

ABSTRACT

To apply Industry 4.0 technologies and accelerate the modernization of continuous pharmaceutical manufacturing, digital twin (DT) and advanced process control (APC) strategies are indispensable. The DT serves as a virtual representation that mirrors the behavior of the physical process system, enabling real-time monitoring and predictive capabilities. Consequently, this facilitates the feasibility of real-time release testing (RTRT) and enhances drug product development and manufacturing efficiency by reducing the need for extensive sampling and testing. Moreover, APC strategies are required to address variations in raw material properties and process uncertainties while ensuring that desired critical quality attributes (CQAs) of in-process materials and final products are maintained. When deviations from quality targets are detected, APC must provide optimal real-time corrective actions, offering better control performance than the traditional open loop-control method. The progress in DT and APC is beneficial in shifting from the paradigm of Quality-by-Test (QbT) to that of Quality-by-Design (QbD) and Quality-by-Control (QbC), which emphasize the importance of process knowledge and real-time information to ensure product quality.

This study focuses on four key elements and their applications in a continuous dry granulation tableting process, including feeding, blending, roll compaction, ribbon milling and tableting unit operations. Firstly, the necessity of a digital infrastructure for data collection and integration is emphasized. An ISA-95-based hierarchical automation framework is implemented for continuous pharmaceutical manufacturing, with each level serving specific purposes related to production, sensing, process control, manufacturing operations, and business planning. Secondly, investigation of process analytical technology (PAT) tools for real-time measurements is highlighted as a prerequisite for effective real-time process management. For instance, the measurement of mass flow rate, a critical process parameter (CPP) in continuous manufacturing, was previously limited to loss-in-weight (LIW) feeders. To overcome this limitation, a novel capacitance-based mass flow sensor, the ECVT sensor, has been integrated into the continuous direct compaction process to capture real-time powder flow rates downstream of the LIW feeders. Additionally, the use of near-infrared (NIR)-based sensor for real-time measurement of ribbon solid fraction in dry granulation processes is explored. Proper spectra selection and pre-processing techniques are employed to transform the spectra into useful real-time information. Thirdly, the

development of quantitative models that establish a link between CPPs and CQAs is addressed, enabling effective product design and process control. Mechanistic models and hybrid models are employed to describe the continuous direct compaction (DC) and dry granulation (DG) processes. Finally, applying APC strategies becomes feasible with the aid of real-time measurements and model predictions. Real-time optimization techniques are used to combine measurements and model predictions to infer unmeasured states or mitigate the impact of measurement noise. In this work, the moving horizon estimation-based nonlinear model predictive control (MHE-NMPC) framework is utilized. It leverages the capabilities of MHE for parameter updates and state estimation to enable adaptive models using data from the past time window. Simultaneously, NMPC ensures satisfactory setpoint tracking and disturbance rejection by minimizing the error between the model predictions and setpoint in the future time window. The MHE-NMPC framework has been implemented in the tableting process and demonstrated satisfactory control performance even when plant model mismatch exists. In addition, the application of MHE enables the sensor fusion framework, where at-line measurements and online measurements can be integrated if the past time window length is sufficient. The sensor fusion framework proves to be beneficial in extending the at-line measurement application from just validation to real-time decision-making.