REVIEW PAPER

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Energy efficient smart manufacturing of pharmaceutical solid oral dosage forms

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ABSTRACT

The global pharmaceuticals market is a trillion-dollar industry which grows more than 5% annually. However, in comparison to other manufacturing industries (e.g., oil refining, automotive), the pharmaceutical sector lags in manufacturing innovation and automation. In the production of pharmaceutical solid dosage forms, the use of energy utilization as a performance measure of production efficiency has neither been implemented extensively, nor been optimized to maximize efficiency. This study will focus on the development and implementation of a smart manufacturing platform to optimize energy productivity whilst maintaining tablet quality via the consideration of different manufacturing scenarios.

This study will consider three main unit operations (wet granulation, drying and milling) which are relatively more energy intensive in pharmaceutical downstream processing, used to produce solid dosage forms, such as tablets. Four case-studies will be considered, which are 1: baseline batch, 2: baseline continuous, 3: optimized batch and 4: optimized continuous. Smart manufacturing is implemented to present optimized cases 3: and 4: Improvements in the energy and performance metrics are quantified and compared to the baseline cases.

The smart manufacturing platform used in this study, integrates advanced process model development, optimization, technoeconomic analysis and data integration. The utilization of this framework contributed to a ~70% and ~80% improvement in energy utilization in the optimized batch and continuous cases, respectively, when compared to the baseline batch case. In the optimized cases, tablet quality was maintained within targeted specifications and was comparable to the baseline batch case. This smart manufacturing framework can be generalized for drug product manufacturing and other particulate-based industries such as food, agriculture, and fine chemicals.

Introduction & objectives

The pharmaceutical industry is currently undergoing a paradigm shift in manufacturing practices, going from batch to continuous, where improvements in product quality and healthcare are largely anticipated [1–3]. The impact of continuous manufacturing (CM) is evidenced by data

showing that on an average, product development is 3 months faster for time to approval and 4 months faster for time to market. This translates to ~$171-$537M USD in early revenue [4]. Data also shows that there are no substantial regulatory barriers to the transition from batch to CM, in terms of pre-approval inspections [4]. It should be noted that there could be additional energy consumption costs for scale-up of batch process operations which could be significant compared to continuous process operations which typically not require substantial scale-up. For optimal operation of CM processes, advanced process modeling, optimization, and smart manufacturing (SM) capabilities need to be integrated into the manufacturing platform [5–7]. The benefits of such an integrated system includes faster time-to-production of high-quality tablets which can be manufactured with minimal energy utilization [8]. The overall impact would be the development of an agile and flexible manufacturing process that is robust to market changes [1]. The overall objective of this study is to adopt a SM framework in process development phase via the use of advanced process models, sensors and data integration architecture and optimization of key pharmaceutical performance metrics such as energy and quality. The development of an advanced process modeling framework that is integrated with a smart manufacturing platform capable of data integration will ultimately lead to process intensification of production which could lead to overall reductions in cost and carbon footprint. This will be accomplished via an advanced process modeling framework that is integrated within a smart manufacturing platform.

Methods

Solid oral drug product manufacturing involves a sequence of unit operations that transforms powders into tablets. These processes start from material (active pharmaceutical ingredient and excipient) feeding and ends with tablet compaction and coating, where the final drug form is tested for its dissolution performance. The four major routes in solid drug product manufacturing are direct compaction, dry granulation, wet granulation, and spray drying (**Figure 1**). For this study, the wet granulation route was chosen due to its higher energy utilization compared to the other routes, due to the presence of larger amounts of motors, compressors and heating elements which are highly energy intensive [9]. Within the wet granulation configuration, the unit operations of granulation, drying and milling were focused on as case-studies to improve energy efficiency.

Four manufacturing cases were established for this study, all of which were performed at Rutgers University. These were cases 1: baseline batch, 2: baseline continuous, 3: optimized batch and 4) optimized continuous. Cases 1: and 2: represent the current state-of-the-art batch and continuous manufacturing processes in the pharmaceutical industry, respectively. These cases represent typical scenarios whereby the processes development is focus on achieving product quality compliance with minimal regard to any other performance metric such as energy. Cases 3: and 4: represent optimized versions of cases 1: and 2: respectively, which implemented the smart manufacturing framework involving advanced process modeling, optimization, techno-economic analysis, and data integration [5, 8]. Here we will focus on developments in advanced process modeling and data integration in a smart manufacturing platform.

Figure 2 demonstrates the advanced process modeling framework which was developed. Levels 1, 2, and 3 represents the incorporation of process parameters, material attributes and design properties in the model equations, respectively. In this study, we will implement a Level 1–2 model representation of the granulation, drying and milling unit operations.

The framework combines a modular development of intermediate, output, process and product models that are ultimately integrated to simulate product performance at each stage of the unit operations. Intermediate models are model representations that provide a quick estimation of output that is usually not measured and is only an indirect and/or partial indicator of product quality. Output models are model representations that take input from intermediate models and predict process outputs that can be measured but are not a descriptor of product quality. Product models are model representations that take input from output models and predict metrics that are direct indicators of product quality.

Subsequently, a smart manufacturing compliant data management framework (**Figure 3**) was developed. Different types of data were first collected using on/in/at/off-line methods, at the process and analytical equipment level and spectral data were pre-preprocessed via statistical algorithms to provide product quality data. These data were then sent to either an electronic laboratory notebook (ELN) or a data historian via a control platform, depending on the method of data acquisition. All data

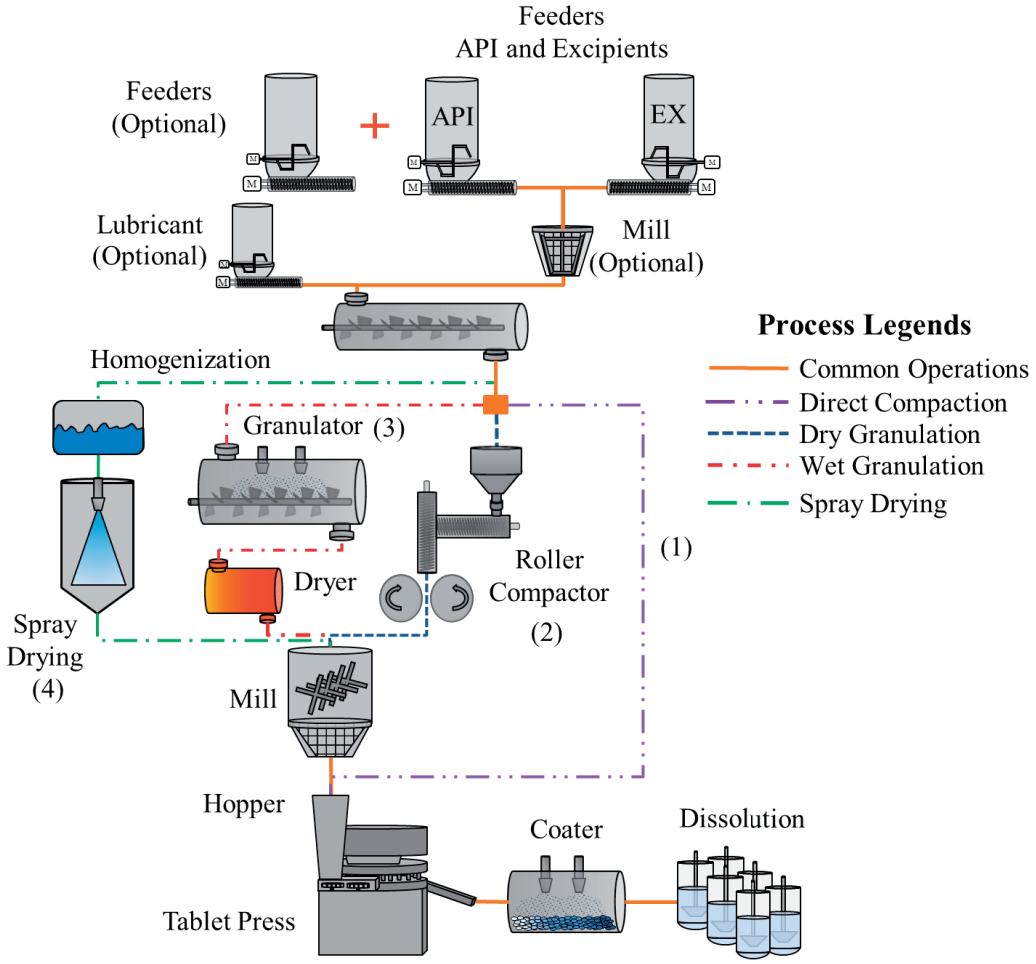

Figure 1. Schematic of drug product manufacturing routes.

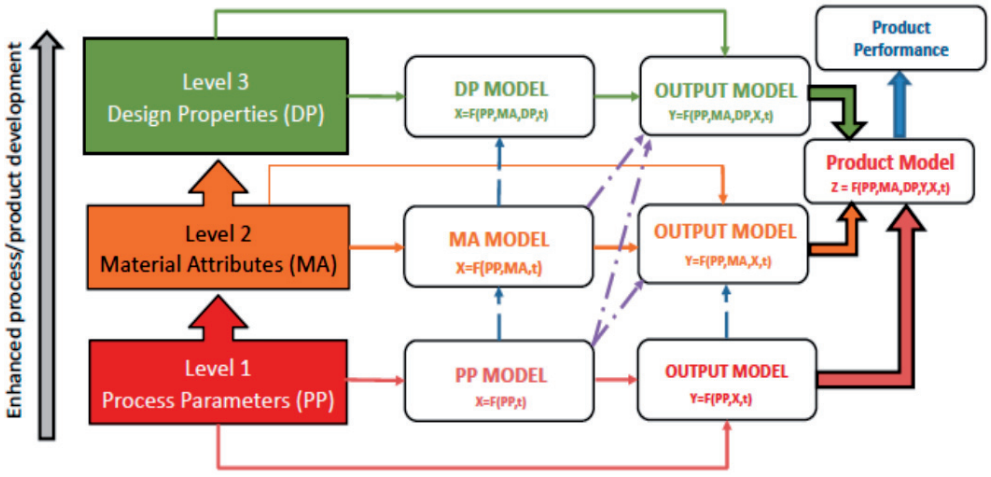

Figure 2. Advanced modeling framework.

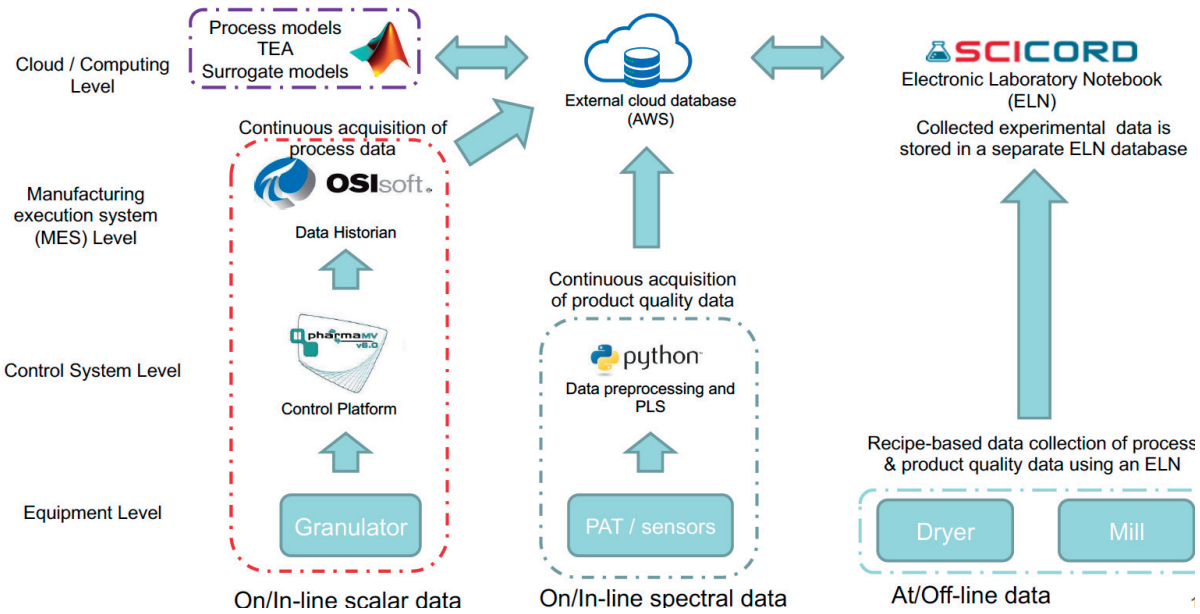

Figure 3. Smart manufacturing compliant data management framework.

was then made accessible through a cloud-based repository whereby the model, optimization and techno-economic algorithms were also implemented and deployed. In such a manner, the framework is bi-directional and can utilize in-process data for model calibration, verification, refinement etc., and the model can then be optimized. Real-time data can be accessed through the cloud, to be used for model predictions and optimization, which can provide updates to process for any necessary course correction required to continue production of tablets within desired specifications.

Results and conclusions

Results from technoeconomic analysis [5, 10] confirmed that the energy requirements for a baseline batch case is ~6K GJ/year. With the use of advanced model development and data integration framework from which optimization was performed, improvements to the energy utilization were made. The experimentally verified advanced process models, which contained both product quality and energy models, provided a framework for optimization, where the optimal operating conditions for the processes that led to energy reduction was identified. These include a 25.6% energy reduction from baseline batch to baseline continuous, a 71.7% energy reduction from baseline batch to optimized batch and an 83.3% energy reduction from baseline batch to optimized continuous. In all cases, the product yield and drug release kinetics of the tablets (demonstrated through USP standard dissolution testing) produced were similar, confirming that tablet quality was maintained. Other metrics such as time-to-market of key therapeutic drugs will also be minimized Such innovations can also be adapted to other similar manufacturing industries such as biologics, food, and fine chemicals.

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Conflict of interest statement
The authors declare no conflict of interest.

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