Process Analytical Tools for Flow Analysis: A Perspective

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Received: 17 November 2017; accepted: 20 November 2017

1. Introduction

Continuous-flow manufacturing is an attractive alternative to traditional batch processes as it affords the potential for a more flexible approach to manufacturing. This is particularly relevant in the pharmaceutical industry where the increased potency of new active pharmaceutical ingredients (APIs) means that smaller quantities of drug are required to deliver the desired therapeutic outcome [1]. In addition, continuous manufacturing limits the risk of large batch failures and opens up the possibility of just-in-time manufacturing for compounds that have a limited shelf life [2]. Just-in-time manufacturing could significantly reduce production costs for APIs and is expected to make continuous manufacturing an attractive alternative for drug manufacturing. The focus of this article is to review the present and future roles of flow analysis for reaction control and monitoring in small molecule fine chemical synthesis.

At present, pharmaceuticals are largely manufactured in batch reactors. Stringent rules are in place to regulate all manufacturing practices ranging from the synthesis of the API to the formulation of pills. Regulatory agencies (e.g., the United States Food and Drug Administration [USFDA], Pharmaceuticals and Medical Devices Agency [PMDA], Health Canada, and others) continue to provide valuable guidelines to ensure that the manufacturing methods do not adversely impact the ultimate pharmaceutical product. There has been a paradigm shift in pharmaceutical drug manufacturing in the current decade towards cleaner and more efficient manufacturing processes. In 2015, Vertex pharmaceuticals received the first new drug application (NDA) approval for using continuous manufacturing technology for the preparation of Orkambi™, a mixture of lumacaftor and ivacaftor (Figure 1) [3]. Soon after, Janssen, a pharmaceutical company of Johnson & Johnson, was awarded with the first NDA supplement approval for switching from batch production to continuous manufacturing for Prezista®/darunavir, a USFDA-approved drug for human immunodeficiency virus (HIV) treatment (Figure 1) [4]. Fundamentally, the expectations from batch and continuous productions have not changed; both production methods are required to deliver APIs in their purest possible form. However, continuous manufacturing, which is based on dynamic flow technology, must be subjected to continuous monitoring to ensure that the production conditions are not compromised over time.

There have been significant advancements in the area of flow analysis research [5]; however, there is a disconnect between integration of the best-suited flow analysis technologies with the best available flow reactor technologies. For example, reactor technologies that primarily deal with the flowability of matter under harsh reaction conditions have evolved significantly. It is now possible to conduct flow reactions under very high temperature and pressure [6–10] with and without introducing restrictive flow-path technologies, both of which have noteworthy merits based on the nature of the flow application [11]. Almost all sources of radiative and convective energy have been applied to flow reactors, delivering fast and efficient access to a wide range of reaction conditions [12–14]. Depending on the intensity of the supplied energy, phase transitions (e.g., liquid to gas or solid to gas) are possible in the reactor and so high-pressure flow reactors were introduced to prevent reagents undergoing undesirable phase transitions during heating. Conversely, the vast majority of advanced flow analysis technologies are still suited to ambient temperature and pressure conditions. Most analytical samplers, which bridge the fluidic gap between the reactor and the analytics, are not compatible with reaction matrices that may contain solids or gases, common by-products of typical organic reactions. Therefore, an effective overlap between flow reactor technology and flow analysis is a necessity, especially when the regulatory agencies are seemingly urging inventors to come up with new technologies for better control of continuous manufacturing. To achieve this, in 2004, the USFDA introduced the Critical Path Initiative, which was designed to monitor existing and emerging technologies in manufacturing sectors and to identify areas of product development in need of improvement. Process analytical technology (PAT), which is defined as "a system for designing, analysing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality," was proposed by the USFDA soon after [15]. In essence, PAT aims to establish a standard for product quality by careful regulation of manufacturing standards to eliminate preventable risks in pharmaceutical products originating from the manufacturing conditions. PAT-enabled tools are defined as tools that allow process understanding for scientific, risk-managed pharmaceutical development, manufacture, and quality assurance. The guidance for pharmaceutical development in ICH Q8 (International Conference on Harmonization of technical requirements for drugs) calls for continuous process verification wherein manufacturing process performance is continuously monitored and evaluated as opposed to full-scale singular batch verification methods, which are essentially treated as pass-fail qualifiers for an entire batch of API. In continuous format, the risk of losing an entire batch due to a single failure is somewhat mitigated as the effluents in the flowed format are tested at regular intervals to monitor a compartmentalized portion of the production stream over a time period. Real-time release testing (RTRT), which is also included in ICH Q8(R2) [16], was proposed to evaluate the quality of in-process and/or final product from continuous manufacturing and to ensure that the quality standards are met during a production run [17]. The ultimate goal for a RTRT-enabled PAT tool is to reliably extract and analyze a sample from flow reactors in order to ascertain that the process parameters that are critical to the fate of the product (critical process parameters; CPP) are kept unchanged over a selected period of time during a production run. According to document 21 CFR 210.3, the current definition of a "lot" is "a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit time or quantity in a manner that assures its having uniform character and quality within specified limits." [17] Identification of CPP for a process (batch or continuous)

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DOI: 10.1556/1846.2017.00032

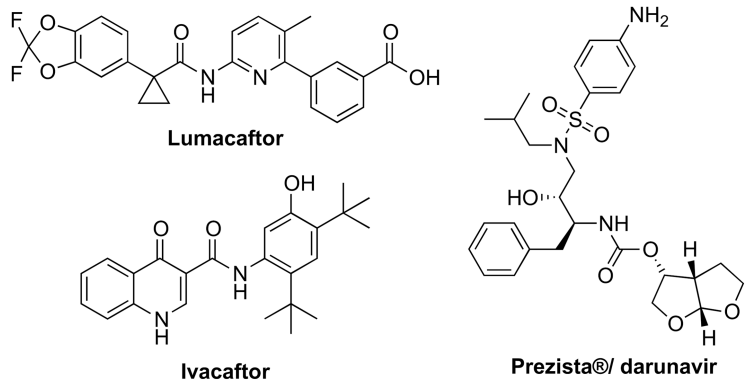

Figure 1. Structure of lumacaftor/ivacaftor (Orkambi™) and Prezista®

relies on the ability to measure certain critical quality attributes (CQA). For continuous-flow formats, the measurements of CQAs are expected to occur in real time as per the suggested guidelines for RTRT. It is important to note that the ultimate objective of including PAT in flow analysis is to transform continuous-flow chemistry from a cutting-edge research science to an alternative production platform for industrial applications. The objectives can be summarized in 5 steps:

- Development of on-line, in-line, and at-line measurement tools to improve production quality and consistency. This could be achieved using an automated sample withdrawal mechanism using either an array of fluid diverting devices [18–23], or by directly inserting an analytical probe in the reactor flow-path [24–28]. A PAT tool that includes a fluid diversion mechanism could be used to extract a sample for analysis at the completion of a flow experiment either from an offline analytical setup or at-line using a local analytical instrument. Manual interference is needed in both which may also include a sample preparation step prior to the analysis. The fluid diverting device can be also placed between the flow reactor and a bulk product collection vessel, so a sample can be analyzed in-line. Alternatively, a detector probe can be placed directly in the flow-path of the reaction mixture to obtain reaction information real-time.
- Development of real-time release testing (RTRT) to ensure the quality of in-process and/or the final product. The strategy currently relies on the ability to communicate with all analytical tools from a single platform or software. Inline strategies, when integrated to a suitable controller for automations, can qualify as an online PAT tool for flow analysis. A universal online PAT-enabled flow-analysis tool, in theory, could allow flow analysis to be free from human errors and traceable in accordance with the guidelines of data integrity by the USFDA. Introduction of online flow-analysis strategies would also allow computer scheduling of high frequency sampling thereby drastically increasing overall sensitivity in the purity measurement of the bulk product. For example, an increase in sampling frequency could allow production scientists to detect traces of impurities at an early stage and reject non-conforming materials which can be temporarily held in compartmentalized confinement (e.g., a loop) until an analytical confirmation is received from the computer-controlled analytical platform [29].
- To prevent or limit rejects and batch re-processing. Online feedback in continuous flow could help to prevent contamination of an entire batch by simply diverting the contaminated reactor stream into a different flow path. Additionally, small segments of effluent stream could be isolated and assayed in a "pre-lot" before they are added to the main reactor output, if the desired analytical purity is achieved [20].
- Another aspect of PAT-enabled inline or online tools lies in the ability to perform multi-variate analysis of multiple quality attributes in parallel. For example, information on reactor performance and product stability could be obtained in parallel thereby lowering the risk of pursuing an undesirable design space during the early phase of the drug discovery. Quality-by-design (QbD), which is gaining widespread popularity in current manufacturing practices, would be ideally included in the campaign for online PAT strategies for flow analysis [17].
- Increase the use of automation to improve operator safety. Two key advantages in flow chemistry lie in the ability of the reaction format to give products just in time and on-demand. Online automated analysis technologies, which would eliminate the need for human interference, would enable scientists to synthesize chemical entities that are challenging to prepare under current manufacturing practices.

2. The Current State: Flow Chemistry and Flow Analysis

Conducting a flow reaction under high pressure or using a multiphase reaction mixture is viewed as difficult, but attainable. As previously outlined (vide supra), flow reactor technologies have advanced considerably in the last decade to allow the application of forcing reaction conditions to flow streams. However, the scarcity of suitable PAT tools for pharmaceutical processing that are operational under the reaction conditions and reliably provide information on the state of matter inside the flow reactor is a significant drawback for flow chemistry as a routine process development platform. There are examples of high-pressure and high-temperature sampling tools that are capable of handling challenging conditions in other sectors (e.g., petrochemicals [30]). However, because the pharmaceutical industry typically utilizes a significantly larger range of functional groups, and a wide variety of organic and inorganic reagents, there is still a need to develop a universal PAT solution for pharmaceutical manufacturing.

Recently, there have been enormous advances in the availability of emerging analytical technologies from injections [31] to detection [5]. Sensitivity and resolution of analytical data originating from modern analytical instruments has reached a level where it is possible to detect chemicals at very low concentrations meaning higher purity products and safer chemical processes. However, analytical products evolved independently of PAT and so a disconnect remains between the analytical technologies available to a researcher and PAT enabled tools. One of the primary criteria of qualifying a technology as a PAT tool for flow-analysis lies in its ability to tolerate a wide range of chemicals and also function in the presence of all phases (i.e., solids, liquids, gases and mixtures). There are up to two crucial steps for the analysis of a sample from a flow reactor, namely, sampling and analysis. For flow experiments where analysis is performed directly using an inline probe at the flow-path of the reactor, a sampling step is not necessary. However, this strategy requires