particularly when scaling from laboratory reaction conditions to the 1000 MT/year production basis assumed here.

5. Conclusions

This study presented the design, simulation, and techno-economic assessment of an integrated downstream separation and purification process for the simultaneous recovery of four bioenzymatic HMF derivatives (BHMF, AMFM, R-PEAM, and S-PEA) at a production scale of about 1000 t per year per product, combining vacuum distillation, liquid-liquid extraction, ion exchange, nanofiltration, and bipolar membrane electrodialysis within a pinch-optimized, heat pump-assisted heat exchanger network.

Water evaporation represents 71.7% of the total downstream energy demand (5.38 MW_{th}), making it the main design driver. A heat pump operating at a minimum temperature approach of 5 °C was identified as optimal, achieving a coefficient of performance of ~4.3 and reducing the total cost of ownership by 3% relative to a conventional 10 °C design. This underscores the importance of heat pump optimization in DSP with high aqueous evaporation loads.

Among the five amine separation scenarios evaluated, the DWC implementation of Route 2 with cyclohexane as solvent (Case c) CH) achieved high product recovery (>99.88%) and a 39% reduction in equipment costs for the amine separation section of the process relative to the base case, resulting in the production cost of 42.94 \$/kg of pure product. However, this configuration has marginally higher energy intensity (9.33 vs. 9.22 kWh/kg) and material intensity (0.0425 vs. 0.0420 kg_{waste}/kg) relative to the base case. This is a trade-off that must be explicitly weighed against recovery requirements. Nonetheless, the key differentiator in favour of Case c) CH is its process intensification benefit (reduction of equipment units through DWC integration) and its lower solvent toxicity profile (cyclohexane vs. toluene), not a distinct cost advantage.

The production cost is most sensitive to electricity and phenylsilane prices, with electricity showing the highest amplification factor, however, its practical impact remains limited due to the expected small variation in electricity costs. Changes in CEPCI have a negligible effect due to the operating expenses outweighing the capital costs. The economic feasibility is mainly determined by the AMFM-to-phenylsilane price ratio. At current market prices, AMFM's value substantially exceeds the estimated production cost, supporting process viability, while BHMF's contribution to overall economics remains marginal.

The principal limitations of this work include idealized assumptions for the ion-exchange and membrane separation steps, the lack of

experimental validation of thermodynamic model parameters for several binary pairs, and the exclusion of upstream bioreactor integration. Addressing these issues (particularly through experimental characterization of BHMF thermal stability and AMFM phase equilibria) is a priority for advancing this process toward pilot-scale demonstration. Overall, the quantitative framework developed here addresses the previously identified gaps in multi-product bioenzymatic DSP by integrating TEA with advanced process intensification strategies. Consequently, this framework provides a replicable basis for TEA of multi-product bioenzymatic separation systems, contributing to the development of economically viable downstream processing routes for bio-based specialty chemicals.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.seppur.2026.140025>.

Data availability

Data will be made available on request.

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