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RESEARCH ARTICLE

Integration of Continuous Flow Reactors and Online Raman Spectroscopy for Process Optimization

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Abstract The pharmaceutical industry has great need to reduce costs and improve manufacturing efficiency while consistently manufacturing quality drug product. Continuous flow reactors (CFRs) offer an option for a flexible, leaner, and cleaner process. CFRs are flow cells optimized for the continuous production of a target compound. Small-volume CFRs avoid some of the reaction control problems associated with scale-up to large-batch chemistry, while still allowing for process intensification through modular scale-out. Compared to batch reactors, CFRs are more energy efficient due to their superior mixing schemes and heat transfer properties. Reactions typically proceed much faster than in batch and require less excess solvent. Currently, CFRs are limited by the technologies available for online monitoring, which require product stream sampling and off-line analytics. This work addresses the analytical challenges inherent to CFRs by demonstrating the ability to assess the quality of product from a reactor stream rapidly, using effective online sampling and monitoring systems. Additionally, following the Quality by Design paradigm, techniques such as statistically based design of experiments, process analytical technologies, and multivariate statistical modeling methods were implemented to facilitate enhanced product and process understanding. An online sampling system that is able to interface with CFRs was developed, with custom software to monitor and control process variables using online analytics. Knowledge of these in-process parameters, combined with appropriate online process analytical technologies, provided a complete understanding of both the physical and chemical system. These improvements reduced the time and effort required to develop and optimize a chemical reaction for large-scale continuous production.

Keywords Process monitoring · Continuous flow reactor · Process analytical technology (PAT) · Raman spectroscopy

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Introduction

Continuous flow reactors (CFRs) are an emerging technology that offer several advantages over traditional batch synthesis methods, including more efficient mixing schemes, rapid heat transfer, and increased user safety [1–3]. CFRs are capable of producing thousands of pounds of target chemicals through scale-out of production by using multiple parallel flow reactors. Modular scale-out reduces extensive engineering challenges associated with the scaling-up of a pilot batch reaction to a larger production volume. For example, if a CFR yields 1 ton of target product per year, 100 identical, parallel systems would yield 100 tons of target product per year with no reaction adaptation required [4]. To achieve a similar increase in production using a batch reactor would require extensive engineering and adaptation to account for the extensive changes in heating and mixing profiles.

Currently, quantitative quality confirmation of chemical synthesis on flow reactors largely requires off-line validation [5–8]. This requires acquiring an aliquot from the reactor and performing quantitative analysis using the appropriate off-line instrument. The delay between the formation of product and the determination of product quality, negatively affects the ability to make informed process control decisions. The longer