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Optimization of Process and Improvement in Continuous Production of Synthesis of Methyl Anthranilate

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The synthesis of methyl anthranilate (MA) from phthalimide is widely used in the production of sodium saccharin because of its accessible raw materials and stable products. In the traditional semi-batch production mode, difficulties to control the temperatures of strong exothermic reactions and the large energy consumption greatly limit its wide applications and sustainable development. In this paper, a new method of MA synthesis by microchannel reactor is proposed, which realizes the transformation of MA synthesis from semi-batch production to continuous production.The effects of different parameters on the conversion rate of raw materials and the purity of products were studied in the experiment part. For comparison, specific experiments were both set up in semi-batch and continuous production process. The optimal synthesis condition of the continuous process is finally determined as below: the molar ratio of the reactants (phthalimide: sodium hypochlorite: methanol) is 1: 1.1: 3.7; the reaction temperature is 0 °C; the reaction time is 97 s. The MA with high yield and purity (80.3 % and 98.5 %) are successfully synthesized. Compared with the semi-batch process, the yield and purity of the continuous products are increased by 5.1 % and 1.2 %. This study provides fundamental data for process optimization, clean production and energy consumption reduction by continuous process. This continuous synthesis method provides a more safe, efficient and energy-saving production mode for industrial production.

1. Introduction

Methyl anthranilate (MA) is an important intermediate product of fine chemical industry, which has dual characteristics of ester and amine. Synthesis of MA from phthalimide by Hofmann rearrangement and esterification is widely utilized in saccharin production because of its accessible raw materials and stable product (Li et al., 2007). With the advancement of technology and the increasingly severe environmental situation, the disadvantages of this traditional semi-batch method of synthesizing MA are increasingly apparent. The synthesis process is sensitive to reaction temperature and needed to be carried out under low temperature conditions according to the large heat release (Zhu, 2012). These characteristics determine the high energy consumption, potential risk of thermal runaway, low stability and high waste emissions (Wang and Wu, 2012) in the synthesis process. These characteristics limit the sustainable development of MA-related industries. The synthesis method of MA has been attracting much attention. A method of microwave-assisted synthesis of MA has been reported. The application in industry is limited because of its complicated process and high cost (Godeau et al., 2016). Lee et al. (2019) synthesized MA and its derivatives by using engineered strains of escherichia coli. Luo et al. (2019) continued to use the synthesis scheme of microbial strains on the basis of predecessors. These synthetic processes can obtain high quality MA, but most of them are based on biological synthesis. Compared with chemical synthesis, biological synthesis has higher cost of raw materials and lower synthesis efficiency, which make it difficult to be use for large-scale industrial production. Under this present situation, it is necessary and urgent to find a more stable, efficient, energy-saving and clean solution to solve these industrial production problems.

As a new type reactor, microchannel reactor has unique advantages in reducing consumption of raw materials and energy, increasing mass (Zhang et al., 2011) and heat transfer, improving raw material conversion rate (Duan et al., 2020) and safety performance (Hassimi et al., 2018). These characteristics make microchannel

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reaction technology widely used in clean, efficient production and energy conservation fields in recent years. Gholami et al. (2019) synthesized biodiesel with salvia leriifolia oil as raw material in microchannel reactor. The utilization rate of raw material is as high as 93.36 %, which effectively solved the problems of high energy consumption and large waste production in the traditional process. By using the microchannel reaction technology, Li et al. (2018) solved the problem that the large amount of exothermic heat in the acylation of 2-methylnaphthalene affected the conversion and selectivity of raw material. Under the optimal conditions, the yield of 2-methyl-6-propionylnaphthalene is 85.8 %, and the selectivity is 87.5 %. A green and facile synthesis of an industrially important quaternary heterocyclic intermediates for baricitinib has been developed by Cui et al. (2019), who reported that the reaction in the microchannel reactor had the advantages of less by-products, easy operation and environmental protection compared with the traditional process. These studies show that microchannel reactor is an effective way to improve the utilization rate of raw materials, save energy and reduce the generation of waste. This kind of reactor is quite suitable for reactions with large heat release and unstable intermediates. To sum up, the characteristics of microchannel reactor coincide highly with the features of synthesis process of MA. MA synthesis based on a microchannel reactor, which has not been reported, may provide a new vision in solving the problems of MA production. Based on the above considerations, this paper optimizes the process parameters of semi-batch MA synthesis and takes this as the control group. The continuous synthesis of MA is carried out in Corning AFR^{TM}-G1 microchannel reactor, and the influence of various process conditions on the reaction is studied.

2. Experiments

The reaction shown in Figure 1 was the research object, the effects of different parameters on the conversion rate of raw materials and the purity of products were investigated. For comparison, specific experiments were set up in semi-batch and continuous production process.

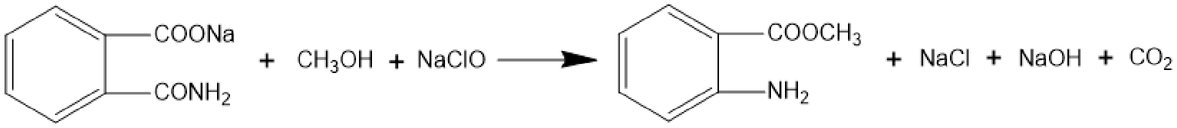


Figure 1: Synthesis of MA by Hofmann rearrangement and esterification

2.1 Experimental materials

- Phthalimide (molecular formula: $C_8H_5NO_2$, molecular weight: 147.13, purity: 99.5 %)
- Methanol (molecular formula: CH_3OH, molecular weight: 30.24, purity: 99.5 %)
- Sodium hypochlorite (molecular formula: NaClO, molecular weight: 74.44, purity: 13 %)
- Sodium hydroxide (molecular formula: NaOH, molecular weight: 39.996, purity: 14 wt%)
- Methyl anthranilate (molecular formula: $C_8H_9NO_2$, molecular weight: 151.16, purity: 99 %)

2.2 Experimental method of semi-batch synthesis

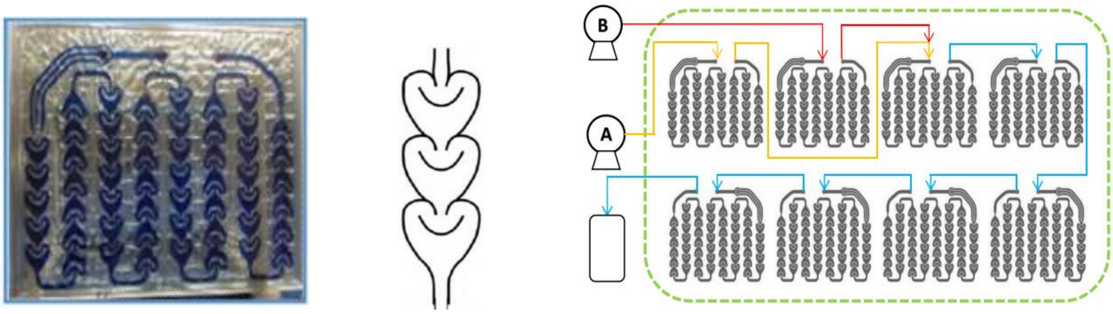
All exploration experiments were set up according to the standard operating procedures. The phthalimide and 14 wt% sodium hydroxide solution were added into the glass reactor with jacket at the molar ratio of 1: 1. The reaction temperature was kept on 70 °C for 120 min by agitation. Sodium o-formamide benzoate ($C_8H_6NO_3Na$) could be obtained by controlling the pH between 8.5 and 9.

For further production of MA, sodium o-formamide benzoate solution and methanol were mixed at required ratio. The temperature of the mixed solution should be kept below -10 °C. The 13 % sodium hypochlorite solution at -12 °C was added at a required molar ratio with stirring. A lot of heat was released during the mixing, so it need to be added slowly to ensure the reaction temperature below -5 °C. After 20 min, a large number of white paste like intermediates were produced. Then the cooling system of the reactor was turned off. When the reaction temperature was naturally raised to 50 °C (about 20 min), 70 °C water was added to the reactor. The paste intermediate was quickly dissolved and the solution was delaminated. The methyl anthranilate product could be finally obtained after standing.

2.3 Experimental method of continuous synthesis

In the experiment, AFR^{TM}-G1 reaction module was used as the reaction carrier, and its structure is shown in Figure 2a. The reactor is composed of glass module and connection module. The glass module is separated into three hollow spaces by four layers of glass. At both ends of it are two heat exchange layers (liquid holdup about 14 mL), and the reaction layer (blue part in Figure 2a, liquid holdup about 8 mL) is in the middle. The reaction channel is composed of a series of miniature "heart-cell" structural units (the internal diameter is 1 mm) with full mixed flow characteristic as shown in Figure 2b. The length of the reaction channel of each reaction layer is about 2 m, and the unit heat exchange area can reach 2,500 m^2/m^3. The reactants were delivered to the reaction module by the middle pressure plunger pump (models for TBP5002T) at the required flow rate.

Figure 2c shows the experimental process. Feed A (solution formed by mixing sodium o-formamide benzoate and methanol at a certain required molar ratio) was transferred to the G1 reaction module by pump A and entered the third module after being pre-cooled in module 1. Feed B (13 % sodium hypochlorite solution) was transported by pump B to the second module for pre-cooling, and then feed A was mixed with it in the third module. The reaction mixture flowed out from the outlet of the eighth module and entered the sample collection tank. In the collection tank, the paste intermediate was produced rapidly (about 1 min). Then the subsequent hydrolysis reaction was carried out. The proportion of materials was controlled by the feed speed of the pump, and the residence time was controlled by the number of modules. The effects of residence time, reaction temperature and material ratio on the purity and yield of MA could be investigated by these modules.



(a) (b) (c)

Figure 2: (a) G1 reaction module; (b) Reaction channel; (c) Continuous synthesis process

2.4 Analytical method

The purity of MA could be analyzed by gas chromatography (He et al., 2017). In this study, the purity of MA was analyzed by external standard method. By using MA as the solute and methanol as the solvent, solutions with concentration of 5.0, 10.0, 30.0, 50.0 and 80.0 g/L were configured. The standard curve obtained by linear fitting is shown in Eq(1).

$$y = 0.9520x + 0.3771 \tag{1}$$

Coefficient of determination: $R^2 = 0.9939$. The results showed that the concentration of MA had a good linear relationship with the peak area in the range of 5.0 to 80.0 g/L. By using MA obtained from experiment as the solute and methanol as the solvent, solution with concentration of 30.0 g/L was configured. The solution was analyzed by GC, and then the purity of the MA could be calculated by Eq(1).

3. Results and Discussion

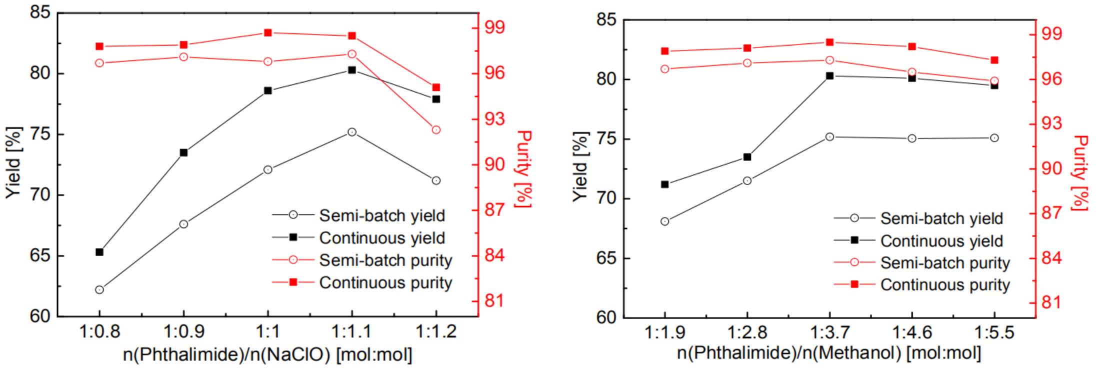
Table 1: Operating variables, detailed parameters, experimental results of continuous synthesis

Group	Flow of A g/min	Flow of B g/min	Temperature/°C	Molar ratio/ (mol: mol: mol)	Time/s	Number of module	Purity/%	Yield/%
1	16.2	19.1	-5	1: 1.1: 3.7	97	8	98.8	80.2
2	16.2	19.1	0	1: 1.1: 3.7	96	8	98.5	80.3
3	16.2	19.1	5	1: 1.1: 3.7	97	8	97.6	79.1
4	16.2	19.1	15	1: 1.1: 3.7	100	8	-	-
5	16.2	19.1	0	1: 1.1: 3.7	79	7	92.9	74.5
6	16.2	19.1	0	1: 1.1: 3.7	46	5	91.5	68.4
7	17.1	18.3	0	1: 1.08: 3.7	98	8	97.8	65.3
8	15.4	19.8	0	1: 1.2: 3.7	94	8	95.1	77.9
9	15.6	19.7	0	1: 1.1: 2.8	96	8	98.1	73.5
10	16.9	18.3	0	1: 1.1: 5.5	97	8	97.3	79.3

In this study, molar ratio of reactants (Phthalimide: Sodium hypochlorite: Methanol), reaction temperature and reaction time were taken as the operating variables in a series of experiments. The experimental data shown in Table 1 were the average value of three experiment results under the same process conditions. Yield (%) is the percentage of the actual mass (g) to theoretical mass (g) of MA; Purity (%) is the percentage of the mass (g) of MA in the product to the total mass (g).

3.1 Effect of NaClO

In the process of the Hofmann rearrangement, [R-CONH$_2$] reacts with [Cl$^-$] to form [R-CONHCl]. The hydrogen on the nitrogen atom is dissociated under alkaline conditions, and then quickly rearranges to [R-NCO] (Hofmann, 1881). NaClO provided alkaline conditions and halogen for rearrangement, which greatly affect rearrangement efficiency. As shown in Figure 3a, the molar ratio of NaClO had a significant effect on the product yield and purity. When the molar ratio of NaClO was 1: 0.8 during semi-batch synthesis, the purity of MA was high but the yield was extremely low (96.7 % and 62.2 %). The reaction didn't proceed sufficiently because the amount of NaClO was insufficient. When the molar ratio of NaClO was 1: 1.2, the purity was decreased to 92.3 %. When the molar ratio of NaClO was too elevated, the strong oxidability of NaClO oxidizes [R-NH$_2$] in MA to [R-CN], which results in the aggravation of product color. Excessive alkalinity would cause partial hydrolysis of the product, leading to the decrease of the yield. The molar ratio of NaClO of 1: 1.1 was selected as the optimal synthesis condition.



(a) (b)

Figure 3: The change trend of MA yield and purity with (a) sodium hypochlorite and (b) methanol

In the continuous synthesis experiment, the influence of MA yield and purity with the molar ratio of NaClO was the same with that of semi-batch synthesis. From Figure 3a, it can be seen that the highest yield of the product was 80.3 %, which was 5.1 % higher than the semi-batch synthesis. During the semi-batch synthesis, the viscosity of the reaction system increased with the formation of the paste intermediate, resulting in uneven concentrations of various parts of the reaction system. If the local proportion of NaClO was too high or too low, the reaction would be both negatively affected. It would not only reduce the utilization rate of reactants, but also cause additional side reactions. This conventional phenomenon was almost inevitable in semi-batch production.

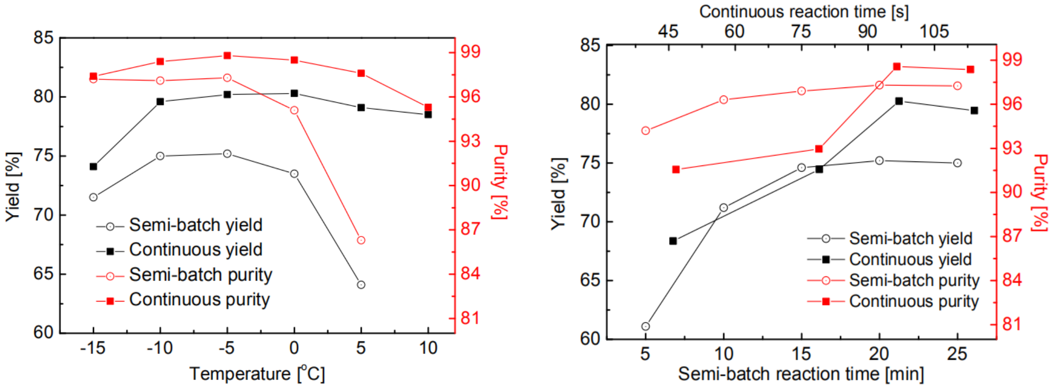
3.2 Effect of methanol

Methanol was both solvent and reactant in the reaction. Methanol with excessive ratio was added to promote the positive reaction, resulting in a large amount of residual methanol in mother liquor. As can be seen from Figure 3b that when the molar ratio of methanol in the semi-batch synthesis was 1: 3.7, the yield and purity of MA reached the peak value (75.2 % and 97.3 %). As the molar ratio of methanol continued to increase, the yield remained almost unchanged, but the purity decreased to 95.9 %. The reason for this phenomenon might be that too much methanol would increase the mutual solubility of MA with methanol.

As shown in Figure 3b, the yield and purity of MA both reached peak values (80.3 % and 98.5 %) when the molar ratio of methanol was 1: 3.7 in continuous process. When the molar ratio of methanol was 1: 5.5, the turbidity and viscosity of the solution increased from the seventh reaction module. The high concentration of methanol leaded to the formation of paste intermediates, so the reaction pipeline might be blocked. To avoid this phenomenon, the molar ratio of methanol for microchannel synthesis should be 1: 3.7. At present, the molar ratio of methanol used in industrial production was usually 1: 5.5, but experimental results showed that when the molar ratio of methanol was 1: 3.7, the purity and yield of MA were the highest. Compared with the current process, the methanol consumption was reduced by 32.7 %.

3.3 Effect of temperature

The reaction temperature was the most important factor affecting the Hofmann rearrangement. When the temperature was too high, phenyl couldn't be accurately transferred to the negatively charged nitrogen atom resulting in the decrease of the [R-NCO] concentration. As can be seen from Figure 4a, the yield of MA increased with increasing temperature from 71.5 % to 75.2 %, and then decreased from 0 °C. When the temperature was -15 °C, the reactants showed low reactivity, leading to the low conversion of raw materials. When the temperature was between -5 °C and -10 °C, there was little difference in the yield and purity of MA. When the temperature was between 0 °C and 5 °C, it is very difficult to accurately control the reaction temperature, because the exothermic rate increases with the increase of reaction temperature. The overtemperature phenomenon appeared in the experiment leaded to a sharp drop in yield and purity, especially at 5 °C. The reactivity of the reactants increased in high temperatures; but the probability of side reactions also increased. In the actual production process, slight deviation might cause sharp changes in temperatures, but too low reaction temperatures would increase cost consumption. Considering these two factors, the reaction temperature was set to -5 °C.



(a) (b)

Figure 4: The change trend of MA yield and purity with temperature (a) and reaction time (b)

Figure 4a shows the same trend of temperatures in continuous process. At the same temperature, the yield of the products obtained in the continuous process was greater than semi-batch process, and the difference was more obvious with the increase of temperature. When the temperature was 5 °C, the yield of MA obtained in the continuous experiment was 15.1 % higher. High yield and purity MA could be synthesized stably in the microchannel reactor even at a reaction temperature of 0 °C. This trend can prove that the microchannel reactor could quickly remove the large amount of heat generated in the material mixing process, and avoid the side reactions caused by local high temperature.

3.4 Effect of reaction time

The appropriate reaction time could not only obtain high-quality products, but also reduce the power consumption. As shown in Figure 4b, the yield and purity of MA increased with the increase of reaction time, and the growth trend became stable from 15 min. After 20 min, there was no significant change in the purity and quality, indicating that the reaction has proceeded sufficiently and the intermediate has good stability at -5 °C. Although the rearrangement process was very fast, the formation of paste intermediates led to the increase in viscosity of the reaction system. In order to ensure the completion of the reaction while reducing energy consumption, the optimal reaction time was selected to be 20 min.

To make the [R-CONH$_2$] be rearranged to [R-NCO], lower reaction temperatures are more favorable. For the reaction, paste intermediates which were generated by [R-NCO] and methanol, low temperature is not a favorable choice. Materials could not be moved out in time in semi-batch production process, so only long-term low temperature could be selected to ensure the accurate synthesis of [R-NCO]. In continuous synthesis, the materials could be removed in time at the appropriate time. But this required that the rearrangement reaction must be completed in the reactor channel before outlet. As shown in Figure 4b and Table 2, when the retention time was 46 s, the yield of MA was only 68.4 %. The unreacted reactants could not be rearranged to [R-NCO] accurately in the hydrolysis tank without cooling device, resulting in a low yield. So the appropriate residence time determined the success of continuous synthesis. According to the experimental results, the residence time was finally selected to 97 s.

4. Conclusions

A robust and continuous flow process for the Hofmann rearrangement and esterification reaction in a microchannel reactor to produce MA was successfully developed. Comparing with the traditional MA synthesis process, the new synthesis method of MA permits the reaction to be supported under reduced process costs with higher conversion rate and higher production efficiency. The consumption of methanol can be reduced by 32.7 %. In terms of raw material conversion rate, the microchannel process is significantly better than the conventional semi-batch process (increased from 75.2 % to 80.3 %) and the purity of MA is higher (98.5 %). The reaction time was greatly shortened (from 20 min to 97s at 0 °C). This new synthesis method reduces the generation of waste from the source, alleviates the pressure of "end-of-pipe treatment" to a certain extent, and improves the environmental self purification ability. The problems of low synthesis efficiency, high energy consumption and low safety performance in the semi-batch production process have been effectively solved. It can be used as a more clean, efficient, safe and low energy consumption production method for MA production. This technology might be promising as a useful tool for similar MA synthesis reaction of other organic compounds and industrial drugs.

Microchannel synthesis technology has many advantages, but as a new technology, there are still some limitations, especially the application of microchannel reactor in industrial production scale. To fulfill the industrial needs, the technology on the synthesis of MA in microchannel reactor still requires deeper study to minimize the gap between industry and laboratory.

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