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INHERENTLY SAFER DESIGN OF A NOVEL INDUSTRIAL SCALE REACTOR FOR ALKYLPyRIDINE DERIVATIVES PRODUCTION

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Abstract
Alkylpyridines and their derivatives are chemical compounds widely used in pharmaceutical industry and agriculture. In recent years, alkylpyridine-N-oxides have received attention due to their increased reactivity provided by the N-oxide group. In our paper, design of an industrial scale continuously stirred tank reactor for production of 3-methylpyridine-N-oxide with the focus on process safety was discussed. 3-methylpyridine was converted into 3-methylpyridine-N-oxide by homogeneously catalysed reaction in the presence of hydrogen peroxide as the oxidizing agent and phosphotungstic acid as the catalyst. Reactor dimensions were proposed based on a scale-up of a laboratory unit. Sensitivity and uncertainty analyses of selected key process parameters were performed to determine optimal operating point within the safety constraints. The proposed continuous process presents a suitable inherently safer alternative to conventional semi-batch production.

Introduction
With the recent development in process intensification activities, detection of possible hazardous events and operability problems has become more difficult. One of the basic concepts of process intensification is the transition towards continuous productions. Continuous reactor is a preferred alternative to batch or semi-batch reactor not only from the economic point of view (size reduction), but also because of its inherently safer character. Inherent safety principles have been applied to the N-oxidation process and design of continuous production of 3-methylpyridine-N-oxide (3-MPNOX) in a continuous stirred-tank reactor (CSTR) as an alternative to the conventional semi-batch process is presented. 3-MPNOX belongs to alkylpyridine derivatives that are frequently used in pharmaceutical industry due to their increased reactivity provided by the N-oxide group.

This paper compiles necessary activities for safe reactor operation and optimization of the reaction conditions towards higher product yield utilizing computer simulations. Key operating parameters and construction dimensions of CSTR were proposed based on a scale-up of a laboratory unit and consequently optimized based on sensitivity analyses and a complex process hazard identification procedure. Mathematical model for process simulation was built in the MATLAB® environment. Impact of model parameters’ uncertainties on the optimization results and proposed operating points of reactor was also studied.

Case study
In pharmaceutical industry, 3-MPNOX (C₆H₇NO) is produced by the N-oxidation of 3-methylpyridine (C₆H₇N, 3-MP) in the presence of phosphotungstic acid (H₃PW₁₂O₄₀) as a metal catalyst and aqueous hydrogen peroxide (H₂O₂) solution as an oxidizing agent (Equation 1). N-oxidation is carried out at temperatures close to the boiling point of the reaction mixture in an open semi-batch reactor to allow discharge of oxygen generated by competitive decomposition of hydrogen peroxide (Equation 2). Recent research proposed transition from a semi-batch to a continuous reactor at elevated pressure (200 – 300 kPa) and temperature (110 – 125 °C) to achieve more efficient N-oxidation with inherently safer operation. A scheme of the proposed manufacturing process is depicted in Figure 1. For the proposed reactor configuration, hydrogen peroxide decomposition reaction is significantly reduced and can be neglected. Although N-oxidation is a complex reaction system, reaction rate for the given range of pressures and temperatures can be calculated from Equation 3 representing simplified reaction kinetic model where C represents the molar concentration of the corresponding component. Values of kinetic parameters used in this case study are summarized in Table I. Constant reaction enthalpy of N-oxidation of -160×10³ J.mol⁻¹ was considered. Key operating parameters were taken from a laboratory unit model with the reaction mixture volume of 1 L. After the appropriate scale-up (Tables II and III), further process intensification and hazard identification were performed. Mathematical modeling of products’ separation and purification steps is not discussed in this paper.

$$\text{C}_6\text{H}_7\text{N} + \text{H}_2\text{O}_2 \xrightarrow{\text{H}_3\text{PW}_{12}\text{O}_{40}} \text{C}_6\text{H}_7\text{NO} + \text{H}_2\text{O}$$

(1)
parameters were performed to determine optimal operating point within the safety constraints. The proposed modeling of products' competitive decomposition of hydrogen peroxide (Equation 2) 4. Recent research proposed transition from a semi-batch to a continuous reactor at elevated pressure (200 MP) in the presence of phosphotungstic acid (H3PW12O40) as a metal catalyst and aqueous hydrogen peroxide (H2O2) solution as an oxidizing agent (Equation 1)3. N-oxidation is carried out at temperatures close to boiling point of the reaction mixture in an open semi-batch reactor to allow discharge of oxygen generated by hydrogen peroxide decomposition (Equation 3). The mathematical model was used to describe the competitive decomposition of hydrogen peroxide (Equation 2) and to predict the reaction kinetics. The kinetic parameters used in the model are summarized in Table I, which includes values of the Arrhenius equation for the reaction of interest (Table I).

\[ \text{Molar ratio of } \text{H}_2\text{O}_2 : 3\text{-MP} = 1.05 \]

Table II: Reactor inlet and outlet streams after the scale-up of a laboratory unit

<table>
<thead>
<tr>
<th>Process variable</th>
<th>Feed 1</th>
<th>Feed 2</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass flow [kg.h⁻¹]</td>
<td>219.9</td>
<td>151.3</td>
<td>371.2</td>
</tr>
<tr>
<td>Temperature [°C]</td>
<td>50</td>
<td>50</td>
<td>118.9</td>
</tr>
<tr>
<td>Mass composition [%]</td>
<td>3-MP</td>
<td>-</td>
<td>1.6</td>
</tr>
<tr>
<td>H₂O₂</td>
<td>-</td>
<td>55.9</td>
<td>1.6</td>
</tr>
<tr>
<td>H₂O</td>
<td>-</td>
<td>44.1</td>
<td>29.1</td>
</tr>
<tr>
<td>3-MPNOX</td>
<td>-</td>
<td>-</td>
<td>67.7</td>
</tr>
</tbody>
</table>

Table III: Selected parameters of CSTR after the scale-up of a laboratory unit

<table>
<thead>
<tr>
<th>Reaction mixture volume [L]</th>
<th>Molar ratio of H₂O₂ : 3-MP [-]</th>
<th>Agitator speed [rpm]</th>
<th>Cooling water inlet temperature [°C]</th>
<th>Cooling water mass flow [10³ kg.h⁻¹]</th>
<th>Overall heat transfer coefficient [W.K⁻¹.m⁻¹]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 000</td>
<td>1.05</td>
<td>180</td>
<td>25</td>
<td>12.3</td>
<td>255</td>
</tr>
</tbody>
</table>

Process intensification, hazard identification and results analysis

The goal of process intensification is to maximize the production rate of 3-MPNOX. The effect of feed temperature, molar ratio of H₂O₂ : 3-MP, catalyst concentration and cooling medium inlet temperature was...
studied. Process variable „feed temperature“ represents the temperature of streams Feed 1 and Feed 2 leaving the heat exchanger (e.g. operating setpoint for both feed streams). Figure 2 represents one of the obtained results from two-parametric optimization of reaction conditions where the production rate of 3-MPNOX as a function of feed temperature and molar ratio of H$_2$O$_2$ : 3-MP is depicted. As it is shown, increase of feed temperature and decrease of molar ratio of H$_2$O$_2$ : 3-MP leads to gradual increase of 3-MPNOX production rate.

However, process safety limitations have to be considered. As previously mentioned, operating regime of the reactor was determined in the temperature range from 110 °C to 125 °C. If the reactor temperature exceeds 125 °C, vaporization of the reaction mixture can occur, which leads to possible over-pressurization of the reactor. Below 110 °C, secondary reaction of H$_2$O$_2$ decomposition is triggered and thermal runaway occurs. Therefore, safe operating regime has to be monitored. Possible application of these safety constraints is depicted in Figure 3, where the temperature in reactor was analyzed. Red zone represents hazardous operating regime and yellow-to-green zone represents the safe one.
Figure 3. Effect of feed temperature and molar ratio of $\text{H}_2\text{O}_2 \, : \, \text{3-MP}$ on the temperature in the reactor after safety constrictions’ application (red zone – hazardous operating regime)

As it can be seen in Figure 3, only a limited number of simulated steady states of CSTR can be considered safe. Numerical algorithm for finding maximum production rate of 3-MPNOX (in the matrix visualized in Figure 2) considering temperature limitations (Figure 3) was developed. User-dependent parameter in the searching procedure was maximum allowed operating temperature in the reactor. For the parameter uncertainty analysis, six different operating points are proposed (Table IV). For every operating point, optimal molar ratio of $\text{H}_2\text{O}_2 \, : \, \text{3-MP}$ was found in the region of ca. 0.91.

Table IV
Proposed operating points after safety constrictions’ application

<table>
<thead>
<tr>
<th>Process variable</th>
<th>Operating points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Maximum allowed operating temperature in the reactor [°C]</td>
<td>125</td>
</tr>
<tr>
<td>Feed temperature [°C]</td>
<td>55.0</td>
</tr>
<tr>
<td>Production rate of 3-MPNOX [kg.h⁻¹]</td>
<td>267.8</td>
</tr>
</tbody>
</table>

**Parameter uncertainty analysis**

Most model parameters involved in the prediction of reactor behavior are uncertain. The influence of uncertainties in the reaction kinetic parameters (Table I) and reaction enthalpy on the proposed reactor operating points was analyzed. Reactor behavior was found to be most sensitive to changes in the reaction enthalpy. Therefore, reaction enthalpy uncertainty was further examined. The original value of the reaction enthalpy in this case study was $-160 \times 10^3 \text{ J.mol}^{-1}$. However, the reaction enthalpy value for 3-MP N-oxidation varies in literature significantly (from ca. $-120 \times 10^3$ to $-190 \times 10^3 \text{ J.mol}^{-1}$). For the purposes of parameter uncertainty analysis, the range of reaction enthalpy from $-10 \%$ to $+10 \%$ was studied. The position of the proposed operating points (Table IV) for various values of the reaction enthalpy is depicted in Figure 4.

Figure 4. Location of the proposed operating points as a function of relative change of reaction enthalpy value from the original value of $-160 \times 10^3 \text{ J.mol}^{-1}$
As it can be seen in Figure 4, none of the proposed operating points is located in the safety operating regime for every uncertainty of the reaction enthalpy in the studied value range. However, if the reaction enthalpy was decreased only by 5 %, all proposed operating points are still satisfactory. In case of a reaction enthalpy decrease by 10 %, operating point F was shifted to the hazardous operating regime because of the reactor temperature decreased below 110 °C and the consequent decomposition of hydrogen peroxide leading to a runaway would take place. An increase of the reaction enthalpy had a more significant impact on the position of the proposed operating points. In case of a reaction enthalpy increase by only 5 %, all but one (F) operating points were shifted to the hazardous operating regime because of the temperature in the reactor exceeded the upper safety constraint of 125 °C, which leads to possible over-pressurization of the reactor. If the reaction enthalpy was increased by 10 %, every proposed operating point was in the hazardous operating regime.

Conclusion

Simulation-based approach for process intensification and hazard identification combination was proposed. As a case study, the production process of 3-methylpyridine-N-oxide was selected. First, a mathematical model suitable for scale-up and reaction conditions optimization of the CSTR for 3-methylpyridine-N-oxide production was developed in the MATLAB® modelling environment. In the next step, reaction conditions were optimized towards maximizing the production rate of 3-methylpyridine-N-oxide with process safety constraints’ implementation. Six different reactor operating points with the production rate increased by ca. 6 % were proposed based on process simulation and multi-parametric optimization. Consequent model parameter uncertainty analysis was performed. For the studied range of reaction enthalpy relative change by ± 5 % from the original value, only one from the proposed operating points was found to be satisfactory for safe operation. If the range of reaction enthalpy relative change was increased (relative change by ± 10 % from the original value), none of the proposed operating points was satisfactory for safe operation.

This study has shown that an appropriate safety analysis is always required prior to the implementation of an intensified process. The need for model parameter uncertainty analysis in the simulation-based process intensification and hazard identification was underlined. In our future work, implementation of the presented procedures into smart software solution for supporting hazard identification techniques will be studied. Such software tool can be used to design inherently safer processes and also to train operators and process engineers in existing industrial plants.

Acknowledgment

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Literature