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Hybridizing Simulated Moving Bed and Electrodialysis: Product Purification and Eluent Regeneration

Complex streams in bio-based industries require efficient downstream processing units. Simulated moving-bed (SMB) chromatography is known to improve process efficiency by reducing resin and buffer requirement, but it can be further enhanced by technology hybridization. In the current experiments, an SMB system has been integrated with a bipolar electrodialysis (BPED) system. SMB purified γ-aminobutyric acid (GABA) from a clarified fermentation broth while BPED processed the product-containing eluent stream into recyclable eluent and purified product streams. The continuous operation did not result in any impurity accumulation.

Keywords: Bipolar electrodialysis, Hybrid system, Simulated moving bed, Technology integration

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1 Introduction

The product stream from a fermentation is water-based (> 80 wt %) and contains both dissolved and suspended impurities. As the choice of technology defines the downstream process efficiency and resulting costs, it is critical to apply innovative unit operations to achieve people, planet, and profit demands [1].

As described in Fig. 1, one or more unit operations are employed in each block of downstream processing. In the current article, the emphasis will be on the adsorption-based unit operation for selective product capture and removal of dissolved impurities in simulated moving-bed (SMB) mode. In addition, the impact of buffer recycling on the efficiency of the SMB process is investigated by employing bipolar electrodialysis (BPED).

1.1 Adsorption and Chromatography Resins

Adsorption technology involves a solid stationary phase interacting with a mobile liquid stream containing one or more target compounds. Adsorption is controlled by different interactions as indicated in Fig. 2. Ion exchange is one of the common adsorption mechanisms and includes weak acid cation (WAC), strong acid cation (SAC), weak base anion (WBA), strong base anion (SBA) exchange resins [2].

1.2 Simulated Moving Bed

In the batch process, fluid flows through the resin bed and equilibrium is attained between resin and process fluid. This results in a mass transfer zone that gradually moves through the bed. The product "breaks through" as the mass transfer zone reaches the exit of the resin bed. The resin then needs to be washed, eluted, and regenerated before it can be loaded again. The aim of the SMB process is to keep the mass transfer zone effectively at the same location by moving the resin beds in the opposite direction of the input streams. This approach ensures an optimal resin utilization and superior resolution, leading to a more efficient and compact separation process. In a true moving-bed concept, the resin flows countercurrently to the liquid flow, whereas in an SMB concept the resin flow rate is simulated by periodically shifting the different inlet/outlet ports in the direction of fluid flow.

1.3 Electrodialysis

Membrane separation processes allow separation of compounds through a semipermeable barrier. The nature of separa-

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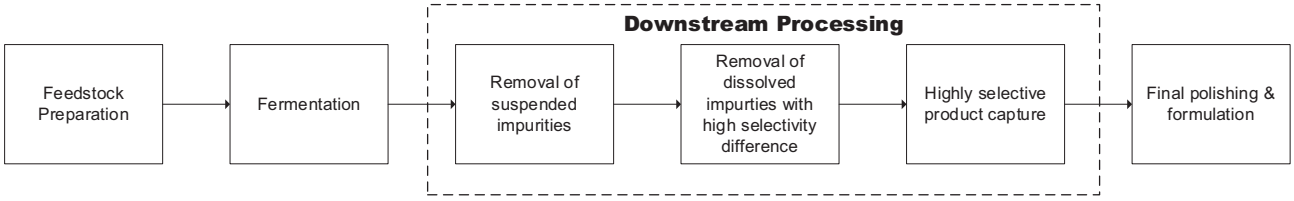

Figure 1. Typical flow of a fermentation-based process.

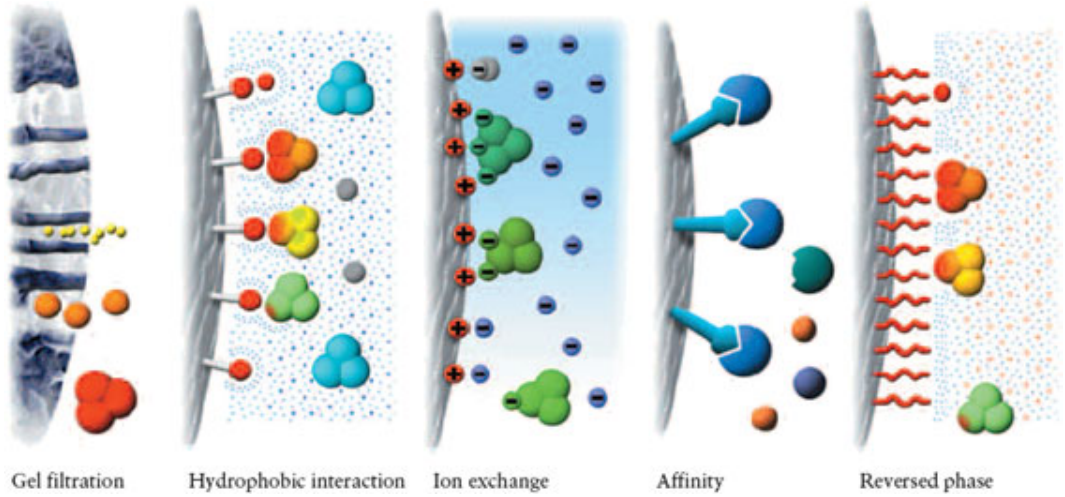

Figure 2. Simplified (artist) impression of the different mechanisms for chromatographic separations commonly used in protein chromatography [2].

tion is determined by the choice of the membrane, characteristics of the feed mixture, and process conditions [4]. Electrodialysis is a membrane technology, where electrodes and current enables selective permeation of electrolytic compounds from the feed stream. Membranes used can be either anion-selective or cation-selective. Depending on the membrane selectivity and current between anode and cathode, anions or cations permeate through the membrane, while keeping water impermeable. Therefore, BPED is a suitable technology to separate and recycle electrolytic eluting compounds like sodium hydroxide (NaOH) in the current case.

2 Process Design by Technology Integration

Technology integration is a potential driver towards techno-economically viable process solutions. One of the best examples is the concept of biorefinery, where several subprocesses are integrated to valorize both feedstock and side streams into biomaterials, biochemicals, and biofuels [3]. A similar integration approach when introduced at unit operation level can improve the step efficiency. The technology integration approach in the current article involved six steps:

(a) Understanding the basis of the process and defining the problem.
(b) Identifying suitable process technologies to address the problem.
(c) Hybridization of chosen technologies.
(d) Defining technology-specific critical process requirements.
(e) Designing hardware and software for optimal performance of the integrated technology.
(f) Testing of the integrated technology.

2.1 Problem Definition for an Exemplary System

Purification of γ-aminobutyric acid (GABA) from *Escherichia coli* sugar fermentation broth was chosen as the exemplary system to develop the SMB-ED process. GABA was considered a representative component for renewable materials that are produced using state-of-the-art biotechnology. Fig. 3 shows the molecular structure of GABA.

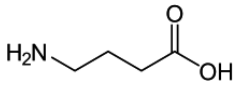

Figure 3. Schematic molecular structure of GABA.

Using the current process, it is required to purify GABA from clarified broth in continuous mode and achieve > 90 % product purity, while at the same time to ensure that: (i) the hybrid system enabled reduction in buffer consumption, (ii) the system control was able to observe and react to changes in process conditions without impacting process performance,

and (iii) a control strategy was established and maintained a steady-state operation. Within this article, the focus is on testing the SMB-ED system for consistency to achieve the above requirements.

2.2 Identifying a Suitable Technology

Based on physiochemical properties of the feed stream described in Tab. 1, the strong acid cation-exchange resin Amberlite 252H was chosen for the SMB process. NaOH was used as elution buffer and H_2SO_4 for regeneration. BPED base stack membranes were then used to recover NaOH from the GABA-containing elution stream.

Table 1. Feed composition.

Compound	Value
GABA [g L^{-1}]	100.02
Glutamate [mmol L^{-1}]	3.0
Glycine [mmol L^{-1}]	1.4
Alanine [mmol L^{-1}]	7.6
Valine [mmol L^{-1}]	1.0
Lysine [mmol L^{-1}]	2.2
Proline [mmol L^{-1}]	1.8
Phosphoric acid [g L^{-1}]	0.8
Malic acid [g L^{-1}]	0.4
Succinic acid [g L^{-1}]	1.3
Glycerin [g L^{-1}]	0.4
Acetic acid [g L^{-1}]	0.3
Ethanol [g L^{-1}]	0.8
Sulfate [g L^{-1}]	13.5
Phosphate [g L^{-1}]	0
Ammonia [g L^{-1}]	5.9
Calcium [g L^{-1}]	0.2
Potassium [g L^{-1}]	0.4
Sodium [g L^{-1}]	0.1

2.3 Hybridization of Technologies

Fig. 4 depicts the steps involved in the exemplary process. In the BPED, bipolar base stack membranes were used to recover NaOH and remove the remaining cations. The ion-free and impurity-free GABA can be further used for product formulation. The process input-output flow scheme of the SMB-ED hybrid system is depicted in Fig. 5.

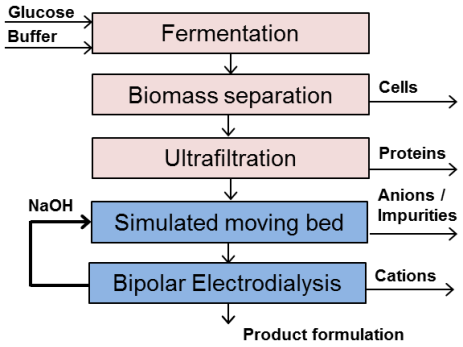

Figure 4. Process steps for the exemplary system containing the SMB and BPED hybrid system.

2.4 Critical Process Requirements

Critical process requirements are key variables that can indicate the efficiency and techno-economic viability of a process. By monitoring these parameters, corrective actions can be taken to maintain the performance of a process within a desired window.

The following process parameters were identified to be critical and monitored during the SMB-ED experiments:

1. pH profiles and binding capacity of the cation-exchange resin in the SMB; measured by pH and conductivity electrodes in the eluate stream.
2. GABA recovery in SMB, BPED, and in the combined system. The GABA recovery is defined by the total percentage of GABA recovered in the product stream from the total feed.

$$X_{GABA} = \frac{w_{GABA\_product} m_{GABA\_product}}{w_{GABA\_Feed} m_{GABA\_feed}} \quad (1)$$

3. Accumulation of impurities in the recycled eluent and the impact of these impurities on process efficiency.
4. The complete mass balance (average GABA recovery and ion removal efficiencies) and the needed energy for desalination in BPED.

2.5 Control Strategy

ED and SMB technologies bring specific requirements for system design and control strategy. A deviation from the steady state in SMB processes can have a direct impact on the process efficiency and, therefore, the control strategy should enable steady-state operation [5]. As the SMB and BPED are linked to each other through the product and the regenerated NaOH stream, it is important that both units are actively connected to each other's state of operation and thus sufficient volumes of liquids with defined compositions have to be available.

As the BPED works in a semi-batch process compared to the continuous process of the SMB, the liquids that are exchanged between these systems are collected in intermediate storage vessels. By monitoring these vessels over time, the SMB and BPED system can take appropriate action on the input flow rates for the hybrid system. These control strategies are

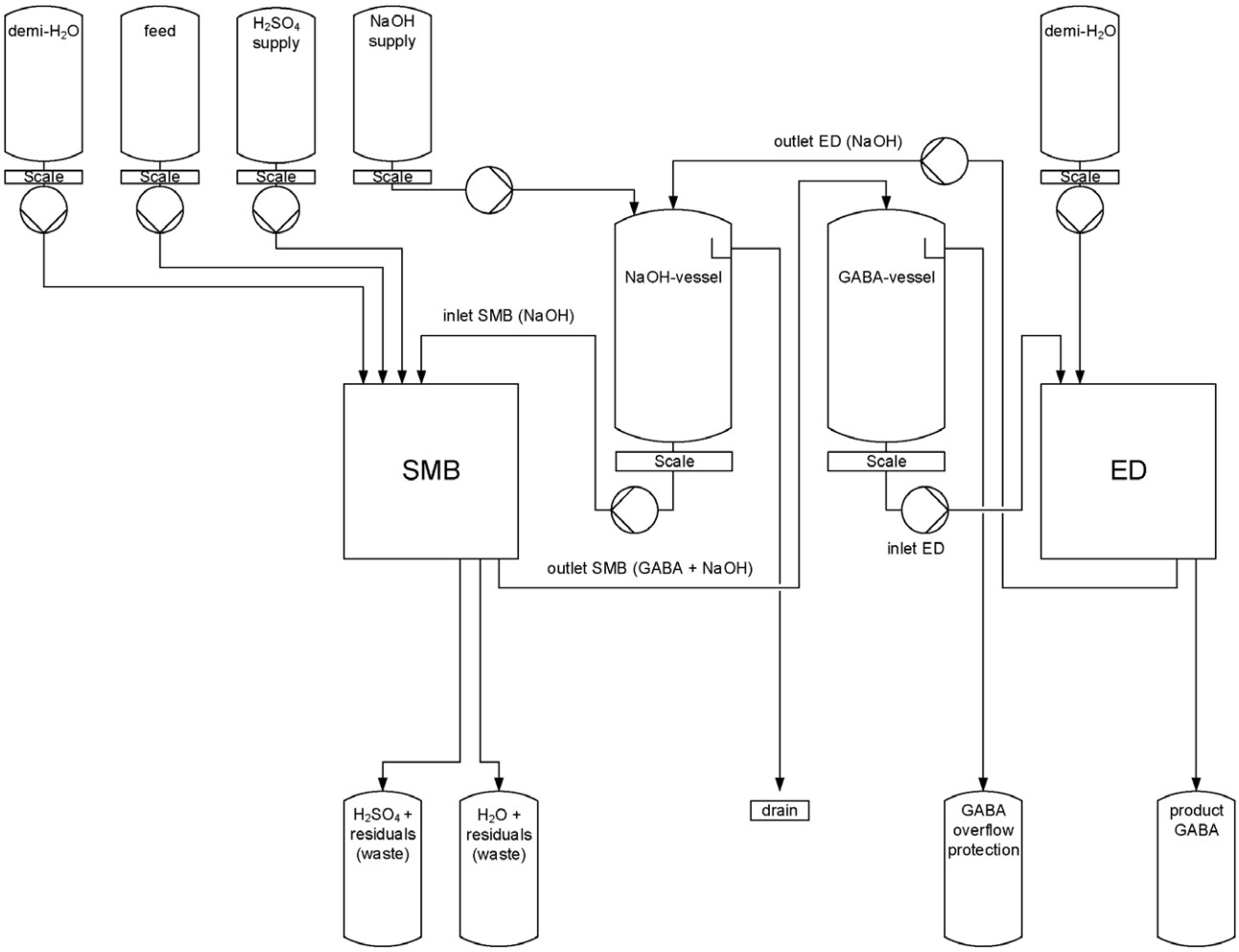

Figure 5. Process flow scheme of the SMB and BPED hybrid system.

described in Tab. 2. In general, the BPED system has the option to pause the SMB system in a master-slave control fashion.

3 Hybridization Studies

3.1 Experimental Plan

The hybrid system was in continuous operation for over 25 days. All waste streams from the loading, wash, and regeneration were purged from the system. Samples of all relevant streams and vessels were taken on day 3, 12, and 18 of the operation. On day 18, the SMB mode was changed to increase productivity, allowing higher flow rates of input streams. After completion of the hybrid experiment, a standalone SMB run was performed to provide a comparison between a standalone and hybrid experiment. An overview of SMB modes used is given in Tab. 3.

Table 2. Control strategies of SMB and BPED systems based on GABA and NaOH vessels.

Event	SMB	BPED
Weight of GABA vessel falls below lower weight setpoint	SMB remains active	BPED pauses
Weight of NaOH vessel exceeds higher weight setpoint	SMB pauses	BPED remains active
Weight of NaOH vessel falls below lower weight setpoint	Pause SMB	Speed up process
Weight of NaOH vessel exceeds higher weight setpoint	SMB remains active	BPED pauses
Concentration NaOH in NaOH vessels fall below setpoint	No action	25 wt % NaOH added to NaOH vessel

Table 3. Overview of SMB modes used during experiments.

Day	SMB mode	Recycling in hybrid process
3	SMB normal run	Yes
12	SMB normal run	Yes
18	SMB run with higher productivity	Yes
25	SMB normal run	No

3.2 SMB Setup and Method

A lab-scale SMB system was designed and constructed with capacity to operate a maximum of eight adsorption columns. The columns were connected to a modular valve block, which consisted of 88 solenoid valves that allowed the user to have a precise control over the flow paths. Each column was connected to a flow path with five inlet valves, five outlet valves, and one series valve. As the valves were controlled independently from each other, flexibility was granted to control the conditions per individual column. The system could execute a maximum of eight zones at the same time, handling a maximum flow rate of 6 L h^{-1}.

The setup was controlled by the XPure-S software program (XPure is Xendo's trademark for SMB continuous chromatography systems) executing experimental conditions based on the recipes generated in the XPure recipe editor. The experimental recipe defined the total number of columns in an SMB cycle, the number of column positions, and the configuration per position with respect to inlet or outlet valve, flow rate, sensor control, and switch time per position. Further, the control software obtained information from sensors (e.g., pH, conductivity, bed level) connected to the system and sent information to pumps and valves. All relevant data (e.g., sensor data, column position within process) was logged for easy post experiment analysis.

In the current case, seven PVC chromatography columns (bed height 490 mm, 42.6 mm ID) were packed with Amberlite 252H. The seven columns were switched between nine defined positions as described in Fig. 6 and the recipe used until 18 days is given in Tab. 4. After 18 days, the flow rates were increased by 8 %, to enhance productivity.

3.3 BPED Setup

The electrodialysis experiments were conducted in a BPED unit built at BASF. Fig. 7 presents the flowsheet of the experimental

Table 4. Recipe controlling the SMB during GABA purification.

Zone	Stream	Inlet no. in use	Outlet no. in use	Total number of columns	Number of columns in series	Flow rate [mL min^{-1}]	Switch time [min]
Adsorption	Clarified fermentation broth	1	1	2	2	13.5	35.5
Adsorption wash	Demineralized water	4	1	1	1	85.7	11.8
Elution	8 wt % NaOH	2	3 and 1	3	3	24.2	35.5
Elution wash	Demineralized water	4	2	1	1	85.7	11.8
Regeneration	4 wt % H_2SO_4	3	4	1	1	38.2	35.5
Regeneration wash	Demineralized water	4	4	1	1	85.7	11.8

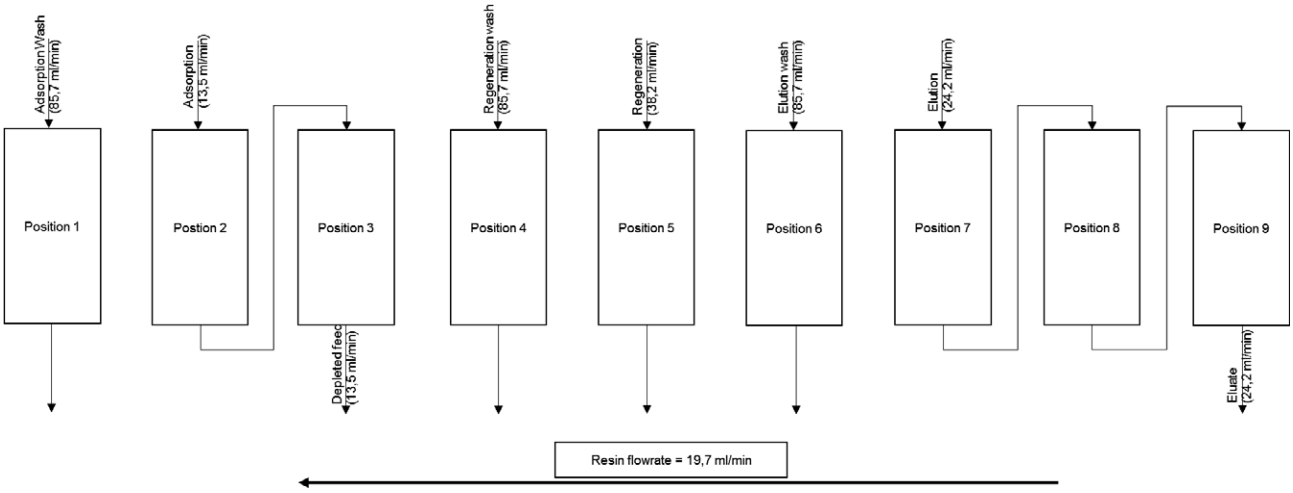

Figure 6. The nine positions defined in the SMB recipe.

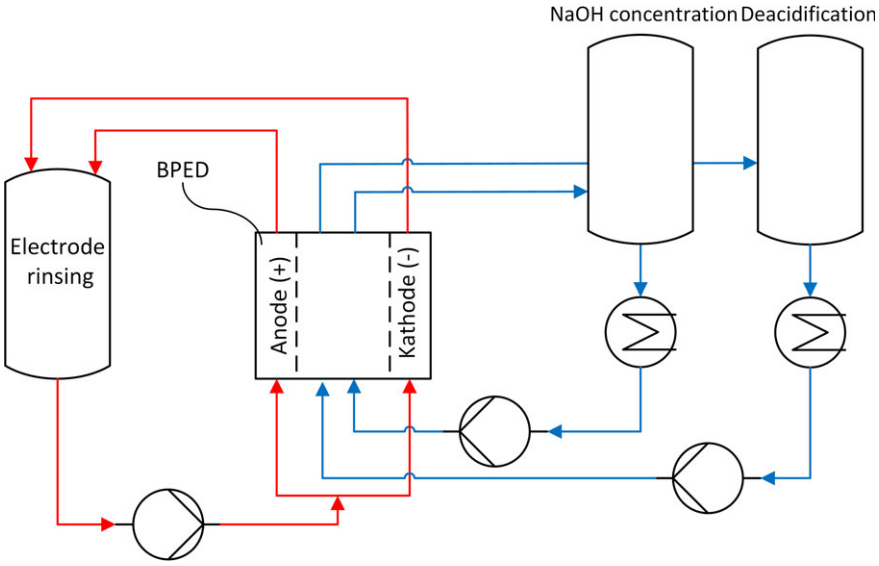

Figure 7. Flowsheet of the BPED apparatus showing the membrane unit and the loops for desalination and concentration of GABA-Na^+.

setup emphasizing the BPED unit, the caustic concentration and desalination loop, as well as the electrode rinsing loop. The unit used had a capacity to process 5 L batch streams of the elution output from the SMB in 8.2 h. The BPED unit is a membrane stack consisting of two electrodes (anode and cathode) and an alternating arrangement of bipolar and anion-exchange membranes. Within the separation process, Na^+ ions move into the caustic concentration loop by passing the cation-exchange membranes. In this way, these Na^+ ions then start the formation of sodium hydroxide. The current between the electrodes was varied from 5 to 9.5 A to study its impact on BPED performance. Due to the formation of electrode gases and to avoid side reactions, the anode and cathode chambers were constantly flushed. The NaOH lost in the product stream was compensated by a 25 wt % NaOH stock.

3.4 Analytics

Analytically, the following streams/vessels were analyzed periodically over the time course of the hybrid experiment:

- GABA inlet stream to check the consistency of the feed
- Waste stream to check the efficiency of the SMB
- GABA vessel to check the efficiency of the SMB
- NaOH vessel to check accumulation of impurities
- GABA product vessel to check the efficiency of the BPED.

By that, it was possible to determine the efficiency of the hybrid process as well as the product quality over time. Moreover, the mixture of all GABA product vessels was analyzed to check the complete mass balance and to calculate the overall average GABA recovery.

As analytical values, the following concentrations were determined:

- GABA, both by in-house titration and HPLC
- Other amino acids (glutamate, glycine, alanine, valine, lysine, proline) by HPLC
- Organic acids (phosphoric acid, malic acid, succinic acid, acetic acid) by HPLC
- Ethanol and glycerin by HPLC
- Anions (sulfate, phosphate) and cations (ammonia, calcium, potassium, sodium) by ion chromatography.

4 Results and Discussion

4.1 Hybrid Process: GABA Recovery over Time

In Fig. 8, the GABA recoveries over time are summarized for SMB, BPED, and for the hybrid process. The recovery for the hybrid process is indicated (a) without desalinating the electrode rinsing compartment and (b) with rinsing the electrode rinsing compartment.

Up to day 12, the SMB was run according to the initial recipe and the GABA recovery was approximately 100 %. At day 18, a different SMB mode was run which increased the productivity of the SMB resulting in a large eluent stream but with reduced recovery (decrease from 100 % to 96.5 %). The overall GABA recovery by the BPED remained stable at about 91 % after an initial decrease from 95 %. Performing a desalination of the BPED rinsing compartment improved the GABA recovery from 93.7 % to 96.2 %.

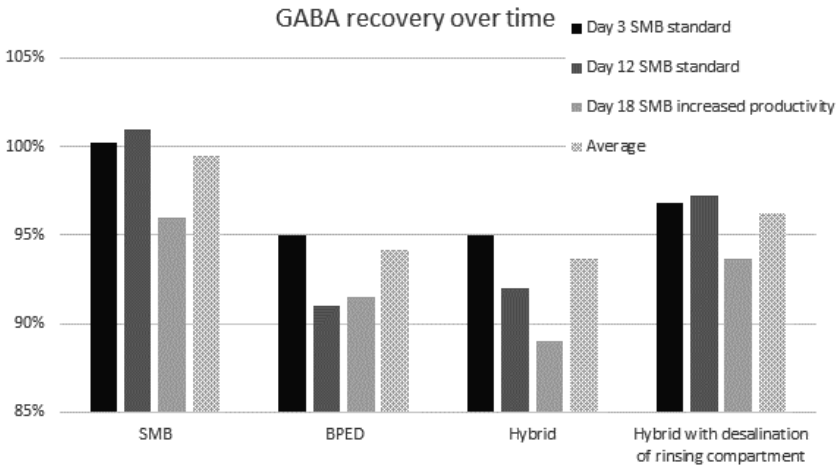

Figure 8. GABA recovery over time for SMB, BPED, the hybrid system, and the hybrid system with rinsing of the desalination compartment.

4.2 SMB Performance over Time

In Fig. 9, the performance of the SMB is presented in the form of conductivity profiles over time. The profiles were consistent over time and do not indicate any decrease in performance over time. This indicates that the recycle of NaOH and the accumulated impurities within this recycle do not have a significant impact on elution efficiency.

4.3 ED Performance over Time

In Fig. 10, voltage curves over bipolar and cation-exchange membranes as a function of conductivity in the GABA desalination cycle during cycles 1–102 are depicted are depicted. The membrane resistances of a membrane pair (bipolar and cation-exchange membrane) for each 10th desalination cycle are indicated (cycle 1, 10, …,100) with currents varying between 5 and 9.5 A. The membrane resistances were constant during most of the desalination process, increasing towards the end of each cycle because of lower total ion concentrations. Most importantly, no significant changes in membrane resistances over time were observed, thus indicating no impact of impurities on the membranes.

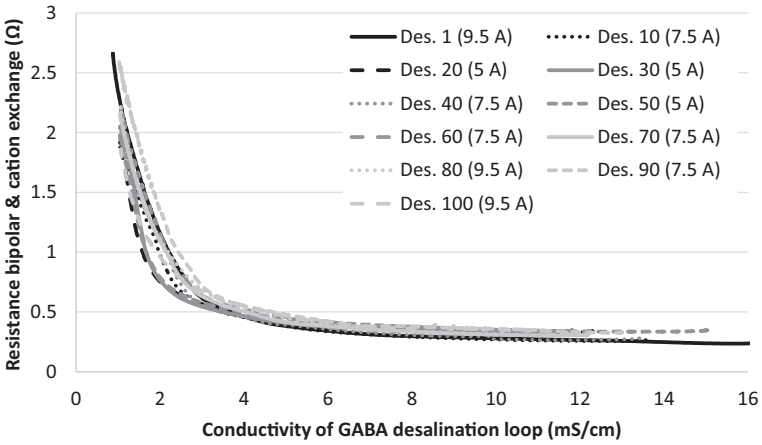

Figure 10. Voltage curves over bipolar and cation-exchange membranes as a function of conductivity in the GABA desalination cycle during cycle 1–102.

4.4 Overall Mass Balance and Savings in NaOH

The overall mass balance is presented in Tab. 5. A complete overview of analytics on GABA, ions, sugars, and other amino and organic acids is given. In total 337 kg of GABA solution was produced out of 274 kg of clarified broth. The total calculated GABA recovery was close to the theoretical average value presented in Fig. 8. The analytics yield a GABA recovery of 93.4 % versus 93.7 % according to the analytics done during the hybrid run.

It was noted that the concentration of amino acids increased in the product stream compared to the feed stream. The organic acids and most ions were effectively removed from the product streams. The ammonium and sodium cations that remained are a result of the defined conductivity threshold of 1.04 mS cm^{-1}. This threshold was selected to reach a sufficient level of desalination. Ammonium and sodium cations were transported through the cation-exchange membrane and subsequently recycled to the SMB together with NaOH.

Fig. 11 presents the composition of the final purified GABA product. The GABA purity was 96.7 %. No anions were detected in the solution. The impurities were the remaining cations (ammonium and sodium, as defined by the conductivity threshold) and several amino acids. Since several amino acids were detected, it can be concluded that the hybrid system in principle can also be used for purification of other amino acids.

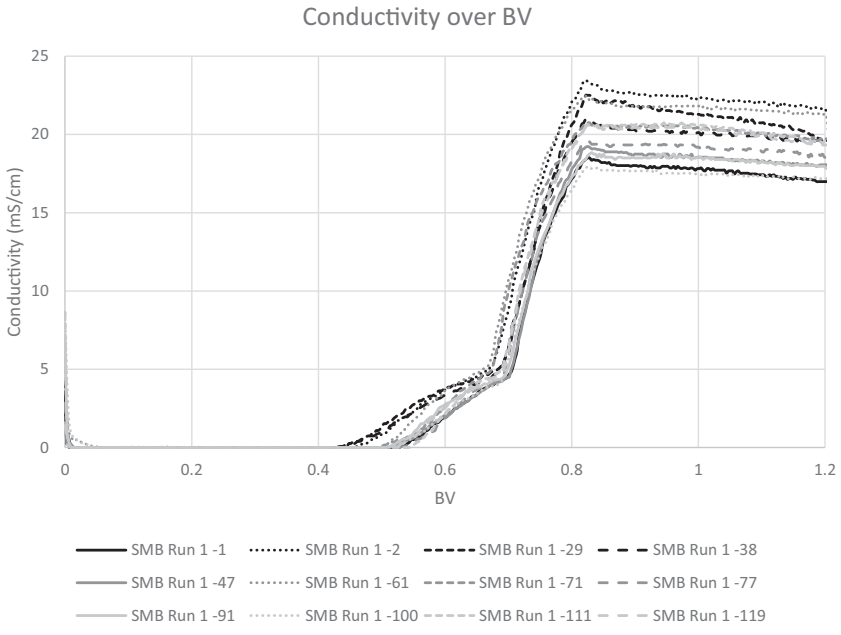

Figure 9. Conductivity profiles of several hybrid SMB elution steps.

4.5 Savings in Eluent

Tab. 6 gives an overview on NaOH consumptions in the hybrid SMB-BPED process using standard and increased productivity recipes. For the normal SMB recipe without NaOH recovery by BPED, the SMB columns needed 466 kg of NaOH (8 wt %) for 75 cycles based on a consumption of 2.77 kg NaOH per day. When the SMB was operated in hybrid form, the NaOH consumption was 356.9 kg, giving a 23.4 % reduction in NaOH consumption.

When changing the SMB from the normal mode to the increased productivity, the NaOH consumption by the SMB decreased by 27.1 % from 2.77 kg to 2.02 kg NaOH

Table 5. Overall mass balance of the hybrid SMB-BPED purification of GABA.

Compound [g]	GABA feed	Product GABA
Overall mass	274 500	337 500
GABA	27 455	25 650
Glutamate	121	207
Glycine	29	60
Alanine	186	185
Valine	32	72
Lysine	88	0
Proline	57	135
Phosphoric acid	220	0
Malic acid	110	0
Succinic acid	357	0
Glycerin	110	0
Acetic acid	82	0
Ethanol	220	0
Sulfate	37 058	0
Phosphate	0	0
Ammonium	16 196	1181
Calcium	549	0
Potassium	1098	0
Sodium	275	979

per day. Operating the SMB in hybrid form with increased productivity, the theoretical NaOH consumption was calculated to be 1.64 kg NaOH per day. Thus, by combining an increase in the SMB productivity and implementing NaOH recovery by BPED, a reduction in NaOH consumption of 41 % or 1.13 kg NaOH per day was realized. When comparing the SMB-BPED hybrid system with increased productivity with the standalone normal SMB without BPED, a NaOH consumption reduction of 40.8 % was calculated.

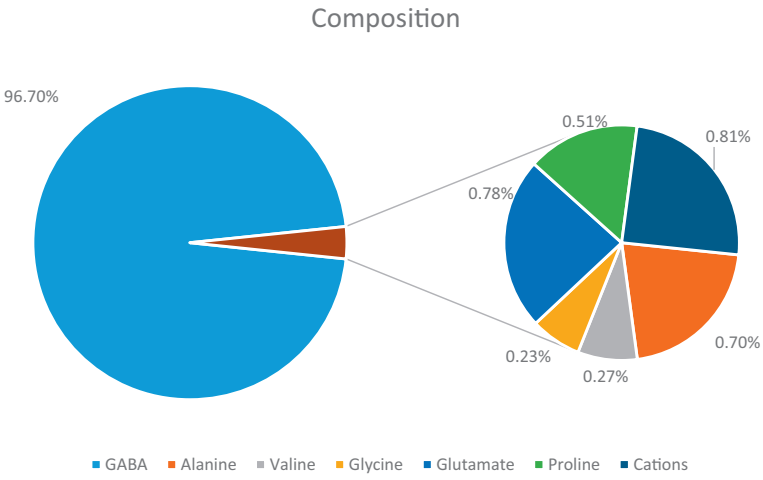

Figure 11. Composition of the solid part of the final GABA product (mixture of all GABA product vessels).

Table 6. Overall mass balance of the NaOH savings of the hybrid system SMB-BPED.

	NaOH consumption [kg d^{-1}]	
	SMB standalone	SMB-BPED hybrid process
SMB normal mode	2.77	2.25[a)]
SMB with increased productivity	2.02	1.64 [a)]

[a)] Based on a saving of 23.4 % of NaOH due to BPED.

5 Conclusions

The SMB and BPED systems were successfully run in hybrid form for nearly 25 days. Integrating the SMB system with the BPED resulted in a decrease in NaOH consumption of approximately 40.8 %. The purity of the GABA obtained was 96.7 % and the recovery was approximately 95 %. Therefore, operating in hybrid form did not impact the overall performance over time of either the SMB or the BPED. Even though two impurities, namely, ammonium and sodium ions, were found to be accumulating, the overall product purity was still maintained in the required range.

Acknowledgment

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The authors have declared no conflict of interest.

Abbreviations

BPED	bipolar electrodialysis
GABA	γ-aminobutyric acid
SMB	simulated moving-bed

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