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RESEARCH ARTICLE

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Abstract In this work, a dynamic flowsheet model for the production of pharmaceutical tablets through a continuous wet granulation process is developed. The unit operation models which are integrated to compose the process line form a hybrid configuration which is comprised of a combination of mechanistic models, population balance models, and empirical correlations, based on the currently available process knowledge for each individual component. The main objective of this study is to provide guidance in terms of the necessary steps which are required in order to move from the unit operation level to the simulation of an integrated continuous plant operation. Through this approach, not only significant process conditions for each individual process are identified but also crucial interconnecting parameters which affect critical material properties of the processed powder stream are distinguished. Through the integration of the dynamic flowsheet with a final component of tablet dissolution, the connection of the processing history of a set of powders which undergo wet granulation and are contained in each produced tablet to the release rate of the pharmaceutical ingredient is enabled. The developed flowsheet is used for the simulation of different operating scenarios and disturbances which are often encountered during operation for the assessment of their effects towards critical material attributes, product properties, and the operation of further downstream processes. Simulation results demonstrate that granulation and milling which control the particle size distribution of the processed powder mixture highly affect the hardness and dissolution of the produced tablets.

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Introduction and Objectives

The pharmaceutical industry is a tightly regulated industry where all production must comply with good manufacturing practices and quality requirements should be strictly satisfied. Historically, manufacturing in the pharmaceutical industry has been carried out in batch mode which potentially results in expensive, inefficient, and poorly controlled processes [18, 26]. Recently, both pharmaceutical industries and regulatory authorities have recognized that continuous manufacturing has a significant potential to improve product quality and reduce manufacturing cost [1, 2, 14, 27, 28, 34, 38, 49, 55, 61, 62]. Moreover, environmental, health, and safety issues are driving the industry towards more efficient and more predictive manufacturing. Therefore, a great opportunity arises for developing a generic continuous manufacturing platform that will benefit from state-of-the-art strategies, modeling tools, and enabling technologies to implement this transition. In this work, we focus on the manufacturing of oral solid dosage drugs which consist of approximately 85 % of the entire pharmaceutical production. A typical manufacturing process for a powder-based product (e.g., tablets and most capsules) involves multiple processing steps, of which the most common are powder feeding, blending, granulation, and tableting or capsule filling.

Dynamic flowsheet modeling and simulation is a prerequisite for the design, analysis, control, and optimization of an integrated process. While several integrated modeling and simulation tools (commercial and noncommercial)

have proven to be effective for fluids processes, their use has been fairly limited for solids processes [52]. As a result, the simulation for processes involving solids is not as advanced and very often; each unit operation is designed and optimized separately from the others, neglecting its influence and dependence on neighboring processes. For simulating the solids process, mathematical models of each individual process are used and the results are manually transferred between the various unit operations [21]. This approach results in loss of information between unit operations and is known to especially fail when there is a recycle loop which feeds back an outlet stream from a unit into another unit that is placed upstream [21]. In cases where recycle loops are present, such as in powder blending [5] and granulation [15], the entire flowsheet simulation has to be done iteratively, which in a limited manner can be done by manual sequencing, and is an extremely time-consuming process. Unit by unit simulation also results in local operating conditions being found and not necessarily a globally optimal solution. Other reasons for the lack of a rigorous solid dynamic flowsheet simulation include (1) lack of adequate mathematical descriptions of solids processes, as solids processes are typically characterized by distributed parameter systems which require a more complex description, (2) lack of process control schemes for individual process and for the entire process, and (3) lack of dynamic optimization strategies to ensure that overall process is running optimally and efficiently.

Solids processes play an important role in todays' chemical industry. It is estimated that about 60 % of the values of the products produced in the chemical and allied industries are either solids (e.g., pharmaceuticals) or have properties which strongly depend on their particulate ingredients [12]. Optimization of solids processes is usually achieved by laboratory-scale tests which are scaled up to plant size after verification of their applicability. Such tests are time consuming and expensive. Therefore, the process engineers cannot afford to examine all possible alternatives for an involved process step in order to find the optimum design. A state-of-the-art method for fast and reliable design studies in the design of fluid/gas processes is the application of flowsheet simulation software. Here, the engineer is able to simulate the different process alternatives without the need of expensive and time-consuming tests. This facilitates the identification of an optimal design. Another possible application of such a simulation system is operator training. Changes in operating conditions can be simulated and the effect on pollution and energy consumption can be estimated. In this manner, critical situations can be simulated, which allows for a faster and more reliable reaction by the operating personnel [57]. Furthermore, the shift of operating conditions to desired targets after simulation can be performed in order to minimize energy consumption and waste production. These benefits make the application of simulation systems for solids processes highly desirable. Unfortunately, compared to fluid/gas processes, the characterization of solids processes leads to much higher complexity of information structures that is required in such a simulation system. Several studies exist in the literature which describe the dynamic simulation of solids processes [10, 19, 35, 45, 46, 50, 51, 56]. However, their aims were to study detailed sensitivity analysis or unit-operation modeling and did not consider the integrated operation of the entire process. Recently, several solids simulation software packages (e.g., SuperPro®, SolidSim®, and gSOLIDS®) have become commercially available. However, their use has been either restricted to steady-state modeling and/or simpler dynamic models or they were used for the study of batch processes [36]. Moreover, their models are not exhaustive and many of the detailed models required for a pharmaceutical process (e.g., tablet compaction, blending, coating) are absent or in their infancy in terms of development.

The objectives of this study are to (1) implement a WG, drying, and dissolution model that is amenable to flowsheet simulation and (2) identify the effect of input parameters on key output variables and CQAs, via an integrated dynamic flowsheet simulation. The remainder of the paper is organized as follows: Section "Pharmaceutical Manufacturing Process—Wet Granulation Step" provides a general description of the manufacturing of pharmaceutical tablets through multiple scenarios. The developed unit operation models are described in Section "Model Development for Flowsheet Simulation", where the focus is given specifically on the wet granulation, drying, milling, and dissolution steps which are introduced in this work. Section "Model Integration" is a detailed description of the integrated flowsheet simulation, while the simulation results are presented in Section "Simulation Results". Finally, the paper concludes with Section "Conclusions", with a general discussion of the results and future goals.

Pharmaceutical Manufacturing Process—Wet Granulation Step

A typical pharmaceutical manufacturing process for an oral solid dosage form (e.g., tablet/capsule) involves multiple processing steps. Considering the case-specific variability in the way in which these processing steps are implemented, flexibility requires that any characterization be, to a large extent, modular (i.e., enabling multiprocessing capabilities in a single manufacturing line), and this requires the

modeling and characterization of a variety of different unit operations in different sequential configurations.

Therefore, the unit operations typically encountered in the processing line of a solid dosage form are the following: (1) feeding, where a desired flow rate of individual ingredients and/or preblends is delivered, (2) blending/mixing, in which the active pharmaceutical ingredient (API) is mixed with excipients and additives in a certain ratio, (3) wet granulation, in which the powder blend is consolidated into solid granules to improve powder flow properties and prevent segregation in downstream processes, (4) roller compaction, in which the powder blend is pressed to form ribbons, (5) milling, in which the granules or ribbons are milled to a desirable size distribution, (6) tablet compaction in which the powder or granulated blend is compressed mechanically into a solid tablet, and (7) coating, in which the solid dosage form is covered with a thin layer of polymer. It must be noted that tablet compaction also involves the consideration of the hopper (which acts as a buffer for powder that exits from the blender and feeds into the tablet press) and the feed frame which is responsible for establishing the flow rate of powder from the hopper into the tablet press. Multiple scenarios, addressing various relevant configurations of the manufacturing setup, are always dictated by the type of formulation, such as concentration of active, flow properties, compressibility, sensitivity to temperature of active, etc. Tablet dissolution can also be considered as a product model since a tablet is ingested and passed through the esophagus to the stomach, which is an aqueous environment. This is the first place where the tablet may dissolve and the rate of dissolution is a key target for monitoring and regulating the duration and intensity of the drug's effect.

A flexible manufacturing platform may support multiple designs, such as the three scenarios shown in Fig. 1, which together encompass the majority of solid dosage products manufactured in the pharmaceutical industry. In scenario 1, the tablets are produced using direct compression (feeder–blender– tablet press–coater), which can be used for moderate to high active ingredient loading products. Scenario 2 involves roller compaction (feeder–blender–roller compactor–mill–tablet press–coater) and is applicable for the production of tablets when higher loading of an active ingredient is required or for the cases that the ingredients are sensitive to moisture. Scenario 3 addresses wet granulation (feeder–blender–granulator– mill–tablet press–coater), which is typically the platform of choice for low drug content products or for formulations that segregate intensely.

In the previous work [4, 5], we had identified the challenges in flowsheet model development and simulation for solid-based pharmaceutical processes such as direct compaction (scenario 1) and dry granulation (scenario 2).

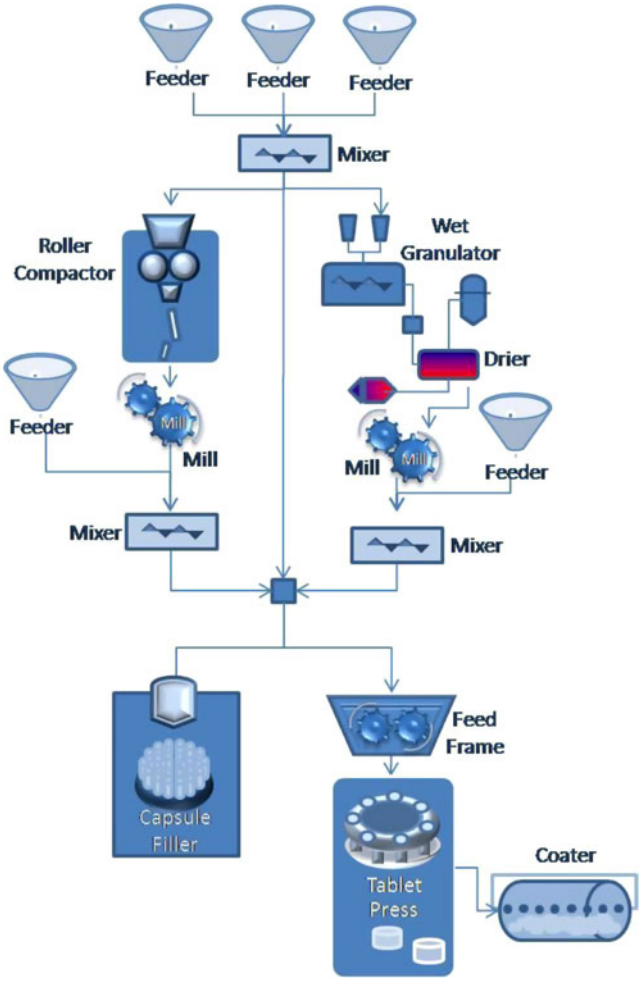

Fig. 1 Schematic of a flexible and modular pharmaceutical manufacturing platform

Results had demonstrated the effect of input properties (e.g., flow rate variability, change in processing parameters) on key tablet properties. A dynamic global sensitivity analysis was also performed to ascertain which input parameters are critical and have the most effect on output variables. In this work, the focus is shifted to study the incorporation of wet granulation (scenario 3) as a key step in the overall processing line. The incorporation of tablet dissolution as a product model is also studied within the dynamic flowsheet simulation environment in order to further quantify the effect of input parameters on one of FDA's most critical quality attribute, such as tablet dissolution. The development of a dynamic flowsheet simulation environment incorporating wet granulation will also complement and integrate well with the research on process control done by the current authors [42, 43].

Model Development for Flowsheet Simulation

Wet Granulation and Drying

Granulation is an important process involved in the manufacturing of pharmaceutical products. It is a size-enlargement process which aids in obtaining a product of more uniform particle size distribution and also helps in optimizing the bioavailability of the drug product. The process of granulation is still not very well understood and is carried out with large recycle ratios, thus making the operation extremely inefficient [48]. Many approaches have been into existence which can be used to model such processes [17, 20, 47], but population balance modeling is very suitable for describing granulation because of its discrete nature and its ability to depict particulate processes. Although agglomeration of fine particles is most prominent, the final outcome of granulation is a combined effect of the various subprocesses like aggregation, breakage, growth, and nucleation, acting together. Apart from the particle size, binder content and particle porosity are also very important attributes that affect granulation, so lumping these parameters would not be advisable. Hence, the hyperbolic integrodifferential equation representing granulation was obtained for a multidimensional case by recasting the attributes in terms of their respective solid, liquid, and gas volumes in order to decouple each mechanism in the overall process [59]. The three-dimensional population balance equation for granulation can be written as

$$\begin{aligned}\frac{\partial}{\partial t}F(s,l,g,t) &+ \frac{\partial}{\partial s}\left[F(s,l,g,t)\frac{ds}{dt}\right] \\ &+ \frac{\partial}{\partial l}\left[F(s,l,g,t)\frac{dl}{dt}\right] \\ &+ \frac{\partial}{\partial g}\left[F(s,l,g,t)\frac{dg}{dt}\right] \\ &= \Re_{\text{aggregation}} + \Re_{\text{breakage}} + \Re_{\text{nucleation}} \end{aligned} \quad (1)$$

where $F(s,l,g,t)$ represents the population density function and s, l, and g are the internal coordinates, namely, solid, liquid, and gas volumes, respectively. The partial derivative terms with respect to the internal coordinates represent the various growth terms that indicate an overall increase or decrease in the particle size but there is no change in the number of particles associated with it. The partial derivative with respect to the solid volume denotes layering, which shows the growth due to fines getting deposited on the bigger particles, the partial derivative with respect to the liquid volume expresses the drying or rewetting of particles due to the addition or evaporation of liquid, and the partial derivative with respect to the gas volume represents consolidation, which is a negative growth term and is associated with the compaction of granules while gas escapes out of it. The right-hand side of Eq. 1 represents the source terms, comprising of aggregation, breakage, and nucleation. Aggregation and breakage are accompanied by a change in the number of particles. It is important to represent all of the underlying mechanisms in the population balance equation. In this paper, we are considering a continuous multicomponent granulation consisting of Avicel and acetaminophen. The necessary microscopic properties for describing the kernel were unavailable for acetaminophen; so for a qualitative purpose, we have used the values for mannitol in our calculations. Also, in order to simplify the model due to computational limitations, we are neglecting the gas volume as an internal coordinate. Therefore, the population balance equation is modified as

$$\begin{aligned}\frac{\partial}{\partial t}F(s_1,l,s_2,t) &+ \frac{\partial}{\partial s_1}\left[F(s_1,l,s_2,t)\frac{ds_1}{dt}\right] \\ &+ \frac{\partial}{\partial l}\left[F(s_1,l,s_2,t)\frac{dl}{dt}\right] \\ &+ \frac{\partial}{\partial s_2}\left[F(s_1,l,s_2,t)\frac{ds_2}{dt}\right] \\ &= \Re_{\text{aggregation}} + \Re_{\text{breakage}} \\ &\quad + \Re_{\text{nucleation}}. \end{aligned} \quad (2)$$

Aggregation can be considered to be the most important mechanism governing granulation. Calculation of the aggregation term is quite intense due to the presence of integral terms. Besides evaluating the integrals, another challenge faced while modeling aggregation is the appropriate choice for the aggregation kernel. Most works found in literature were focussed on single-component granulation, but lately, some research has also been involved in addressing multicomponent granulation [31, 32, 54]. In this paper, a multicomponent granulation is considered, and hence, an appropriate kernel that can adequately address the interaction between the multiple components is necessary.

For this purpose, the aggregation kernel proposed by [41] is found to be the most appropriate and is expressed as

$$K_{12} = \psi_{12}\beta d_{43}^{\gamma}(d_1+d_2)^2\left(\frac{1}{d_1^3}+\frac{1}{d_2^3}\right)^{0.5} \quad (3)$$

where ψ_{12} is the nondimensional collision factor consisting of the composition dependence of the kernel, β is the aggregation constant (assumed value $4 \times 10^{1}7$) and d_{43} is the average particle diameter, and d_1 and d_2 are the particle diameters for the two colliding particles. However, a slight modification of the multicomponent aggregation kernel suggested by [41] has been performed, by replacing the size-dependent component of the kernel with the kernel proposed by [30] instead of the kernel based on the equipartition of kinetic energy (EKE kernel) [22]. The size-dependent part is represented by the Madec kernel since it takes into account the fractional liquid of each particle,

thus addressing the size and liquid dependence of the kernel instead of just the size dependence as in the case of the former kernel (EKE).

$$y_{12} = (L_1^3 - L_2^3)\left((c_1 + c_2)^{\alpha}\left(100 - \frac{c_1 + c_2}{2}\right)^{\delta}\right)^{\alpha}, \quad (4)$$

where

$$c_i = \frac{\text{volume of liquid}}{\text{volume of agglomerate}}100. \quad (5)$$

Since the grids which are used in this work are in terms of the volumes, the L_1^3 and L_2^3 in the size-dependent component of the kernel can be replaced by v_1 and v_2. Also, in order to introduce least nonlinearity, α and δ have been assigned the value of 1.

The concentration-dependent term, ψ_{12} is the success factor that imparts the multicomponent attribute to the kernel and can be expressed as

$$\psi_{12} = \psi^{\text{geom}}\psi^{\text{phys}}. \quad (6)$$

It is defined as the product of the geometric success factor and the physical success factor. The geometric success factor is obtained as a sigmoidal function, defined as

$$\psi_{\text{geom}} = 1 - (1 - \eta_1)(1 - \eta_2) \quad (7)$$

where

$$\eta_i = \frac{1}{1 + e^{-b(z_i - c)}}. \quad (8)$$

Here, z_i is the binder-to-solid ratio and b and c are constants specific to the different components and have been listed in previous works by [54]. Table 1 consists of the values for these constants for Avicel and mannitol, which are used in this work.

The physical success factor is based on analyzing the Stokes' number [13, 29, 40, 41] as

$$\psi^{\text{phys}} = \begin{cases} 1, & \text{if } St \le St^* \\ 0, & \text{if } St \ge St^* \end{cases} \quad (9)$$

where the Stokes number and the critical Stokes number are defined as

$$\text{St} = \frac{8\tilde{m}u_0}{3\pi\mu\tilde{d}^2} \quad (10)$$

$$\text{St}^* = 2ln\frac{\lambda_{12}}{h_a} \quad (11)$$

Here, u_0 is the velocity of collision (in meter per second), μ is the binder viscosity (in kilogram per meter-second), λ is the binder layer thickness between the two colliding particles, and h_a is the surface asperities of the particle. The information on the surface asperity of the particle can be obtained from the morphological analysis of the particles and can be given as $h_a = (a/2)r_g$, where a is the dimensionless surface roughness amplitude. The Stokes number can be expressed using the information of the two colliding particles by substituting $\tilde{d}$ and $\tilde{m}$ into Eq. 10. The reduced particle diameter and mass, $\tilde{d}$ and $\tilde{m}$, can be defined as

$$\tilde{d} = \frac{d_1 d_2}{d_1 + d_2} \quad (12)$$

$$\tilde{m} = \frac{m_1 m_2}{m_1 + m_2}. \quad (13)$$

The binder layer thickness for the two colliding particles [54] can be expressed as a function of the mean radius of gyration, r_g as

$$\lambda_{12} = r_g\phi_1^{1/3} + r_g\phi_2^{1/3} \quad (14)$$

where ϕ_i is the relative displaced binder volume which is a function of the binder-to-solid ratio, y_i, and is defined as

$$\phi_i = e^{f(y_i - g)} \quad (15)$$

The values for f, g, and h_a have been listed in Table 2 and were obtained from [41].

In the performed simulations, we have considered the mean radius of gyration, $r_g = 60\mu$ is considered, and also in order to reduce the calculation complexity and to avoid making the kernel dynamic, parameter λ has been set to 0; thus, the dependence of the aggregation kernel on the average particle diameter is neglected. The main two mechanisms addressed in our simulations are aggregation and the addition of liquid binder.

The next processing step after wet granulation is drying of the formed granules. Drying of granulated particles using fluidized beds is a common and important step in the pharmaceutical industry. Compared with other drying methods, fluidized bed drying provides more efficient air–solids contact and, hence, faster drying rate because better mixing and uniformity can be achieved through the process of fluidization. In this work, a simple mathematical model is developed to consider the change of particle size distribution (PSD) during drying after granulation.

Table 1 Constants for various components

Excipient	b	c
Avicel	35.1	0.129
Mannitol	27.4	0.182

Table 2 Constants for various components

Excipient	f	g	h_a
Avicel	25.9	0.327	6.3
Mannitol	26.8	0.394	10.5

Specifically, the evaporation rates of water in all periods of drying can be determined by the following equation [7]:

$$m_{\text{evap}} = A_{\text{p}} H_{\text{s}} \rho_{\text{g}} (X_{\text{s}} - X_{\text{e}}) L \tag{16}$$

where m_{evap} represents the evaporation rate of liquid of each particle, ρ_{g} represents density of the hot air used for drying, H_{s} denotes the mass transfer coefficient, L is the length of the dryer, and X_{s} and X_{e} stand for the saturated moisture content of drying medium on the particle surface and the equilibrium moisture content of the particle, respectively. Specifically, H_{s} can be expressed based on the diffusion coefficient [39]:

$$H_{\text{s}} = 2D/(10^{-6} d_{\text{p}}) \tag{17}$$

$$D = 2.6 \times 10^{-5} \left(\frac{T_{\text{p}}}{273.15} \right)^{1.5} \tag{18}$$

where D represents the diffusion coefficient of water and d_{p} and T_{p} denote respectively the diameter and temperature of the particle. Finally, X_{s} is dependent on the saturation pressure of water in the prewarming and constant-rate period. The relationship between saturation moisture content and saturation pressure is shown below [60]:

$$X_{\text{s}} = 0.622 \frac{p_{\text{sat}}}{(p_{\text{sat}} - p_{\text{oper}})}. \tag{19}$$

$$p_{\text{sat}} = 101{,}325 e^{13.869 - \frac{5{,}173}{T_{\text{p}}}} \tag{20}$$

where p_{sat} and p_{oper} are the saturate pressure of water and operating pressure of the fluidized bed dryer, respectively. Here, it should be noted that it is assumed that the particle size distribution of the granules will only change in the prewarming and constant-rate periods.

Finally, the parameters used within the current drying model are based on literature and empirical knowledge about the operation of drying. Specifically, the temperature of the particles is assumed to be 348 K; the temperature for the drying air is set to 393 K and therefore its corresponding density is equal to 0.898 kg/s based on ideal gas law. Finally, the operating pressure (p_{oper}) and equilibrium moisture content (X_{e}) are set at 1 atm and 0.05 kg/kg, respectively.

Feeding, Mixing, Milling, Tablet Compaction, and Hoppers

In this subsection, the remaining unit operation models are described in less detail, since these are components which have been previously described in the previous work [4].

In the majority of powder-handling industries (i.e., pharmaceutical, food, ceramics, catalysts), feeding of powder materials into a continuous processing line is performed through gravimetric feeders, whose purpose is the supply of raw materials to the next unit operation at desired and consistent flow rates in order to match the desired mixture composition and total material throughput. A typical loss-in-weight (LIW) feeder is comprised of a hopper that can hold up to a certain amount of powder material, which is fed to the next processing unit through a rotating screw. Throughout the process of feeding, the material is assumed to retain its original particle size distribution and bulk density, which is something that is validated experimentally for the types of fine excipients, active ingredients that are handled in this work. However, such an assumption must be validated for materials which are complex, show tendency to break or aggregate, and especially in cases where mixtures are fed through a LIW feeder. Feeders are operated in closed loop, where a built-in controller manipulates the feed screw rotation speed, in order to achieve the desired output mass rate. In order to capture the dynamics of the unit operation of feeding, a differential delay equation model is employed, whose parameters are determined based on experimental studies. More details about the feeder model and parameters can be found in Boukouvala et al. [4, 5].

Powder blending is described through a two-dimensional population balance model which accounts for $n = 2$ solid components, two external coordinates (axial and transverse directions in the blender), and one internal coordinate (size distribution due to segregation). The equation of the population balance model (PBM) model is shown below, while the model is described in detail in Boukouvala et al. [4]:

$$\begin{aligned} \frac{\partial}{\partial t} F(n, x_1, x_2, r, t) &+ \frac{\partial}{\partial x 1} \left[F(n, x_1, x_2, , r, t) \frac{dx_1}{dt} \right] \\ &+ \frac{\partial}{\partial x_2} \left[F(n, x_1, x_2, r, t) \frac{dx_2}{dt} \right] \\ &+ \frac{\partial}{\partial r} \left[F(n, x_1, x_2, r, t) \frac{dr}{dt} \right] \\ &= \Re_{\text{formation}} - \Re_{\text{depletion}}. \end{aligned} \tag{21}$$

As opposed to the PBM model which is developed to describe the granulation process, the focus in mixing is on the spatial movement of the particles since no aggregation or breakage is assumed between the particles during this process step. This assumption is based on previous experimental studies for the materials which are handled in this work, as well as results from the discrete element method simulation models [6, 58].

A three-dimensional population balance model is implemented to describe the dynamics of the milling process [4]. Similarly to the granulation model, milling is assumed to be homogenous with respect to spatial position, but heterogeneous with respect to its internal coordinates which in this case are particle size, bulk density, and API composition. Similar to Verkoeijen et al. [59], a volume-based

PBM is employed in this study, in which one of the basic parameters is the breakage function, which describes how fragments, resulting from the breakup of larger particles, are distributed in terms of their volumes. The breakage function used in this study is based on the work of Pinto et al. [37]. Based on the probabilities of particles in a particular finite volume (bin) breaking to form daughter particles in one or more smaller finite volumes, a numerical operation was performed that was able to describe the distribution of these fragments [44]. The milling model also incorporates product classification (essentially two sieves) which sorts particles of particular size. These sorted particles are tracked to monitor the bulk density and API composition, with the intention of maintaining their values within certain specifications.

Hoppers are unit operations which are a supplementary component of processes such as tablet presses and roller compactors and aim to collect powder from an upper opening and feed material to the actual process from the bottom orifice. In general, the properties of the processed raw materials (i.e., cohesiveness, angle of internal friction, flowability) can suggest the optimal design in order to attain the operation of the hopper in the mass flow rate regime, where all of the material inside the hopper is moving towards the exit, where it is discharged with a relatively constant flow rate. The output flow rate from a hopper in tableting is sometimes controlled through the presence of a feeding screw (system equivalent to gravimetric feeders) or through the feed frame in the tablet press. It is important, however, to make sure that the hopper is carefully designed (height, angle, and outlet diameter) such that mass flow is achieved and stagnation of material in dead zones is avoided. The model employed in this work is a buffer tank equation model, in which the following assumptions are made: (a) mass flow, (b) no mixing, and (c) particle size distribution and bulk density of the material are not changed [4]. The main purpose of this simplified model is to capture the residence time of the material inside the hopper, while a mass flow regime is assumed. This allows the "tracking" of the material properties of the powders which reach the tablet press and filters out upstream flow rate disturbances which may occur during feeder refilling.

Subsequently, the powder material enters the feed frame which is a small chamber with rotating blades that fill the dies of the tablet press, where the powder is finally compressed into a tablet. The model which is implemented in this work is a combination of well-known literature correlations and was firstly implemented in Singh et al. [53]. In this model, the powder granules are filled in each die, which is the control volume of the model, and subsequently, pressure is applied to compress the granules in order to make the tablet. The effect of the precompression and main compression stages on the final tablet porosity are modeled through the Kawakita equation [23], while the final tablet hardness is described as a function of the relative density of the tablet, based on the work of Kuentz and Leuenberger [25].

Tablet Dissolution

The bioavailability of the API, which is a critical quality characteristic of the end product, is determined mainly from the dissolution profile of the tablet. Therefore, the integration of a dissolution component as the final unit of the dynamic flowsheet simulation is valuable since there are several physical tablet and powder properties determined upstream, which affect the drug release mechanism. These properties are tablet porosity and composition, as well as the particle size distribution of the powder after milling. Through this integration, the factors which affect the final tablet dissolution time will be determined in order to be able to identify and propose strategies for mitigating upstream disturbances before they reach the final product.

In most low-dosage drug formulations, the set of excipients added form the bulk of the tablet and control the dissolution mechanism of the entire tablet. On the other hand, interactions between the different components as well as the granule arrangement and homogeneity of the final tablet structure have been found as critical towards the final dissolution time. Dissolution has been studied both experimentally as well as from a modeling perspective in literature, leading to a variety of models ranging from empirical [8] to even two- or three-dimensional distributed rigorous models [3, 24, 33], which allow the investigation of effects such as tablet homogeneity and granule structure to the final release profile.

The model which is implemented in this work is based on the work of Kimber et al. [24], and it is a first-principle distributed model in which drug dissolution is captured by Fick's second law equations.

$$\frac{\partial}{\partial t} C_i = -\nabla(-D_i \nabla C_i) + s_i \tag{22}$$

where

$$s_i(x) = k_i(c_i^{\text{sat}} - c_i(x)) \tag{23}$$

where (s_i) is the source term which is not equal to zero when the presence of the API component in location (x) is true. Otherwise, the source term is equal to zero. The term (C_i) represents the dissolved concentration of each component i, while D_i is the diffusion coefficient of each component which is related to the solid fraction of the component as well as its mean particle size based on the following equations:

$$D_i = D_{i0}\left(1 - \sum \phi_j\right)^{\alpha_i} \tag{24}$$

and

$$D_{i0} = \frac{k_i T}{6 d_{50i} \pi \mu}. \tag{25}$$

The first equation ensures that the diffusivity is lower when location x is purely filled with solid component, and as it is filled with liquid (diffuses), the value of diffusivity will reach the bulk diffusivity of the component(D_{i0}). The bulk diffusivity is a function of the temperature (T), viscosity (μ), mean particle size of the granule (d_{50}), and k which is Boltzmann's constant. This equation holds due to the fact that diffusion is the result of thermal fluctuations in the suspension and is often referred to as Brownian motion [9].

The overall evolution of the dissolution process is described by the following equation:

$$\frac{\partial}{\partial t}\phi_i = -\frac{s_i}{\rho_i} \tag{26}$$

where the local change of the solid fraction (ϕ_i) is correlated to the local change of dissolution or else the source term (s_i).

For initialization, each tablet is represented as a discretized square shape, with dimensions that approximate the actual circular surface of a typical tablet. Initially, each element within the tablet is assigned a random porosity value of solid fraction (ϕ_i), making sure that the inner part of the tablet is denser than the section which is closer to the outer radius, which is something that has been validated experimentally . Next, however, we need to take into account the actual effect of the particle size of the granules which have formed the tablet. For this purpose, a similar approach to the one followed in [24] is used, where the discretized elements are smoothed through Gaussian smoothing, and the characteristic length (L_c) plays the role of the mean particle size of the granule.

$$\phi_i^{\text{new}} = \sum \exp\left(\frac{-d_{ij}^2}{L_c^2}\right) \phi_j^{\text{old}} \tag{27}$$

where (d_{ij}) is the distance between two points in x. This smoothing procedure creates the effect of granules (clusters of discretization elements) which is relative to the characteristic length.

The integration of this final step of tablet dissolution to the flowsheet model is a challenging problem due to the significant increase in computational cost as well as the introduction of an additional time domain, that of the dissolution profile of the group of tablets produced in each second of the simulation time domain. In order to overcome this issue and avoid the significant increase in simulation time, the dissolution model component is activated only when significant changes are detected in the set of properties of the powder or tablets, which will affect the dissolution profile. These properties, which are dependent on the upstream processing, are the ones that are used to initialize the distribution of the particle size, composition, and porosity of the tablet.

Model Integration

The integrated system consists of two feeders (API and excipient) that feed raw material into a blender where the components are mixed due to both convective and diffusive forces. The mixture of API and excipient is then continuously transported into a granulator whereby through the addition of liquid binder, the particles are transformed into larger granules. Next, drying of particles is necessary for the decrease of the moisture content which may have detrimental effects in compaction and in the final tablet properties. The dry granules are then passed through a mill in order to achieve the desired particle size distribution, and finally, the milled granules enter the hopper which feeds material to the feed frame and the tablet press for the production of tablets at a desired production rate. At the final stage, a dissolution component is included which provides the characteristic dissolution rate in real time based on the properties of the produced tablets.

Once each unit operation model is developed and validated individually, the formation of the aforementioned integrated system is achieved through the creation of a flowsheet model with the desired configuration. The major challenge involved in the integration of unit operation modules of different types and complexity is the identification of the necessary interconnecting variables which should be included in the process streams which connect process i to process $i + 1$. This information should include the necessary properties which characterize the powder stream as well as the required input data for each downstream process $i + 1$ which depends upon the output of process i. In certain cases, certain properties remain unaffected during one processing step but should be passed on through the process streams since they are considered as inputs to a further downstream process. Once again, it should be noted at this point that even though this procedure may seem trivial for a fluid/gas based flowsheet, it is a great challenge in solids handling where there is still a lot of uncertainty in terms of the properties which characterize the powder material and the models which characterize each process are of different fidelity and detail. In fact, the authors realize that there are still gaps in the integration of specific unit operation steps, due to the nonexistence of a critical parameter that is a result of process i in process model $i+1$. These missing links are described in the following paragraph and will be the focus of future work, either though the incorporation of empirical correlations or significant model modifications

to account for additional effects. The integrated design is shown in detail in Fig. 2.

Specifically, PSD, bulk density, and mass flow rate are tracked throughout the process across units up to the tablet compaction step. The API concentration which is initially defined in the mixer and then is further affected through granulation, drying, and milling is also a critical property which affects the average concentration of the drug present in the tablets. Moisture content and porosity are introduced after granulation and drying and are critical to downstream processes such as milling, tablet compaction, and dissolution. The outlet stream of the tablet press should be expressed in terms of tablets instead of powder, where additional parameters such as tablet hardness, porosity, density, and production rate are included. Finally, the critical inputs to the dissolution are the PSD of the powder which reaches the tablet press, tablet porosity, and the API concentration, which are all properties defined in upstream processes. In terms of the aforementioned missing links, the most significant deficiencies of the current flowsheet model are the ignorance of the effect of tablet hardness on the disintegration and dissolution mechanism and the effect of moisture content of the powder after drying in all downstream processes and dissolution. Even though it has been experimentally observed that the above quality attributes affect the quality of the final product, the simplified models which are used for the hopper, tablet press, and dissolution cannot explain or predict the effects caused the additional variability introduced by these inputs.

Simulation Results

The software which is used to perform this simulation (gPROMS) is equation-oriented, which is a great advantage when the flowsheet contains models of different level of detail. Moreover, gPROMS is inherently dynamic which is also a desirable aspect for simulation of start-up conditions as well as step changes in process conditions and time-dependent noise. In addition, the transfer of multi-dimensional properties such as PSD, population balance density functions, and parameters from one process to the

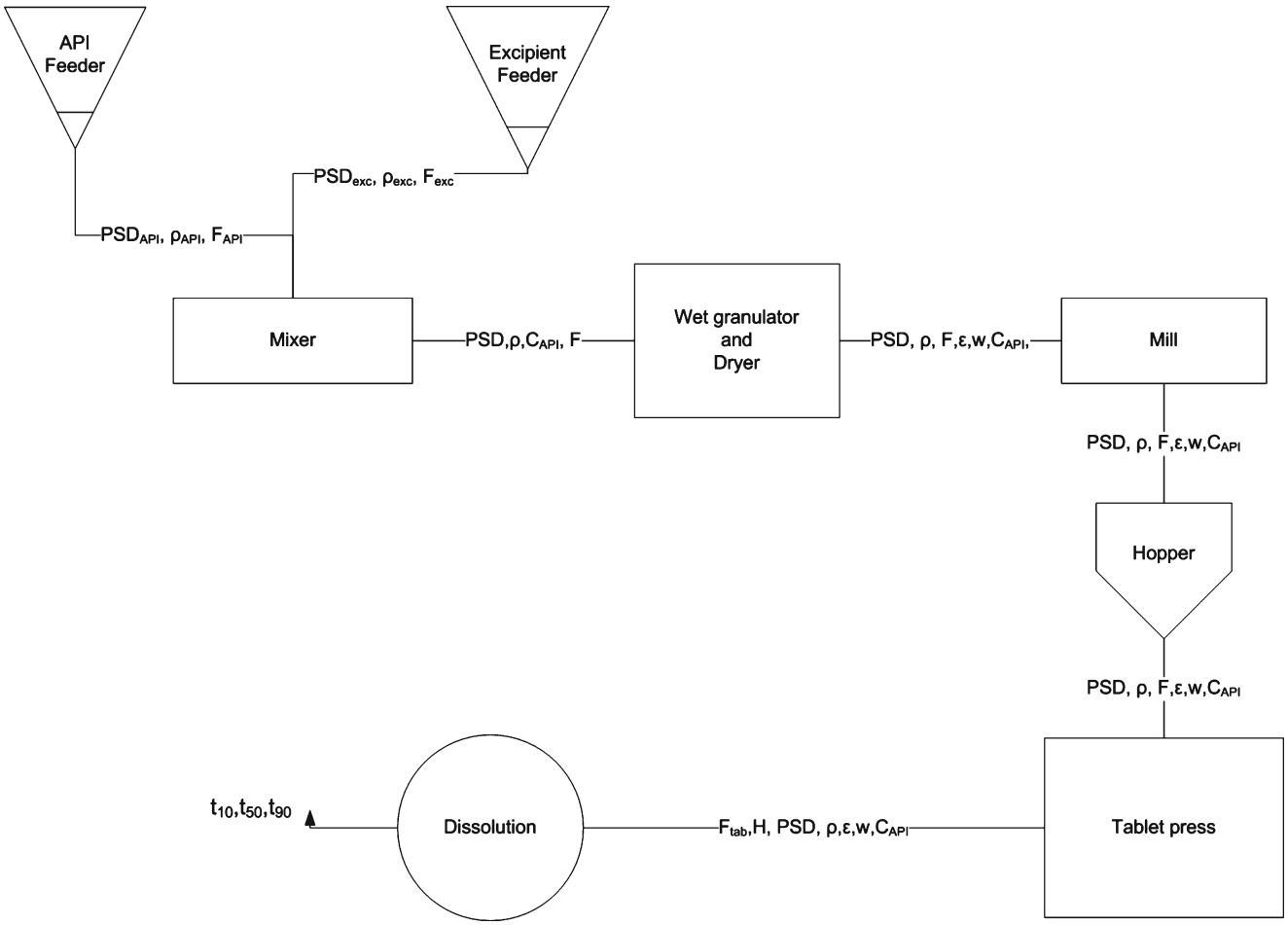

Fig. 2 Schematic of the integrated process design for continuous wet granulation

next is fairly simple based on the capabilities of the software. Overall, the goal of this work is the development of a unique library of unit operation models and process streams (connection types) which can then be combined to create a flowsheet model using the standard "drag-and-drop" approach.

The simulation requires the input of the desired total throughput and mixture composition in order to calculate the required operating conditions of the two feeders which will introduce the correct ratio of material to the entire system. In addition, material properties of each individual component such as particle size distribution parameters and bulk density are necessary input parameters of the simulation. If more than two materials are introduced into the system (i.e., lubricant), then this can be achieved by the addition of more feeders into the flowsheet which is possible in the current setting. However, the prediction of the behavior of multiple materials through the multidimensional population balance models is an aspect that still requires further validation; thus, a two-component mixture is described in this case study. Specifically, a mixture of 30 % acetaminophen and 70 % Avicel at a total throughput of 80 kg/h is simulated, producing tablets at a rate of 800,000 tablets/h.

Initially, it is important to verify the overall performance of the flowsheet through validating that the mass balances are satisfied throughout the process and the residence times of the powder material inside each process are correctly captured.

In Fig. 3, the dynamic profiles of the mass flow rate, the API concentration, and the bulk density of the processed powder stream are shown at different locations along the process line. It can be observed that the process reaches steady state at approximately 1,100 s, where all of the powder streams have obtained constant characteristics. The mean residence times of the granulator and the mill are set to 100 and 200 s, respectively. In addition, the results

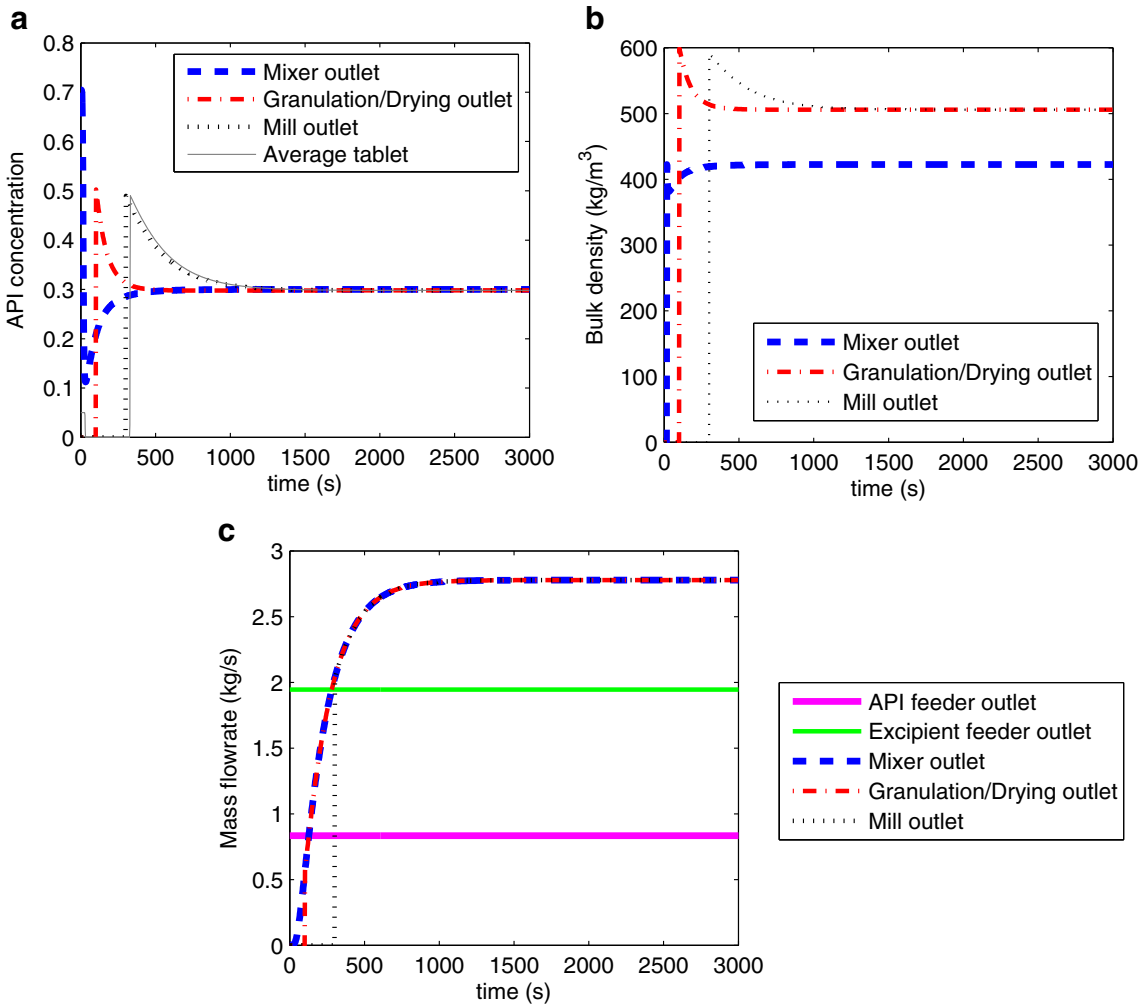

Fig. 3 **a** API concentration of process streams, **b** bulk density of process streams, and **c** mass flow rate of material, during dynamic simulation

verify the assumption of zero loss of mass, since all of the incoming material is equal to the material which reaches the tablet press. Moreover, the results validate the approach which was used to integrate the processes of granulation and milling, since not only the conservation of mass but also that of the desired concentration of API is achieved. Finally, the model can capture the expected change in the bulk density of the material as it is transformed from dry particles to dried wet granulated agglomerates. Specifically, the bulk density of the material has increased from the point of the blender to the granulator, which can be explained due to the transformation of the particle size of the material. In fact, experimental studies have shown that there are many process parameters, such as wetting conditions and mean residence time, as well as raw material properties, such as particle size composition, which affect the final bulk density of the granulated material. Thus, by choosing the optimal operating conditions, a material with high bulk density can be produced, which is easier to store and transport. In T. Gluba [16], it was shown that droplet diameter, mean particle size of raw materials, and saturation of the granulated bed were the most critical towards the final bulk density of silica flour. In addition, it is certain that the drying process also affects the bulk density of the material significantly, since once the liquid binder is removed, the particles may retain their granules or break into smaller particles. One of the limitations of this work, however, is the inability to decouple the effects of granulation and drying, since they are modeled as one unit operation. Based on the results, it can also be observed that the process of milling does not affect the bulk density of the material significantly in this case, under the specific operating conditions. This fact implies that the configured milling process does not significantly change this material attribute; however, this does not mean that the particle size distribution of the material has remained unchanged, and this will be shown through Figs. 4 and 5.

Figure 4 is a representation of the evolution of the frequency of different grades of particle sizes during wet granulation and milling. The size ranges that are most common during granulation are of sizes 2 and 3, which correspond to the particle size ranges shown in Table 3. In fact, based on the used parameter values, the population of size 3 particles is increasing at a constant rate and does not reach steady state even after 3,000 s. The remaining finer and larger sizes (1, 4, and 5) have negligible concentrations. On the contrary, after the process of milling, the mean particle size has decreased in value, which is reflected by the significant increase in the population of the smallest size particles relative to the total amount of particles (sizes 1 and 2). There exist a certain amount of size 3 particles, which can be explained by the continuous birth in the previous process step, but their population reaches a steady state at 2,000 s, due to their simultaneous depletion, and the fraction of this grade of material within the entire population of particles is smaller. The largest grades of particles (sizes 4 and 5) are depleted at a much faster rate. In Fig. 5, only groups of 1, 4, and 5 are included in order to distinguish their behavior

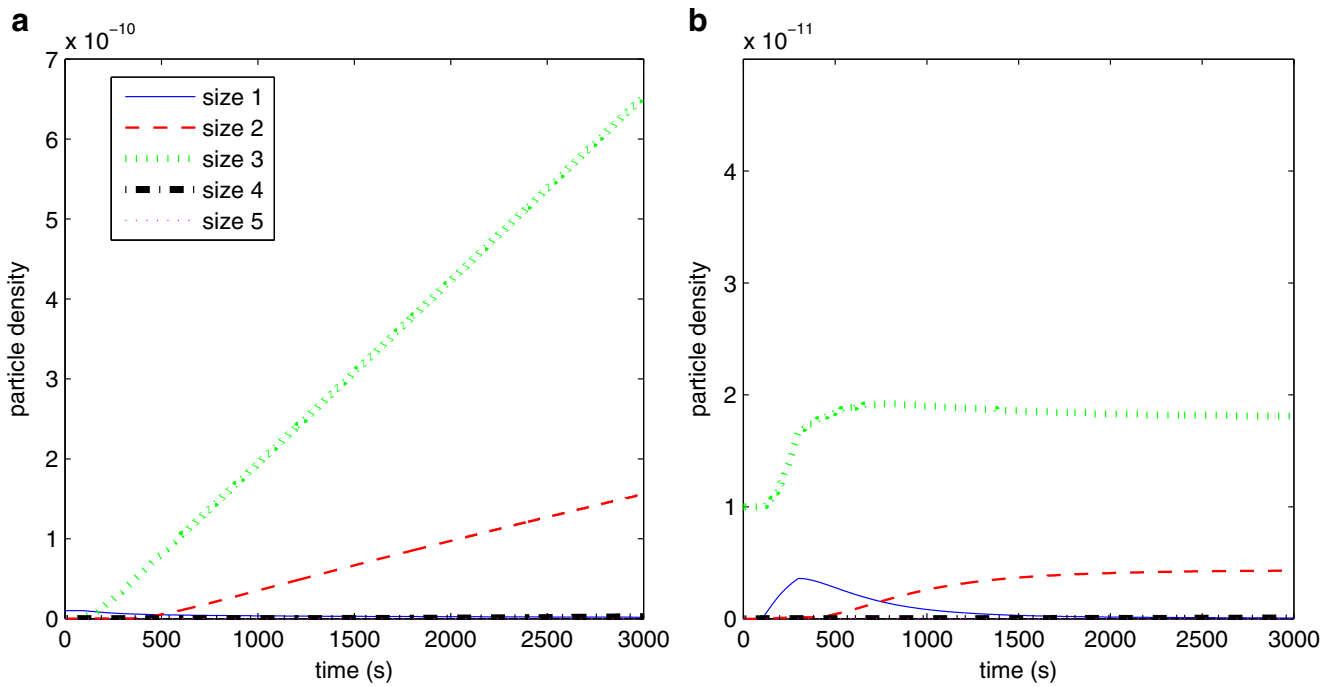

Fig. 4 **a** PSD evolution of granules during wet granulation and **b** PSD evolution of particles during milling

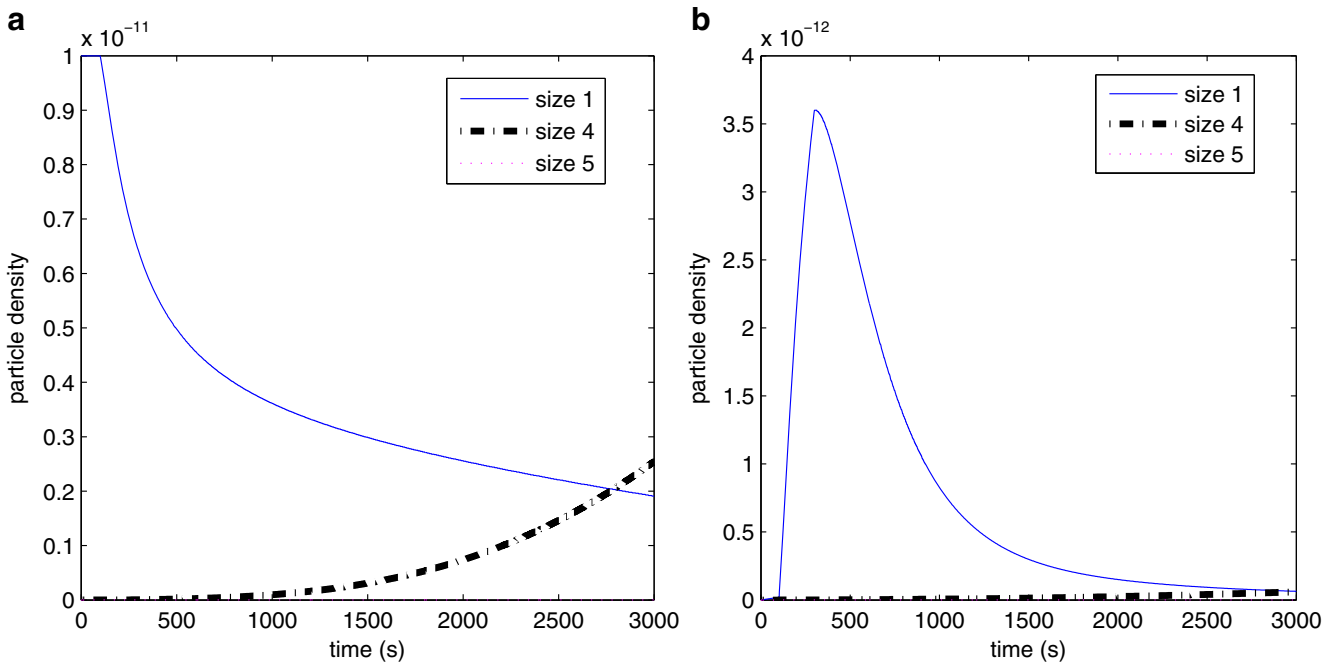

Fig. 5 **a** PSD evolution of granules during wet granulation and **b** PSD evolution of particles during milling, only of sizes 1, 4, and 5

better, since their frequency ranges are much lower compared to groups 2 and 3. During granulation, smaller size particles are depleted and larger size particles are formed. On the contrary, during milling, coarse particles are not formed and the finest size particles increase initially but later are depleted. The above results are encouraging since the desired particle size should lie in the middle-size groups after milling, in order to avoid not only agglomerates but also fines which can cause flowability issues in the hoppers.

Feeder Refilling

In a continuous operation of a wet granulation line, the refilling of the materials in the feeder hoppers is inevitable, and it has been shown that this procedure introduces significant perturbations in the system in the form of a feedrate pulse of the material that is being refilled [11]. Experimentally, this pulse has been shown to propagate downstream, and therefore, efficient control strategies or design modifications (i.e., recycling) are necessary to mitigate this effect. The objective is to correct the perturbation in the composition of the powder stream before it reaches the final step of compaction and it significantly affects the composition and dissolution of the tablets. Thus, it is important to investigate whether the current flowsheet model can capture the propagation of effects caused by a pulse in the feedrate of the API, since this is the first step in the identification of the optimal strategies which could be used to filter this perturbation further.

Table 3 Grid size bounds for particle size distribution

Bounds	Minimum radius	Maximum radius
Size1	0.0	5.05×10^{-5}
Size2	5.05×10^{-5}	6.08×10^{-5}
Size3	6.08×10^{-5}	7.10×10^{-5}
Size4	7.10×10^{-5}	8.12×10^{-5}
Size5	8.12×10^{-5}	9.14×10^{-5}

The simulated pulse of the active ingredient material is shown in Fig. 6a, and it is of a relatively large magnitude in order to better observe the effects of the perturbation downstream. However, the magnitude of this pulse is realistic, since experimental studies have verified that the size of the overshoot is highly dependent on the fill level of the gravimetric feeder hopper. According to the model results, the perturbation at 2,500 s affects the bulk density of the powder blend exiting the mixer, but this effect is mitigated further downstream during granulation and milling. Similarly, even if mixing process has not filtered out the API flow rate pulse completely, the effects are further filtered out during granulation and milling. In other words, it is not probable to get significant effects on macroscopic properties of granulated materials after such a short-time perturbation. This result is very encouraging for the continuous simulated design; however, it needs further experimental validation. Finally, in Fig. 6c, the effects of the performed perturbation on microscopic properties, such as particle density, are shown to be clearer and more significant. Specifically,

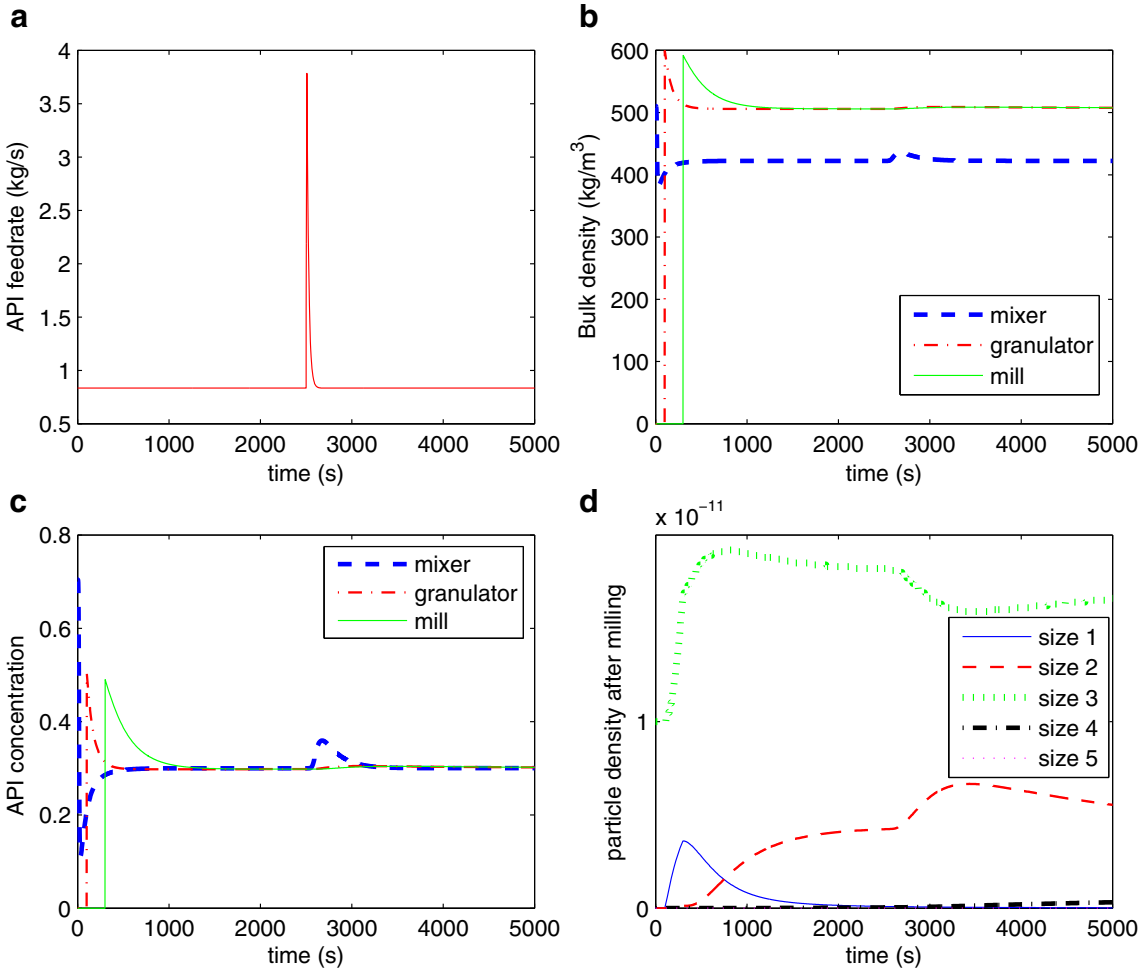

Fig. 6 **a** Pulse of API material during API feeder refilling and **b** effect of feeder refilling on API concentration in downstream process units

after the API refilling perturbation, the larger size particles (size 3) decrease, while the smaller grade of material (size 2) increases in population. This effect suggests a shift in the mean particle size of the milled particles towards smaller sizes.

Step Change in Critical Operating Conditions

The performance of each unit operation is controlled by a set of critical operating conditions which will affect the properties of the outlet powder stream and thus affect the operation of further downstream processes and the final product properties. Therefore, it is important that the developed flowsheet model can capture the effects of modifications in certain key operating conditions, based on experimentally observed results. If this is validated, then the flowsheet model can be further used for the identification of optimal control strategies of the integrated granulation line. As an example, the most important in-process parameter which has been studied here is the liquid binder addition rate during granulation.

According to T. Gluba [16], experimental studies have shown that the moisture content of particles, which is dependent on the rate at which the liquid binder is added in the process, is very critical towards the properties of the final granules. In another study that was performed using a batch wet granulation process [63], it was observed that the agglomerate density increased with moisture content, up to the point where it reached a maximum and then the effect was inverted. In Fig. 7, it is observed that the simulation results agree with experimental findings in the sense that an increase in the binder addition rate causes an increase in the bulk density of the produced material. Since this is a continuous operation, where granules are simultaneously removed from the process, it is expected that this effect will not have a maximum but rather reach a new steady state. In terms of the PSD of the granules, an increase in the binder rate modifies the slope of the birth of larger size agglomerates, such that they are produced at a higher rate. This result shows that the developed granulation model accurately captures the expected favoring of agglomerate formation, when the amount of liquid binder is more.

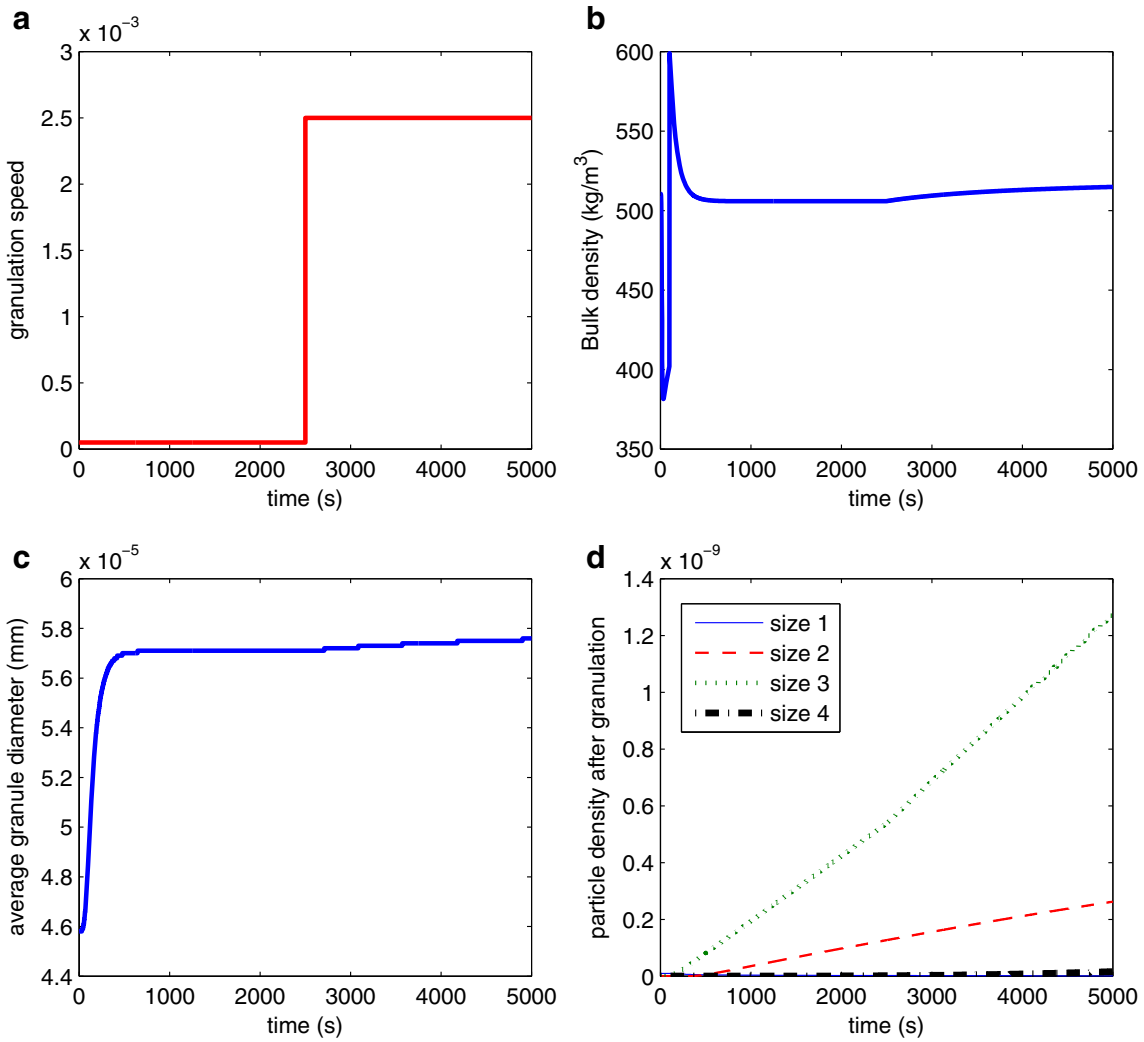

Fig. 7 **a** Step change in granulation binder rate addition, **b** effect of binder rate step change on granule bulk density, and **c** effect of binder rate step change on PSD of granules

Effects on Dissolution

The properties of the powder stream reaching the tablet press as well as the properties of the produced tablets at each time interval highly affect the disintegration and dissolution of each of the produced tablets. In order to quantify the performance of dissolution through a singe metric, the ratio $\frac{t_{10}}{t_{90}}$ is introduced which corresponds to the ratio of the time needed for the dissolution of 10 % of the API over the time needed for the dissolution of 90 % of the API (see Fig. 8). This metric should lie between strict and specific upper and lower bounds based on the specifications of the produced tablet, which are the most critical especially in controlled release products. Any tablets which are produced and which violate these bounds should be discarded; hence, it is very valuable for a simulator to be able to predict the exact time interval within which a fraction of the continuous production should be diverted. In Fig. 9, it can be seen that the dissolution profile metric of the tablets produced while feeder refilling and after a step change in the granulation operating conditions is affected. In the first case, the feeder refilling has affected the tablet properties after a significant time interval and is shown to have a wide time range effect. In other words, the effect of the instantaneous pulse has been delayed and dispersed over time, at the point it has reached the tablets. The slight increase of the $\frac{t_{10}}{t_{90}}$ index signifies that the API has been released faster, which can be explained by the slight decrease in the mean particle size of the powder which reaches the tablet press. On the other hand, after the step change in the binder amount, and due to the slight increase in the mean particle size of the granules, a slight decrease in the dissolution metric is observed. Even though the magnitude of the effects is not large, it is a matter of how strict the product quality specifications are in order to decide whether the produced tablets are out of specifications.

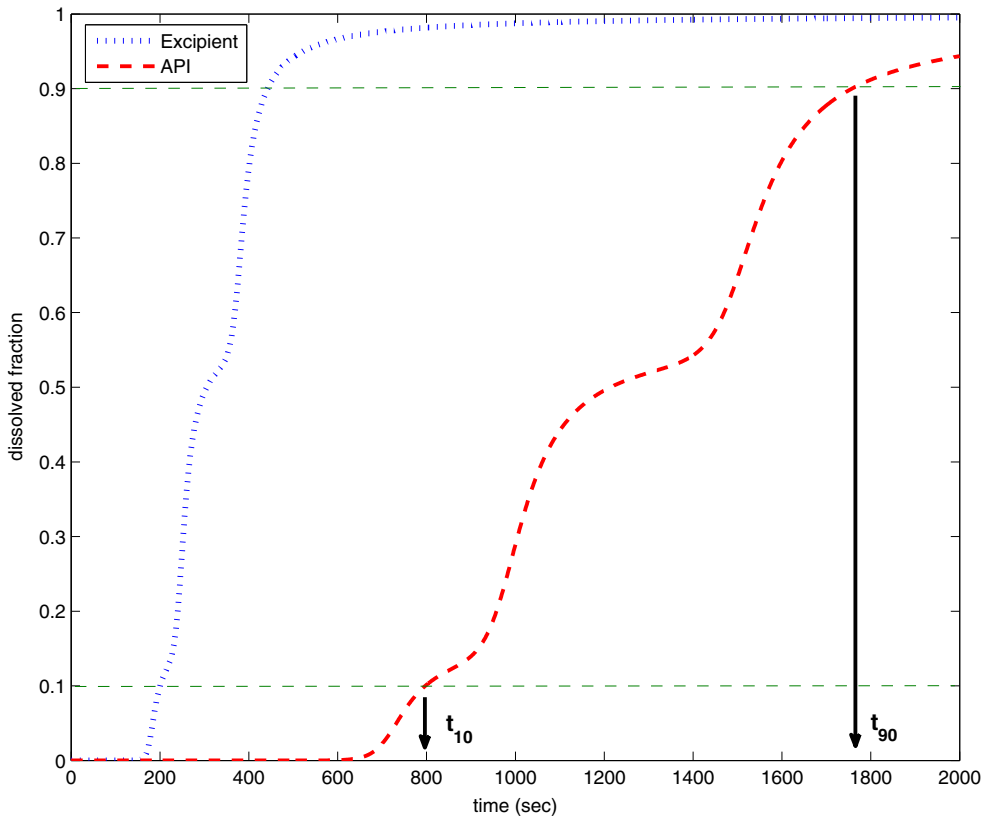

Fig. 8 Dissolution profile of API and excipient for steady-state operation

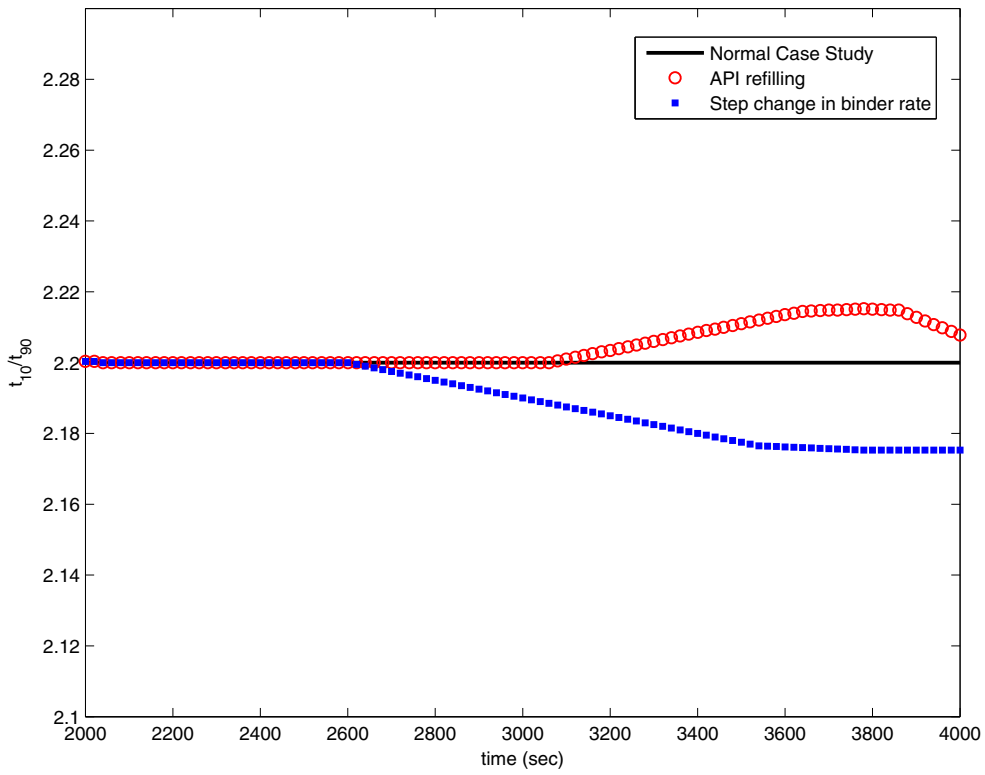

Fig. 9 $\frac{d_{10}}{d_{90}}$ for normal steady-state operation, during feeder refilling and after step change in binder addition rate

Conclusions

Tablet manufacturing through wet granulation is a very commonly employed approach in the production of pharmaceuticals, which is not efficiently designed through the use of process systems engineering tools. In this work, a novel continuous wet granulation configuration is simulated, from the initial feeding of the powder mixture ingredients to the final stage of tablet compaction and their dissolution. This work aims to outline the necessary steps and challenges associated with solid-based flowsheet modeling which include the integration of different types of model types, ranging from semi-mechanistic population balances to purely empirical models, as well as the identification of the critical connecting variables and parameters within and across different unit operations.

Results show that the developed flowsheet model can capture the effects of feedrate perturbations as well as step changes in critical operating conditions such as binder addition rate and milling speed. The novelty of this work lies in the combination of various types of models to describe a continuous powder handling process, where powder and liquid binder are continuously fed into the system and tablets are produced at a constant rate. However, even though the models used in this work have been individually experimentally validated previously, the results of the integrated model need further experimental validation for accurate parameter estimation in order to increase the quantitative accuracy of the developed model. This will be the focus of future work; however, through the current work, the authors aim to propose a general framework for the development of an integrated continuous wet granulation process for the production of pharmaceutical powders.

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References

1. Basu P, Joglekar G, Rai S, Suresh P, Vernon J. Analysis of manufacturing costs in pharmaceutical companies. J Pharm Innov 2008;3:30–40.
2. Betz G, Junker-Purgin P, Leuenberger H. Batch and continuous procesing in the production of pharmaceutical granules. Pharm Dev Technol 2003;8:289–97.
3. Borgquist P, Krner A, Piculell L, Larsson A, Axelsson A. A model for the drug release from a polymer matrix tablet—effects of swelling and dissolution. J Control Release 2006;113(3):216–25.
4. Boukouvala F, Niotis V, Ramachandran R, Muzzio FJ, Ierapetritou MG. An integrated approach for dynamic flowsheet modeling and sensitivity analysis of a continuous tablet manufacturing process. Comput Chem Eng 2012a;42(0):30–47.
5. Boukouvala F, Ramachandran R, Vanarase A, Muzzio FJ, Ierapetritou MG. Computer aided design and analysis of continuous pharmaceutical manufacturing processes. Comput aided Chem Eng 2011;29:216–20.
6. Boukouvala F, Vanarase A, Dubey A, Ramachandran R, Muzzio F, Ierapetritou M. Computational approaches for studying the granular dynamics of continuous blending processes ii: Population balance and data-based methods. Macromol Mater Eng 2012b;297:9–19.
7. Burgschweiger J, Tsotsas E. Experimental investigation and modelling of continuous fluidized bed drying under steady-state and dynamic conditions. Chem Eng Sci 2002;57(24):5021–38.
8. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001;13(2):123–33.
9. Crowe CT. Multiphase flow handbook. Boca Raton: Taylor & Francis; 2006.
10. Dosta M, Heinrich S, Werther J. Fluidized bed spray granulation: analysis of the system behaviour by means of dynamic flowsheet simulation. Powder Technol 2010;204:71–82.
11. Engisch W, Ierapetritou M, Muzzio FJ. 2010. Hopper refill of loss-in-weight feeding equipment. In : Proceedings of the AIChE Annual Meeting 2010. Salt Lake City, UT, USA.
12. Ennis BJ. Particle technology: the legacy of neglect in the US. Chem Eng Prog 1990;90:32–6.
13. Ennis BJ, Tardos G, Pfeffer R. A microlevel-based characterization of granulation phenomena. Powder Technol 1991; 65(1–3):257–72.
14. Fung KY, Ng KM. Product-centered processing: pharmaceutical tablets and capsules. AIChE J 2003;49(5):1193–215.
15. Glaser T, Sanders CFW, Wang FY, Cameron IT, Ramachandran R, Litster JD, Poon JMH, Immanuel CD, Doyle III FJ. 987 Model predictive control of drum granulation. J Process Contr 2009;19:615–22.
16. Gluba T, Obraniak A, Gawot-Młynarczyk E. The effect of granulation conditions on bulk density. Physicochem Probl MI 2004;38:177–86.
17. Goldschmidt M. Hydrodynamic modeling of fluidized bed spray granulation. Ph.D. Thesis. Netherlands: University of Twente; 2001.
18. Gorsek A, Glavic P. Design of batch versus continuous processes: part 1: single-purpose equipment. Chem Eng Res Des 1997;75:709–17.
19. Grunh G, Werther J, Schmidt J. Flowsheeting of solids processes for energy saving and pollution reduction. J Clean Prod 2004;12:147–51.
20. Hapgood KP, Litster JD, Smith R. Nucleation regime map for liquid bound granules. AIChE J 2003;49(2):350–61.
21. Hartge EU, Pogodda M, Reimers C, Schwier D, Gruhn G, Werther J. Flowsheet simulation of solids processes. KONA 2006;24:146–56.
22. Hounslow M. The population balance as a tool for understanding particle rate processes. KONA 1998;16:179–93.
23. Kawakita K, Ldde K-H. Some considerations on powder compression equations. Powder Technol 1971;4(2):61–8.
24. Kimber JA, Kazarian SG, Stephanek F. Microstructure-based mathematical modelling and spectroscopic imaging of tablet dissolution. Comput Chem Eng 2011;35(7):1328–39.
25. Kuentz M, Leuenberger H. A new model for the hardness of a compacted particle system, applied to tablets of pharmaceutical polymers. Powder Technol 2000;111(12):145–53.
26. Leuenberger H. New trends in the production of pharmaceutical granules: batch versus continuous processing. Eur J Pharm Biopharm 2001;52:289–98.

27. Leuenberger H. Scale-up in the 4th dimension in the field of granulation and drying or how to avoid classical scale-up. Powder Technol 2003;130:225–30.
28. Leuenberger H, Betz G. Chapter 15 granulation process control—production of pharmaceutical granules: the classical batch concept and the problem of scale-up. In: Salman AD, Seville J, Hounslow M, editors. Handbook of powder technology: granulation, vol 11; 2007, pp. 705–33.
29. Liu LX, Litster JD, Iveson SM, Ennis BJ. Coalescence of deformable granules in wet granulation processes. AIChE J 2000;46(3):529–39.
30. Madec L, Falk L, Plasari E. Modelling of the agglomeration in suspension process with multidimensional kernels. Powder Technol 2003;130(1–3):147–53.
31. Marshall Jr CL, Rajniak P. Multi-component population balance modeling of granulation with continuous addition of binder. Powder Technol 2012. doi:10.1016/j.powtec.2012.01.027.
32. Matsoukas T, Marshall Jr CL. Bicomponent aggregation in finite systems. EPL 2010;92(4):46007.
33. Muschert S, Siepmann F, Leclercq B, Carlin B, Siepmann J. Prediction of drug release from ethylcellulose coated pellets. J Control Release 2009;135(1):71–9.
34. Ng KM. Design and development of solids processes: a process systems engineering perspective. Powder Technol 2002;126:205–10.
35. Pantelides CC, Oh M. Process modelling tools and their application to particulate processes. Powder Technol 1996;87:13–20.
36. Papavasileiou V, Koulouris A, Siletti C, Petrides D. Optimize manufacture of pharmaceutical products with process simulation and production tools. Chem Eng Res Des 2007;85:1086–97.
37. Pinto MA, Immanuel CD, Doyle III FJ. A feasible solution technique for higher-dimensional population balance models. Comput Chem Eng 2007;31(10):1242–56.
38. Plumb K. Continous processing in the pharmaceutical industry: changing the mindset. Chem Eng Res Des 2005;83:730–8.
39. Radford R. A model of particulate drying in pneumatic conveying systems. Powder Technol 1997;93(2):109–26.
40. Rajniak P, Mancinelli C, Chern R, Stepanek F, Farber L, Hill B. Experimental study of wet granulation in fluidized bed: impact of the binder properties on the granule morphology. Int J Pharm 2007;334(1–2):92–102.
41. Rajniak P, Stepanek F, Dhanasekharan K, Fan R, Mancinelli C, Chern R. A combined experimental and computational study of wet granulation in a wurster fluid bed granulator. Powder Technol 2009;189(2):190–201.
42. Ramachandran R, Ansari MA, Chaudhury A, Kapadia A, Prakash AV, Stepanek F. A quantitative assessment of the influence of primary particle size polydispersity on granule inhomogeneity. Chem Eng Sci 2012;71:104–10.
43. Ramachandran R, Arjunan J, Chaudhury A, Ierapetritou M. Model-based control-loop performance of a continuous direct compaction process. J Pharm Innov 2011;6:249–63.
44. Ramachandran R, Chaudhury A. Model-based design and control of a continuous drum granulation process. Chem Eng Res Des 2011;90(8):1063–73.
45. Reimers C, Werther J, Grunh G. Flowsheet simulation of solids processes: data reconciliation and adjustment of model parameters. Chem Eng Process 2008;47:138–58.
46. Reimers C, Werther J, Grunh G. Design specifications in the flowsheet simulation of complex solids processes. Powder Technol 2009;191:260–71.
47. Rynhart PR. Mathematical modeling of granulation processes. Ph.D. thesis. New Zealand: Massey University; 2004.
48. Salman AD, Hounslow MJ, Seville JPK. Granulation. Handbook of powder technology. Amsterdam: Elsevier; 2007.
49. Schaber SD, Gerogiorgis DI, Ramachandran R, Evans JMB, Barton PI, Trout BL. Economic analysis of integrated continuous and batch pharmaceutical manufacturing: a case study. Ind Eng Chem Prod Res Dev 2011;50(17):10083–92.
50. Schwier D, Hartge E, Puttman A, Grunh G, Werther J. Sensitiviy analysis in the simulation of complex solids processes. Comput aided Chem Eng 2006;21:601–6.
51. Schwier D, Hartge E, Werther J, Grunh G. Global sensitivity analysis in the flowsheet simulation of solids processes. Chem Eng Process 2010;49:9–21.
52. Seider WD, Seider JD, Lewin DR. Process design principles: synthesis, analysis and evaluation. Hoboken: Wiley; 1999.
53. Singh R, Gernaey KV, Gani R. ICAS-PAT: a software for design, analysis and validation of pat systems. Comput Chem Eng 1108–1136;34(7).
54. Stepanek F, Rajniak P, Mancinelli C, Chern R, Ramachandran R. Distribution and accessibility of binder in wet granules. Powder Technol 2009;189(2):376–84.
55. Suresh P, Basu P. Improving pharmaceutical product development and manufacturing: Impact on cost of drug development and cost of goods sold of pharmaceuticals. J Pharm Innov 2008;3:175–87.
56. Toebermann J, Rosenkranz J, Grunh G., Werther J. Block-oriented process simulation of solids processes. Comput Chem Eng 2000;23:1773–82.
57. Truss Jr CL. The future of operator training. J Am Water Works Assoc 2000;92:80–1.
58. Vanarase A, Muzzio FJ. Effect of operating conditions and design parameters in a continuous powder mixer. Powder Technol 2011;208:26–36.
59. Verkoeijen D, Pouw GA, Meesters GMH, Scarlett B. Population balances for particulate processes—a volume approach. Chem Eng Sci 2002;57(12):2287–303.
60. Wang H, Dyakowski T, Senior P, Raghavan R, Yang W. Modelling of batch fluidised bed drying of pharmaceutical granules. Chem Eng Sci 2007;62(5):1524–35.
61. Werani J, Grunberg M, Ober C, Leuenberger H. Semicontinuous granulation—the process of choice for the production of pharmaceutical granules. Powder Technol 2004;140:163–8.
62. Werther J, Heinrich S, Dosta M, Hartge E-U. The ultimate goal of modeling—simulation of system and plant performance. Particuology 2011;9(4):320–9.
63. Yu A, Standish N, Lu L. Coal agglomeration and its effect on bulk density. Powder Technol 1995;82(2):177–89.