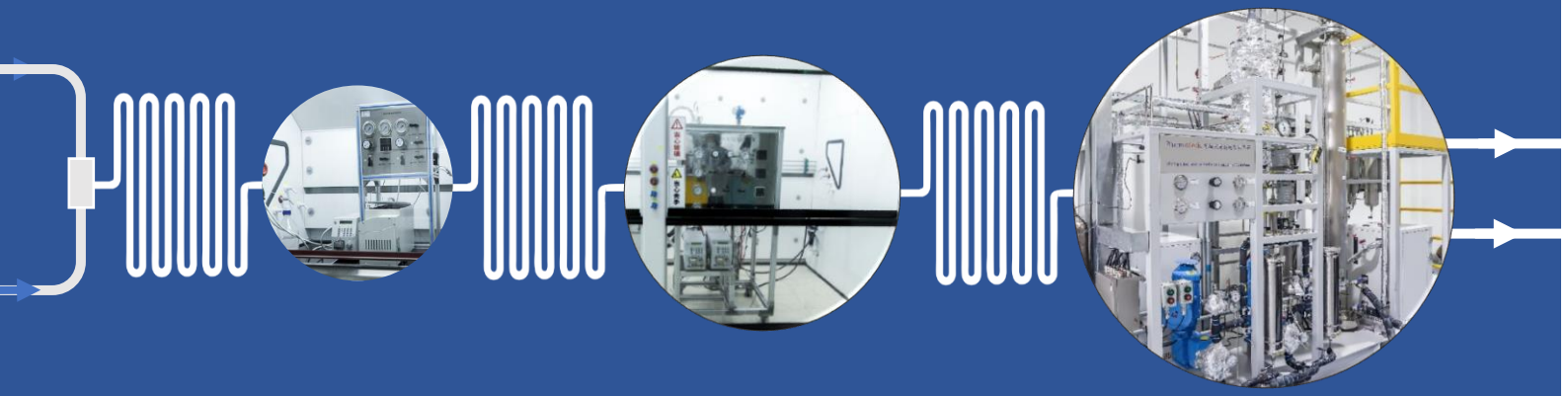
Technical Research Whitepaper

Application of Continuous Flow Hydrogenation with Micropacked Bed Reactors on Manufacturing Scale



PharmaBlock

In the pharmaceutical industry, the hydrogenation reaction represents about 14% of all chemical reactions. With the demand for more environmental and safe pharmaceutical manufacturing, this common transformation has been more of a love-hate reaction[1].

In the past, such reactions are carried out using excess quantities of costly reducing agents, such as hydrides ($LiAlH_4$, $NaBH_4$) or borane reagents. Although effective, these reagents cause problems with the coproduction of large amounts of metal salts which require separation and disposal. There is also the lack of control over selectivity during reduction[2].

Alternatively, catalytic hydrogenolysis with high pressure H_2 is a greener and more atom efficient option. The most widely used process for catalytic hydrogenation is batch production, which is limited by a few drawbacks[3-6]:

- Long reaction time: a major challenge for this method is the poor solubility of H_2 in liquid phase solvents coupled with slow gas-liquid transfer limitation. A long reaction time (6-12 hours) is required.
- Large reactors with storage of excess H_2 gas: to shorten the reaction time, large reactors (1000-5000L) are usually designed for high-pressure hydrogenation. However excess H_2 gas in the large equipment is highly dangerous.
- Labor intensive with higher safety risk: multiple gas replacement operations and separation of the catalysts are required in each batch production. Plus the storage of a large amount of pressurized hydrogen.

The continuous flow technology has been identified as the most prominent green engineering research area by the ACS GCI Pharmaceutical Roundtable. A continuous flow process has many inherent advantages over conventional batch production, including reducing impurities, increasing yields, reducing the footprint on the environment and enhancing stability and safety, featuring improved heat and mass transfer properties, while avoiding formation of hot spots, thus providing high selectivity towards desired products. Application of continuous flow process in hydrogenation with micro-packed bed reactors is a promising option for overcoming the barriers of conventional usage of batch reactors for hydrogenation[4-5].

How does a micro-packed bed reactor work?

The solid-supported catalyst is packed inside of the reactor. The substrate solution mixes with gas in a mixer which is usually installed or connected at the inlet end of the reactor. The mixed gas-liquid solution is pumped into the reactor and makes effective contact with solid catalysts[2].

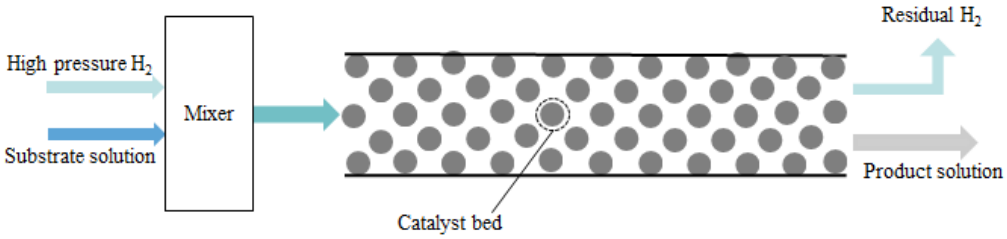


Figure 1. Micro-packed bed reactor.

The basic process flow chart is shown below in Figure 2. The process consists of liquid feed preheating system, reaction system, and separation system. The configured raw material solution is preheated by an inlet preheater and mixed with hydrogen in a micromixer. After fully mixing, the gas-liquid flow enters a micro packed bed reactor. In the reactor, the mixed raw materials and hydrogen undergo a hydrogenation reaction under the action of a catalyst fixed on the reactor bed to produce a final product. A small amount of purge gas is discharged, and the product in solution goes to the collection tank and enters the post-processing system for refining[7-8].

This method can significantly enhance the mass transfer process, which effectively improves the reaction rate[5]. As it has great advantages of easy replacement and fixation of the catalyst, simple and efficient operation, it is becoming a more popular and widely adopted technical route in the current chemical industry. However, it also has some problems with solubility issues, large pressure drops, and difficult scale-up[6]. Therefore, micro-packed bed reactors are mostly used at lab-scale or up to kilo scale in pharmaceutical industry rather than manufacturing scale.

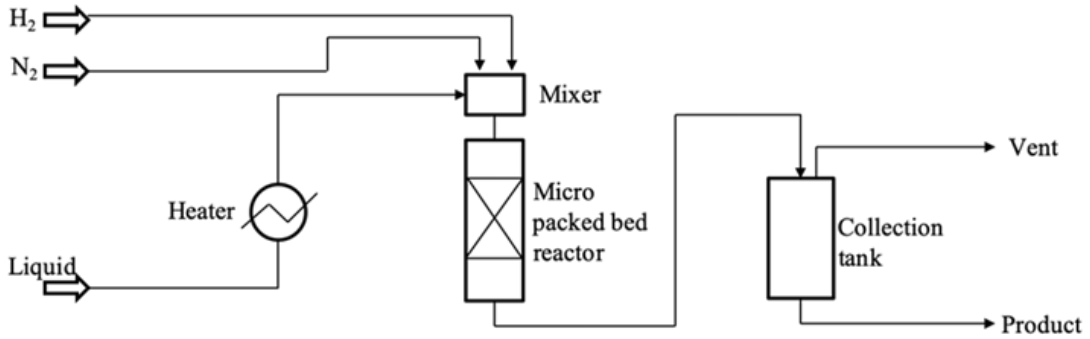


Figure 2. Micro-packed bed hydrogenation reactor process flow chart.

Table 1. Comparison between conventional batch production and micro-packed bed hydrogenation technology.

Batch production	Micro-packed bed technology
Long reaction time: Interfacial surface area limits mass transfer, and requires long reaction time	**High efficiency:** Rapid gas-liquid-solid mass transfer with higher yield
Possible high level of Impurities: Hydrogen starvation will lead to elevated levels of impurities	**Reduced impurities:** Impurity issues associated with hydrogen starvation is eliminated as the required hydrogen gas inventory is minimal. **Consistent quality**: with no batch variation
High Safety Risk: a large amount of hydrogen gas storage, coupled with labor requirements for multiple gas replacement operations and separation of the catalysts	**Safer Process:** ✓ Minimal hydrogen gas inventory and control of injection rate ✓ In situ catalyst regeneration or recyclability and automated mode for reduced manpower
Large high pressure reactor	**Much smaller equipment footprint**
Costly: Lower yield and high consumption of precious metal catalyst	**Cost effective:** improved yield and less precious metal catalyst utilization

What makes PharmaBlock unique?

PharmaBlock's experience with **Continuous Flow Hydrogenation** has occupied a leading position at manufacturing scale in the pharmaceutical industry.

- **Capacity:** Nowadays, most of the applications of micro-packed bed reactors are still at lab-scale or up to kilo scale in the pharmaceutical industry. However, PharmaBlock currently has designed and assembled several sets of **manufacturing-scale** equipment, and **yearly output has reached hundred-metric ton scale**.
- **Catalyst development, screening and production capabilities:** PharmaBlock's chemistry and engineering team is able to **develop and produce the suitable catalysts**, made of palladium (Pd(I/II)), platinum (Pt) or ruthenium (Ru), etc., for a better solution to reduce cost and extend catalyst service life.
- **Automatic process detection and control:** The micro-packed bed reactor system at PharmaBlock is also designed with the DCS (distributed control system) to achieve automatic detection and automatic control of the entire device. It is currently the internationally advanced control system dedicated to small and medium-sized devices and is equipped with low-, high-, ultra-high-alarm and multi-level safety protection logic to ensure high accuracy, safety and reliability, easy operation, and easy maintenance.
- **Extensive experience:** This technology supports various solvents (MeOH, EtOH, EtOAc, etc.) and is proven to be efficient on diverse transformations, including

debenzylation as well as nitro and alkene reduction. Table 2 below summarizes our extensive manufacturing experience.

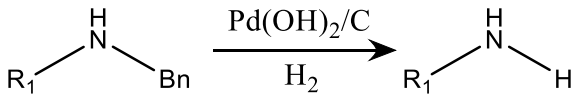
Figure 3. (A)Manufacturing scale micro-packed bed reactor; (B) Digital Automated Control System-DCS.

Table 2 Brief summary of PharmaBlock's manufacturing experience.

Catalytic bed: Pd ,Pt, Ru, or Rh		
Supports various solvents: MeOH, EtOH, EtOAC, HOAc, THF		
-NRBn $-NO_2$ $-CHO+NH_2$ = -CN -NHOH	H_2,cat	-NRH $-NH_2$ $-CHNH_2$ -- CH_2NH_2 NH_2

Application Cases

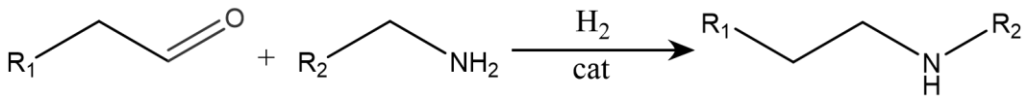
1.Bn Deprotection



Here is a hydrogenation project case of Bn deprotection in a micro-packed bed reactor. It is estimated that debenzylation is required during the synthesis of more than 1,000 drugs[11]. This technlogy reduced the consumption of the calalyst to 0.1~0.2% of the coventional batch method. Meanwhile, the yield of target product is improved from 85% to 95%. And the annual output exceeds hundred Metric tons.

	The batch process	The continuous flow process
Catalyst cost	150+ USD/Kg	The catalyst consumption is 1/10~1/15 of the previous batch process.
Yield	85%	95%
Operability	Complex, dangerous, and costly catalysts.	Continuous operation, robust process.
Production Scale	Depending on the size of the high-pressure hydrogenation reactor.	The annual output of each unit is 100 metric Tons.

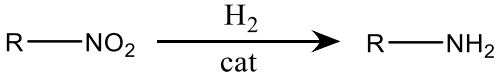
2. Reductive Amination



The second case is one of the commonly used methods for the synthesis of pharmaceutical intermediates - reductive amination[10]. Due to the continuous operation and simple process operation, the labor cost also has been reduced and a safer operation condition has been developed. Compared to the batch process, the yield increased from 70% to 95%.

	The batch process	The continuous flow process
Catalyst cost	Higher	Lower
Yield	70%	95%
Operability	Complex, dangerous, and more reaction step.	One step synthesis to final product. Continuous operation, simple process operation.
Production Scale	Depending on the size of the high-pressure hydrogenation reactor.	The annual output of each unit is 100 tons.

3. Nitro Reduction



Last but not least, in the nitro reduction case, PharmaBlock also reduced the catalyst cost, improved the yield to 95% and completed the annual output of product to over 100 Metric tons. Also, there was no Dehalogenated impurities detected. This is a significant breakthrough as functionalized anilines are an important class of intermediates in the

pharmaceutical industries, which can usually be prepared by direct hydrogenation of nitro compounds.

	The batch process	The continuous flow process
Catalyst cost	higher	lower
Yield	80%	95%
Operability	Complex, dangerous, and costly catalysts.	Continuous operation, robust process.
Production Scale	Dehalogenated impurities > 2%.	No dehalogenated impurities is detected.

A GLIMPSE INTO THE FUTURE

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. The usage of micro-packed bed reactors is a viable option for application of continuous flow technology in hydrogenation. However, most of the applications are still at lab-scale. PharmaBlock will continue exploring more types of reduction transformations at manufacturing scale, and enhance the automated control systems.

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