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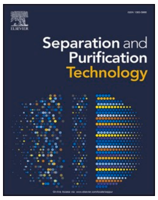

Multi-Objective Bayesian Optimization of Continuous Purifications with Automated Phase Separation for On-Demand Manufacture of DEHiBA

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ABSTRACT

The optimization of purifications has received little attention in an era of machine-learning driven optimization technologies that focus on synthesis, despite purifications being equally challenging and critical. This work utilizes lab-scale continuous purification equipment to automate the mixing and separation of phases for the purification of *N,N*-Di-2-ethylhexylisobutyramide (DEHiBA), a specialized ligand in demand for advanced nuclear reprocessing. Bayesian optimization drove the purifications via feedback from HPLC and GC-FID quantitative analysis to maximize purity and product recovery via a weighted single objective. Batch purification screening found removal of *N,N*-Di-2-ethylhexylamine (DiEHA) to be problematic with aqueous only extractions, adding complexity to the purification. Three purification routes were optimized in continuous flow and compared for their efficacy after a single extraction stage. Optimization of both product purity and recovery process metrics was crucial to identify optimum Pareto conditions. Product purities >95% were attainable for all routes, but the target of >99.9% was eluded after a single extraction in continuous flow. Product loss to the aqueous phase could be limited to <5%, but at the expense of product purity for all routes. Ultimately, a two-step process was devised from this work, employing a combination of water or 0.2 M nitric acid and acetonitrile to remove DiEHA and ~90% isobutyric acid, subsequent sodium bicarbonate extraction yielded >99.9% purity.

1. Introduction

Product purification is a key step in chemical manufacture, particularly for highly selective, specialized pharmaceuticals and extractants. Whilst high purities are prioritized, other metrics like waste reduction, sustainability, and cost are factors that can be optimized alongside purity, attaining a similar product with a reduced impact [1]. Publications that optimize processes focus on synthetic optimization with purification optimization escaping the spotlight [2,3]. Purification screening and optimization can be time consuming and labor intensive but can be overcome via the adoption of automation and machine-learning (Industry 4.0) for batch or flow processes [3,4].

Industrial batch chemistry traditionally involves discrete steps with intermittent transfer or storage of crude products and intermediates, often necessitating downtime for cleaning and preparation between batches [5]. This not only limits productivity but increases the risk of human error and contamination [6]. In contrast, flow chemistry facilitates the uninterrupted flow of reactants and products through reactors and purification equipment, resulting in constant product output [7]. The nature of continuous processes boosts productivity whilst improving product quality and consistency, with the telescoping of multiple steps into a single platform enabling robust on-demand product manufacture [8]. Despite recent advancements focusing on multi-step synthetic optimization [9], optimized continuous purification has garnered lesser attention, with focus on synthesis [10]. Traditionally purification methods consume large volumes of solvents and aqueous phases to remove impurities, leading to poor process sustainability and economics [11]. The application of machine-learning algorithms to chemical purifications offers the possibility to improve multiple process metrics whilst yielding pure material [12,13]. Self-optimizing purification platforms explored in this work provide opportunity to simplify and automate the optimization of operating conditions reducing the cost and time required to develop profitable, sustainable, and effective industrial processes from start to end.

Liquid-liquid extraction is well-suited for continuous flow, and the development of lab-scale purification equipment [14], such as

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membrane separators and coalescing filtration [15,16], presents new opportunities for streamlined chemical manufacture. Access to highly capable and scalable equipment facilitates the optimization of process conditions in the lab before pilot-plant operations, reducing the cost and complexity. Advantageously liquid–liquid extractions in flow can be automated, requiring little human intervention, reduced equipment downtime, and no solid waste disposal costs. By adapting self-optimizing flow reactor platforms to incorporate continuous separation/purification equipment, the automated optimization of purification routes and conditions is increasingly feasible. AD Clayton et al. [17] has demonstrated the self-optimization of an amine purification in continuous flow focusing on a single objective, purity, for this purification. To develop a balanced process, the work described herein optimizes product purity and recovery alongside sustainability, and economic process metrics.

Optimized and telescoped continuous synthesis and purification promises enhanced efficiency, improved safety, reduced environmental impact, and greater scalability [18]. Thus positioning continuous processes at the forefront in advancing the modern chemical industry, driving progress and innovation for the production of a wide range of chemical products.

The complete on demand manufacture of DEHiBA is a crucial step towards improving the economics and accessibility to ligands for advanced nuclear reprocessing [19,20,21,22]. Therefore, as previous work has optimized the synthesis of DEHiBA in continuous flow [22], this work aims to achieve a fully optimized and integrated process by optimizing the purification of crude DEHiBA. Thus, the optimized, on-demand manufacture of other ligands and chemicals can follow. The objective for these optimizations is to produce DEHiBA with >99.9% purity, recovering maximum product with minimal waste across the whole platform. By optimizing the purification of crude DEHiBA (the output material from the synthetic optimization of DEHiBA [22]) for product purity and recovery whilst minimizing aqueous waste, this work overcomes the challenge of multi-step process optimization where early changes impact later steps. Ultimately, the optimum synthetic and purification conditions can then be combined into a single platform, yielding a complete and efficient continuous manufacture route to pure DEHiBA on demand, granting improved accessibility to large volumes of industrially relevant extractants with less economic burden.

Additionally, insights gained from this work can be used to guide the development of purification (solvent wash) steps in nuclear reprocessing flowsheets to overcome challenges with removing fatty amines like DiEHA (*N,N*-Di-2-ethylhexylamine) or *N,N*-dioctylamine, typical degradation products of popular amide ligands like DEHiBA or TODGA (*N,N,N',N'*-tetraoctyldiglycolamide) [23,24,25,26,27].

2. Materials and methods

2.1. Materials

2.1.1. Chemicals and crude materials

All compounds were used as received. Acetonitrile (MeCN; HPLC grade), biphenyl (99%), naphthalene (99%), sodium bicarbonate, and hexane were purchased from Fisher Scientific Ltd. Nitric acid (68%) was purchased from VWR Chemicals. Ethyl acetate was purchased from Merck Life Science UK Ltd. Sodium naphthalenesulfonate (99%) was purchased from Fluorochem.

Two crude DEHiBA materials were purified in this work, batch work utilized the less pure (44%) DEHiBA via the high throughput synthesis, whilst the continuous flow work used purer (49%) DEHiBA from the reagent efficient synthesis. Compositions and synthetic conditions can be found in the ESI, **Fig. S8**.

2.2. Methodology

2.2.1. Optimization platform and procedure

The flow platforms are detailed individually in the ESI and were setup as per Fig. 1 for all optimizations, only the aqueous reservoir was changed between optimizations between nitric acid, water and sodium bicarbonate. Industrially available 2 mL fReactors (CSTRs) were used to mix the phases whilst a 2 mL coalescing separator was employed to automate the phase separation via conductivity measurements and a needle valve connected to a servo motor (see ESI and [16] for more details). The platform was controlled via a custom written MATLAB script, where the optimization algorithms were also written and implemented. Automated multi-point sampling facilitated online analysis: each experiment was allowed to stabilize over a total flow equal to eight times the volume of the entire platform to reach steady state (**Fig. S3**); then the sampling valve was triggered, sampling the aqueous outlet to the HPLC initializing the analysis, after 3 min the sampling valve for the organic outlet was triggered, again sampling to the HPLC [18]. During this time samples of the organic phase were collected and quantified via GC-FID analysis. Process metrics were determined automatically from these chromatograms for feedback to the optimization algorithm to generate the next batch of conditions.

The concentration of DEHiBA in the aqueous and organic phases was quantified via online HPLC analysis using internal standards to determine volume changes and thus the loss of DEHiBA. Sodium naphthalenesulfonate (NSA) was used as the aqueous internal standard and was not found in the organic phase post extraction. As the starting materials and by-products are not UV-active their concentrations were quantified by GC-FID analysis, therefore organic samples were collected at steady state and diluted for GC-FID analysis using naphthalene as the external standard.

Bayesian Optimization with Adaptive Expected Improvement (BOAEI) [18] was integrated for the closed-loop self-optimization of chemical purification routes, identifying global optima in minimal experiments and thus minimal waste, time, and cost. This optimization approach minimized periods of inactivity due to the time cost of GC-FID analysis, by suggesting new experiments in batches of four.

A weighted objective was used with BOAEI to target high purity, low product loss conditions whilst avoiding excessive material consumption needed to explore the whole Pareto front, solving this expensive-to-evaluate optimization with minimal experiments. The weighted objective combines and normalizes purity and product loss metrics, favoring purities >95% and minimal product loss (see ESI). A weighted objective function was used as opposed to a multi-objective algorithm as identifying the Pareto front was not the objective of this work, instead the weighted objective allowed the algorithm to focus on the process criteria of interest. The weighted objective was refined in initial work following use of TSEMO to ensure the objective worked as intended and did not avoid areas of interest. The algorithm employs a Bayesian optimization methodology utilizing Gaussian processes as the surrogate models for the objective. The acquisition function uses adaptive expected improvement to balance exploration and exploitation. The algorithm was terminated once convergence on the optimum was realized or crude material was exhausted.

3. Results and discussion

3.1. Purification goals

This work sets out to optimize the purification of crude products, specifically DEHiBA in continuous flow using Bayesian optimization algorithms to optimize both product purity and recovery alongside minimizing the volume of aqueous waste. Ultimately, a product purity >99.9% is required but can be achieved whilst optimizing sustainability and economic process metrics. The automated extraction/separation equipment benefits economics further by reducing time and labor required for process optimization. Batch purification screening was utilized to identify a suitable purification route to optimize in continuous flow.

Removal of DiEHA from the crude product proved challenging with

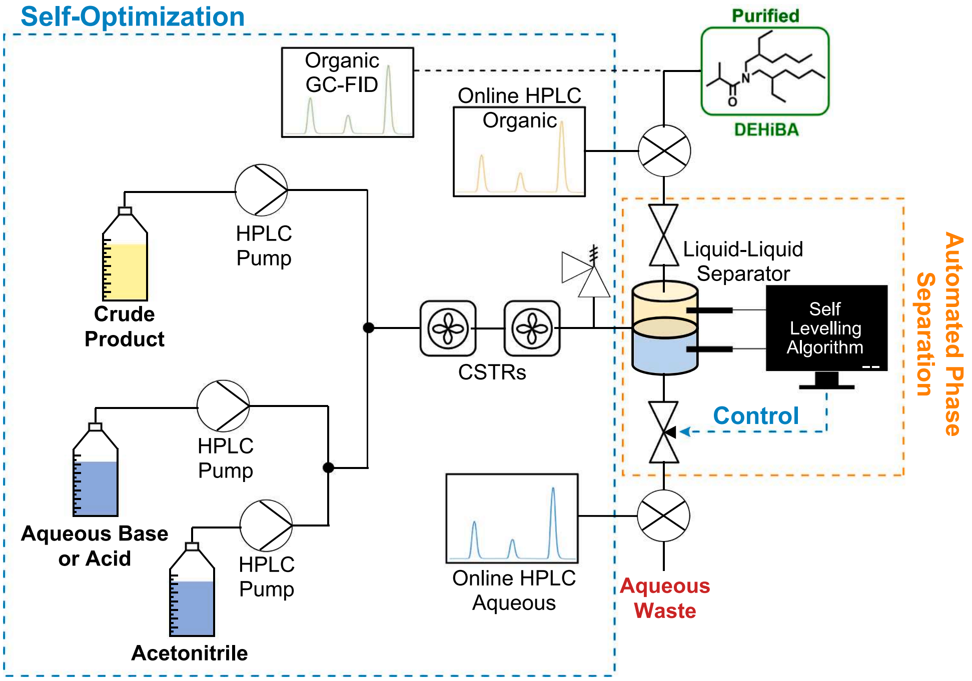


Fig. 1. The self-optimizing flow purification platform employed in this work to automate the optimization of purification conditions.

an aqueous only liquid–liquid extraction. Overcoming this challenge led to product losses due to addition of acetonitrile to the aqueous phase, it was therefore paramount that both product purity and recovery were maximized in this work. Although it may be possible to achieve the desired purity in a single stage with a large volume ratio of aqueous to organic phase or other wasteful methods, the goal is to minimize waste, risk and thereby cost so limits for volume ratios were set for the optimizations (Table S4).

Ideally the optimum purification route here maximizes purity and product recovery, whilst minimizing the number of extraction stages/steps, cost, and waste. This work prioritizes maximizing product purity and recovery using the defined weighted objective and BOAEI to optimize a single stage/step, with minimal aqueous waste a secondary objective. This work only uses one stage to identify ideal conditions and compare routes to simplify the optimization and minimize costs, but the incorporation of multiple stages and steps is calculable and can be verified.

3.2. *Batch purification screening*

Batch purifications were employed to screen a range of purification routes and conditions to develop a promising system that could be transitioned into continuous flow. Key considerations were to ensure homogeneity of the system to avoid blockages, separation of phases to avoid emulsions, a two-phase system as three liquid phases would be problematic with the flow setup, and the refinement of reagents to reduce the number of optimization runs and time. The goal of the batch screening was to identify a promising route capable of removing all impurities from DEHiBA, with the ability to reach the desired product purity >99.9%. The crude material used was collected from a 5-hour synthesis run using high throughput conditions identified in previous work, to yield 72 kg $L^{-1}h^{-1}$ DEHiBA from iBAnhydride and DiEHA [22]. The composition of the crude material before and after base extraction is quantified via GC-FID analysis (Tables 1 **& S1**), where purity is calculated using moles. The starting material has a 44% product purity with ~ 1% DiEHA and 55% iBA.

As iBA is the major impurity, purification screening began with bases such as saturated sodium bicarbonate and 1 M sodium hydroxide. The volume ratio of crude DEHiBA to aqueous phase was varied for each extraction, and hexane was added as a variable to aid separation and compare performance. Hexane improved separation in all cases, reducing the separation time, though separation was possible without.

Table 1
Comparison of batch purifications varying the amount of base and hexane.

Volume Ratio and Composition		Purity (%)	mol% DiEHA wrt DEHiBA	mol% iBA wrt DEHiBA
	Crude DEHiBA	44.0	2.9	125.4
1:1	DEHiBA : sat. NaHCO3	85.4	3.3	13.7
1:2		97.6	2.4	0.0
1:3		97.6	2.4	0.0
1:1:1	DEHiBA : hexane : sat. $NaHCO_3$	84.1	2.3	16.6
1:1:2		97.8	2.2	0.0
1:1	DEHiBA : NaOH	97.5	2.6	0.0
1:2		97.7	2.4	0.0
1:3		97.7	2.4	0.0
1:1:1	DEHiBA : hexane : NaOH	83.0	2.6	17.9
1:1:2		85.8	2.2	14.4

Purifications with base targeted iBA removal, with little to no removal of DiEHA as expected. Saturated sodium bicarbonate was selected as a cheap, relatively benign reagent, for comparison with 1 M NaOH, a more powerful, but toxic and corrosive base.

1 M NaOH proved to be more volume effective, but both were only able to achieve purities <98%. Inclusion of hexane hindered iBA extraction when using NaOH, leading to a drop in product purity, but did not reduce product purity when using $NaHCO_3$. Overall, the combination of $NaHCO_3$ and hexane was most promising, offering a benign, cost-effective route, with the addition of hexane improving phase separation reducing operational complexity. Alternative bases like methylamine, pyridine, and ammonium hydroxide were also screened but afforded no benefit (**Table S2**). To improve purity to >99.9% a different purification route was needed to remove DiEHA and iBA, ideally in a single step to minimize complexity and cost

Next, DiEHA was targeted for its removal via acid extractions, this fatty amine oxidizes over time from colourless to yellow interfering with UV–Vis analysis a technique often employed to monitor and quantify uranium extraction [28,29,30]. It was therefore paramount that this material be removed to avoid complications downstream when performance testing DEHiBA. An efficient methodology for DiEHA removal would also support reprocessing development. 1 M sulfuric acid, 2 M nitric acid, and saturated ammonium chloride were compared for the purification of crude DEHiBA (**Table S3**). However as nitric acid is already utilized in nuclear reprocessing and to avoid entrainment of ions like sulfate or chloride, as these are known to interfere with UV–Vis absorption of uranium(VI) [31], nitric acid is the preferred acid for this work. Nevertheless, the performance of these acid must be assessed.

Screening of these acids alone did not achieve the desired >99.9% purity, instead achieving up to ~76% purity via the extraction of iBA but not DiEHA. Removal of DiEHA was unexpectedly poor and did not improve when increasing the amount of acid, likely due to the insolubility of the fatty chains in the polar aqueous phase. Nitric acid performed best with 70–77% purities, whilst sulfuric acid and ammonium chloride produced purities between 64–71%, both benefitting from the inclusion of hexane, nitric acid purifications were seemingly unaffected by the presence of hexane here. Notably, no significant benefit was gained by increasing the amount of each acid present.

To overcome this lack in performance and the poor extraction of DiEHA with acid alone, acetonitrile (MeCN) was incorporated into the aqueous phase, hoping to aid solubilize the greasy DiEHA and improve product purity. This study (**Table S4**) utilized the same acids, again with and without hexane, incorporating equal volumes of acetonitrile whilst increasing the amount of acid. These extractions achieved up to 88% purity using nitric acid, MeCN and hexane, again with nitric acid outperforming the other acids that achieved a maximum of 80% purity for sulfuric acid and no significant improvement for ammonium chloride. For both nitric acid and sulfuric acid, lower acid content in the aqueous phase improved DiEHA removal.

As nitric acid outperformed the other acids it proved to be most suitable for further investigation, this time increasing the ratio of MeCN to DEHiBA (Table 2). This work highlights the importance of the DEHiBA to MeCN ratio for extracting DiEHA where increased MeCN improves extraction, but increased nitric acid hinders DiEHA extraction. Additionally, the absence of hexane reduced the overall purity and extraction of DiEHA. >99.9% purity was achieved in a single step for the greatest ratios explored using equal volumes of crude DEHiBA, hexane, and nitric acid, but a large excess of MeCN (4x the volume of crude DEHiBA). These extractions removed DiEHA and iBA without the need for base, streamlining the process potentially to a single step, reducing process complexity.

Overall, nitric acid outperformed sulfuric acid and ammonium chloride even in the presence of acetonitrile, suggesting both nitric acid and acetonitrile facilitated the removal of iBA and DiEHA. The combination of hexane, acetonitrile and nitric acid benefitted the purification most, with hexane improving purity and separation. Ultimately, an excess of acetonitrile provided the best performance, facilitating the complete removal of DiEHA and iBA in a single step. Despite the obvious benefits acetonitrile provides, these extractions are now more complex due to increased solubility of DEHiBA in the aqueous phase leading to greater product losses. This added complexity lends itself to multi-objective optimization where the trade-off between product purity and recovery can be minimized.

3.3. *Continuous flow purifications*

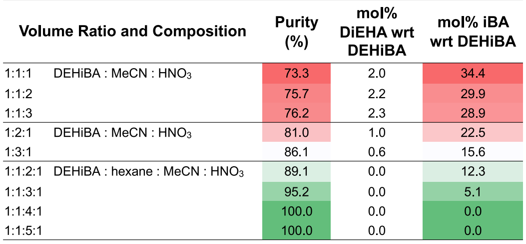
Following the identification of a single-step purification route in batch, focus moved to optimizing this system in continuous flow aiming to achieve similar performance and optimize process conditions. Ultimately, a purity >99.9% is required, whilst minimizing the loss of DEHiBA to the aqueous phase, ideally in a single step or with minimal steps/stages, minimizing aqueous waste and thus cost.

The same crude product was used for the continuous flow purifications for fair comparison (**Fig. S9**), differing from the batch purifications with greater DEHiBA content and less impurity. The DEHiBA content used in the continuous flow purifications is representative of the crude DEHiBA that would be produced from the optimum synthetic conditions to be taken forward for scale-up due to the lesser DiEHA content and lower cost associated with producing this crude DEHiBA. The DEHiBA used in the batch work was employed as a more difficult product to purify to ensure the chosen route could handle greater quantities of impurities and less DEHiBA, the DEHiBA content is unlikely to have significant effect on the product loss but a greater impurity content may saturate the aqueous phase sooner than a purer crude product. DEHiBA makes up 49% of this material with 50% iBA and ~1% DiEHA as a molar composition. This crude DEHiBA composition was used as its synthesis optimum for scale-up, being most cost and reagent efficient with multi-kilogram per hour product throughput.

The nitric acid optimizations utilized BOAEI to maximize purity then moved to TSEMO to maximize purity and minimize DEHiBA loss, however TSEMO did not perform as intended, prioritising minimal product loss avoiding high purity conditions. Therefore, BOAEI was

Table 2

Comparison of batch purifications varying the amount of acid, hexane, and the importance of acetonitrile.



Volume Ratio and Composition		Purity (%)	mol% DiEHA wrt DEHiBA	mol% iBA wrt DEHiBA
1:1:1	DEHiBA : MeCN : HNO_3	73.3	2.0	34.4
1:1:2		75.7	2.2	29.9
1:1:3		76.2	2.3	28.9
1:2:1	DEHiBA : MeCN : HNO_3	81.0	1.0	22.5
1:3:1		86.1	0.6	15.6
1:1:2:1	DEHiBA : hexane : MeCN : HNO_3	89.1	0.0	12.3
1:1:3:1		95.2	0.0	5.1
1:1:4:1		100.0	0.0	0.0
1:1:5:1		100.0	0.0	0.0

reintroduced, this time with the weighted objective which focused on identifying conditions of most interest with little product loss but maximum purity to more effectively solve this expensive-to-evaluate optimization. BOAEI and the weighted objective were solely used for the water and sodium bicarbonate optimizations due to the improved efficacy. The overall flow rate was measured for a range of conditions before each optimization and throughout the optimizations to ensure accuracy of each condition and all provided sufficient accuracy with minimal deviation (<1%) from the expected flow rate.

3.4. Nitric acid and acetonitrile purifications

Nitric acid concentration was reduced from 2 M used in batch work, to 0.2 M for the initial purification optimization in flow, reducing the risk associated with mixing nitric acid with organic materials. Purity and DEHiBA loss data for this optimization is plotted across the design space in Fig. 2, highlighting the effect of each variable. Purity benefitted most from high ratios of MeCN to crude DEHiBA, whilst nitric acid had minimal effect on purity besides providing phase separation, as low nitric acid ratios resulted in miscibility for certain organic, acetonitrile ratios (dark blue markers). To contrast, minimal DEHiBA loss favored opposite trends, favoring lower acetonitrile to crude DEHiBA ratios, crucially increased nitric acid content hindered DEHiBA extraction. Product loss can therefore be minimized at high purity conditions by increasing nitric acid content.

Purity and product loss are the primary process metrics optimized in this work, however, the amount and composition of waste is detailed in Table 3 for comparison of relative cost and sustainability, allowing identification of balanced, yet optimum process conditions. For example, the most optimal condition here only produces 94% pure DEHiBA after a single stage, however low product losses of 1.5% and comparatively low volumes of aqueous waste after a single stage yields optimum overall performance. The target purity of >99.9% is still feasible using this condition but would theoretically require at least three extraction stages, only losing ~ 5% DEHiBA overall. In comparison, conditions that yield 97.8% or even 98.6% purity lose 8–12% DEHiBA and >2 times the aqueous waste without achieving the desired purity in a single stage, justifying the importance of optimizing and comparing these metrics.

A similar optimization was executed using 1 M nitric acid to understand and optimize the influence of nitric acid concentration. Purity and DEHiBA loss comparison, Fig. 3 **& S21** shows little difference between 0.2 M and 1 M nitric acid concentrations, with the optimum conditions highlighted using the weighted objective function as the colourbar for the 4D plot. Thus, indicating that the concentration of nitric acid has little effect on the purification in continuous flow for these conditions.

Both nitric acid concentrations are capable of 98–99% product purity, although product losses >9% are met above 96% purity and increase with higher purity as illustrated in Fig. 3. By operating at 94–95% purity, product losses can be limited to 1–2%. Whereas by operating at 97–98% purity 9–10% DEHiBA is lost per stage, which despite potentially requiring less extraction stages to achieve a product purity >99.9%, overall DEHiBA losses are greater. The performance of each condition must therefore be weighed up with the theoretical minimum number of extraction stages to achieve >99.9% purity before identifying optimum purification conditions and route.

Further work with 0.2 M nitric acid proved this routes capability for removing greater quantities of DiEHA, as well as removal of iBAnhydride. This is highly desirable, as in the event of differing crude product composition from manufacture, this purification route is more than capable, though more extraction stages may be needed to achieve the desired purity. The nature of this continuous process allows integration of inline and online process analytics to monitor purity, regularly ensuring product quality with less manual intervention reducing human error and risk. The process can therefore be understood and adjusted in real-time with this technology to account for any process upset.

As it is unclear whether nitric acid is beneficial to the purification, the next optimization employed water to replace the nitric acid instead of optimizing for nitric acid concentration.

3.5. Evaluating the need for nitric acid: Water and acetonitrile purifications

This purification exchanged nitric acid for deionized water, only using the weighted objective optimization methodology to reach an optimum in fewer experiments saving time and waste. Visually, phase separation was less problematic with water, which advantageously is a cheaper, less hazardous material to store and use, thereby reducing operational and disposal costs. The water, acetonitrile waste stream offers simplified recovery and recycle of starting materials, by-products and solvents, lending to a greener, cleaner process, avoiding concerns with nitric acid, improving safety and sustainability whilst minimizing raw material cost.

Purity and product loss trends from this optimization were analogous to the nitric acid optimizations (**Fig. S13**), with maximum purity favoring high acetonitrile to crude DEHiBA ratios, and seemingly independent of water. Again, the opposite was true for minimal product loss, favoring high crude DEHiBA to acetonitrile ratios, whilst water hindered product loss. As this optimization explored the design space less than the

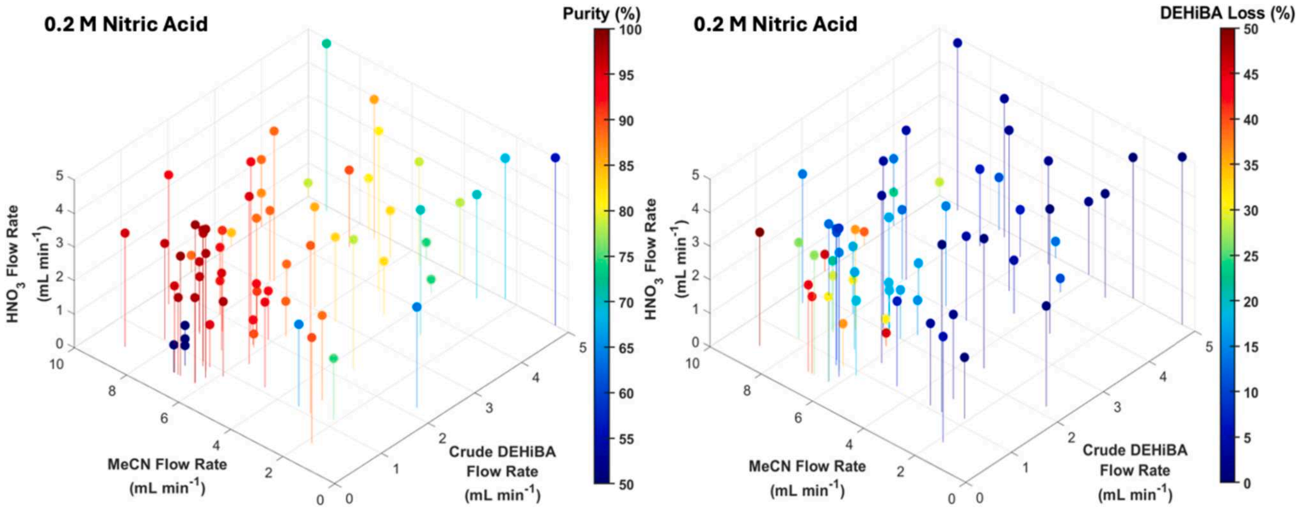


Fig. 2. Purity and product loss across the parameter space for the optimization with 0.2 M nitric acid and acetonitrile.

Table 3
Performance metrics for the optimal conditions when using acetonitrile and 0.2 M nitric acid to purify crude DEHiBA.

Crude DEHiBA Flow Rate (mL min^{-1})	MeCN Flow Rate (mL min^{-1})	0.2 M HNO_3 Flow Rate (mL min^{-1})	MeCN:HNO_3 Flow Ratio	Purity (%)	DEHiBA Loss (%)	Aqueous: Organic Ratio
1.575	5.387	5.000	1.08	94.0	1.5	6.6
1.370	5.746	5.000	1.15	95.4	2.3	7.8
1.481	5.803	2.569	2.26	95.9	9.9	5.7
0.888	6.659	4.071	1.64	97.4	9.6	12.1
0.727	6.239	4.270	1.46	97.8	8.8	14.5
0.705	6.226	4.431	1.41	97.8	8.5	15.1
0.518	6.291	4.703	1.34	98.6	12.7	21.2

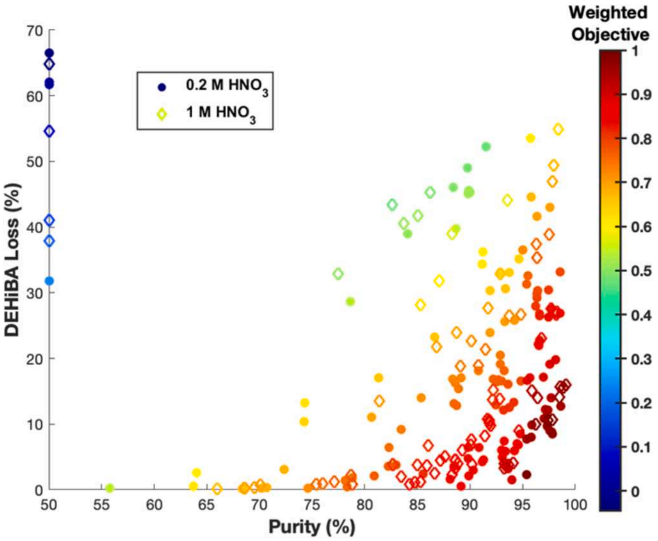


Fig. 3. Comparing purity and product loss metrics for the purifications with 0.2 M and 1 M nitric acid using the weighted objective (defined in the methodology) as a visual aid, 1 indicating the more optimal conditions.

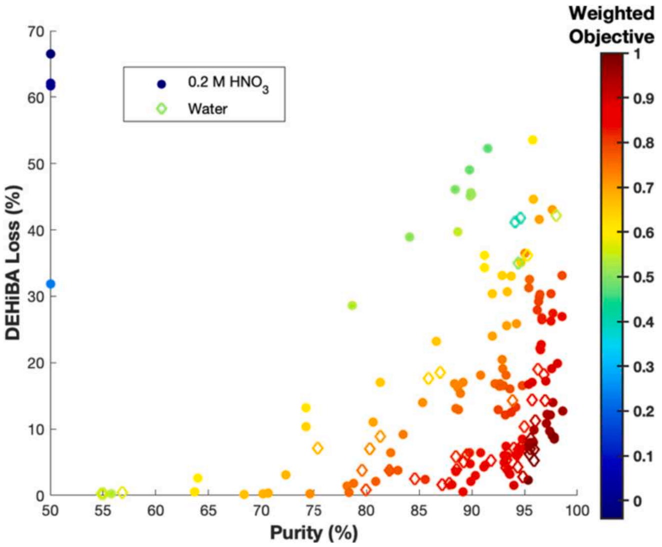


Fig. 4. Comparing purity and product loss metrics for the purifications with water vs 0.2 M nitric acid using the weighted objective indicating the more optimal conditions.

nitric acid extractions, the data was modelled using a quadratic linear regression model (**Fig. S14**) to better understand the interactions between parameters and validate our understanding of this purification route. Overall, these models confirm the influence of water content on DEHiBA loss but no influence on the purity.

The purity and product loss trade-off data for this purification route is overlaid with the data from the 0.2 M nitric acid purifications for comparison Fig. 4; Similar performance is achieved between 94–96% purity yielding similar product losses, however maximum purity is reduced when using water, struggling to exceed 97%. For optimal overall performance 94–95% purity minimizes product losses to ~3% after a single extraction stage. The optimum conditions are highlighted in **Fig. S15** using the weighted objective function, seemingly requiring less MeCN compared to the nitric acid purifications.

Despite sustainability benefits of water over nitric acid these benefits are lessened by the greater volume of aqueous waste for the optimal conditions (Table 4) compared to the nitric acid purifications. For example, the optimum condition yields 94.9% product purity, losing 3% DEHiBA but requiring three times the aqueous volume as the optimum nitric acid condition that produced 94% purity, losing ~ 1.5% DEHiBA. Again, the higher purity conditions here lose a greater percentage of DEHiBA, especially over 96% purity. Lower volumes of aqueous waste are possible but result in greater losses of DEHiBA so this must be assessed from a cost perspective.

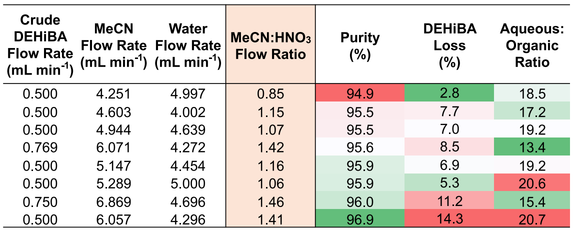
Purities >99.9% are possible via both routes, though require multiple extraction stages to achieve this. Both routes performed best between 94–96% purity due to the trade-off with product loss causing product loss to increase significantly over 95–96% purity. As these conditions require the same number of extraction stages to achieve >99.9% purity, total product loss is important for identifying optimal conditions.

In summary, water offers similar optimal trade-off performance between purity and product loss to the nitric acid purifications. To its benefit water is a more favorable reagent than nitric acid in terms of sustainability and safety. Nitric acid benefits from less aqueous waste for similar purity and product losses, this must be weighed up against the cost and risk of nitric acid storage and disposal. Finally, the aqueous waste stream from the water purifications makes recycle of this phase simpler and likely more cost effective than disposal of the nitric acid waste stream. Both routes have benefits, particularly water being more risk averse than nitric acid, however, a cradle to grave economic analysis is needed to identify the most optimum route.

3.6. Targeting iBA removal: Sodium bicarbonate and acetonitrile purifications

Isobutyric acid (iBA) is the major impurity in the crude DEHiBA used, even after purification via the other routes. Purifications with sodium bicarbonate proved successful in batch with complete removal of iBA, but no removal of DiEHA. The addition of acetonitrile therefore hoped to yield >99.9% purity removing both DiEHA and iBA in fewer stages with less aqueous waste. Preliminary work with saturated sodium bicarbonate and acetonitrile proved challenging due to precipitation and blockages when combined. The concentration of sodium bicarbonate was reduced to 0.4 M to facilitate the mixing of this phase with acetonitrile without precipitation, the result being solubility until a 1:3 ratio of sodium bicarbonate to acetonitrile which then prompted precipitation.

Table 4
Performance metrics for the optimal conditions when using acetonitrile and water to purify crude DEHiBA.



Crude DEHiBA Flow Rate (mL min^{-1})	MeCN Flow Rate (mL min^{-1})	Water Flow Rate (mL min^{-1})	MeCN:HNO_3 Flow Ratio	Purity (%)	DEHiBA Loss (%)	Aqueous: Organic Ratio
0.500	4.251	4.997	0.85	94.9	2.8	18.5
0.500	4.603	4.002	1.15	95.5	7.7	17.2
0.500	4.944	4.639	1.07	95.5	7.0	19.2
0.769	6.071	4.272	1.42	95.6	8.5	13.4
0.500	5.147	4.454	1.16	95.9	6.9	19.2
0.500	5.289	5.000	1.06	95.9	5.3	20.6
0.750	6.869	4.696	1.46	96.0	11.2	15.4
0.500	6.057	4.296	1.41	96.9	14.3	20.7

This was coded into the MATLAB optimization code to avoid exceeding this, preventing blockages. Sodium bicarbonate was chosen over bases like sodium hydroxide due to its lower toxicity and corrosivity, plus similar solubility challenges were also faced with sodium hydroxide.

As fewer experiments were conducted during this optimization, due to limited crude material and a refined objective for the BOAEI algorithm, the purity data was modelled to verify the parameter interactions for this purification. Experimental work suggests (Fig. 5**, a**) that sodium bicarbonate has a greater effect on product purity than water or nitric acid, promoting aqueous solubility of iBA, with high product purities achievable even at low acetonitrile flow rates. The purity model, **Fig. S18** confirms the benefit of increased sodium bicarbonate content for product purity. Additionally, product loss is again hindered when aqueous (base) content increases, therefore this route is capable of high purities at low acetonitrile flow rates, reducing the trade-off between purity and product loss.

This purification appears to better overcome the trade-off between purity and product loss (Fig. 5**, a-b**), benefitting from the reduced acetonitrile content due to enhanced sustainability and lower cost even at high purity low product loss conditions. However, the reduction in acetonitrile content results in incomplete removal of DiEHA as illustrated in four dimensions alongside purity and product loss (Fig. 5, **c-d**), an issue not encountered with the other purification routes. As a result, the observed optimal conditions do not completely extract DiEHA despite its low concentration. This is of great concern especially if the reaction yield falls during manufacture as this route may not be able to handle an increase in DiEHA resulting in an impure product even with multiple extraction stages.

It is possible to operate at less optimal conditions that ensure DiEHA removal, however despite purities up to 99%, 9–10% product loss results in this route being comparable to the higher purity nitric acid purifications (Fig. 5, **e-f**). Additionally, this route did not grant any reduction in aqueous waste with 0.2 M nitric acid generating less waste, though the cost for disposal of nitric acid may outweigh this difference in volume. The most optimal condition for this purification yields 96.9% purity with 0.7% product loss and less aqueous waste compared to the other conditions, though DiEHA is not completely removed and may require numerous stages for removal. Alternatively, for complete DiEHA removal 99% purity is possible but at the cost of 10% product loss and higher volumes of aqueous waste (Table 5).

Ultimately this route demonstrates promise for removing large quantities of iBA, but is let down by the lack of DiEHA removal, leading to the question as to whether acetonitrile is required for this step to achieve similar performance. Removal of acetonitrile from the purification would allow the removal of iBA as demonstrated in the batch purification work, preventing the extraction of DEHiBA, but not facilitating DiEHA removal, requiring an additional step before reaching the target purity.

3.7. An optimum purification route

The optimization of these purification routes has not identified a purification route capable of >99.9% purity in a single stage, yet all routes are capable of this target purity via multiple extraction stages. This has escalated the importance of minimizing product loss and aqueous waste to ensure optimal performance. By first using acetonitrile and water or 0.2 M nitric acid, the organic phase is then contacted with sodium bicarbonate to yield >99.9% product purity (**Fig. S19**) avoiding a multi-stage purification that utilizes the same route and conditions. The second step of this route has not been optimized in this work but represents a successful proof of concept with no DEHiBA identified in the aqueous phase, limiting DEHiBA losses to 1–3% whilst achieving >99.9% product purity. The purified products from the optimum purifications with water and 0.2 M nitric acid were used in batch to achieve the target purity using an equal volume of saturated sodium bicarbonate.

Alternatively, purifying with sodium bicarbonate first, followed by an acetonitrile and water or 0.2 M nitric acid extraction to remove residual DiEHA and iBA could reduce aqueous waste and further minimize product loss, however this would require further testing and optimization. Whereas the first proposed route is more readily implemented.

4. Conclusion

In summary, the development of lab-scale purification equipment for continuous flow, in this case a coalescing filter, has facilitated the development of a self-optimizing continuous purification platform that utilizes machine-learning and automation to test, develop, and optimize purification routes prior to pilot plant. This minimizes material consumption during the development of a suitable and optimized purification route, reducing complexity and labor. The optimization of purification conditions is no less important than synthetic optimization, improving overall process sustainability, economics and ultimately the final product.

The crude DEHiBA used in this work is required to be at least 99.9% pure, requiring removal of iBA and DiEHA, also the degradation products of DEHiBA in nuclear reprocessing. Batch purifications found DiEHA troublesome to remove with a purely aqueous workup, which could cause problems for an industrial reprocessing flowsheet. This work compared three different purification routes in continuous flow, all employing acetonitrile and an aqueous phase (nitric acid, water, and sodium bicarbonate) to purify crude DEHiBA derived from optimum synthetic conditions identified in previously published work. The aqueous phases included two nitric acid concentrations, water and 0.4 M sodium bicarbonate. All routes were capable of purities >95% up to 99%, however the minimization of product loss became an important objective with all routes capable of losing <3% but at the cost of purity. Sodium bicarbonate was most hindered resulting in poor DiEHA extraction or high product losses >9%. 0.2 M nitric acid marginally outperformed water for a single stage extraction losing less DEHiBA, 1.5% vs 3% and a third of the aqueous waste, at the minor cost of 1% purity. Unfortunately, nitric acid adds further complications and increases the cost of the aqueous waste compared to water adding complication to the decision.

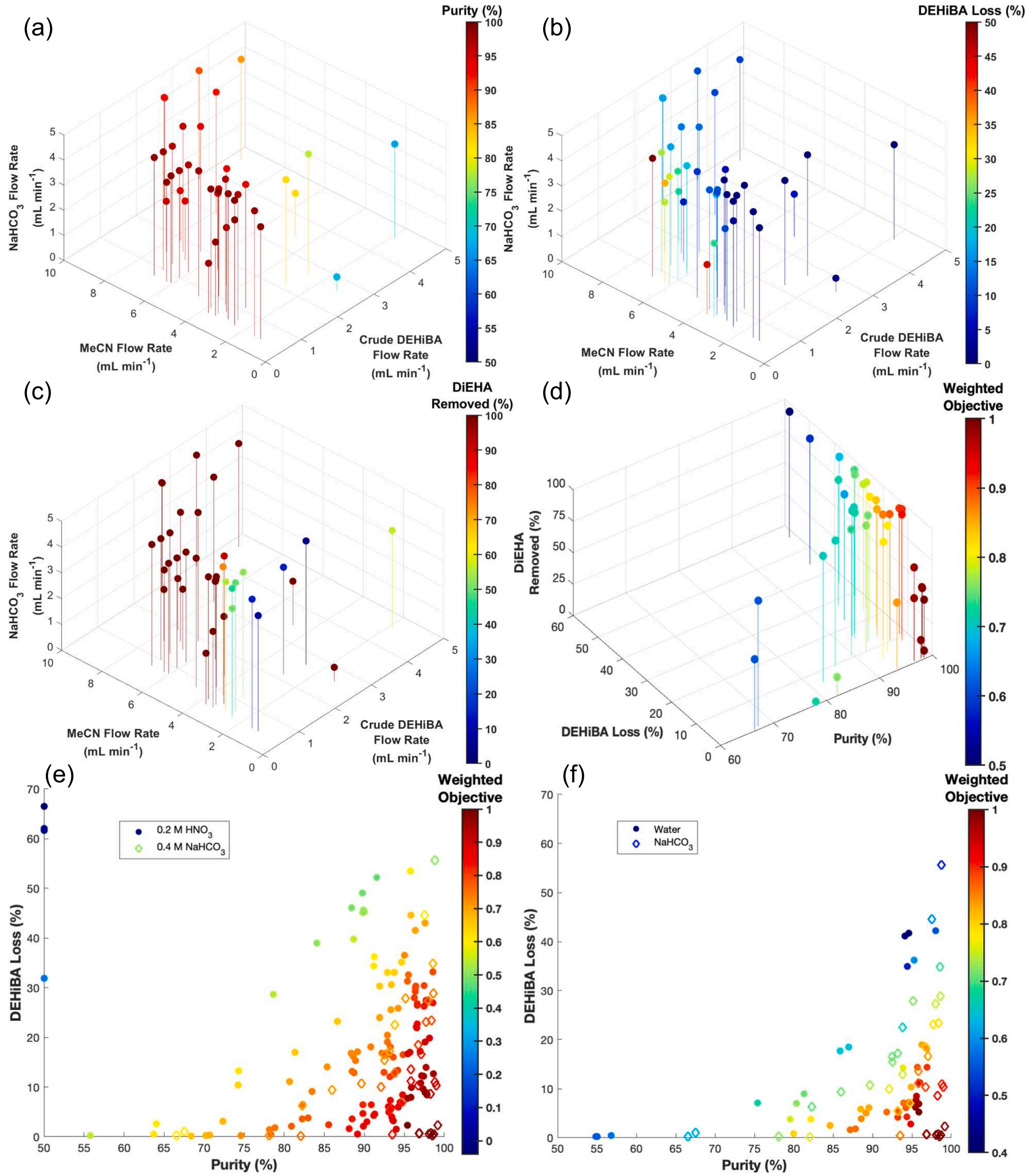
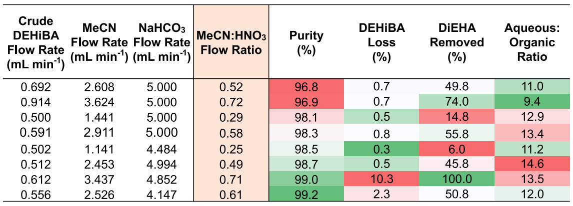


Fig. 5. Purity, product loss and DiEHA removal performance across the parameter space for the optimization with 0.4 M sodium bicarbonate and acetonitrile (a-c) respectively. Comparison of these performance metrics using the weighted objective to highlight that the optimum Purities and product losses lead to incomplete removal of DiEHA (d). The bottom plots (e-f) compare the purity and product loss performance of this route to the other routes.

As cost is difficult to determine for this work, mostly due to unknown disposal costs for the aqueous wastes, it is assumed that the nitric acid containing waste is more costly than the sodium bicarbonate containing waste which is more costly than the water containing waste. The inclusion of further extraction stages will incur some capital cost, although this will be minimal due to the separators/equipment used for this however the increased aqueous waste from multiple extraction stages may significantly increase waste volumes which will add further cost, although the optimum route outlined will avoid this due to the two different purification routes used sequentially. The amount of aqueous waste is likely to incur the greatest cost for the production of DEHiBA, hence the focus on this process metric once the desired purity was achievable with minimal product loss.

A multi-step purification platform has been devised for the purification of crude DEHiBA that is capable of <3% product loss and 99.9% product purity. Pure DEHiBA can be manufactured on demand using this platform, improving accessibility to this specialized ligand for uranium extraction. The development of this platform facilitates the on-demand

Table 5
Performance metrics for the optimal conditions when using acetonitrile and 0.4 M sodium bicarbonate to purify crude DEHiBA



Crude DEHiBA Flow Rate (mL min^{-1})	MeCN Flow Rate (mL min^{-1})	$NaHCO_3$ Flow Rate (mL min^{-1})	MeCN:HNO_3 Flow Ratio	Purity (%)	DEHiBA Loss (%)	DiEHA Removed (%)	Aqueous: Organic Ratio
0.692	2.608	5.000	0.52	96.8	0.7	49.8	11.0
0.914	3.624	5.000	0.72	96.9	0.7	74.0	9.4
0.500	1.441	5.000	0.29	98.1	0.5	14.8	12.9
0.591	2.911	5.000	0.58	98.3	0.8	55.8	13.4
0.502	1.141	4.484	0.25	98.5	0.3	6.0	11.2
0.512	2.453	4.994	0.49	98.7	0.5	45.8	14.6
0.612	3.437	4.852	0.71	99.0	10.3	100.0	13.5
0.556	2.526	4.147	0.61	99.2	2.3	50.8	12.0

manufacture of DEHiBA allowing access to liters of DEHiBA cost effectively for pilot plant scale testing of DEHiBA for the extraction of uranium(VI) this will aid to increase the technology readiness of processes that use this technology and opens up new avenues to research with DEHiBA removing some cost barriers associated with similar specialized materials. Disadvantages with this route mostly reside in the volumes of aqueous waste generated, however this is largely unavoidable and best efforts to reduce waste volumes have been made.

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.2024.131288.

Data availability

Data will be made available on request.

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