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Decarbonizing API Manufacturing: Conceptual Design and Scale-up Analysis of Continuous-Flow Electrosynthesis for Ibuprofen Production

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ABSTRACT

The decarbonization of pharmaceutical manufacturing is critical for achieving the industry's net-zero targets, and electrochemistry is emerging as a promising green technology that could play a key role in this transition. This work evaluates a continuous-flow electrochemical route for ibuprofen synthesis through electrochemical carboxylation of 1-chloro-(4-isobutylphenyl) ethane as a low-carbon alternative that can be directly coupled with renewable electricity. Experimental studies have demonstrated the selective formation of ibuprofen using a silver cathode in the ionic liquid N-methyl-N-propylpiperidinium bis(trifluoromethanesulfonyl)imide (PP13 TFSI). While the reaction mechanism is based on laboratory-scale, batch experiments, this study develops a conceptual design and scale-up methodology for the continuous route to provide an evaluation of the industrial feasibility of this electrochemical pathway through a rigorous plant-wide simulation in AVEVA® Process Simulation. Global sensitivity analysis is employed to identify key operating variables and evaluate their impact on reactor and process performance, energy consumption, and ionic liquid recovery. These insights provide a robust foundation for informed decision-making in process intensification, demonstrating the technical viability and scalability of continuous flow electrosynthesis as a sustainable alternative to conventional API manufacturing.

Keywords: Process Design, Simulation, Renewable and Sustainable Energy, Pharmaceutical Manufacturing

INTRODUCTION

As the pharmaceutical industry is a significant contributor to global emissions, increasing the focus on decarbonizing active pharmaceutical ingredient (API) manufacturing is crucial to achieving global net-zero goals. For this purpose, renewable energy sources should be utilized, and electrosynthesis is one of the green alternatives that offers an electrified synthetic pathway to replace carbon-intensive routes.

However, the feasibility and economic viability of achieving high throughput from electrosynthesis for the pharmaceutical industry remain underexplored. While batch reactors are frequently used for exploration in research due to their simple setup, flexibility, and predictability, they have significant limitations for industrial production. Flow reactors provide improved mass transfer, enhanced safety, and greater control over reaction parameters, ensuring the reproducibility required for pharmaceutical standards. Additionally, they are easier to scale up by using modular stacked-cell configurations. Considering the advantages, the transition from batch to continuous flow reactors is needed to achieve a successful scale-up, and the reliable implementation of this transition depends on the conscious design of the electrochemical flow reactor [1].

This work proposes a conceptual design for a greener, continuous electrochemical alternative to the established Hoechst process [2] for ibuprofen synthesis, which was evaluated in our previous work [3]. Mena et al. [4] demonstrated that using a silver cathode and ionic liquid (IL) allow for selective ibuprofen synthesis from electrochemical carboxylation of 1-chloro-(4-isobutylphenyl) ethane in a divided cell by suppressing side reactions without sacrificial metals. It is demonstrated that using dried ionic liquid, N-Methyl-N-propylpiperidinium

bis(tri-fluoromethanesulfonyl) imide (PP13 TFSI), overcomes significant drawbacks found using other electrolytes, such as imidazolium-based ionic liquids or organic solvents like dimethylformamide (DMF). The main advantage of using PP13 TFSI is the decreased electrochemical reduction potential which improves the energy efficiency of the process [4]. Even though the ionic liquids are more expensive than the conventional electrolytes, their recovery and recyclability capability, along with other advantages, show the potential of industrial scale-up using flow chemistry.

This study presents a rigorous plant-wide simulation of this greener, electrochemical route using AVEVA® Process Simulation. By translating laboratory cyclic voltammetry (CV) data into a modular, scalable filter-press reactor model and expanding the experimental separation logic into a full-scale downstream separation and purification stages, this work provides a methodology for early-stage conceptual design and scale-up analysis.

A global sensitivity analysis is performed to assess the impact of key operating parameters on the performance of the process. This analysis identifies the feasible operating ranges and quantifies the trade-offs between space-time yield, overall process yield, specific energy consumption, and electrolyte recovery efficiency. By identifying the operational limits and quantifying key performance indicators (KPIs), this study provides a comprehensive evaluation of the scalability of the process, offering a robust foundation for transitioning from laboratory-scale electrosynthesis to industrial production.

METHODOLOGY

The process flowsheet, illustrated in Figure 1, is developed in AVEVA® Process Simulation using mass and energy balances to model and simulate the steady-state performance of the individual unit operations.

Reactor Modelling & Scaling Up

To achieve industrial-scale throughput, we follow the technical specifications of the commercial filter-press reactor, Electro Prod Cell, marketed by Electrocell AB, which supports up to 16 m^2 of projected electrode area per module by using multiple electrodes, with a single electrode area of 0.4 m^2 [5]. To achieve higher yields, we assume that we have three reactors in series reaching a total projected electrode area of 48 m^2, each including modular 40 stacked cells having the highest possible area of Electro Prod Cell.

Each reactor is modeled as a steady-state Plug Flow Reactor unit in AVEVA® with uniform mass transfer characteristics. The reactor is modeled using a divided cell configuration, where the cathodic and anodic compartments are separated by a membrane to prevent product crossover and undesired secondary reactions. While the physical system consists of both compartments, we specifically model the cathodic compartment and its associated electrochemical kinetics in this study, as the electrochemical carboxylation of the organic chloride occurs at the silver cathode. The total active electrode area (A_e) and the total catholyte channel volume (V) are calculated as:

$$A_e = LW\sigma_{active}N_{cells} \quad (1)$$

$$V = LWd_sN_{cells} \quad (2)$$

where L and W represent the length and width of each cathode electrode, both set to 0.633 m to support for the maximum allowable area based on Electro Prod Cell specifications, and d_s represents the cathode-to-membrane spacing, which is set to minimum allowable distance 0.001 m, σ_{active} accounts for the effective surface area in contact with the electrolyte, set to 1.

In alignment with the experiments conducted by Mena et al. [4], it is assumed that carbon dioxide (CO_2) is pre-dissolved into the electrolyte until reached saturation before entering the reactor. This assumption allows for the treatment of electrolysis as a single-phase liquid process, simplifying the process by eliminating the complexities associated with gas bubble formation within the narrow electrolyte channels.

To optimize the industrial operation, the cells in one reactor module are configured in parallel for fluid flow and in series for electrical connectivity. The parallel fluid arrangement ensures that the total pressure drop across the stack is minimized while keeping uniform residence time and reactant distribution across all 40 cells per module. On the other hand, electrical connectivity is configured in series to ensure a uniform current across all cells, allowing the stack to operate at an optimized voltage under galvanostatic control.

Electrochemical Kinetics & Parameter Estimation

The electrochemical carboxylation follows an electrochemical-chemical-electrochemical (ECE) mechanism as summarized in Figure 2.

$$\textit{Step 1:} \quad R-Cl + e^- \rightarrow [R-Cl]^{\bullet -}$$

$$\textit{Step 2:} \quad [R-Cl]^{\bullet -} \rightarrow R^{\bullet} + Cl^-$$

$$\textit{Side Reaction:} \quad R^{\bullet} + H \rightarrow R-H$$

$$\textit{Step 4:} \quad R^{\bullet} + CO_2 + e^- \rightarrow R-COO^-$$

$$\textit{Step 5:} \quad R-COO^- + HCl \rightarrow R-COOH + Cl^-$$

Figure 2: Reaction Mechanism for Electrochemical Carboxylation of Organic Chlorides

The initial electron reduction produces a radical

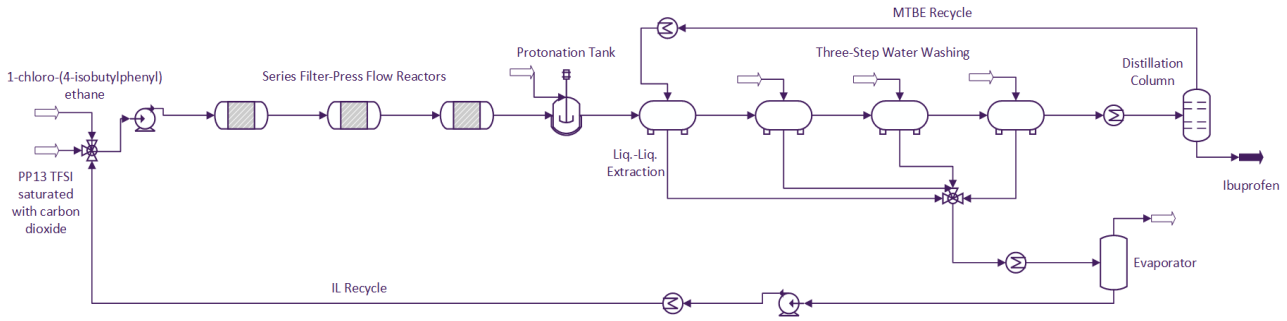

Figure 1. Ibuprofen Synthesis via Electrochemical Carboxylation Process Flowsheet.

anion, which undergoes rapid, irreversible C-Cl bond cleavage. The resulting intermediate can either form ibuprofen anion or a side-product, isobutyl ethyl benzene (IBEB). Following the second electron transfer, the resulting carboxylate anion is protonated to yield the neutral ibuprofen molecule.

The half-cell kinetic parameters are estimated using the established engineering correlations, based on data provided from Mena et al. [4]. The rate equation is derived from Faraday's Law and adapted for plug flow behavior [6].

$$\frac{dC_j}{d\tau} = \upsilon_j \eta \frac{C_j k_{eff}}{1+\frac{k_{eff}}{k_m}} \frac{A_e}{V} \tag{3}$$

Where C_j is the concentration of the compound j, τ is the residence time in the reactor, υ_j is the stoichiometric coefficient for the compound j, η is the Faradaic efficiency, k_{eff} is the effective electrochemical rate constant and k_m is the mass transfer coefficient.

The formation rates for ibuprofen and IBEB are determined by multiplying the absolute consumption rate by a selectivity ratio (S_R) of 0.9 and $(1 - S_R)$, respectively. This ensures a closed mass balance where 90% of the converted reactant is directed toward the target API, ibuprofen.

Because the chemical step is extremely fast and lacks a return peak in cyclic voltammetry, the reaction can be modeled using a single effective rate constant. This simplifies the multi-step sequence into a single rate-determining approximation suitable for plant-wide simulation in AVEVA®. The effective kinetic rate constant (k_0) is estimated using the Tafel approximation of the Butler-Volmer equation.

$$k_{eff} = k_0 \exp\left(\frac{-\alpha_c n F (E_{op,c} - E_{eq,c})}{RT}\right) \tag{4}$$

Where α_c is the cathodic charge transfer coefficient, n is the number of electrons required, F is the Faraday's constant, E_{op} is the cathodic operating potential, E_{eq} is the standard equilibrium potential, R is the universal gas constant, and T is the reaction temperature, which is 25 °C.

To estimate the standard cathodic rate constant for irreversible reactions, the Klingler-Kochi equation [7] is used, and the charge transfer coefficient (α_c) and cathodic peak potential $(E_{p,c})$ values are taken from the cyclic voltammetry (CV) results provided by Mena et al. [4] for the silver cathode and PP13 TFSI ionic liquid as 0.37, and -1.66 V, respectively.

$$k_{0,c} = \sqrt{\frac{D\alpha_c n F \upsilon_{scan}}{RT}} exp\left(\frac{\alpha_c n F (E_{p,c} - E_{0,c})}{RT} + 0.78\right) \tag{5}$$

Where D is the diffusion coefficient and υ_{scan} is the scan rate used for the CV experiment, which is 0.5 V/s.

The mass transfer coefficient is determined by the fluid dynamics inside the filter-press cell, and we assume that we have turbulent promoters to enhance the mass transfer.

$$k_m = \frac{ShD}{d_H} \tag{6}$$

Where the Sherwood number (Sh) is a function of the Reynolds number (Re) and Schmidt number (Sc).

We assume that the process operates under stage-wise galvanostatic conditions, where a constant current is maintained across the 40-cell stack. To estimate the required operating potential for the nth reactor unit for galvanostatic operation, the following equation is used.

$$E_{op,c,n} = E_{eq,c} - \frac{RT}{\alpha_c nF} \ln\left(\frac{i_n k_{m,c}}{k_{0,c}(i_{lim,n} - i_n)}\right) \tag{7}$$

Where i_n is the applied current density, calculated as a fixed ratio of the limiting current density and the limiting current density $(i_{lim,n})$ is calculated by $nFC_b k_{m,c}$ for each reactor unit due to mass-transport limitations.

The total specific cathodic energy consumption per unit mass of product is determined by summing the power requirements of the three individual reactor modules. Each module's voltage $(V_{stack.n})$ is calculated by adding the activation overpotentials and ohmic losses $(V_{ohmic,n})$ of its 40 stacked cells.

$$Specific\ Energy\ Consumption = \frac{\sum_{n=1}^{3}(V_{stack,n} I_n)}{\dot{m}_{ibuprofen}} \tag{8}$$

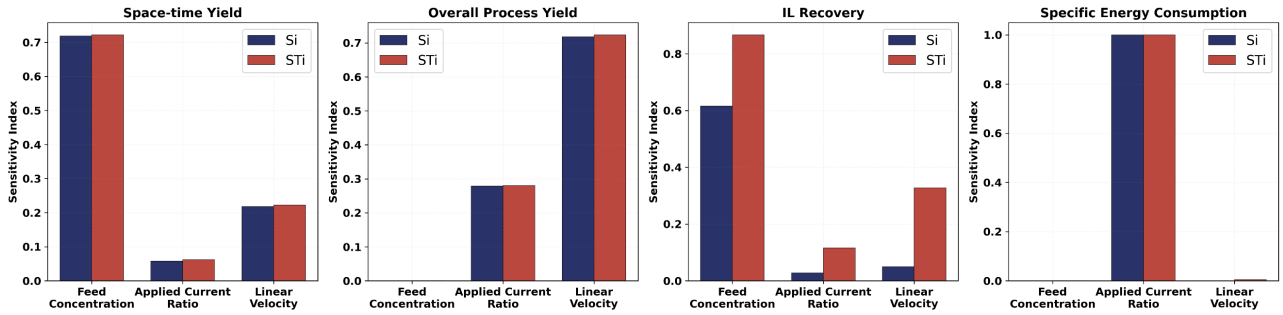

Figure 3. Global Sensitivity Analysis Results.

$$V_{stack,n} = 40\left(|E_{op,c,n}| + V_{ohmic,n}\right) \quad (9)$$

$$V_{ohmic,n} = i_n\left(\frac{d_s}{\kappa}\right) \quad (10)$$

Where κ is the electrolyte conductivity.

Downstream Processes

To model phase equilibria, the NRTL (Non-Random Two-Liquid) property method is utilized for components with established experimental binary parameters. To accurately capture the non-ideal behavior of the ionic liquid and its interactions with organic solutes, the Modified UNIFAC (Dortmund) Group Contribution Method is used to estimate the required thermodynamic parameters. For vapor-liquid equilibrium calculations, the vapor phase is modeled using the Ideal Gas Law, as the system operates at pressures where gas-phase non-ideality is negligible. These enable a rigorous calculation of activity coefficients and phase equilibria during both the reaction and downstream stages.

The reactor effluent enters a Liquid-Liquid Extraction (LLE) unit, where methyl tert-butyl ether (MTBE) is used to separate the ibuprofen from the ionic liquid. In this model, the recovery efficiency for ibuprofen is set at a fixed design specification of 90% for the LLE unit and 92% for the subsequent washing stages to simulate a standardized quality for downstream processes. Under these constraints, initial separation yields a recovery of approximately 30% of the ionic liquid. To enhance this, the ibuprofen-rich stream undergoes a 3-step deionized water wash. Finally, the multi-stage separation achieves a total recovery of the ionic liquid of approximately 70%.

This downstream configuration scales up the laboratory logic established by Mena et al. [4], where ether extraction and a single water wash achieved approximately 80% ionic liquid recovery in a laboratory scale, batch setting.

To ensure the ionic liquid is suitable for recycling and reuse as the electrolyte, an evaporator is used to dry the recovered ionic liquid by removing residual water and ether. Simultaneously, the ibuprofen-rich stream is sent to a distillation column where MTBE is recovered for recycling, and the final ibuprofen product is purified to pharmaceutical standards.

SENSITIVITY ANALYSIS RESULTS AND DISCUSSION

The global sensitivity analysis is conducted using the Sobol variance-based method to estimate first-order sensitivity indices (S_i), which quantify the individual contribution of each parameter to the output variance, excluding interaction effects, and total-order sensitivity indices (S_{Ti}), which quantify the total contribution of each parameter, including all interactions with other parameters [8]. The analysis is performed using a quasi-Monte Carlo (QMC) Sobol sequence sampling [9] and the Saltelli design [10] with a base sample size of 2048, resulting in 10240 simulation runs to construct the required matrices for the three input variables. The indices are then calculated using the Jansen estimator [11].

For this study, the reactor dimensions are kept constant based on the industrial specifications of the Electro Prod Cell. The sensitivity analysis focuses on operational variables, specifically the feed concentration, applied current ratio, and electrolyte linear velocity, to evaluate the process performance.

The feed concentration consisting of 1-chloro-(4-isobutylphenyl) ethane dissolved in CO_2-saturated ionic liquid (PP13 TFSI) is assumed to be varied between 0.2 and 0.3 kmol/m^3. This range is chosen to balance the need for high industrial throughput with the solubility limits and viscosity constraints of the ionic liquid. To evaluate the reactor's performance near its physical limits, the applied current density is defined as a fraction of the limiting current density. The ratio is assumed to be varied between 0.7 and 0.9. This range is selected to investigate the mass-transfer controlled regime, which is of particular interest for industrial scale-up. The linear velocity is assumed to be varied between 0.02 and 0.03 m/s, comparably lower since we use ionic liquids that are highly viscous.

To provide a comprehensive evaluation, four key

performance indicators (KPIs) are selected: space-time yield (STY), which provides a measurement for reactor productivity; overall process yield, which assesses both the upstream and downstream efficiency; specific cathodic energy consumption, which quantifies the electrical energy requirements; and ionic liquid recovery to evaluate the economic viability and sustainability. The results from the global sensitivity analysis are presented in Figure 3.

Results reveal that the space-time yield is dominated by the feed concentration, while the feed concentration has a negligible impact on the overall process yield. This behavior is caused by the first-order kinetics of electrochemical synthesis. The rate of reaction scales linearly with bulk concentration; therefore, increasing feed concentration directly increases the amount of product produced per volume per unit time. However, because conversion and yield are fractional metrics, they remain unchanged. Additionally, because the downstream recovery ratios for ibuprofen are fixed, the overall process yield also remains unchanged. This suggests that the process can achieve higher throughputs by increasing concentration without sacrificing the chemical efficiency of the reactor, considering the solubility limits of the ionic liquid.

While both electrolyte linear velocity and applied current ratio theoretically influence the reaction rate, the Sobol analysis unveils a higher impact of the linear velocity on the overall process yield compared to the applied current ratio. Lowering the velocity increases the residence time, which proves to be the dominant factor in ensuring sufficient duration for the electrochemical conversion.

Even though there is a trade-off since lowering the velocity also decreases the space-time yield, the results guides for a strategic pathway for optimization. Because feed concentration has a more dominant effect on space-time yield than velocity does, by increasing feed concentration, the plant can offset the productivity losses occurred from lowering the velocity. This strategy can allow us to achieve high chemical efficiency and high industrial throughput, reaching the target production without the loss of performance associated with increased residence time.

In contrast to the other input variables, the ionic liquid recovery showed high parameter interactions, with higher total-order indices compared to first-order indices. As the feed concentration increases, the mass of ibuprofen in the effluent also increases. To maintain the fixed recovery specifications, the process scales the consumption of MTBE and water. As more solvent flows through the system, it physically carries away more of the ionic liquid, either as tiny droplets or by slightly dissolving it. This creates a direct trade-off: as production capacity increases, the efficiency of the ionic liquid recycling decreases.

Finally, the Sobol analysis reveals that the specific energy consumption is exclusively governed by the applied current ratio, with a total-order index of approximately 1.0. While the feed concentration and electrolyte linear velocity both fundamentally influence the limiting current density, their impact on the energy intensity is neutralized. Consequently, the only variable that can change the cost per kilogram is the applied current ratio.

As the applied current ratio increases, the cell operates closer to its mass-transfer limit, in this region the specific energy consumption behaves asymptotically, as the cell voltage increases significantly without a matching proportional increase in mass yield. This result proves that the energy cost is decoupled from production throughput; we can increase the plant's capacity by raising the feed concentration without observing an increase in the electricity cost per unit of product.

CONCLUSION AND FUTURE WORK

This work presents a rigorous modeling and simulation framework for the design and scale-up of continuous electrochemical flow reactors, applied to an electrosynthesis route for ibuprofen production. A modular filter-press reactor is selected to reflect industrial electrochemical practice and is modeled using a plug flow reactor, as the electrolyte flows through narrow channels with plug-flow-like behavior and uniform mass transfer characteristics along the electrode surface. For the smooth transition from laboratory-scale data to industrially relevant design parameters, we use governing equations to define electrochemical kinetics, mass-transfer limitations, hydrodynamics, and reactor geometry. The simulation of the process flowsheet demonstrates the technical feasibility and scalability of continuous electrochemical carboxylation for ibuprofen synthesis.

Global sensitivity analysis is used as a guidance tool to explore the simulated process and identify the operating variables that most strongly govern productivity, efficiency, energy intensity, and electrolyte recovery. The results reveal clear trade-offs between throughput, residence time, energy efficiency, and ionic liquid losses that are inherent to the scale-up of electrochemical flow reactors. Importantly, the analysis shows that production capacity can be increased through feed concentration without penalizing specific energy consumption, while electrolyte recovery emerges as a critical bottleneck at higher throughputs.

Beyond demonstrating process feasibility, this study highlights that rigorous reactor and downstream processes modeling combined with the global sensitivity analysis is a necessary early-stage step for scale-up and decision making toward economically viable electrochemical API manufacturing. By identifying the key

operating variables with dominant effects and feasible operating windows, the proposed framework provides a robust foundation for reliable techno-economic and sustainability analysis.

Future work will extend the current framework to include full-cell kinetics, incorporating anodic reactions, additional voltage losses through membrane resistance, and anodic potential. Based on the results from the global sensitivity analysis, the optimization will be performed, and techno-economic and life cycle analysis will be conducted comparing the green pathway with the current manufacturing pathway for the ibuprofen synthesis.

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