

Continuous hydrogenation in micro-packed bed reactors for pharmaceuticals synthesis

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1. Introduction

In recent years, with the advancements in continuous flow technology and the ever-increasing demand for green processes, continuous flow chemistry has become more and more widely adopted in the pharmaceutical industry. In this work, the continuous hydrogenolysis of N-diphenylmethylazetidin-3-ol (DMAOL) to 3-azetidinol in micro-packed bed reactors (μ PBRs) was demonstrated. The effects of different catalysts, solvent types and the pH of the solution on the reaction in a micro-packed bed reactor were investigated. The results indicate that the reaction rate per reactor volume is increased by 100 times due to the larger interfacial area and shorter diffusion distance in micro-packed reactors. To further study the long-term stability of the reaction system and catalyst life, the flow system was successfully operated for 240 h. The reaction kinetics model for the hydrogenation of N-diphenylmethylazetidin-3-ol in methanol was studied after the internal and external diffusion limitations were eliminated. In addition, the type of adsorption of the raw material on the catalyst and the rate-determining step of the reaction were investigated. In addition, the continuous reductive amination and hydrogenation of nitro groups are all investigated in the micropacked bed reactors. The scaling up of the micropacked bed technology is also successfully performed, demonstrating the high safety and efficiency compared with the conventional batch reactors.

2. Methods

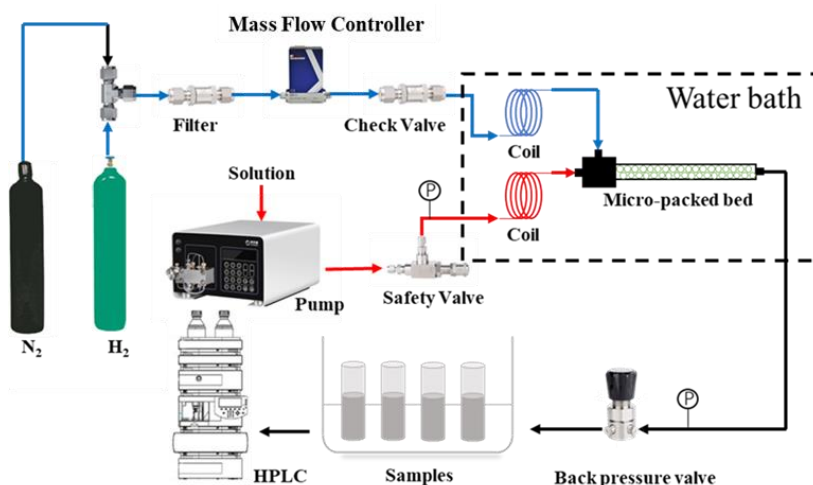


Figure 1. The schematic overview of the flow system for hydrogenation based on μ PBRs.

3. Results and discussion

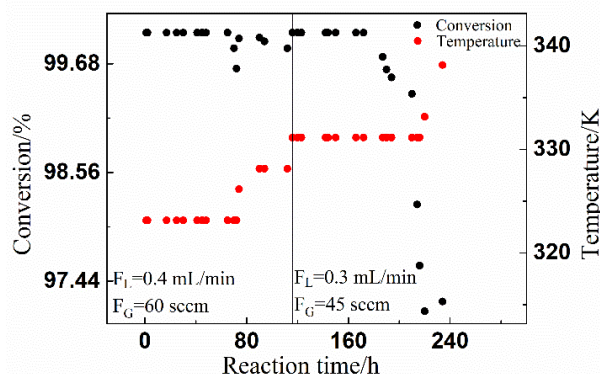


Figure 2. The stability of reaction system in the micro-packed bed reactor

Experimental conditions: initial concentration of 1-(diphenylmethyl)-3-hydroxyazetidine: 10 wt.%; $P=25$ bar; the amount of $\text{Pd}(\text{OH})_2/\text{Al}_2\text{O}_3$ catalyst (7 wt. %): 4.3 g. When the reaction time is less than 116 h, $F_L=0.4$ mL/min, $F_G=60$ sccm; when the reaction time is more than 116 h, $F_L=0.3$ mL/min, $F_G=45$ sccm.

To further study the long-term stability of the reaction system and catalyst life of $\text{Pd}(\text{OH})_2/\text{Al}_2\text{O}_3$, the reaction performance was investigated in the micro-packed bed reactor for 240 h as shown in Figure 2.

4. Conclusions

In this study, a micro-packed bed reactor has been successfully applied to the continuous hydrogenation of DMAOL using hydrogen gas. It is demonstrated that the μPBR s is more efficient for the hydrogenation of DMAOL than the traditional batch reactor. The value of conversion per unit reactor volume per unit time of the micro-packed bed reactor is 100 times of that of the batch. The reaction kinetics model was obtained after the external and internal mass transfer limitations have been eliminated and the reaction is in the kinetics-control region. The reaction rate is found to be 0.53 order with respect to DMAOL concentration and 0.31 order to hydrogen pressure. The activation energy (E_a) of the rate constant is 18.6 kJ/mol and the Arrhenius constant (A) is $2.68 \text{ mol}^{0.47}/(\text{L}^{0.47}\text{bar}^{0.31}\text{s})$. The experimental results were fitted with several kinetic models to determine the rate-determining step, which indicated that the diphenylmethyl removal rate of DMAOL with $\text{Pd}(\text{OH})_2/\text{Al}_2\text{O}_3$ catalyst was controlled by surface reaction rate and the adsorption type of substrate and H_2 on the catalyst are non-competitive and dissociative adsorption.