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PSE PRESS

Process analysis of end-to-end continuous pharmaceutical manufacturing using PharmaPy

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ABSTRACT

As pharmaceutical manufacturing is transitioning from traditional batch to continuous manufacturing (CM), there is a lack of tools for CM design and development, which can integrate drug substance and drug product unit operations for overall evaluation. Recently, a Python-based PharmaPy framework was proposed to advance the design, simulation, and analysis of continuous pharmaceutical processes. However, the initial library of models only addressed upstream drug substance processing. In this work, new capabilities, including drug product unit operations such as feeder, blender, and tablet press, have been added to the PharmaPy framework, enabling end-to-end study and optimizing the effects of material properties and process conditions on solid oral dosage products. The platform supports computational efficiency and model accuracy by allowing the development of different mechanistic and semi-mechanistic models. Sensitivity analysis is performed on the integrated end-to-end simulator to identify critical input variables influencing product quality and control strategies. The analysis lowers the complexity of the model by ranking significant input variables. Finally, feasibility studies are conducted on extracted influential input variables to characterize the process design space and achieve desirable output. The enhanced PharmaPy package can now support decision-making from early research and development stages through manufacturing.

Keywords: PharmaPy, Process synthesis, Process analysis, Pharmaceutical manufacturing

INTRODUCTION

The pharmaceutical regulatory agencies have recognized the need to transition from batch to continuous mode of operation due to its various advantages. Among the several benefits that drives continuous process includes scalability, increase in controllability, reduction in time to product release in the market, product quality consistency, and potential reduction in human involvement and capital costs. These advantages contribute to increased adaptability, agility, and robustness in the continuous manufacturing of pharmaceuticals. At the same time, it also provides a great opportunity for practitioners to develop continuous and efficient manufacturing processes for pharmaceutical production [1].

However, the strict regulatory mechanism of the pharmaceutical industry draws multiple challenges in this transition. In this work, we consider the integration of drug substance process, i.e., active pharmaceutical ingredient (API) manufacturing, with the drug product operations for solid oral-drug production, i.e., tablets. For the end-to-end continuous operation, the first challenge lies in the physics and chemistry-based constraints that may decide the best operation mode for the manufacture of a given API. The API manufacturing process also needs to have necessary control on the raw material properties. In addition, the optimal manufacturing route should be determined based on the process economics and the adoption of effective separation and purification steps to achieve desired API quality attributes. The second challenge is to understand the effects of material attributes on powder flowability and process dynamics between unit operations for drug product manufacturing. Finally, the process design, analysis, and optimization of the integrated process need to be performed through a systems approach which would study the effects of material properties, equipment, and process parameters on the product qualities [2]. Such an integrated system should

also be developed within the quality-by-design (QbD) or quality-by-control (QbC) framework for the construction of design space regions that ensures final product quality.

To address the aforementioned challenges, recently PharmaPy, an open source pythonic framework for flexible flowsheet modeling and simulation of discrete/continuous processes for pharmaceutical manufacturing, was developed [3]. The framework supports parameter estimation and process optimization and adopts a sequential-modular approach towards integrated simulation for drug substance. However, the goal of end-to-end continuous manufacturing using PharmaPy was unrealizable due to the absence of downstream drug product operations. In this work, new capabilities are added to the existing PharmaPy tool, and the drug product framework is presented to integrate and study the effects of raw materials, upstream processes on final product quality. The enhanced PharmaPy framework will act as a complimentary open-source platform to existing commercial flowsheet simulation tools such as Aspen Plus and gPROMS by providing flexible user control while ensuring adequate model fidelity and numerical accuracy.

PHARMAPY FRAMEWORK

PharmaPy is a Python software application that makes use of the language's versatile scripting features and incorporates powerful computational libraries for flowsheet modelling [3]. Several in-built models in the open-source package are drawn as standard unit operations for the manufacture of drug substances and products. Furthermore, it offers the flexibility to design and accommodate customized user-generated unit operation models. These standard (and user-defined) models are used as building blocks to construct the integrated flowsheet models. PharmaPy can be used for simulation, design and optimisation of pharmaceutical manufacturing processes. It uses a sequential-modular equation solving approach and an object-oriented software architecture, which enable to perform efficient process simulation and flowsheet optimization. PharmaPy has been used successfully for drug substance manufacturing applications including its application in a simulation-optimization framework [4], and for techno-economic analysis of various flowsheet alternatives [5]. For the drug product manufacturing, which is the focus of this study, the extended PharmaPy framework adds the downstream processing units where the API is converted into final tablets.

The downstream PharmaPy implementation for flowsheet simulation and optimization starts with the input of API properties from the dryer unit operation which helps connect the upstream process with downstream operations (Figure 1). The dried API properties are estimated using the upstream PharmaPy framework [6] which also includes a filter and deliquorizer (DL) to reduce the liquid present in the pores of the filter cake. The final dried API information flows through the product operations which effects the final product quality. Other participating species such as excipients, lubricants/glidants and their material properties are also fed by the user to the downstream process. Next, the downstream unit operations and their connections are established using object-oriented programming. Following that, the flowsheet model can be executed to perform process simulation and process analysis.

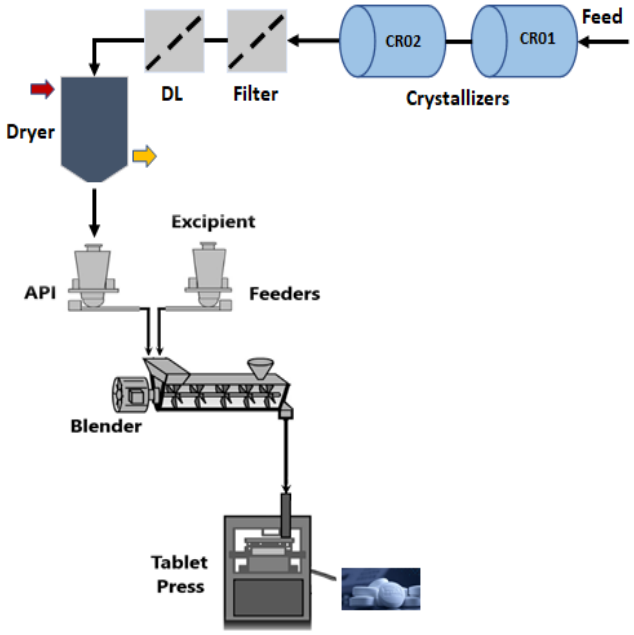

Figure 1. Integrated drug substance-drug product flowsheet used for simulation in PharmaPy (DL represents the deliquoring step in the filtration).

Ultimately, with the help of flowsheet optimization in the second theme which is still in development stages, the users can compare various manufacturing routes for tablet production in an automated framework. In the next section, the first theme of downstream PharmaPy is illustrated with the help of a direct compaction case study, which includes sensitivity analysis to investigate crucial input variables and feasibility studies to determine the process design space that ensures consistent product quality.

RESULTS & DISCUSSIONS

Case Study: Direct Compaction process

Direct Compaction (DC) process is a straightforward and popular tablet production method that directly uses the blended constituent materials and compresses them into tablets. It also requires fewer unit operations, which implies less equipment space and cost, less processing

times, lower manufacturing costs and improved productivity. In the DC process under consideration, the API from the drug substance operations and an excipient, which aids in the drug processing, are fed to loss-in-weigh feeders which deliver the materials at a desired flow rate. The API and excipient are then fed to a continuous blender to achieve a homogenous blend of the constituent ingredients. Finally, the well-mixed ingredients flow through a hopper to a rotary tablet press (TP), which fills the dies with blended powder where the tablet press compresses the mixture into tablets.

The PharmaPy package includes dynamic simulation of a variety of built-in models along with the flexibility to customize and construct their own functions. The flowsheet model includes semi-mechanistic, empirical, hybrid and data-driven models to estimate intermediate and final product quality. The unit operation models that are built and implemented for DC process are explained next.

Feeders

Gravimetric feeders known as "loss-in-weight" feeders use direct weight measurements of the material in the hopper to reach and maintain a pre-set flow rate. The feeder also consists of an impeller to assist material flow and a rotating screw which transports the material out of the feeder. Under the gravimetric mode, the flow rate is automatically controlled by adjusting the screw speed with the help of a PID controller according to the loss in weight of the materials in the feeder over time. A semi-empirical feed factor model is deployed in PharmaPy to model the feeder that accurately predicts the relation between the mass flow rate and screw speed of the feeder [7]. The following equations represent the functioning of the feeder module.

$$F_{out}(t) = ff(t)\omega_{screw}(t) \quad (1)$$

$$ff(t) = \rho_{eff}(t)V_{sp} \quad (2)$$

$$\rho_{eff}(t) = \rho_{sat} + (\rho_{in} - \rho_{sat})e^{-\frac{\sigma(t)}{\beta}} \quad (3)$$

$$\omega_{imp}(t) = \alpha\omega_{screw}(t) \quad (4)$$

$$\sigma(t) = \frac{W(t)g}{A_f} + \cos(2\pi\omega_{imp}t)\frac{M_b R_b \omega_{imp}^2}{A_{sp}} \quad (5)$$

where F_{out} is the outlet mass flow rate of API, excipient, etc. and ff is the feed factor, ω_{imp} and ω_{screw} are the impeller and screw speed, respectively, V_{sp} is the volume of the screw pitch, ρ_{eff} is the effective density of the material, σ is the vertical stress, β is the density constant, A_f is the feeder area, A_{sp} is the screw port area where screws enter the bowl, M_b and R_b are the mass and radius of the impeller blade, g is the gravitational constant, and W is the weight of powder in the feeder.

Blender

The continuous blender is used to reduce the variations which stems from the feeding system and plays a crucial role in maintaining strict quality constraints of the concentration uniformity in the blend and final product. The PharmaPy package uses a two-dimensional multi-compartmental model to describe the blender operation [8]. The model includes axial and radial directions of the compartments which is assumed to be equally sized and well mixed. The blend mass hold-up, flow rate from the blender, API composition and relative standard deviation of the blend samples are estimated using the compartmental model.

$$\frac{dm_{i,j}}{dt} = F_f(m_{i-1,j} - m_{i,j}) + F_b(m_{i+1,j} - m_{i,j}) + F_r(m_{i,j-1} - 2m_{i,j} + m_{i,j+1}) \quad (6)$$

$$F_f = a\omega_{blend} + b \quad (7)$$

$$F_b = c\omega_{blend} + d \quad (8)$$

$$F_r = e\omega_{blend} \quad (9)$$

$$F_{out,b} = \sum_{j=1}^{N_r} F_{f,API}\, m_{N_a,j}^{API} + \sum_{j=1}^{N_r} F_{f,EXCP}\, m_{N_a,j}^{EXCP} \quad (10)$$

$$C_{API} = \frac{\sum_{j=1}^{N_r} F_{f,API} m_{N_a,j}^{API}}{F_{out,b}} \quad (11)$$

where $F_{out,b}$ is the exit blend flow rate, $m_{i,j}$ is the mass hold-up in the ith axial and jth radial compartment, N_a and N_r are the number of compartments in the axial and radial directions. F_f, F_b and F_r are the forward, backward, and radial fluxes respectively, with a, b, c, d and e being the flux parameters, ω_{blend} is the blender speed, and C_{API} is the API composition in the exit blend.

Tablet Press

The incoming blend from the previous unit operation is transported through a hopper and feed frame to a series of dies where the blends are compressed into tablets. The die shape and tablet press process conditions determine the geometry and final quality of tablets. PharmaPy also includes a hopper and feed frame model to predict the hopper level (h_{hopper}) and feed frame flow (F_{fframe}) into the dies. The tablet press functions in two stages, namely pre-compression, to remove entrapped air and reduce material porosity, and main compression, to convert the pre-compressed blend into tablets. Empirical models have been deployed to correlate the material attributes such as bulk density (ρ_b), and process parameters like turret speed (N_T), main compression thickness (M_{thick}), dosing position (H_{fill}), etc., with tablet properties which includes weight (W), main compaction force (F_{main}), density (ρ_{tab}), and strength (σ_T). The tablet press model equations used in PharmaPy framework are summarized below.

$$\frac{dh_{hopper}}{dt} = \frac{F_{out,b} - F_{fframe}}{\rho_b A_{hopper}} \quad (12)$$

$$V_{fill} = \frac{\pi D^2 H_{fill}}{4} + \frac{\pi h(\frac{3D^2}{4} + h^2)}{6} \quad (13)$$

$$F_{fframe} = n_T N_{stat} \rho_b V_{fill} \quad (14)$$

$$W = \rho_b V_{fill} \left(-\varphi_1 \frac{N_F}{N_T} + \varphi_2 \frac{H_{fill}}{D} + \varphi_3 \left(\frac{H_{fill}}{D} \right)^2 \right) \quad (15)$$

$$F_{main} = \frac{\pi D^2 (\rho_{in-die} - \rho_c)}{4b(\rho_{in-die}(a-1) + \rho_c)} \quad (16)$$

$$V_{in-die} = \frac{\pi D^2 M_{thick}}{4} + \frac{\pi h(\frac{3D^2}{4} + h^2)}{3} \quad (17)$$

$$\rho_{in-die} = \frac{W}{\rho_t V_{in-die}} \quad (18)$$

$$\rho_{tab} = \rho_{in-die} (1 - \varepsilon_p) \quad (19)$$

$$\sigma_T = \sigma_0 \left[1 - e^{(\rho_{tab} - \rho_{c,\sigma})} \left(\frac{1 - \rho_{tab}}{1 - \rho_{c,\sigma}} \right) \right] \quad (20)$$

where D, h, A_{hopper}, N_F, ε_p are the die diameter, cup depth, hopper cross section area, feed frame speed, and elastic recovery of the tablet, respectively. $\rho_{c,\sigma}$ and σ_0 are the tablet tensile strength model parameters.

Content uniformity of the tablets (C_V) is also estimated to study the effects of upstream material attributes i.e., mass fraction (x_i) and particle size (d_i) of API, and downstream material conditions (C_{API}) on tablet quality based on a target dosage (T_D) [9].

$$C_V = 100(1 - C_{API}) \left(\frac{\pi \rho}{6 T_D} \right)^{1/2} \left(\sum_{i=1}^{N} x_i d_i^3 \right)^{1/2} \quad (21)$$

The downstream process synthesis for tablet manufacture comprises a dynamic flowsheet model, which includes integrated unit operations as described above for the direct compaction process. This flowsheet model is developed within the PharmaPy framework and combines individual processes by utilizing the output of previous unit operation as the input of the subsequent one. The object-oriented programming structure in Python allows the flexible use of these unit operations and also build customized functions for the flowsheet model. The model parameter values of the individual processes are taken from existing studies towards the manufacture of 10% acetaminophen tablets [6,10-12].

Sensitivity and Feasibility Analysis

Once the flowsheet model is developed, the next step is to perform process analysis. This includes the identification of crucial input variables, i.e., material attributes and process parameters. Then, the influential input factors are examined to estimate feasible design space regions which can then be used to develop control strategies. Statisticians and practitioners have developed various sensitivity analysis methods which studies how uncertainty in model input can be assigned to variations in model output. Among the main techniques, global sensitivity analysis stands out as it allows the determination of effects of uncertain input variables across the whole input space.

Table 1: Input variables for sensitivity analysis with lower (LB) and upper bound (UB).

Input	LB	UB
Crystallizer (CR01)		
Residence time (s)	2470	2730
Coolant jacket temp. (K)	298	328
API feeder		
API flow (kg/hr)	0.95	1.05
Excipient Feeder		
Excp. Flow (kg/hr)	8.55	9.45
Continuous blender		
Blender speed (RPM)	237.5	262.5
Tablet press		
TP fill depth (mm)	7.6	8.4
TP thickness (mm)	2.85	3.15
TP turret speed (RPM)	19	21

PharmaPy performs global sensitivity analysis on a given set of input and output variables by utilizing in-built python libraries for qualitative and quantitative sensitivity analysis. In this study, we use variance-based Sobol's method to study quantitatively, how the variance of flowsheet output can be apportioned into terms based on input variables and their interactions. Sobol's method uses two metrics to provide sensitivity information, S_i for first-order effect, and S_{Ti} for total-effect defined as follows:

$$S_i = \frac{\mathbb{V}(\mathbb{E}(Y|X_i))}{\mathbb{V}(Y)} \quad (22)$$

$$S_{Ti} = 1 - \frac{\mathbb{V}(\mathbb{E}(Y|X_{-i}))}{\mathbb{V}(Y)} \quad (23)$$

where $\mathbb{V}$ is the variance, $\mathbb{E}(Y|X_i)$ refers to the expected value of output Y when parameter X_i is fixed, and X_{-i} denotes all uncertain parameters except X_i. The sum of S_i cannot exceed one and the sum of S_{Ti} is greater than or equal to one. However, if there are no higher order interactions between the input parameters, the sum of S_i and S_{Ti} is one.

Table 2: Output variables for sensitivity analysis, and constraints (LB, UB) on the output for feasibility studies.

Unit operation	Output	(LB, UB)
Blender	API comp. (C_{API}, %)	(9.5,10.5)
Tablet press	Weight (W, mg)	(167,183)
	Compaction force (F_{main}, kN)	(2, 50)
	Strength (σ_T, MPa)	(2,15)
	Content uniformity (C_V, %)	(0,6)

Table 1 lists the input variables with their corresponding ranges for the feeders, blender and the tablet

press. Along with the downstream variables, the first crystallizer's residence time (τ_{CR01}) and its cooling jacket temperature (T_{CR01}) are also considered. These factors affect the crystal size distribution and are investigated to quantify their impact on tablet content uniformity. Other upstream decision variables are fixed at their nominal values and can be found in the work of Inyoung et al. [6]. Table 2 elucidates the considered output variables in this study.

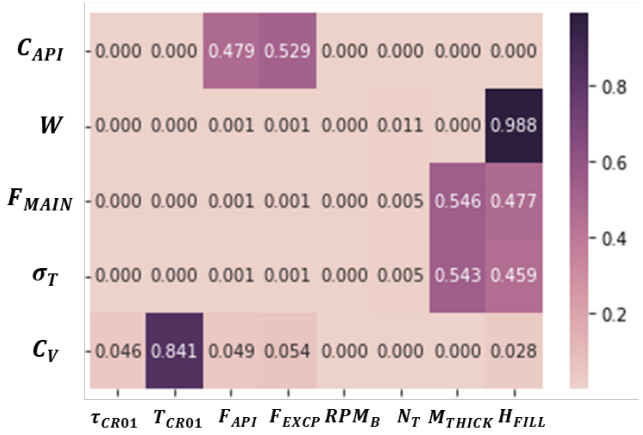

Figure 2. Sensitivity analysis results showing Sobol's total sensitivity index effect (S_{Ti}) on the drug substance-product process.

The sensitivity results based on Sobol's total effect index in shown in Figure 2. It is found that the first order effect (S_i) is similar to the total effect (S_{Ti}) which means that the interaction effect between each input variable is weak and hence the total effects are reported. The Sobol's method concluded that six out of eight input variables are most critical. Blender speed does not affect any of the output variables and turret speed affects the tablet properties only very slightly and therefore has not been retained for feasibility studies. On the other hand, crystallizer's residence time and its operating temperature, API and excipient flow rates, tablet press' main compression thickness and dosing position impact one or more output variables significantly.

After sensitivity analysis, feasibility studies can be performed on the subset of input variables to characterize the process design space. To estimate the design space, the output variables are determined based on the uncertain input variables. Based on whether the maximum and minimum value of output variables obey the constraints or not, the process feasibility is drawn. For the integrated flowsheet, feasibility analysis is conducted on the six most influential input factors and the constraints on the output variables are shown in Table 2. The feasibility studies result in a 6D problem with 10 constraints for the flowsheet model. For this high-dimensional problem, matrix plots are deployed to describe the feasibility as explained in Forrester et al., (2008). The matrix includes 15 plots, each of which represents feasibility of two input variables while the remaining four inputs are fixed at their nominal values. It should be noted that the matrix is symmetric, therefore 15 plots instead of 25 are shown accounting for all possible input combinations for feasibility studies. For each plot, 25 sample grid points are obtained through discretization of inputs, and output variables are estimated at the discretized inputs. The feasible region where all the constraints are jointly satisfied is represented by the olive contours.

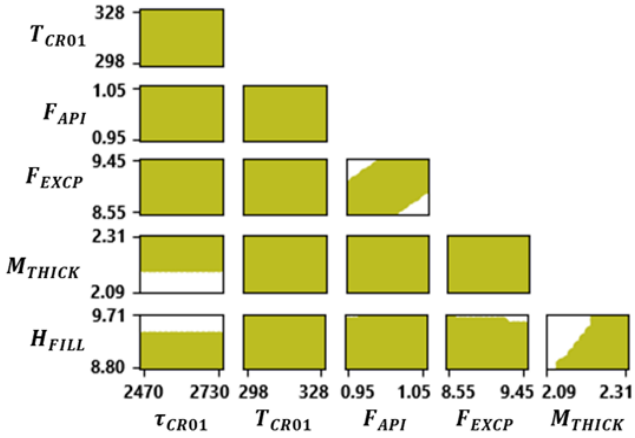

Figure 3. Feasibility analysis results of the DC process using PharmaPy.

The results of the feasibility analysis for the flowsheet model are shown in Figure 3. From the feasibility plots, we can observe that the operating temperature (T_{CR01}) and residence time of the crystallizer (τ_{CR01}) are feasible over their entire range, which directly impacts the crystal size distribution in the upstream process. This implies that the process can sustain all the variations from these sources while ensuring robustness. The API flow rate (F_{API}) and excipient flow rate (F_{EXCP}) are also linearly feasible across their input space. The main compression thickness (M_{thick}) and dosing position (H_{fill}) significantly affect the tablet properties and are found to be feasible for higher and lower values, respectively. But much lower values of thickness and dosing position can result in large deviations from the desired tablet properties like weight, compaction force, and strength. Therefore, the variations in thickness and dosing position need to be strictly controlled to avoid adverse effects on tablet quality.

With the help of in-built python libraries and deployment of matrix plots, PharmaPy can execute sensitivity and feasibility analysis on a given set of input and output variables. This allows to clearly screen the important input variables and quantify the extent of tolerance to process variations which can help build robust control strategies ensuring product quality.

CONCLUSION

This contribution demonstrates the features of the enhanced PharmaPy package to study the effects of upstream and downstream pharmaceutical processes on final tablet quality. Since the downstream processing can operate in a truly continuous mode, a direct compaction case study is used to investigate the effects of process parameters on tablet quality attributes with the help of process analysis. The process analysis helped identify crucial input variables and determined a process design space that ensures consistent product quality.

However, the downstream PharmaPy package can undergo further enhancements to fully realize the open-source prowess of PharmaPy framework. This includes flowsheet optimization and alternate routes to manufacture tablets such as dry granulation and wet granulation where key differences and challenges can be analyzed. In addition, the downstream architecture needs to be equipped with models that help quantify the effects of variations in API attributes, e.g., particle size distributions and moisture content, on the blend and tablet properties. This will help understand the changes a given blend undergoes during the drug production process. Efficient models will be built to capture such effects as part of the overall PharmaPy downstream development.

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