Modelling Continuous Pharmaceutical and Bio-based processes at plant-wide level: A Roadmap towards Efficient Decision-making

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Abstract

The importance of developing simulation models for decision-making in pharmaceutical and bio-based production processes is elaborated in this article. The advantages of modelling continuous processes are outlined and certain barriers in this regard are identified. Although there have been some advancements in the field, there needs to be a larger international collaboration in this regard for providing reliable data for model validation, for development of generic model-based frameworks and implementing them in computer-aided platforms in the form of software tools.

Introduction

Tight regulations together with rising cost of the R&D and production have been a driving force for the pharmaceutical and bio-based industries to seek and adopt more flexible and viable synthesis and purification alternatives, reliable Process Analytical Technologies (PAT) and robust control and monitoring strategies. Many pharmaceutical and bio-based production processes (where upstream is a fermentation or cell culture) are operated in batch mode, and producing high value products from relatively low value raw materials. These processes have typically been scaled up from lab/bench scale with no particular attention paid to improving process throughput and efficiency, recovery or decreasing the overall materials and energy consumption due to the lucrative economics. However, the dynamics of pharmaceutical and bio-based manufacturing are evolving rapidly. Firstly, the costs related to bringing in new drugs have been increasing over time [1] while the time required to get a drug approved is considerable. In addition, generic pharmaceutical and bio-based manufacturing introduces increased competition between various stakeholders by drastically lowering operating costs. Hence, these processes need to adapt new and improved process alternatives such as continuous production towards increased viability, which in turn requires considerable input from process engineers and highlights the importance of process models and simulations in this field.

Effective management and decision-making ensures a reduction in product development costs while reducing the time from discovery of an active pharmaceutical ingredient (API) to establishing a process. In this respect, following the old management adage that says, “You Can't Manage What You Don't Measure” many process efficiency metrics were defined to indicate the performance of the process in terms of, yield, waste generation, solvents and water usage [2]. Furthermore, to achieve more sustainable process options, different, so called green or sustainability metrics are used, with e.g. E-factor [3] and Process Mass Intensity (PMI) being among the most frequently used ones [4]. However, there is a lack of consensus to what extent one should consider an “end-of-pipe” metric reliable and whether a given metric is a better indicator than

some other indicators. It has been shown that often a combination of different indicators are needed [5] to ensure high efficiency of a “green” pharmaceutical process. This is especially a relevant paradigm shift from ‘‘toxic by design’’ to ‘‘benign by design’’ which pushes pharmaceutical industries for more sustainable designs at all stages of development, from conception (low technology readiness levels – TRL) all the way to full-scale implementation and production (very high TRL) [6]. These indicators are helpful to achieve short-term or unit specific initiatives; for example, choosing the right solvent or a solvent swap. Seen from a broader perspective, data analysis would help to distinguish, compare and contrast different chemistries [5]. However creating a comprehensive data catalog for such analysis requires lots of testing and data collection. Moreover, these metrics report on overall process performance in an abstract way and cannot be used as an effective tool for diagnosis and process performance analysis. Hence, as an alternative there have been suggested a number of mathematical models to simulate the pharmaceutical production, predominantly batch processes. Such models can then be used to assess the impact of design parameters; for example, residence time of each production unit, purge ratio on production, the amount of impurities (also byproducts) and yield [7–12]. Furthermore, various tools have been developed to improve the quality of pharmaceutical products including rules of thumb, heuristic techniques or advanced model-based control strategies [13]. However, in view of recent process developments, there is now a need for comprehensively using current state-of-the-art towards developing plant-wide models that can be efficiently used for decision-making.

Why continuous process modelling?

The ever-increasing demand for improved process understanding together with the quest for economically efficient operations makes continuous production in pharmaceutical and biopharmaceutical processes both a necessity and a realizable concept. The development and implementation of these pharmaceutical and biopharmaceutical processes requires a systematic approach that explores a wide range of variations. The advantages of continuous pharmaceutical production over batch operation have been discussed frequently, and include reducing wastes production, product variability and energy consumption as well as enhancing process reliability and flexibility [14,15]. However, carrying out extensive experimentation on bench, pilot and full scale to validate and develop a continuous pharma or biopharma process is impractical due to the associated cost. In fact, the integrated continuous production of API is not widely investigated because of the inherent challenges (e.g. lack of process understanding, technology readiness, mindsets). Nevertheless, continuous secondary manufacturing is increasingly investigated and implemented in industry [16]. At the research level, there exist many modelling frameworks supporting operation and control of batch pharmaceutical production, while there has been no significant progress for continuous operation in terms of predictability and resilience of process components. In the traditional chemical and fine chemical production the use of process models and simulation is widespread, with both academia and industry using these process models for control, design and optimization of whole processes. In these industries, process models play an important role in improving process efficiency through more optimized process designs that increase process throughput and recovery while decreasing the overall energy and materials usage. In comparison, the modelling of continuous pharmaceutical and bio-pharmaceutical processes is still at its infancy. In fact, a plant-wide approach for process monitoring and modelling for continuous pharmaceutical production is not yet well realized. Benyahia et al. [11] have developed a process model of a continuous pharmaceutical production process which is also validated against a pilot scale production facility. Such model describes the plant-wide dynamics and can predict the transient response e.g. start-up and shut

down. It also provides effective opportunities for investigating control of critical quality attributes and to evaluate safety and plant operability.

Towards plant-wide model simulation

Looking at the existing challenges in continuous production of pharmaceuticals (for example, supplementing new knowledge for process and product development), developing a plant-wide and systems approach is necessary for efficient process design and operation. Such a comprehensive modelling approach requires a flexible and robust modelling framework allowing plug-and-play development of various models for the purpose of design analysis and control. A design space for pharmaceutical production should be developed such that the optimal operational strategy can be implemented without the need for process validation. These frameworks, such as the Benchmark Simulation Model №2 [17] for wastewater treatment plants, would allow evaluation of control strategies at the level of the whole plant. For pharmaceutical product-process design Gernaey and Gani [10] have introduced a model-based framework including 4 components, i.e. modelling tool, knowledge base, computer-aided methods and tools as well as a user-interface. This general framework can include components for plant-wide uncertainty analysis and for debottlenecking studies using simulations.

Figure 1 illustrates the plant-wide simulation model to be used as a decision making tool for process development in pharmaceutical and bio-based production processes. As depicted in this figure, the models can be classified into three categories. The first set of models describe physical unit operations such as mixers and filters, the second set describe chemical unit operations such as crystallizers, emulsifiers, ion-exchange separations, etc.; and the third set describe biological unit operations such as fermentation and cell culture. The usability of such a plant-wide model largely depends on availability of data. Moreover, the possibilities for application of process analytical technologies (PAT) can be explored for various operating modes using such models. One important feature of a continuous process is the possibility of recycling un-reacted raw materials and reagents for reuse within the process. This feature is often crucial in reducing operating costs, and a plant-wide model provides the possibility of exploring recycling and resource recovery options without requiring excessive experimentation. However, such an exploration also means added complexity for PAT development and control strategies.

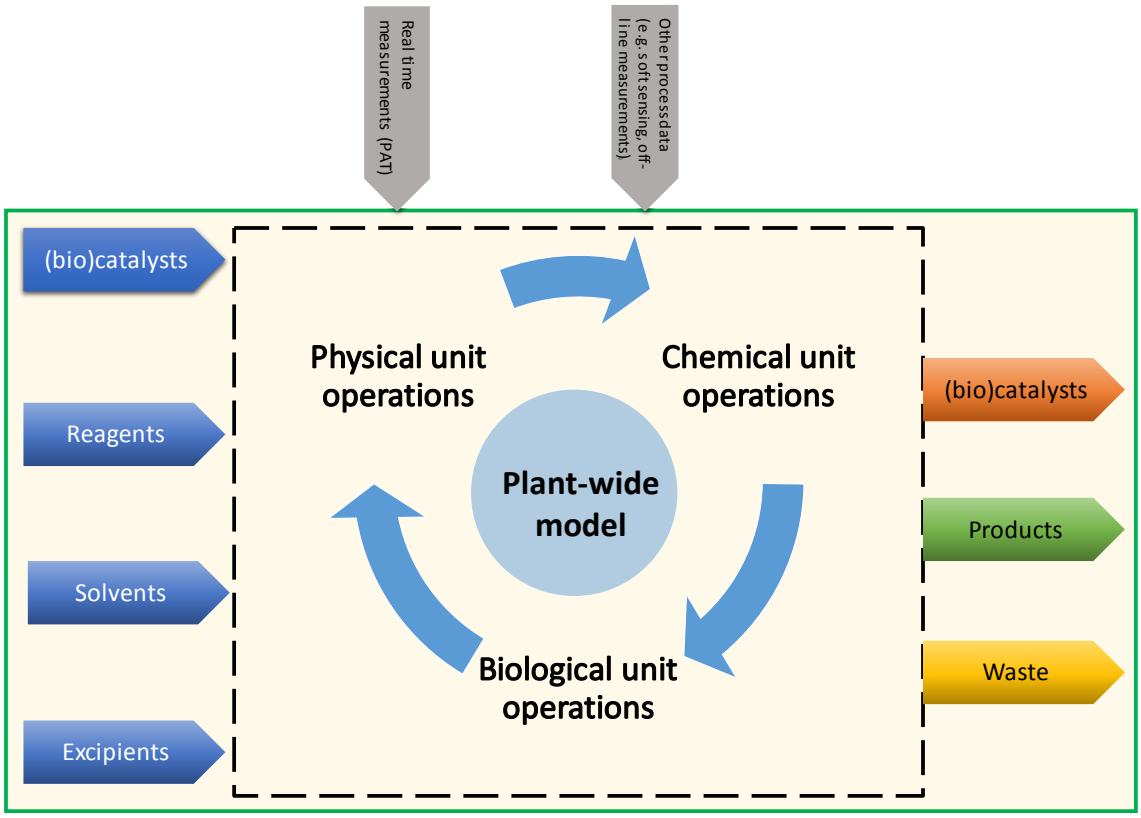

Figure 1: An overview of the components of a plant-wide model

Future perspectives

Currently there are a handful of applications in pharmaceutical and biopharmaceutical processes that are implemented in industry where some elements of continuous processing are used in primary production. However, there have been notable joint academic and industry collaboration projects that have developed continuous pharmaceutical manufacturing processes in pilot scale, such as the MIT-Novartis collaboration. Based on this pilot scale facility, Benyahia et al. [11] have developed a validated process model of a continuous pharmaceutical process which can be considered as a benchmark process model, as it is the only complete end-to-end dynamic model that is publicly available in the literature. However, the developed model is addressing an application for organic synthesis of an API, while there remains a lack of such models for bio-based production processes, i.e. processes where the upstream part contains a bioreactor.

With the ever-increasing drive by pharmaceutical and bio-based manufacturers to transition into continuous production, the importance of process models and simulations will continue to grow. In pharmaceutical manufacturing, there are established process models that can be used as a base case or a benchmark. However, in comparison to the petrochemical and fine chemical industries, the process models available for pharmaceutical processes are limited. Hence, there is a need to further develop process modelling and simulation capabilities for pharmaceutical processes. As we see it, the following would be required:

- Process models currently available should be extended to include alternative unit operations such as in-situ bioconversion of impurities to enhance separation processes.
- Develop a process simulation environment which can be used to “build” a process model of a continuous pharmaceutical production

In comparison, there are no such process models within biopharmaceutical manufacturing, which hinders the refinement of biopharmaceutical manufacturing processes including the transition towards continuous manufacturing. The authors involved in this manuscript have identified this shortfall and are currently working together with industrial and academic partners to address this gap. The development of a process model and simulations for biopharmaceutical manufacturing processes is complicated by the following factors which need to be addressed:

- Lack of common process steps/methodologies in the manufacturing steps
- Difficulty in capturing the complexities of biological pathways involved in reactions
- A lack of comprehensive feed characterisation abilities, especially with micronutrients.
- Variable residence time for different unit operations and often long residence time required for biological reactors

Based on these gaps the authors of the manuscript are currently developing an open source collection of process models (BIOPROSim) as part of the BIOPRO strategic research initiative (www.biopro.nu). The BIOPRO strategic research initiative is a close collaboration between Danish industry and academia in the area of bio-based production. To develop this open collection of process models the following aspects need to be addressed

- A process modelling environment that allows unit operations to be easily changed and deleted to match a particular biopharmaceutical process
- An international collaboration (beyond the BIOPRO collaborators) to map the unit operations
- Industrial collaborations and generic industrial data to validate unit operations.
- Developing more advanced online process analytical technologies
- Designing more smart green processes.
- Compatibility with some of the existing platforms such as VPPD-Lab [18]

Conclusions

Using a plant-wide model, it is possible to assess the environmental impact of the production line beyond the common sustainability metrics. It would help waste-management schemes at each production step not to use only the end-of-pipe indicators. Furthermore, such model provides the possibility of exploring different operating modes, recycle loops and control strategies along with developing PAT alternatives. In future, there is a need for a closer collaboration between academia and industry to systematically develop and validate such models for both pharmaceutical and bio-based production processes.

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