APPLICATIONS OF CONTINUOUS REACTORS IN PHARMACEUTICAL MANUFACTURING

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Abstract

Within the past three years Eli Lilly has scaled up eight different continuous reactions in API manufacturing. Seven of these were operated cGMP to make drug substance used in clinical trials, and two were validation campaigns. Vertical bubble flow pipes-in-series plug flow reactors (PFRs) (360 L, 200 L) were used for reductive aminations with high pressure H_2. A 40 L continuous stirred tank reactor (CSTR) with sequestered Mg solids was used for a highly energetic Grignard formation reaction. Superheated high pressure coiled tube PFRs (8 L, 12 L, 1.5 L) were used for thermal de-protections, and a condensation reaction with hydrazine. A 3 L coiled tube PFR was used for a S_NAr coupling reaction, and a 12 L vertical coiled tube PFR was used an acid de-protection with 2-phase gas-liquid flow. Both of these were integrated into a continuous process that eliminated two isolations of highly potent intermediates.

Keywords

API manufacturing, PFR, CSTR, continuous reaction.

Introduction

There are many reasons why an API manufacturer may choose to run chemical reactions in continuous mode instead of batch. Yield and selectivity may be better for fast reactions in series with unstable intermediates.[1] Safety may be improved for highly exothermic or hazardous reactions.[2] Operating ranges may be wider and safety may be improved for high pressure reactions with hazardous gas reagents such as H2, CO, O_2, and for reactions at extreme temperatures less than -40 °C or greater than 200 °C.[3] Safety is improved for reactions with hazardous reagents like hydrazine, nitro containing compounds, diazo compounds, and cyanides.[4] End to end fully continuous processes offer advantages of quality control, extreme operating conditions, telescoping, and introducing excipients further upstream, which improve processing API to drug product.[5] The use of continuous reactors in the industry is rapidly increasing and it is an important part of modernizing pharmaceutical manufacturing.[6]

Continuous Reactors in Manufacturing

High pressure H_2 reactions pose severe safety risks and require expensive autoclaves and explosion proof bunkers for batch processing. Alternatively, a 360 L vertical bubble flow pipes-in-series PFR was used for reductive amination with 850 psig H_2 homogeneously catalyzed by Ir. The stainless steel reactor was constructed from 45 vertical pipes in series, each 3.7 m tall and 53 mm i.d., connected by 4.57 mm i.d downjumper tubes. It was designed to operate with 12 hour reaction time, >98% liquid filled, low axial dispersion, high vapor-liquid mass transfer, Froude number > 0.3 in the downjumpers to minimize surging, and about 7 bar overall pressure drop. Throughput was 100 kg per day of an advanced intermediate, and the process ran non-stop for 24 days continuous production. Isolated yield was 95% of the highly pure penultimate. The main safety advantages were

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that the amount of H_2 in the reactor at any time was low and that the reactor system operated outside of the building. Capital cost was about 10X lower than 1000 L batch equipment providing an equivalent productivity rate. A Direct Asymmetric Reductive Amination (DARA) was run in a 200 L bubble flow pipes in series reactor, fabricated from 24 pipes in series. The reaction operated at 500 psig H_2 pressure and 130 °C, and produced 3250 kg GMP intermediate in a validation campaign.

A 40 L CSTR with sequestered Mg solids was used for a Grignard formation reaction that had initiation difficulties and runaway potential. The aryl bromide starting material flowed into the CSTR continuously, and the Grignard reagent flowed out of the CSTR continuously, but Mg solids were charged intermittently once every 4 hours and self-initiated immediately. The CSTR operated at 40 °C with a 60 minute residence time, τ, for a total of 96 hours in continuous flow, producing more than 4000 L non-GMP Grignard reagent solution. The amount of solid Mg left at the end of the campaign was small, such that the overall Mg stoichiometry was 1.02 equivalents. CFD was used to help design the Mg sequestering system, which was one of the main engineering challenges of the project. Compared to batch, the reactor was 50X smaller, initiation was done at 500X smaller scale, and 20X less H_2 byproduct was produced during the excess Mg quench.

A thermal BOC de-protection reaction in superheated THF solvent was accomplished in an 8 L Hastelloy® coiled tube reactor, 4.57 mm i.d. and 490 m long. The PFR operated at 140 °C and 200 psig with a 60 minute τ in a validation campaign that produced 120 kg API. An NH_4Cl-catalyzed thermal ethoxy ethyl deprotection in superheated THF was run in a 12 L Hastelloy® coiled tube reactor, 4.57 mm i.d. and 730 m long. The thermal reaction replaced a strong acid deprotection, eliminated the quench and workup unit operations, and minimized impurities associated with the acid and quench. The PFR operated at 150 °C and 250 psig with 100 minute τ in a late phase campaign that produced 100 kg API. A condensation reaction with hydrazine in superheated methanol was run in a 1.5 L stainless steel coiled tube reactor, 4.57 mm i.d. and 91 m long. The PFR operated at 125 °C with a 90 minute τ, and produced 30 kg of GMP intermediate. Compared to batch, the thermal tube reaction conditions allowed a 5X reduction in the amount of hydrazine necessary for complete conversion, and decreased reaction time from 15 hours to 60 minutes. Running the PFR 100% liquid filled eliminated headspace hydrazine. A series of counter-current heat exchangers were used to transfer heat between reagent and product, greatly reducing the required energy input.

Two fully continuous steps eliminated two isolations of highly potent intermediates. The flow chemistry included a S_NAr reaction between aminopyrazole and nitrile, and an acid BOC de-protection, both running in simple inexpensive PFA coiled tube PFRs. The S_NAr reaction was done in a 2.9 L, 91 m long, 6.38 mm i.d.

coiled tube, with 120 minute τ at 80 °C. The acid de-protection was run in a 12 L vertical coiled PFA tube with 2-phase gas-liquid flow, operating at 25 °C and 4 hour τ. The vertical coiled tube was made from 15.9 mm i.d. PFA tubing, coiled with about 40 loops and oriented like a wheel, which maintained consistent 50% liquid filled volume over a wide range of gas/liquid flow ratios. Removal of isobutylene by stripping action of a nitrogen carrier gas suppressed the formation of a process impurity. Metering of total volumetric flow was necessary at the reactor outlet to mitigate surging phenomena. The assay yield for the process was >98% and in production the reactor was found to be robust for > 200 h of continuous GMP production.

All seven PFRs used in these manufacturing runs were designed for low axial dispersion, and all achieved D/uL = 0.001 or less. In other words, the reactors achieved 99% pushout after only about 1.1 volume turnovers. Six of these reactions in GMP manufacturing were monitored for key impurities by custom-designed on-line HPLC systems. Transitions to steady state were monitored with a variety of on-line probes, including RI and IR.

Conclusions

Simple, inexpensive coiled tubes, pipes, and stirred tanks have been utilized for continuous PFRs and CSTRs in GMP pharmaceutical manufacturing. Continuous processing has provided new capabilities not possible or practical in traditional batch processing, and improved safety and process efficiency.

Acknowledgments

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