Optimization with Uncertainty for Pharmaceutical Process Design – Ibuprofen Synthesis as case study

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Abstract

By intensifying the manufacturing processes of active pharmaceutical ingredients, there is potential for enhanced productivity and efficiency. This approach may also contribute to a reduction in environmental impact and result in savings from both energy and cost. In this contribution, optimum operational conditions that maximize the concentration of 1-(4-isobutylphenyl)-ethanol (IBPE), which is an intermediate product for the synthesis of ibuprofen, are studied. The results from deterministic and stochastic optimization techniques are performed and discussed. Since the uncertainties are present in the process/kinetics models, we account for the uncertainties in assessing the robustness of the proposed solution. To this end, MOSKopt stochastic simulation-based optimization framework is used to deal with uncertain parameters in the constraints. The optimization under uncertainty yields different operational conditions with roughly 10 grams less of product in the batch. This optimization with uncertainty approach provides the engineer with the flexibility to generate and test robust design concepts as a trade-off between objective function (such as high yield) and confidence in the expected performance.

**Keywords**: Optimization under uncertainty, simulation-based optimization, Monte Carlo simulations, ibuprofen manufacturing

* 1. Introduction

Awareness surrounding the environmental impact of drug development is continuously growing, which leads manufacturers toward finding greener and more sustainable synthesis methods (Gernaey et al., 2012). In addition to environmental considerations, the increase in costs of creating new pharmaceutical ingredients is another challenge that the pharmaceutical industry is facing. Therefore, it is relevant to study if the existing synthesis methods are both cost-effective and environmentally friendly and can be carried out using methods and tools from the Process Systems Engineering (PSE) domain. Additionally, evaluating the operating conditions and identifying the influential variables or parameters could lead to improvements in achieving process objectives and implementing more advanced control strategies.

There are many studies about the synthesis of one of the widely used active pharmaceutical ingredients, namely ibuprofen. While some of these studies show that continuous manufacturing production is feasible (Jolliffe et al., 2016), however, a significant portion of the industry continues to depend on Hoechst batch production. For some of the production steps, the reaction kinetics and the data could be found in the literature based on the experiments (Thakar et al., 2007). Montes et al. (2018), proposed a dynamic simulation model to study plantwide dynamics and operation including propagation of disturbances in the production of ibuprofen.

In this work, the aim is to study the feasibility of applying simulation-based optimization methods to explore the optimal operating conditions for the hydrogenation step of the ibuprofen synthesis while considering the uncertainties in the parameters. Given that parameters are derived through parameter estimation methods that may not yield precise outcomes, the uncertainties associated with the parameters should be considered to achieve greater robustness.

For the scope of the work, the optimization of the operating conditions is conducted through three different optimization approaches. As the initial approach, the optimization problem is formulated deterministically as a constrained nonlinear problem and solved using an interior-point algorithm implemented in Matlab by running fmincon solver in parallel from multiple start points. A simulation-based optimization with and without uncertainties is used for the other approaches. To this end, MOSKopt optimization framework is used, which employs a surrogate-based modeling approach to deal with uncertainties as described in Al et al. (2020).

* 1. Methodology
     1. Simulation-based optimization: MOSKopt

MOSKopt, a stochastic simulation-based optimization framework, allows for solving constrained complex optimization problems. For efficient exploration of design space, surrogate models are employed which are created based on an initial set of design space using Latin hypercube sampling, and iteratively enhanced with additional samples based on infill criteria. The infill criterion is selected as multiple constrained feasibility enhanced expected improvement in this work since it separately considers the probability of feasibility for each stochastic constraint while simultaneously seeking enhancements in the objective value (Al et al., 2020). Stochastic Kriging model is used as a surrogate model because of the ability to handle intrinsic and extrinsic types of uncertainties of stochastic simulations by introducing an additional noise model (Ankenman et al., 2010).

* + - 1. Monte Carlo uncertainty simulations

Monte Carlo method is widely used to estimate the numerical outcomes of uncertain processes by employing random sampling strategies. Accordingly, Monte Carlo simulations can be integrated into the MOSKopt framework to account for uncertainties while searching for an optimal combination of design and operational decisions. The objective and constraints of the optimization problem can be calculated for each design sample considering the uncertainty scenarios provided by Monte Carlo simulations. To find the optimal design points in the design space, hedging strategies are used against uncertainties (Al et al., 2020). The selected hedging strategy for this work involves keeping the mean plus one standard deviation of constraint observations from Monte Carlo simulations below the constraint limit. This strategy of using mean plus sigma in the objective function is useful as it accounts for both average performance and the associated risk or variability into the decision-making process. Hence the resulting decision variables will be more robust against not only the most expected outcome but a wider range of outcomes (Wang and Ierapetritou, 2018).

* 1. Application to Ibuprofen Synthesis
     1. Upstream Processes

In this work, ibuprofen is produced following the Hoescht synthesis pathway involving three main reaction steps: Friedel-Crafts acetylation, hydrogenation, and carbonylation (Elango et al., 1991). Since no data is available in the literature for the Friedel-Crafts acetylation, the initial reactant is assumed to be the product of the acetylation reaction, 4-isobutyl acetophenone (IBAP). Therefore, the synthesis begins with the reaction of IBAP to produce 1-(4-isobutylphenyl)-ethanol (IBPE) followed by a catalytic carbonylation of resulting IBPE to form ibuprofen along with byproducts. Given the significant influence of catalytic hydrogenation on the final products and its occurrence in the early stages, this work aims to determine the optimum process conditions for the hydrogenation step.

* + - 1. Hydrogenation

A chemical formula with text

Description automatically generated with medium confidenceThe reactions occurring during the hydrogenation step are shown in Figure 1.

Figure 1. Reactions during hydrogenation of IBAP over Pd/SiO2 (Thakar et al., 2007).

Hydrogenation of IBAP to IBPE is the desired reaction while simultaneously occurring oligomerization because of the deactivation of the catalytic activity is the side reaction and hydrogenolysis of IBPE to IBEB is the undesired consecutive reaction.

The kinetic model ordinary differential equations in terms of concentrations for the hydrogenation of IBAP into 1-(4-isobutylphenyl)-ethanol (IBPE) over Pd/SiO2 catalyst are taken from Thakar et al. (2007), assuming batch process occurring in a perfectly mixed batch reactor at isothermal conditions. The reaction rates are expressed as follows:

|  |  |
| --- | --- |
|  | (1) |
|  | (2) |
|  | (3) |

Where accounts for the loss of catalytic activity due to oligomerization.

The rate and equilibrium constants are reparametrized considering the dependence of temperature as follows:

|  |  |
| --- | --- |
|  | (4) |

The parameters are taken based on the results of the parameter estimation of Thakar et al. (2007). Optimization without uncertainty is made by using the mean values of the parameters and optimization with uncertainty is made by using uncertainty space of the parameters considering their 95% confidence intervals. The uncertain parameters and their 95% confidence intervals when temperature is 373 K are given in Table 1.

Table 1. Estimated values of uncertain parameters and their 95% confidence intervals.

|  |  |  |
| --- | --- | --- |
| Rate constants | k1 (L/gcatatm.s) | 1.14±0.25 |
| k2 (L/gcatatm.s) | 0.095±0.02 |
| k3 (L2/gcatatm.s) | 0.024±0.004 |
| Adsorption constants | KIBAP (L/mol) | 76.4±23.7 |
| KH2O (L/mol) | 529±106 |
| Activation energies | Ea1 (kJ/mol) | 102±15 |
| Ea2 (kJ/mol) | 105±14 |
| Ea3 (kJ/mol) | 117±15 |

* 1. Results and Discussion

The optimization problem is defined to maximize IBPE concentration in the catalytic hydrogenation reaction, with IBPE yield calculated relative to initial IBAP concentration, by optimizing the temperature, hydrogen partial pressure, catalyst concentration, and residence time. Increasing the partial pressure of hydrogen can increase the yield of IBPE if the hydrogenation is more favorable than catalyst deactivation until the hydrogenolysis of IBPE to IBEB becomes favored. Beyond this point, increasing pressure may contribute to the undesired consecutive reaction. On the other hand, lower pressure may favor catalyst deactivation which allows a slower decrease of IBPE to form an undesired product which is also affected by the catalyst amount. Therefore, optimizing these decision variables is crucial for achieving the maximum yield of IBPE because of the tradeoffs inherent in the process.

Thakar et al. (2007) investigated the reaction kinetics of hydrogenation at various temperatures, hydrogen partial pressures, and catalyst concentrations, ranging from 333 to 373 K, 10 to 40 bar, and 0.26 to 0.78 g/L respectively. Consequently, in this work, the decision variable limits are selected based on these specified ranges. Additionally, the lower and upper bounds for the residence time are set at 10 and 60 minutes, respectively. The volume of the hydrogenation batch reactor is taken as 185 L and the initial concentration of IBPA is taken as 0.27 mol/L aiming to obtain approximately 7 kg per batch of IBPE.

Three different optimization procedures are applied in this work. The mean values of the parameters from the parameter estimations results are used for the deterministic solvers. On the other hand, using the mean and the standard deviation of the parameters, it is assumed that the uncertainties follow multivariate random normal distribution and employed for sampling for the stochastic solver. The maximum number of iterations for the optimization task is set to 150 for each MOSKopt algorithm. To account for the influence of the uncertainties on objective and constraints, 250 Monte Carlo simulations are performed for each iteration.

The optimal objective values along with the values of decision variables at the optimal for three different optimization approaches are given in Table 2.

Table 2. Optimization results.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Decision  variable | Lower bound | Upper bound | Optimal values | Best obj.  (mol/L) |
| Interior-point algorithm | Temperature (K) | 333 | 373 | 333 | 0.2192 |
| H2 partial pressure (bar) | 10 | 40 | 19.93 |
| Catalyst amount (g) | 48.1 | 144.3 | 58.95 |
| Residence time (min) | 10 | 60 | 32.06 |
| MOSKopt deterministic | Temperature (K) | 333 | 373 | 333 | 0.2192 |
| H2 partial pressure (bar) | 10 | 40 | 14.36 |
| Catalyst amount (g) | 48.1 | 144.3 | 77.39 |
| Residence time (min) | 10 | 60 | 26.11 |
| MOSKopt  with uncertainties | Temperature (K) | 333 | 373 | 333 | 0.2189 |
| H2 partial pressure (bar) | 10 | 40 | 31.77 |
| Catalyst amount (g) | 48.1 | 144.3 | 88.59 |
| Residence time (min) | 10 | 60 | 17.5 |

The ideal residence time is significantly influenced by catalyst concentration. If the catalyst concentration is low, it takes more time to reach the maximum yield and therefore more time to complete the production batch. On the other hand, for higher catalyst concentrations, the residence time becomes smaller causing a slight reduction in the yield of product. (Thakar et al., 2007). The tradeoff between the catalyst amount and residence time as explained above can be observed from the optimization results.

From Table 2, there are three competing design candidates. Multiple running of a local nonlinear programming solver with interior-point algorithm and MOSKopt using deterministic approach provided the same optimal objective value, albeit with different values for the decision variables. MOSKopt including uncertainties provided slightly lower objective value, approximately 10 g less desired product produced per batch volume of 185 L. Since the latter accounts for a range of likely outcomes, due to uncertainties inherent in the process, the provided solutions are considered more robust to the uncertainties considered.

A graph of a line graph

Description automatically generated with medium confidenceSelectivity dynamics, illustrated in Figure 2 using optimal values of the temperature, hydrogen partial pressure and catalyst amount reveal an increase up to optimal residence time and decrease beyond this point, emphasizing the importance of optimizing residence time for desired selectivity. The influence of the uncertainties can also be observed from Figure 2.

Figure 2. Selectivity of IBPE.

From a production capacity point of view, small residence time is preferred, however, it comes with the expense of increased production cost with a higher catalyst amount. A multi-objective optimization accounting for different priorities in the operation can be formulated to address this tradeoff. To this end, this study will be complemented with techno-economic metrics as well as sustainability to generate a holistic view of the process design.

* 1. Conclusions and Future Work

The study optimizes the hydrogenation step in ibuprofen synthesis, focusing on maximizing the yield of IBPE. Three optimization approaches: constrained nonlinear programming solver with the interior-point algorithm, and MOSKopt framework without and with the inclusion of uncertainties are employed. The uncertainties in the rate and adsorption constants and activation energies derived from experimental data are accounted for to assess the robustness of the optimization results. Considering their great influence on the reaction kinetics, incorporating uncertainties provides a more comprehensive understanding. It is observed that accounting for the uncertainties leads to variations in the optimal operating conditions causing a slight decrease in the objective value as expected since the variations of the performance are also accounted for in addition to the expected performance. Optimization with uncertainty favors faster batch completion but incurs higher production costs. To navigate the tradeoff, a multi-objective optimization approach can be developed encompassing perspectives from both techno-economic and sustainability considerations. The MOSKopt framework, coupled with Monte Carlo simulations for uncertainties, proved to be a valuable tool for addressing uncertainties and enhancing the robustness and reliability of the optimization of pharmaceutical processes. The pharmaceutical processes are sensitive to variations in conditions and parameters, therefore, the identification of optimal solutions that perform well across a range of likely outcomes enhances the adaptability to real-world variations. The findings can contribute to the ongoing efforts in pharmaceutical manufacturing to achieve greener, more sustainable, and cost-effective processes.

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