Conceptual Modular Design for Continuous Pharmaceutical Processes: A Case Study on Ibuprofen

Asrav, T.; Alvarado-Morales, M.; Sin, G.

Published in:
ESCAPE 35: 35th European Symposium on Computer Aided Process Engineering 2025

Publication date:
2025

Document Version
Publisher's PDF, also known as Version of record

Research Article - Peer Reviewed Conference Proceeding
ESCAPE 35 - European Symposium on Computer Aided Process Engineering
Ghent, Belgium. 6-9 July 2025
Jan F.M. Van Impe, Grégoire Léonard, Satyajeet S. Bhonsale,
Monika E. Polańska, Filip Logist (Eds.)

Conceptual Modular Design for Continuous Pharmaceutical Processes: A Case Study on Ibuprofen

T. Asrav, M. Alvarado-Morales, G. Sin

[a] Process and Systems Engineering Center (PROSYS), Department of Chemical and Biochemical Engineering, Technical University of Denmark (DTU), 2800, Kgs. Lyngby/Denmark
* Corresponding Author: tusas@kt.dtu.dk

ABSTRACT

Modular process design offers product, volume, and location flexibility to meet the dynamic needs of the pharmaceutical industry. This study highlights volume flexibility by utilizing small-scale process units that can be scaled efficiently by numbering up or down to adapt to different production scales in response to uncertain market demands. Through an ibuprofen manufacturing case study, the modular design's series reactor configuration with bypassing capability is shown to enable rapid capacity adjustments, optimize resource use, and minimize downtime. Unlike conventional plants, modular design demonstrates less sensitivity, greater adaptability, and economic efficiency across varying production scales, offering an innovative pathway for future pharmaceutical manufacturing.

Keywords: Modular Process Design, Design Under Uncertainty, Continuous Pharmaceutical Manufacturing

INTRODUCTION

The pharmaceutical industry faces high manufacturing costs, strict regulations, and varying market demands, necessitating efficient and adaptive manufacturing processes. Modular process design addresses these challenges by using standardized, interchangeable, small-scale process units that can be rearranged for fast adaptation. Bertran et al. (2023) demonstrate its potential for streamlining facility design in batch API purification [1]. This study investigates modularity's role in adjusting production capacity to variable market demand and its economic impact on continuous manufacturing. The significance of flexibility was evident during pandemics, where quick adaptation to demand shifts was crucial. This case study focuses on a two-step catalytic continuous ibuprofen manufacturing process involving hydrogenation and carbonylation. Unlike previous studies on continuous ibuprofen manufacturing that focus on fixed production scales, this study explores the scalability and adaptability of modular reactor configurations under varying demand conditions. The process is simulated using AVEVA Process Simulation, incorporating reaction kinetics and reliable thermodynamic models for modular and conventional design configurations [2][3]. Monte Carlo simulations evaluate the minimum selling price (MSEP) as a key economic metric. The findings provide insights into the economic and operational advantages of modular process design in the pharmaceutical industry.

METHODOLOGY

The design process determines the optimal conditions and reactor sizing for the conventional configuration to accommodate the mean production scale. For the modular design, small-scale reactors are sized and arranged in series. The modular system allows for reactor bypassing without disrupting the process flow ensuring that the number of reactors in operation are dynamically adjusted. Reactor bypassing decisions are guided by observed conversion and yield, ensuring that efficiency is maintained while adapting to varying demands.

Conventional & Modular Process Design

In the conventional design, the manufacturing process is structured using two fixed-size Plug Flow Reactors (PFR). Two configurations were evaluated: the first uses 5 m^3 and 7.5 m^3 reactors for hydrogenation and carbonylation respectively, while the second uses 5 m^3 reactors for both. In the modular design, the manufacturing process is structured using a series of two PFR reactors for hydrogenation and three PFR reactors for carbonylation with each reactor having a 2.5 m^3 volume.

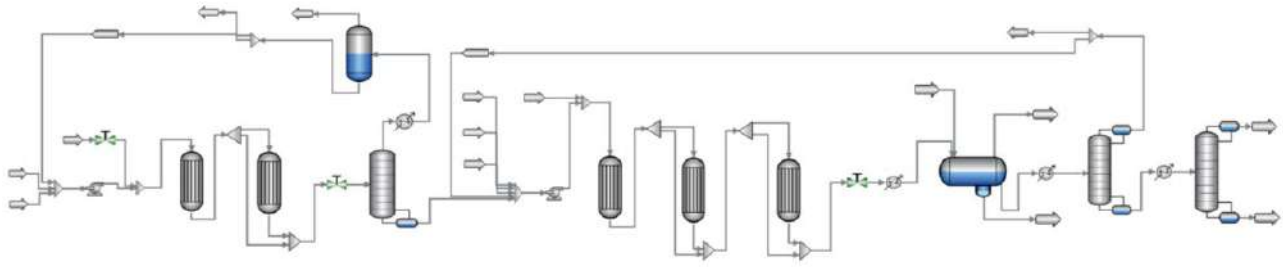

Figure 1. Modular Process Design

CASE STUDY RESULTS AND DISCUSSION

To evaluate the performances under varying production scales, 500 Monte Carlo simulations are conducted. The production demand, assumed to follow a uniform distribution with a minimum value of 155 kg/h and a maximum value of 565 kg/h representing approximately 10% of the global market size is sampled using Latin Hypercube Sampling (LHS). The results shown in Figure 2 highlight the differences in how each design adapts to varying demand levels, with the sorted values presented.

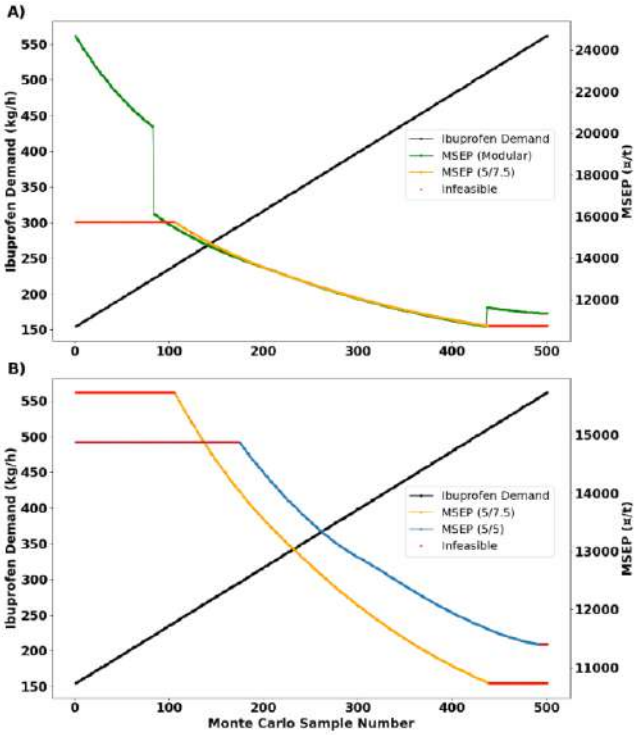

Figure 2. Sorted Monte Carlo Results

Figure 2A shows that the modular design successfully accommodates the demand across the specified range, demonstrating enhanced flexibility. In contrast, the conventional designs result in infeasible regions due to their limited adaptability constrained by the fixed reactor sizes. Figure 2B illustrates that changing the size of the carbonylation reactor enables accommodating higher demand values; however, this modification introduces a trade-off, leading to higher minimum selling prices.

CONCLUSION

This work highlights the advantages of modular design in continuous ibuprofen manufacturing, enabling adaptation to evolving market demands with precise capacity adjustments and fast responses to changes without compromising economic performance. In contrast, the choice of reactor sizes in conventional designs is critical to maintaining performance and avoiding infeasibilities under varying demand scenarios.

ACKNOWLEDGEMENTS

This work has received funding from the European Union's Horizon 2021 Research and Innovation Programme under the Marie Sklodowska-Curie Grant Agreement No. 101073003.

REFERENCES

1. Bertran, M. O., & Babi, D. K. (2023). Exploration and evaluation of modular concepts for the design of full-scale pharmaceutical manufacturing facilities. *Biotechnology and Bioengineering*.
2. Asrav, T., Alvarado-Morales, M., Sin, G. Optimization with Uncertainty for Pharmaceutical Process Design - Ibuprofen Synthesis as case study. *Computer-Aided Chemical Engineering*.
3. Seayad, A. M., Seayad, J., Mills, P. L., & Chaudhari, R. v. (2003). Kinetic modeling of carbonylation of 1-(4-isobutylphenyl) ethanol using a homogeneous PdCl2(PPh3)2/TsOH/LiCl catalyst system. *Industrial and Engineering Chemistry Research*.