Flow Chemistry:

A New Technology to Enhance the Traditional Batch Process in the Delivery Requirement

Introduction

In the pharmaceutical manufacturing of active pharmaceutical ingredients (APIs), scale-up production often faces significant challenges. Some reactions carry substantial safety risks, while others suffer from drastically reduced efficiency compared to laboratory-scale reactions or are even difficult to achieve. By transforming chemical reactions into inherently small-scale, continuously fed and discharged micro-reactions through flow chemistry technology, these scale-up challenges can be largely overcome.

The characteristics of flow chemistry technology primarily include:

1. Enhanced Mixing Capability: Improved mass transfer eliminates concentration gradients;
2. High Surface-to-Volume Ratio: Structural features enable rapid heat transfer (fast cooling/heating) and precise temperature control;
3. Accurate Residence Time: Residence time is strictly determined by reactor characteristics (channel length, volume) and flow rate.

Compared to batch reactors, continuous reactors are hundreds to thousands of times smaller in volume. Leveraging their excellent heat and mass transfer properties, reaction parameters are far easier to control, enabling conditions that would be nearly impossible in batch reactors

Continuous reaction can effectively solve the problem of "amplification effect" in batch processes from research and development to pilot testing, and then again to commercial production. Porton’s continuous reaction capabilities include low-temperature lithiation reaction, ozone oxidation reaction, nitrification reaction, high-temperature reaction, and organic azide reaction, etc., which can achieve process development and technology transfer from research and development to production application. This article will explain the actual cases of the results separately.

Application Scenario 1:

Highly hazardous reactions

Background:

The project of a big pharma company applied ozone reaction technology for production delivery, shortening the project delivery time by more than a month.

- Highly Exothermic Reactions: Examples include nitration, ozonolysis, radical polymerization;
- Reactions Involving Hazardous Intermediates: These involve high-energy/highly reactive intermediates such as azides, diazo compounds, and peroxides;
- Reactions Involving Highly Toxic or Flammable Substances: Examples include the use of phosgene, cyanides, sodium azide, and hydrogen;
- Hazardous Gas Reactions: Examples include reactions involving hydrogen, oxygen.

Figure 1. Ozonolysis reaction with the low temperature conditions in Continuous Stirred Tank Reactor (CSTR) systems

Figure 2. Continuous hydrogenation with fixed bed reactor in pilot production scale

Application Scenario 2:

Reactions conditions that batch mode is hard to perform

Background:

The project was performed three times production in Porton with many tons' product delivery.

In traditional batch reactors, steps such as material addition, heating, and cooling require extended time, leading to significantly prolonged reaction durations. For reactions with unstable intermediates or products prone to further conversion, the operable time window is extremely narrow, making ideal

outcomes nearly unachievable in scale-up synthesis. Continuous reactors, with their high efficiency and controllability, enable precise control of reaction time and temperature, allowing reactions to proceed within narrower time windows for successful scale-up or optimized performance.

Examples include:

1. Reactions Generating Unstable Organometallic Intermediates: Such as those involving lithium reagents;
2. Reactions Requiring Specific Conditions with Unstable Products/Intermediates: Such as reversible Diels-Alder reactions;
3. Reactions Where Products Further React Under Reaction Conditions: Such as benzylic bromination.

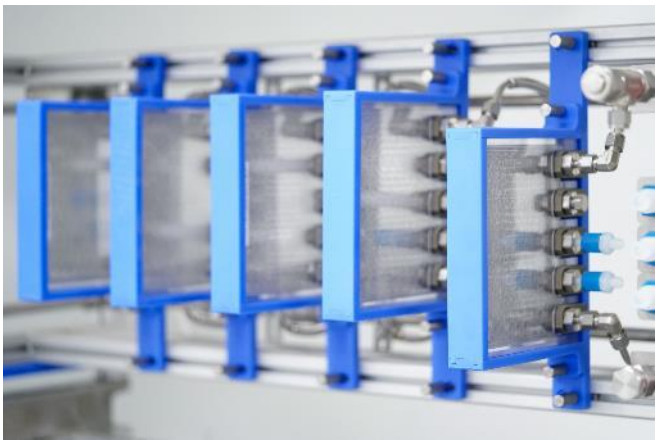

Figure 3. Tow phase fast reaction (less 10s) with Microchannel systems

Application Scenario 3:

Reactions conditions that batch mode is hard to reach

Background:

The project involving the conversion of alcohol to aldehyde utilized a microchannel reactor, enabling the production of 200 kg of product per day.

Flow chemistry also enables reactions unachievable by conventional methods. Due to its superior mass/heat transfer and inherent safety, continuous reactions can operate under extreme conditions, including:

1. Ultra-Low or Ultra-High Temperature Reactions;
2. Photochemical/Electrochemical Reactions with significant scale-up effects;
3. High-pressure Reactions: Such as chlorination and supercritical fluid reactions.

Figure 4. Photochemistry reaction with the Plug Flow Rector (PFR) systems

Conclusions

Flow chemistry is a high effective method to improve the delivery capability in some reaction types as to the batch mode in the pharmaceutical production. In the commercial production of bulk product, it will have more advantages over the traditional method in the future.

About Porton Continuous Reaction Technology Platform

The Porton Continuous Reaction Technology Platform boasts ton-scale continuous reaction production capabilities and is equipped with dedicated GMP-compliant workshops. The platform covers a wide range of reaction types, extending from traditional hazardous reactions such as nitration, diazotization, and ozonolysis, to advanced processes including lithiation, Grignard addition, catalytic hydrogenation, and substitution reactions. Focused on enhancing efficiency and reducing costs, Porton leverages innovative, efficient, safe, and environmentally friendly continuous reaction solutions to accelerate the commercialization of new drugs. This commitment drives industry development and progress, ensuring that effective medications reach the public sooner.

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With 17+ years of experience in organic synthesis and process R&D, along with more than 7 years as a senior director in the flow chemistry department, there is in-depth knowledge and rich project experience in flow chemistry, as well as plenty experience in flow team management and platform establishment.

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