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RESEARCH ARTICLE

Latent Variables-Based Process Modeling of a Continuous Hydrogenation Reaction in API Synthesis of Small Molecules

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Abstract
Introduction Continuous manufacturing can be benefited by the use of the Quality by Design (QbD) strategy for robust process development and by the use of Process Analytical Technology (PAT) for real-time process monitoring and control. A successful implementation of QbD and PAT for continuous processes relies on a robust and information-rich process model as a basis for process understanding, monitoring, and control. Compared to first principles and other empirical models, a latent variables-based process model is capable of decomposing multidimensional process data into a few orthogonal latent variables and of providing accessible process understanding/visualization and control within the latent variable space. This study is an extension of our group's earlier effort (Liu et al., J Pharm Innov 6:170–180, 2011) to explore the utility of latent variables-based process modeling in pharmaceutical manufacturing processes.
Methods The case presented here is the first application of latent variables-based modeling to a reaction process in small-molecule active pharmaceutical ingredient route synthesis, i.e., a continuous-flow hydrogenation. A particular reactor configuration and operation was used in this proof-of-concept study.
Results It was found that time-variant profiles of pressure in the flow tube reactor served as an effective indicator of gas–liquid interaction within the reactor, thus determining process outcomes, i.e., the extent of reaction and enantiomeric excess (ee), given the importance of process set points. In addition, a design space of process parameters predicted to produce optimal outcomes, i.e., extent of reaction greater than 98 % and ee higher than 93 %, was established in order to provide a flexible operation space for performing the reaction with desired process outcomes.
Conclusions The capabilities of latent variables-based process modeling have been well demonstrated as applied to a continuous-flow hydrogenation reaction, regarding its improved process understanding and the potential for process optimization & control as well. Future efforts will be focused on continuing understanding of the capabilities and limitations of such a methodology on a fully-automated control scheme for continuous flow reaction.

Keywords Continuous manufacturing · Latent-variable modeling · Hydrogenation · Design space

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Introduction

Hydrogenation is a commonly used reaction in bulk active pharmaceutical ingredient (API) synthesis of small molecules to reduce or saturate organic compounds, typically using molecular hydrogen as a reductant in the presence of a catalyst. Hydrogenations used in pharmaceutical industry are often complicated processes, with end-product quality variables dependent on a variety of process parameters. These are typically performed batchwise at pressures of 10 to 100 psig, with elevated pressures increasing operational difficulty and resulting in process safety issues due to the large molar amounts of hazardous hydrogen gas present in a batch vessel headspace during commercial autoclave hydrogenation. Alternatively, the use of continuous manufacturing to perform flow hydrogenation in tubular reactors provides a safer and more efficient method of hydrogenation, both from R&D and manufacturing perspectives.

Performing hydrogenations in a continuous-flow tubular reactor allows for extended processing without the need to depressurize, to empty and clean the reactor, or to refill it