Hybrid Model-based Design Space Determination for an Active Pharmaceutical Ingredient Flow Synthesis using Grignard Reaction

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Abstract

This work presents a hybrid model-based design space determination for active pharmaceutical ingredient flow synthesis using Grignard reaction. A set of flow experiments was conducted to gather kinetic data for model development. One of the significant challenges encountered during this modelling process was the incorporation of impurity generation, specifically halohydrin, the mechanism of which remains elusive. To tackle this challenge, a hybrid modelling approach was adopted, integrating a mechanistic component to capture the main product and a data-driven component to account for the impurity. The resulting hybrid model was then employed to simulate various evaluation indices such as yield and temperature change towards the identification of the design space. Furthermore, the analysis of potential disturbances was conducted by leveraging this model, which can aid in the sensor monitoring and the management of disturbances.

**Keywords**: Flow chemistry; Drug substance; Machine learning; Continuous manufacturing; Random forest regression model

* 1. Introduction

Flow synthesis has recently attracted significant attention especially in the pharmaceutical industry. This growing interest can be attributed to the advantages offered by compact reactors in flow synthesis, including efficient heat and mass transfer, improved yields, cost savings, reduced ecological impact of manufacturing plants, and minimized waste and energy consumption. As such, extensive research has been conducted on the flow synthesis of active pharmaceutical ingredients (APIs) (Nqeketo, *et al.* 2023, Xu, *et al.* 2023, Burange, *et al.* 2022). These advancements encompass not only experimental work but also extend to the application of modelling and simulation techniques towards optimising pharmaceutical processes (Kim, *et al.* 2023a, Diab, *et al.* 2021).

The utilization of modelling and simulation techniques in API synthesis holds the potential for alignment with regulatory frameworks like the design space (ICH Q8) and state of control (ICH Q13). Design space is a concept within the framework of Quality by Design (QbD), referring to the multidimensional combination of input parameters that ensures product quality. Meanwhile, the state of control is a crucial notion, particularly in flow synthesis, signifying a condition that ensures ongoing process performance and product quality assurance. Creating a design space and assessing the state of control involves analysing various parameters, which requires a substantial volume of experimentation. The digital techniques can offer a promising avenue to reduce reliance on extensive experimentation, as exemplified by the works of García-Muñoz, *et al.* (2015) and Sagmeister, *et al.* (2023). Nonetheless, model-based investigations within this domain are still in their early stages of development, highlighting the need for ongoing efforts to seamlessly integrate new methodologies, such as digitalization and flow synthesis, into established regulatory frameworks. Process systems engineering can serve as a powerful tool for addressing this aspect (Gani, *et al.* 2022).

This work presents the model-based design space determination for an active pharmaceutical ingredient flow synthesis using Grignard reaction. The Grignard reaction is fast and highly exothermic reaction, making it difficult to collect kinetic data in batch synthesis. Thus, a set of flow experiments was conducted to collect kinetic data for model development. One of the key challenges encountered during this modelling process was incorporating the generation of impurities, such as halohydrin, the mechanism of which remains unknown. To address this challenge, a hybrid modelling approach was adopted, integrating a mechanistic component to capture the main product and a data-driven component to account for the impurity. The design space was then determined based on simulations using the developed hybrid model. Furthermore, the study conducted an assessment of process robustness in the presence of pulse disturbances.

* 1. Materials and Methods
		1. Target Reaction and Flow Experiment

**Figure 1** shows the target Grignard reaction and the overview of flow experiment (modified from Kim et al. (2023b)). In this reaction, (2R)-2-(Phenoxymethyl)oxirane (SM, starting material) undergoes a reaction with allylmagnesium chloride (RMgCl, Grignard reagent). The reaction is subsequently quenched with methanol, resulting in (2R)-1-phenoxy-5-hexen-2-ol (DP, desired product). As a by-product of this reaction, (2R)-1-chloro-3-phenoxy-2-propanol (BP, by-product) is also produced.

In the flow experiments, the inner diameter, temperature, concentration of RMgCl, and residence time were varied in different runs. High performance liquid chromatography (HPLC) was used to quantify the concentrations of SM, DP, and BP in the samples. The heat of reaction was measured by reaction calorimeter, and it was –258 kJ mol–1.



**Figure 1. Target Grignard reaction and flow experiment**



**Figure 2. Overview of the hybrid model**

* + 1. Hybrid Model Development

In this study, the hybrid model was developed to quantify both DP and BP. **Figure 2** shows the overview of the model (modified from Kim et al. (2023b)). The mechanistic component of this model involves the mass and energy balance models, while the data-driven part of the model incorporates the application of a random forest regression model to estimate the trace amount of produced by-proudct. Although the miniscule amount of BP produced during the reaction is problematic from a product quality point of view, the effect on the overall mass and energy balances is negligible. Thus, the mechanistic component of the hybrid model considered only the main reaction to give DP. The mechanistic model is presented in Eqs. (1)–(4).

|  |  |
| --- | --- |
|  | (1) |
|  | (2) |
|  | (3) |
|  | (4) |

Here, [mol m–3] is the concentrations of (SM, RMgCl, and DP), [m s–1] is the flow velocity, [m2 s–1] is the diffusion coefficients, [mol m–3 s–1] is the reaction rate, [K] is the temperature, [m2 s–1] is the thermal diffusivity, [J mol–1] is the heat of reaction, [kg m–3] is the density of the solvent, [J kg–1, K–1] is the specific heat capacity, and [m] are the inner and outer radius, [J s–1 m–2 K–1] is the heat transfer coefficient, [J s–1 m–1 K–1] is the thermal conductivity of the PTFE tube.

For BP, it was not feasible to develop a mechanistic model due to the unresolved nature of the underlying mechanism. Instead, a random forest regression model was constructed in this work. To evaluate the reliability of the model, a Leave-One-Out (LOO) cross-validation process was conducted.

* + 1. Evaluation Model Development and Conditions Settings for Design Space Analysis

To assess the design space, several evaluation indices were determined in this work. Evaluation models were developed for yields (DP and BP) and maximum temperature change as shown in Eqs. (5)–(7). The constraints for each evaluation index are defined as follows: , , and .

**Table 1. Variables and their ranges**

|  |  |
| --- | --- |
| Parameter | Range |
| Inner diameter | mm | 1.0–2.4 |
| Set temperature | K | 263–293 |
| Equivalent amount of RMgCl | eq. | 1.0–2.0 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | (5) |  | (6) |  | (7) |

Here, and [–] are the yields of DP and BP, [K] is the maximum temperature change, [mol m–3] is the initial concentration of SM at the inlet, and [mol m–3] are the concentrations of DP and BP at the outlet, [K] is the maximum temperature in the reactor, and [K] is the initial temperature.

The design space was investigated for a steady-state process, as outlined in Eq. (8). The process variables and their ranges are summarised in **Table 1**. Furthermore, the process was assessed in the presence of pulse disturbances, as defined in Eq. (9). These disturbances, characterised by their intensity and duration, were applied to the steady-state process. This study conducted two case studies involving variations in inlet and coolant temperature, considering the highly exothermic nature of the Grignard reaction.

|  |  |
| --- | --- |
|  | (8) |
|  | (9) |

Here, is the design space, is the element of the set of variables , is the element of the set which represents whether the results of each evaluation index fulfil the constraints, is the element of the set of disturbance variables , is the time point when the system reaches the steady state, and is the time point when the system reaches the steady state after the occurrence of the disturbance. When equals to 1, it indicates compliance with the constraint, while a value of 0 indicates non-compliance.

* 1. Results and Discussion
		1. Kinetic Analysis and Regression Results

The kinetic analysis and regression results are shown in **Figure 3** (modified from Kim et al. (2023b)). The average coefficient of determination (*R*2) of SM and DP for all experimental conditions was 0.96. For the random forest regression model, the *R*2 was calculated using the mean values of prediction results by the LOO cross validation, and the resulting value was 0.96.

* + 1. Assessment of Design Space

The simulation was conducted using the predefined ranges of variables outlined in **Table 1**, with the aim of investigating the design space for the Grignard reaction. **Figure 4** presents the results of (a) yield of DP, (b) yield of BP, (c) maximum temperature change, and (d) design space.



**Figure 3. Prediction results of the hybrid model**



**Figure 4. Individual evaluation results and design space**



**Figure 5. Design space considering pulse disturbances, with the x-axis representing pulse duration and the y-axis representing intensity**

In general, the simulation results show that a smaller inner diameter and higher set temperatures significantly enhance the yield of DP, albeit concurrently escalating the maximum temperature change. Furthermore, as illustrated in **Figure 4(b)**, elevated temperatures lead to increased production of BP. A notable increase in BP production is observed when the inner diameter falls within the intermediate range of 1.4 to 1.8 mm. This trend aligned with the experimental observations, and the data-driven model successfully reflected the trends identified in the experimental data.

**Figure 4 (d)** shows the design space which fulfils the predefined constraints (, , and ), indicated by the white area. Within the domain of larger inner diameters and lower temperatures, the process violated the DP yield constraint. In the case of larger inner diameters and elevated temperatures, the process could not satisfy the maximum temperature constraint, surpassing the predefined value.

Finally, the process robustness was assessed in the presence of pulse disturbances. **Figure 5** shows the results when the disturbances of inlet and coolant temperature were occurred. Maintaining pulse durations of less than two seconds demonstrated that the process could operate within predefined constraints under specific conditions.

* 1. Conclusions and Outlook

This work presents the hybrid model-based design space determination for an active pharmaceutical ingredient flow synthesis using Grignard reaction. A set of flow experiments was conducted to gather kinetic data, and a hybrid model was developed. For design space exploration, the evaluation models were developed regarding yields and temperature change. Leveraging the developed model, the design space was assessed. Furthermore, the analysis of potential disturbances related to temperature variables was conducted. Expanding this analysis of disturbances can provide valuable insights for sensor monitoring and effective disturbance management.

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