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Research Article

Simulation Modeling of a Pharmaceutical Tablet Manufacturing Process via Wet Granulation

Zhengsong Wang,[1] **Zhen Pan**,[1] **Dakuo He**,[1,2] **Jiahui Shi**,[1] **Shouxin Sun**,[3] **and Yue Hou**[4]

[1]*College of Information Science and Engineering, Northeastern University, Shenyang 110004, Liaoning, China*
[2]*State Key Laboratory of Synthetical Automation for Process Industries, Northeastern University, Shenyang 110004, China*
[3]*H3C Technologies Co., Limited, Beijing 100102, China*
[4]*College of Life and Health Sciences, Northeastern University, Shenyang 110169, China*

Correspondence should be addressed to Dakuo He; hedakuo@ise.neu.edu.cn

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The pharmaceutical tablet manufacturing process (PTMP) via wet granulation holds a critical position in pharmaceutical industry. The interest in integrating mechanistic process modeling into the pharmaceutical development has been increased because simulation model is a prerequisite for process design, analysis, control, and optimization. So the simulation modeling for PTMP via wet granulation is very necessary and significant. This study aims at proposing a simulation modeling framework for PTMP via spray fluidized bed granulation (SFBG), which is one of the most widely used wet granulation techniques in pharmaceutical industry. For SFBG, a simulation model that simultaneously involves the influences of operating variables and material attributes on average particle size (APS) is firstly developed, and then a drying model to determine the particle moisture content is introduced to be coupled with the established model predicting APS. For PTMP, considering the important effect of porosity on tablet qualities, a model describing the changes in tablet porosity is developed based on a promoted form of the Heckel equation, and then several recognized models that are all related to porosity are introduced or constructed to calculate important tablet quality indexes. The feasibility and effectiveness of the developed simulation models are validated by performing a computational experimental study to explore the scientific understanding of process and process quality control.

1. Introduction

Oral dosage forms, such as tablets, account for the most popular drug delivery systems for treating patients today [1–3]. So a pharmaceutical tablet manufacturing process (PTMP) holds a critical position in pharmaceutical industry. It is well known that tablet manufacturing via wet granulation is the most common processing route and mainly consists of several consecutive steps, including mixing, wet granulation, drying of wet granules, milling (if necessary), and tabletting [4–6]. The spray fluidized bed granulation (SFBG) is one of the most widely used wet granulation techniques in pharmaceutical industry since the mixing, granulation, and drying of the granules can be achieved in a single operation [7].

Simulation model is a prerequisite for the design, analysis, control, and optimization of processes [5], and the pharmaceutical industry is showing increasing interest in integrating mechanistic process modeling into the workflow of pharmaceutical development, which is mainly motivated not only by quality and cost concerns but also by the need to improve understanding of the influence of materials and processes on the final product [8]. First of all, mechanistic simulation models can in fact be used for increasing scientific understanding by summarizing available process knowledge which would help to understand the influence of input variables on the pharmaceutical process and the product quality [4, 8]. Secondly, the models can also be used to explore a design space or develop control strategies during pharmaceutical development, and an advantage of using

models is their solution speed, allowing to compute many different scenarios as opposed to performing expensive experiments [4, 8, 9]. Furthermore, simulation modeling is also an important segment of Quality by Design [9]. Therefore, the simulation modeling for SFBG-based PTMP is of great significance both theoretically and practically.

In the SFBG-based PTMP, although some of the unit operations considered can be run continuously and also growing attention has been paid to continuous manufacturing, they are still operated in a batchwise manner due to the presence of intermediate bulk mixing steps [8]. Additionally, with the introduction and development of Industry 4.0 and intelligent manufacturing, product customization will be an inevitable trend in the future, with applications such as drug customization, which further reinforces the importance of batch processes in the pharmaceutical industry especially in small batch drug customization. Consequently, the simulation modeling for SFBG-based PTMP operated in a batchwise manner is necessary. However, to the authors' knowledge, research studies on simulation modeling for such an integrated process, i.e., PTMP via wet granulation, are very limited and mainly focused on continuous tablet manufacturing [5, 10]. And even few studies have been reported in the simulation modeling for SFBG-based PTMP. Furthermore, SFBG is a complicated process influenced by both the material- and process-related factors, but not much attention has been paid to the modeling considering material attributes except for Hussain's work [11, 12], in which the effects of process parameters and material attributes are modeled in the kernel. However, the limitation of this model is that it contains only one critical operating variable.

The primary aim of the present study is to develop a simulation modeling framework which can link the key operating variables and material attributes with the properties of granules or tablets to predict the granulation and tabletting behavior in the SFBG-based PTMP. The contributions and limitation are listed as follows:

(i) A simulation model for SFBG, which simultaneously involves the influences of operating variables and material attributes on a key quality index, i.e., average particle size (APS), is developed using population balance model (PBM), in which a Hussain's aggregate kernel [11, 12] and a Walzel's model [13, 14] are applied to, respectively, introduce the material attributes and the critical operating variables into modeling framework.

(ii) A drying model to determine the particle moisture content (another critical particle quality significantly affecting tabletting) [15] is introduced to be coupled with the established PBM predicting APS, so that the simulation model for a multiple-input multiple-output SFBG is developed.

(iii) Considering the important effect of porosity on tablet quality, a model describing the change in tablet porosity is developed based on a promoted form of the Heckel equation, in which several empirical models for state variables such as initial porosity and punch pressure are constructed according to the widely accepted analysis and conclusions in the field, and then the model parameters are identified using experimental data from the literature. Following the porosity model, several recognized models relating to porosity are introduced or constructed to calculate important tablet quality indexes, such as tensile strength, hardness, disintegration time, and dissolution rate so that the simulation modeling for tabletting is achieved.

(iv) The simulation modeling for a SFBG-based PTMP is developed by integrating the models of SFBG and tabletting. And then a computational experimental study is carried out by exploring the scientific understanding of process and process quality control to validate the feasibility and effectiveness of the simulation models. But this work is limited to a simulation study and lacks validation based on actual process data. Therefore, this paper only puts forward a preliminary simulation modeling framework. Once the actual experimental data are available in the future studies, the modeling framework can be identified and validated with the actual process data to make it practical for simulation, which is important for intending to use the models as a tool for the pharmaceutical Quality by Design.

The remainder of this paper is arranged as follows. Section 2 gives the process description of SFBG-based PTMP. In Section 3, the simulation models for SFBG-based PTMP are, respectively, developed. In Section 4, the computational experimental study is performed to verify the feasibility and effectiveness of simulation models, and then the results and discussions are given. Section 5 concludes this paper.

2. Process Description

As shown in Figure 1, a typical PTMP via wet granulation can be subdivided into a number of stages [4, 5]: (1) mixing/blending, in which the active pharmaceutical ingredients (APIs) are mixed with excipients in a certain ratio; (2) wet granulation, in which the particles are consolidated into granules to obtain a desirable size distribution, improve powder flow properties, reduce the dust formation, promote the compressibility, and so on; (3) drying of wet granules, in which the wet granules are dried to the desired moisture content level that is suitable for tabletting; (4) milling (if necessary), in which the lumps or oversized granules formed during the wet granulation are broken; (5) tabletting, in which the granules are compressed into a solid tablet by mechanical means; and (6) coating (if necessary), in which the tablet is covered with a thin layer of polymer.

2.1. Spray Fluidized Bed Granulation. SFBG is a well-known process that forms particles into larger granules by spraying a binder solution onto fluidized particles with a spray nozzle

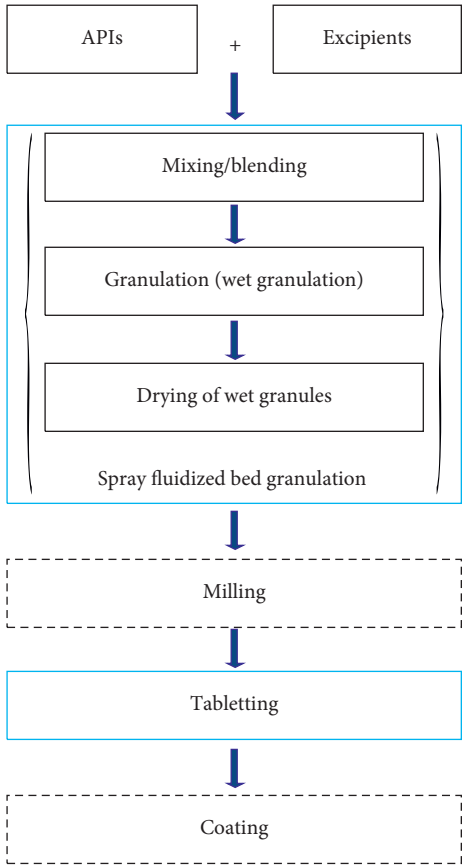

Figure 1: Schematic diagram of typical PTMP via wet granulation.

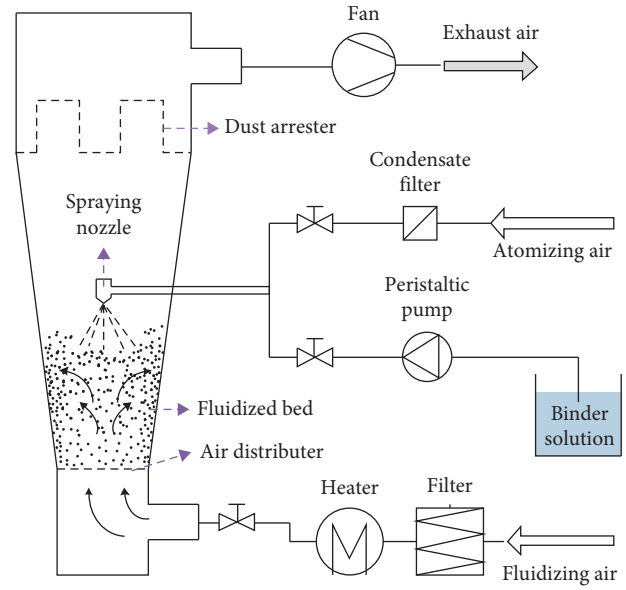

Figure 2: Schematic diagram of a top-spray fluidized bed granulator.

at the top of the fluidized bed. Since the mixing, granulation, and drying of the granules can be achieved in a single operation (Figure 1), which helps avoid transfer losses, enables dust containment, and saves labor costs and time, SFBG is thus widely used in pharmaceutical industry [7, 16, 17].

The overall granulation process in a top-spray fluidized bed granulator shown in Figure 2 is divided into three stages. Initially, in order to sufficiently blend materials, the powder particles circulate within granulator by pumping fluidizing air from a distributor at the bottom of the fluidized bed. Next, liquid binder is atomized into fine droplets by atomizing air and then sprayed onto fluidized bed. The droplets are dispersed over the surface of fluidized particles, which contributes to the agglomeration of surface-wetted particles to form granules. During granulation, the particle size increases due to agglomeration. Lastly, the final granules are dried to a predetermined moisture content level by continuously pumping fluidizing air into the bed.

SFBG is a complicated process influenced by both the material- and process-related factors [17–19]. The material-related factors include wetting properties of solid particles and its solubility, load and micrometric properties of powder, and properties of binding agents, and among them, the important material attributes affecting SFBG consist of primary particle size, particle density, binder viscosity, and so forth [20–23]. Among many process-related factors, such as the geometry of granulator chamber, airflow rate, and inlet air temperature, it has been found that the particle quality changes remarkably due to variations in the operating conditions of binder solution spray, including binder feed rate and atomizing air pressure [17, 19]. Particle quality can be evaluated by many factors, and among them, APS is the key factor to be controlled [17, 18]. Additionally, moisture content is another important particle quality index because of its influences on tabletting.

2.2. Tabletting Process. Tabletting on rotary tablet presses, where the powder material is compressed into tablets in a die between rigid punches, is widely used in pharmaceutical industry [1, 3]. The schematic diagram of a rotary tablet press is shown in Figure 3. The central part of a rotary press is the turret (or die table) which is equipped with a number of tool stations consisting of upper punch-die-lower punch assemblies, and each station passes successively through the following mechanisms as the die table rotates [3]:

(1) Feed frame, where the powder is introduced into the die

(2) Precompression and main compression, where the powder is compressed into a tablet

(3) Ejection cam, where the tablet is ejected from the die

The rotary tablet presses have many adjustable process parameters affecting the tablet properties, and among them, the most important ones during compression include turret speed, rolling reduction, and compression pressure [3]. Additionally, it is reported that the critical quality attributes of tablets can be represented by the properties of tensile strength, hardness, disintegration time, and dissolution rate [24–26].

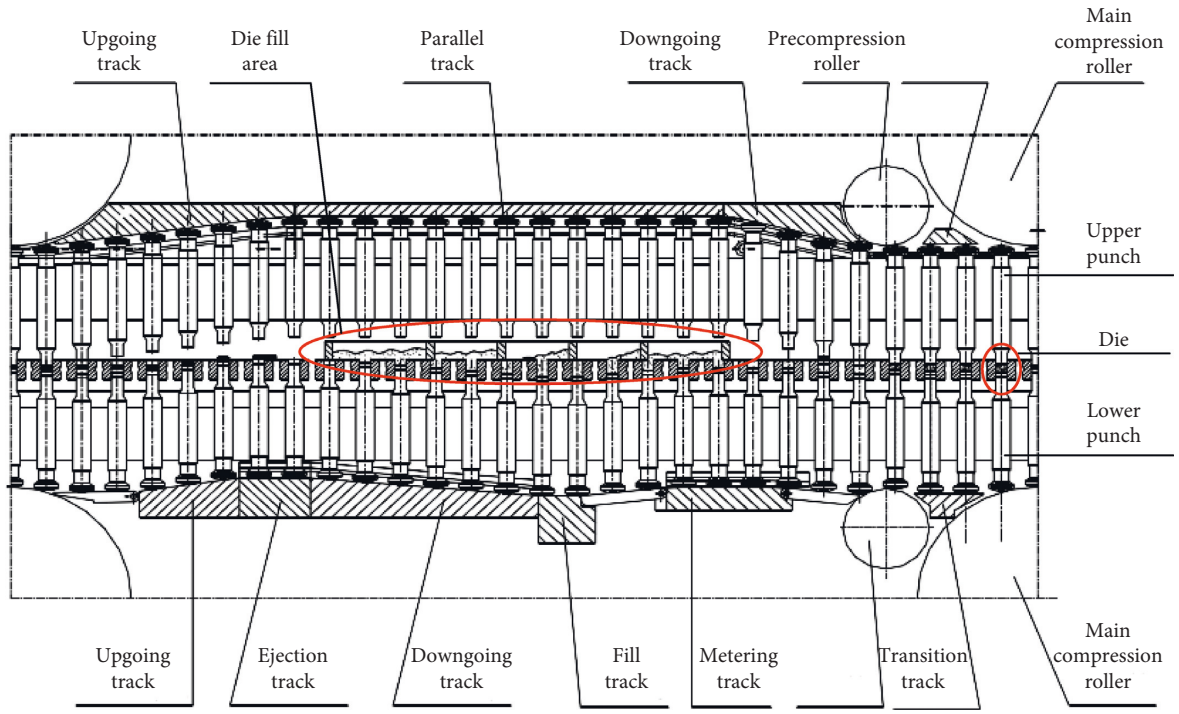

Figure 3: Schematic diagram of unfolded view of a rotary tablet press.

3. Simulation Modeling for SFBG-Based PTMP

The process to be modeled is comprised of SFBG and tabletting in series, and the models should be connected so that a change in materials or operating conditions can be related to intermediate and final product attributes. Figure 4 gives the framework overview of simulation modeling for SFBG-based PTMP.

3.1. Simulation Modeling for SFBG

3.1.1. The Model Predicting APS. In this subsection, a simulation model which simultaneously links the operating variables, including binder feed rate and atomizing air pressure, and material attributes such as binder viscosity, particle density, and primary particle size with the APS is developed using PBM. Population balance is simply a number balance around each size fraction of particle size distribution based on number conservation law, and it describes the change rate of number of particles entering and leaving that size interval by different occurring phenomena within a granulation system, such as nucleation, aggregation, and breakage [27]. But many studies paid attention to pure agglomeration and ignored other mechanisms when constructing PBM framework [11, 12, 28–31]. Pure agglomeration is not only considered for simplicity but also justified for SFBG because raw materials and operating conditions, in the practical application, are chosen as to avoid other mechanisms [31].

The discrete form of a general one-dimensional and length-based PBM for pure agglomeration is given by [32, 33]

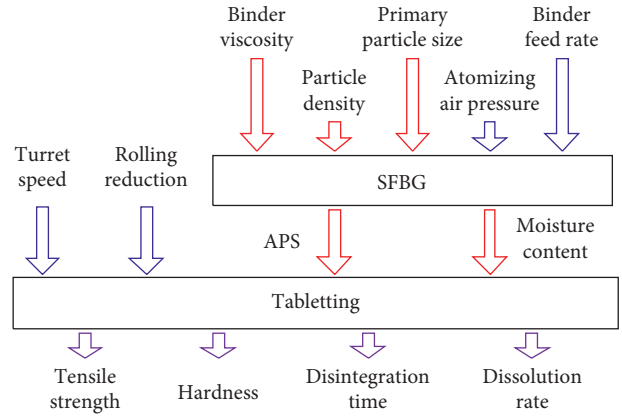

Figure 4: The framework overview of simulation modeling for SFBG-based PTMP.

$$\frac{dN_i}{dt} = \sum_{j=1}^{i-2} 2^{j-i+1}\beta_{i-1,j}N_{i-1}N_j + \frac{1}{2}\beta_{i-1,i-1}N_{i-1}^2 - N_i\sum_{j=1}^{i-1} 2^{j-i}\beta_{i,j}N_j - N_i\sum_{j=i}^{n_{\max}}\beta_{i,j}N_j, \quad (1)$$

where N_i is the number of particles within particle size interval (L_i, L_{i+1}), L_i and L_{i+1} are the lower and upper limits of i-th size interval with a geometric ratio of $L_{i+1}/L_i = \sqrt[3]{2}$ and the particle size in i-th size interval is represented by the left edge L_i, $n_{\max}$ is the number of size intervals, and $\beta_{i,j}$ is the aggregation kernel between particles from i-th and j-th size intervals.

The aggregation model $\beta(t, l, \delta)$ can be generally formulated as [11, 17]

$$\beta(t,l,\delta) = \beta_0(t)\beta^*(l,\delta), \tag{2}$$

where β_0 is the aggregation rate constant which depends on the time, operating conditions, and material attributes except particle size, $\beta^*(l,\delta)$ reflects the influence of particle size on the probability of aggregation between particles with different diameters of l and δ, and $\beta^*(l,\delta)$ is set as a shear form [17]:

$$\beta^*(l,\delta) = (l+\delta)^3, \tag{3}$$

and β_0 is given by [11, 12]

$$\beta_0 = \frac{\psi f_c N_{wet}}{N_{tot}^2}\left(\frac{2(N_{tot}-N_{wet})}{N_{tot}-1}\eta_{wd} + \frac{N_{wet}-1}{N_{tot}-1}\eta_{ww}\right). \tag{4}$$

Here, f_c is the collision frequency per particle which should be given in advance; N_{tot} is the total number of particles in the granulation system; N_{wet} is the number of wet particles; ψ is the success factor concerning the dissipation of kinetic energy according to Stokes criterion [34]; η_{wd} is the probability of collision at wet parts in a wet-dry collision; and η_{ww} is the probability of collision at wet parts in a wet-wet collision.

By substituting (3) and (4) into (1), we have

$$\begin{aligned}\frac{dN_i}{dt} = {} & \frac{\psi f_c N_{wet}}{N_{tot}^2}\left(\frac{2(N_{tot}-N_{wet})}{N_{tot}-1}\eta_{wd} + \frac{N_{wet}-1}{N_{tot}-1}\eta_{ww}\right) \\ & \times\left(\sum_{j=1}^{i-2} 2^{j-i+1}\left(L_{i-1}+L_j\right)^3 N_{i-1}N_j + 4L_{i-1}^3 N_{i-1}^2\right. \\ & \left. - N_i\sum_{j=1}^{i-1} 2^{j-i}\left(L_i+L_j\right)^3 N_j - N_i\sum_{j=i}^{n_{max}}\left(L_i+L_j\right)^3 N_j\right),\end{aligned} \tag{5}$$

where L_i and L_j represent the particle sizes in i-th and j-th size interval, respectively.

Then, N_{tot} and N_{wet} can be modeled as [11, 12]

$$\begin{aligned}\frac{dN_{tot}}{dt} &= -\frac{f_c\psi N_{tot}}{2}\left(\frac{2(N_{tot}-N_{wet})}{N_{tot}-1}\eta_{wd} + \frac{N_{wet}-1}{N_{tot}-1}\eta_{ww}\right), \\ \frac{dN_{wet}}{dt} &= \dot{N}_{drop} - N_{wet}\left(\psi f_c\left(\eta_{wd} - (\eta_{wd}-\eta_{ww})\left(\frac{N_{wet}-1}{N_{tot}-1}\right)\right)\right. \\ &\quad \left. + \left(1-\frac{t_{dry}}{t_g}\right)\frac{N_{wet}}{\dot{N}_{drop}t_{dry}^2}\right),\end{aligned} \tag{6}$$

where $\dot{N}_{drop}$ is the number addition rate of binder droplets and t_{dry} and t_g are the mean drying time of a binder droplet and the granulation time, respectively. Besides, ψ is determined by Stokes criterion [34, 35]:

$$\begin{aligned}St_{coal} &= \frac{4\rho_p u_c d_p}{9\mu_b}, \\ St_{coal}^{crit} &= \left(1+\frac{1}{e}\right)\ln\left(\frac{h}{h_a}\right).\end{aligned} \tag{7}$$

If $St_{coal} < St_{coal}^{crit}$, then $\psi = 1$, which reveals that the colliding particles are merged to form one agglomerate. Otherwise, $\psi = 0$. Here, ρ_p and d_p are the particle density and APS during granulation, respectively; μ_b is the binder viscosity. Refer to [12, 36] for the other parameters; they will not be covered here.

The above discussions clearly indicate that the material attributes including binder viscosity, particle density, and primary particle size (primary particle size is a necessary initial condition for solving PBM) are involved in modeling framework. But the current model has only one operating variable, $\dot{N}_{drop}$. Therefore, by introducing a Walzel's model described in the following equation [13, 14], in which binder feed rate and atomizing air pressure are used to predict binder droplet size, the operating variables of binder feed rate and atomizing air pressure can be introduced into modeling framework.

$$d_{drop} = \frac{0.35 d_{noz}\left(P_{air}d_{noz}\right)^{-0.4}}{\left(\sigma\left(1+\left(\dot{M}_{liq}/\dot{M}_{air}\right)\right)^2\right)^{-0.4}\left(1+\left(2.5\mu_b/\left(\sigma\rho_{liq}d_{noz}\right)^{0.5}\right)\right)}, \tag{8}$$

where d_{drop} is the diameter of binder droplet, d_{noz} is the diameter of spray nozzle, σ is the surface tension of binder solution, P_{air} is the atomizing air pressure, $\dot{M}_{liq}$ is the binder feed rate, $\dot{M}_{air}$ is the atomizing air flow rate, and ρ_{liq} is the density of binder solution. Then, $\dot{N}_{drop}$ can be expressed as

$$\dot{N}_{drop} = \frac{\dot{M}_{liq}}{\rho_{liq}V_{drop}} = \frac{6\dot{M}_{liq}}{\rho_{liq}\pi d_{drop}^3}. \tag{9}$$

Because the above PBM is built based on a discrete calculation method, and in order to facilitate the coupling of this model with the model predicting moisture content, the SFBG is discrete into multiple stages and the schematic diagram of simulation modeling for a segmented SFBG is shown in Figure 5. The PBM is solved by "ode45" in MATLAB to obtain the number of final particles in i-th size interval at m-th stage, $N_{f,i,m}$, where $i = 1, 2, \ldots, n_{max}$, $m = 1, 2, \ldots, n_s$. Then, the APS of final granules at m-th stage is calculated by

$$d_{p,m} = \sum_{i=1}^{n_{max}} V\left(N_{f,i,m}\right)d_{gm,i}, \tag{10}$$

where $V(N_{f,i,m})$ is the volume fraction of end particles in i-th size interval at m-th stage and $d_{gm,i}$ is the geometric mean of lower limit and upper limit of i-th size interval. By taking $d_{p,0}$ as the initial APS and solving PBM n_s times according to the sequence shown in Figure 5, the final APS, d_{p,n_s}, can be calculated by (10).

3.1.2. The Model of Moisture Content and Its Coupling with the Model Predicting APS. The focus of this subsection is on the introduction of a drying model that determines the particle moisture content and its coupling with the above-described PBM predicting APS. The basis of their coupling is the commonality in a discrete calculation method, by which the SFBG process is discrete into multiple stages in series.

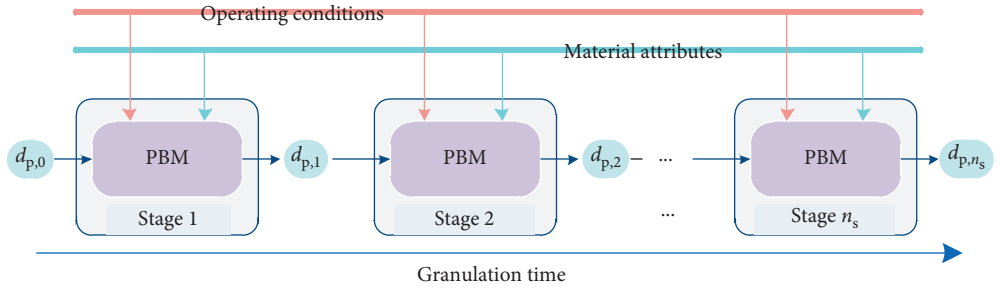

Figure 5: Schematic diagram of the simulation modeling for a segmented SFBG.

Next, we first briefly introduce the drying model, and for its detailed derivations, refer to [15].

The following formula can be used to evaluate the mean moisture content,

$$X_{mc} = \frac{M_w}{M_{s,dry}}, \tag{11}$$

of the solid, i.e., water mass M_w per mass of dry solid $M_{s,dry}$.

The drying of droplets can be expressed by the mass balance as follows:

$$\frac{dM_{drop}}{dt} = -\dot{M}_{evap} \approx \frac{\Delta M_{drop}}{\Delta t}, \tag{12}$$

with the kinetics,

$$\dot{M}_{evap} = \rho_g k_{mt} A_{drop} (Y_{sat} - Y_{out}), \tag{13}$$

where Y_{sat} and Y_{out} are the adiabatic saturation moisture content and the steady-state moisture content of the gas phase, respectively, and ρ_g is the gas density. (Y_{sat}) can be calculated by [37]

$$Y_{sat} = 0.622 \frac{p_{sat}}{P_t - p_{sat}}, \tag{14}$$

where P_t is the total pressure of wet air and p_{sat} is the saturation vapour pressure and can be obtained from the Antoine equation which links p_{sat} to the bed temperature T_{bed}. The expression Y_{out} can be calculated by assuming maximum evaporation of liquid ($\dot{M}_{liq}$) added via the nozzle:

$$Y_{out} = Y_{in} + \frac{\dot{M}_{liq}}{\dot{M}_g} (1 - w_b), \tag{15}$$

where Y_{in} is the inlet moisture content, $\dot{M}_{liq}$ and $\dot{M}_g$ are the mass flows of binder liquid and gas, respectively, and w_b is the solid mass fraction of the binder liquid. The mass transfer coefficient can be computed as

$$k_{mc} = \frac{S_h \delta_{wg}}{d_p}, \tag{16}$$

where S_h is the dimensionless Sherwood number, δ_{wg} is the diffusion coefficient of water in gas, and d_p is the primary particle diameter. The total evaporation of water per time step i is a cumulative measure of all liquid droplets j being present:

$$\Delta M_{w,i} = \sum_{j=1}^{N_{drop}} M_{evap,j} \Delta t_i. \tag{17}$$

The water mass carried by the particles can now be calculated by

$$M_{w,i} = M_{w,i-1} - \Delta M_{w,i}. \tag{18}$$

Then, two models are coupled to form the simulation model of SFBG, as shown in Figure 6.

3.2. Simulation Modeling for Tabletting. Porosity is an important concept in the study of tablets because it is related to various quality indexes of tablets. The tablet press model calculates tablet porosity from the tablet reduced density as a function of the pressure [8]. The Heckel equation is a widely studied model to calculate this relationship. A lot of research works by Picker et al. [38–49] have studied the influences of pressure, compression time, and compression distance (rolling reduction) on the porosity through a promoted form of the Heckel equation:

$$-\ln \varepsilon = \ln \frac{1}{1 - \rho_{rel}} = e_t t_c + e_p p_c + e_0, \tag{19}$$

where $\varepsilon = 1 - \rho_{ref}$ is the porosity; ρ_{ref} is the relative density of the tablet (the ratio of tablet density to true density of powder); e_t represents the densification over the compression time; e_p represents the densification over the pressure; and e_0 represents the intersection with y-axis $\ln(1/(1 - \rho_{rel}))$ and it is described as

$$e_0 = \ln \frac{1}{1 - \rho_{ref,0}} + K = \ln \frac{1}{\varepsilon_0} + K, \tag{20}$$

where ε_0 is the initial porosity and K represents the change in porosity due to the rearrangement of particles in the initial state [50].

Picker et al. [38–49] carried out a large number of experiments, by which we give the following models in (21)~(23) to be identified after the analysis of each variable, and then the model parameters are calibrated with the experimental data from literature studies:

$$e_t = a_{11} d_p + a_{12} d_r + \frac{a_{13}}{n_r} + a_{14}, \tag{21}$$

$$e_p = b_{11} d_p + b_{12} d_r + b_{13}, \tag{22}$$

$$K = c_{11} d_p + \frac{c_{12}}{n_r} + c_{13}, \tag{23}$$

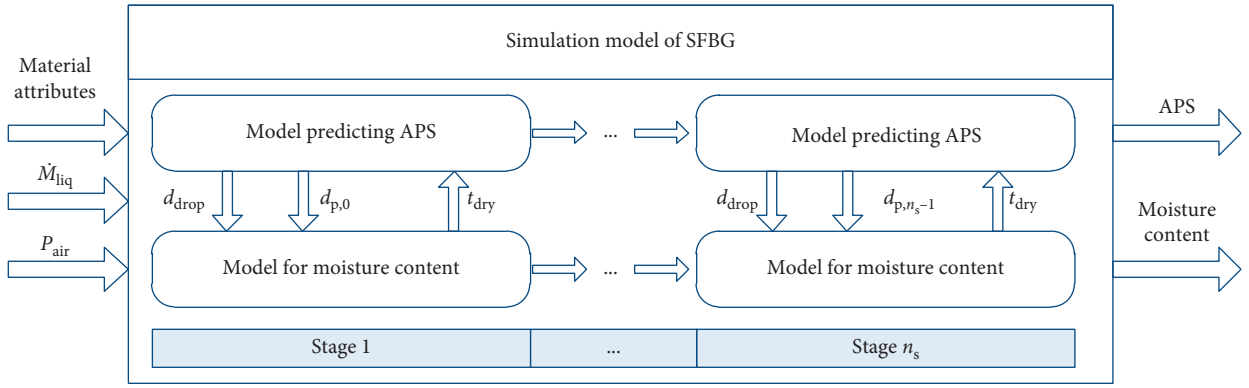

Figure 6: The coupling structure of the two models for SFBG.

where d_p is APS, d_r is the rolling reduction, n_r is the turret speed (rpm), and the others are the parameters to be identified.

The initial porosity is related to the APS of particles. Generally speaking, the initial porosity increases as the APS increases due to the gradually increasing space between the particles [50]. But when the particle size increases to a threshold, the initial porosity no longer changes with increasing APS, that is, the initial porosity has a maximum value. By referring to the form of Cooper–Eaton equation [51], we give the following form of initial porosity model:

$$\varepsilon_0 = d_{11}\exp\left(d_{12}d_p\right) + d_{13}\exp\left(d_{14}d_p\right), \tag{24}$$

where d_{11}, d_{12}, d_{13}, and d_{14} are the coefficients to be identified with the experimental data from literature studies.

The compression time t_c can be divided into process time t_p and dwell time t_d, i.e., $t_c = t_p + t_d$, as shown in Figure 7, in which d_e is the diameter of the upper punch head and also is the punch displacement during the dwell time.

Because the punch follows the turret for circular motion, the punch velocity is given by $v_p = 2\pi R_t n_r$, and then

$$\begin{aligned} t_p &= \frac{h_p}{v_p} = \frac{R_{cr}\sin\left(\arccos\left(\left(R_{cr} - d_r\right)/R_{cr}\right)\right)}{2\pi R_t n_r}, \\ t_d &= \frac{d_e}{v_p} = \frac{d_e}{2\pi R_t n_r}, \end{aligned} \tag{25}$$

where R_t is the radius of turret, t_p and t_d are closely related to the tablet quality, and t_d plays a major role in the tabletting.

The powder in the die has both viscous and elastic properties, and the punch pressure p_c is related to this viscoelasticity. The existing viscoelastic model in powder mechanics [52] is quite complicated so that it has theoretical analysis significance but is not applicable in practical applications. Therefore, based on the analysis of the viscoelastic model and the effect of each state variable on the pressure, we try to establish a model for pressure. Firstly, the smaller pressure required during tabletting for the greater sized particles can be attributed to a smaller surface area, smaller contact points, and a lower cohesion or frictional force, which requires less pressure to offset [50, 53]. So there is an inverse relationship between pressure and particle size.

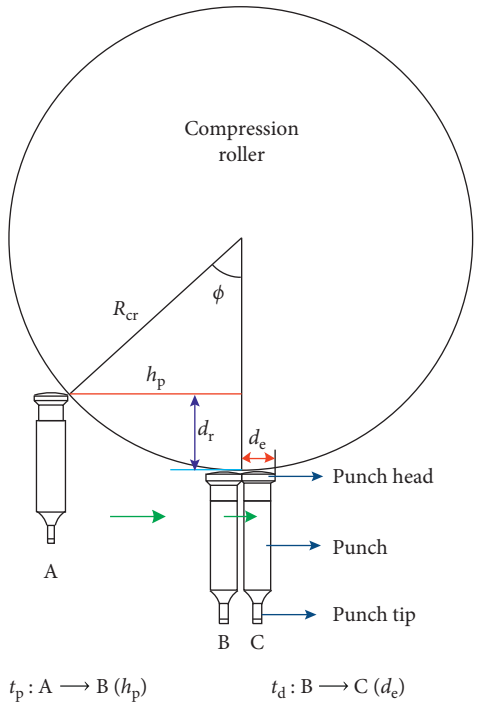

Figure 7: Two time periods of tabletting.

Secondly, the moisture content represents the viscous properties of the particles to some extent. The smaller pressure required to form a tablet when the particles have a larger moisture content. So there is also an inverse relationship between pressure and moisture content. Thirdly, if the total amount of particles is constant, the smaller the thickness of the tablet, i.e., the greater the degree of compression, the greater the rebound force of the particle column [50]. So the punch pressure is inversely proportional to the remaining particle column height. Additionally, the pressure is also proportional to the compression speed [54]. Therefore, the following empirical equation is used to model the punch pressure:

$$p_c = k_p\frac{\left(1 - X_{mc}\right)v_c}{d_p\left(l_0 - d_r\right)}, \tag{26}$$

with a compression speed model [55]:

$$v_c = \frac{\pi R_t n_r}{15}\sqrt{\frac{d_r}{r}}, \tag{27}$$

where k_p is the pressure coefficient that is related to the viscoelasticity of particles and l_0 is the initial powder column height without compression.

With this, we have constructed the simulation model for the porosity, based on which the following models are introduced to calculate the tablet quality indexes, including tensile strength H_{ts}, hardness H_h, disintegration time D_t, and dissolution rate D_r.

Tensile strength is obtained by solving the following equation [25]:

$$H_{ts} = H_{ts,max}\left(1 - \exp\left(\varepsilon_0 - \varepsilon + \ln\frac{\varepsilon}{\varepsilon_0}\right)\right), \tag{28}$$

where $H_{ts,max}$ is the maximum tensile strength representing the strength of tablets at a theoretical zero porosity, and it is a regressed parameter based on the experimental data from [25].

Hardness is obtained by solving the following equation [24]:

$$H_h = H_{h,max}\left(\varepsilon - \varepsilon_0 - \ln\frac{\varepsilon}{\varepsilon_0}\right), \tag{29}$$

where $H_{h,max}$ holds for the maximal hardness.

For disintegration time, we give the following polynomial model according to the known influence trend of the tablet porosity on the disintegration time [3, 56]:

$$D_t = f_{11}\varepsilon^2 + f_{12}\varepsilon + f_{13}, \tag{30}$$

where f_{11}, f_{12}, and f_{13} are the coefficients to be identified with the experimental data.

Dissolution rate is obtained by solving the following equation [26]:

$$\frac{3}{2}\left(1 - \left(1 - \frac{M_t}{M_\infty}\right)^{2/3}\right) - \frac{M_t}{M_\infty} = \frac{3D_f C_{fs}\varepsilon}{r_0^2 C_0 \tau}t, \tag{31}$$

and refer to [26] for details.

4. Computational Experimental Study: Results and Discussions

In this section, the feasibility and effectiveness of simulation models are tested through a computational experimental study—simulations. The influences of process parameters and material attributes on the intermediate or final quality attributes are firstly studied by implementing simulation experiments, whose results are compared with the widely accepted conclusions in the field. The feasibility and effectiveness will be confirmed by the consistencies of simulation results and recognized analysis or conclusions. On another level, in order to verify the effectiveness of simulation models in process quality control, a validated control method is applied to determine whether the simulated SFBG-based PTMP can be used for designing or testing control algorithms.

Table 1: The simulation experiment settings for SFBG.

Property (unit)	Value
$d_{p,0}$ (μm)	[50, 126]
μ_b (Pa·s)	[0.025, 0.15]
ρ_p (kg/m^3)	[300, 1200]
M_{liq} (10^{-5}kg/s)	[0.5, 3.0]
P_{air} (10^5Pa)	[1.5, 4.5]
T_{bed} ($^\circ$C)	[30, 60]
M_g (kg/s)	1.6×10^{-5}
ρ_{liq} (kg/m^3)	1014
ρ_g (kg/m^3)	1.225
w_b (%)	6
$M_{s,dry}$ (kg)	0.05
S_h	4
δ_{wg} (10^{-4}m^2/s)	2.9
n_{max}	12
L_1 (μm)	50
$L_{n_{max+1}}$ (μm)	800
f_c (s^{-1})	1
η_{wd}	0.5
η_{ww}	0.75
σ (mN/m)	43.1
t_g (s)	1200

4.1. Computational Experiments on Model Verification for SFBG. The focus of this section is on the study of influences of critical material attributes and important process parameters on the APS and moisture content. The simulation experimental conditions are shown in Table 1.

The simulation results about the influences of material attributes on APS are shown in Figure 8. Firstly, APS increases with the increase of binder viscosity up to maximum at a critical value, and then, APS decreased with the continuous increase of binder viscosity, which is consistent with the conclusion in [35]. As stated in [35], binders of viscosity less than a critical value will be referred to as "lower viscosity" binders and binders of viscosity larger than this critical value will be referred to as "higher viscosity" binders. With "lower viscosity" binders, the degree of size enlargement increases with increasing binder viscosity because the granule growth occurs by layering and, conversely, the extent of size enlargement decreases with increasing viscosity with "higher viscosity" binders because the growth occurs by coalescence [35, 57]. Secondly, APS increases as the primary particle size increases when keeping operating variables and other material attributes constant, which agrees with the conclusions in [20, 22]. This is attributed to the fact that an increase in the particle initial size leads to an enhancement of the layering mechanism and further results in an increase in final particle size [20, 22]. Thirdly, APS decreases as the particle density increases. The mechanism of particle density affecting particle growth can be reasonably explained from the kinetic energy level of the particle. The increase in particle density directly leads to an increase in the weight of particles, which directly increases the kinetic energy of particle motion. Therefore, in the case where the operating variables and the binder viscosity are constant, the probability that the adhesive layer dissipates the kinetic energy of particles is reduced, and the probability of collision

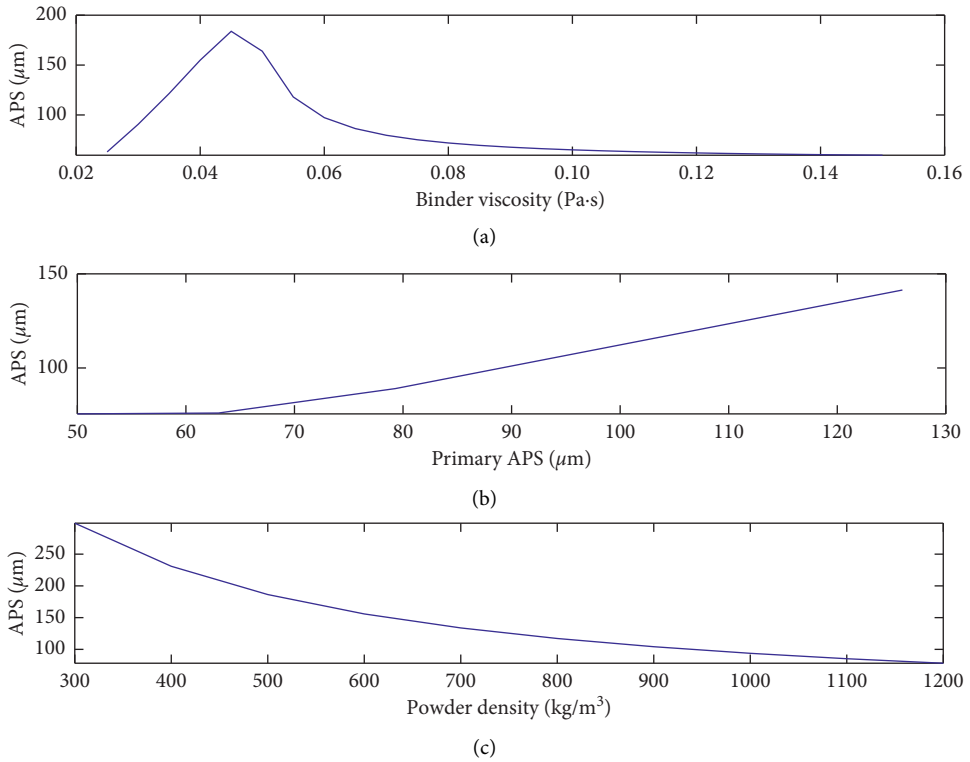

Figure 8: The simulation results for SFBG: influences of material attributes.

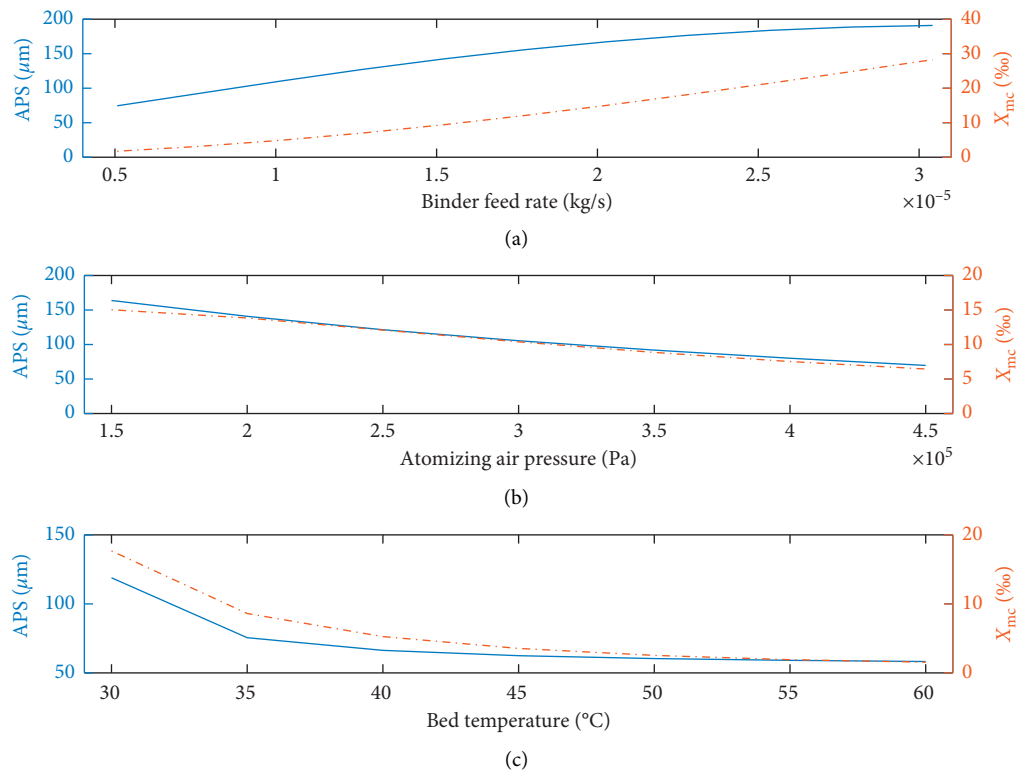

Figure 9: The simulation results for SFBG: influences of process parameters.

Table 2: The simulation experimental conditions for tabletting.

Property (unit)	Value	Parameter	Value	Parameter	Value
n_r (rpm)	[40, 100]	a_{11}	7.19×10^{-4}	d_{11}	0.4500
d_r (mm)	[1, 4]	a_{12}	0.0049	d_{12}	-6.27×10^{-5}
d_p (μm)	[80, 150]	a_{13}	−0.0164	d_{13}	−0.0106
X_{mc} (‰)	[10, 300]	a_{14}	0.0114	d_{14}	−23.44
R_t (mm)	250	b_{11}	−0.0063	f_{11}	167.2125
R_{cr} (mm)	50	b_{12}	−0.0005	f_{12}	−173.4375
d_e (mm)	15	b_{13}	0.0072	f_{13}	44.5875
l_0 (mm)	10	c_{11}	-6.98×10^{-4}		
$H_{ts,max}$ (Mpa)	8.2927	c_{12}	0.0155		
$H_{h,max}$ (N)	250	c_{13}	−0.0128		

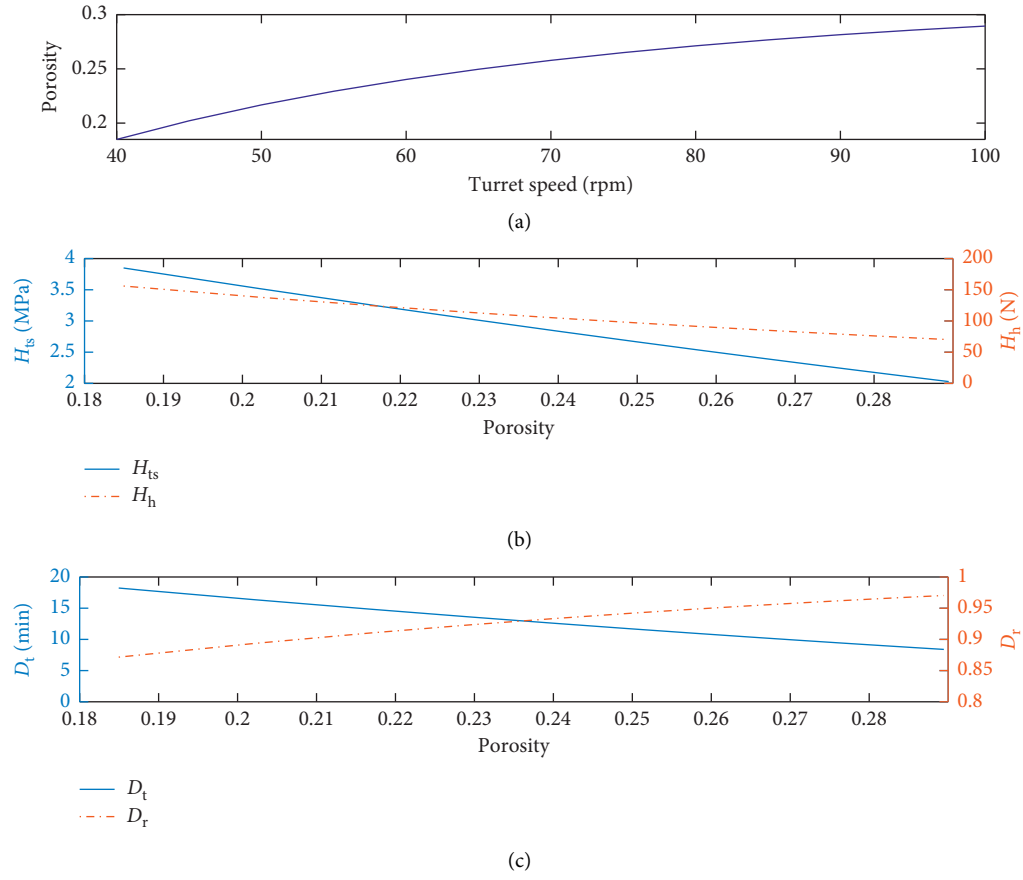

Figure 10: The experimental results for tabletting: the influences of turret speed.

between particles merged into one larger granule is reduced [11, 12], so that the final APS is reduced.

The simulation results about the influences of process parameters on APS and moisture content are shown in Figure 9. Firstly, the granules with larger APS will be generally produced by increasing the binder feed rate because of the significant enhancement on moisture content, which explains that both moisture content and APS increase with the increase of binder feed rate and agrees with the conclusions in [16, 18, 21, 58]. Secondly, as the atomizing air pressure increased, a smaller value of the liquid droplets size is obtained and the moisture in the droplets is more likely to evaporate, leading to the reduction of moisture content and final APS, which is consistent with the conclusion in [16, 21]. Thirdly, the bed temperature is found to be dependent on the inlet air temperature and the APS decreases with the increase of bed temperature [21, 59]. In addition, the moisture content decreases as the bed temperature increased because of the faster evaporation rate [58].

4.2. Computational Experiments on Model Verification for Tabletting. The input variables of tabletting process such as APS, moisture content, turret speed, and rolling reduction first affect the tablet porosity, which in turn affect the tablet quality. Refer to Table 2 and Figures 10–13 for the experimental conditions and results, respectively.

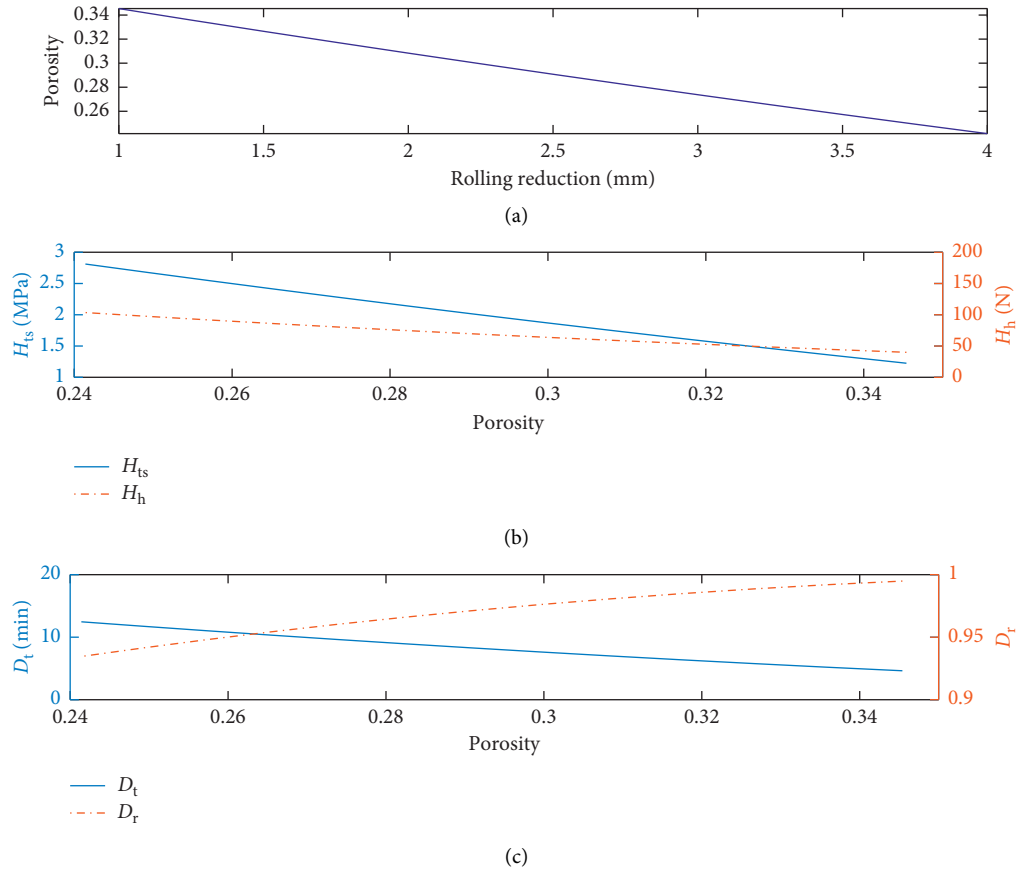

Figure 11: The experimental results for tabletting: the influences of rolling reduction.

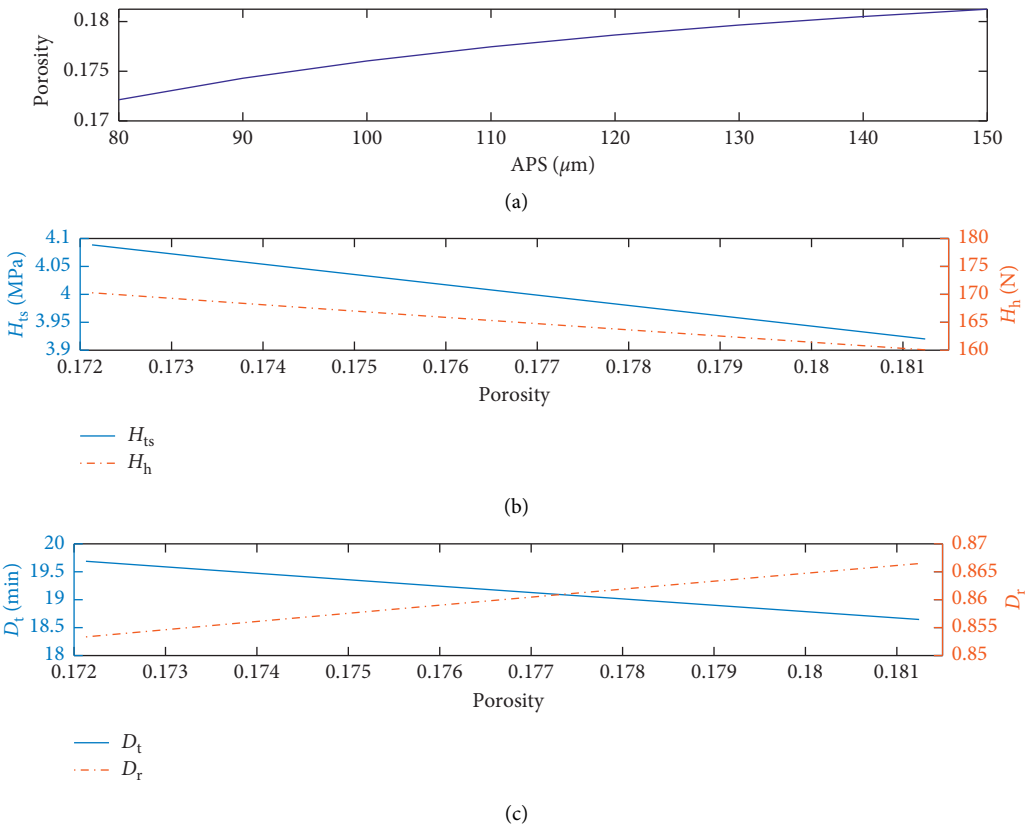

Figure 12: The experimental results for tabletting: the influences of APS.

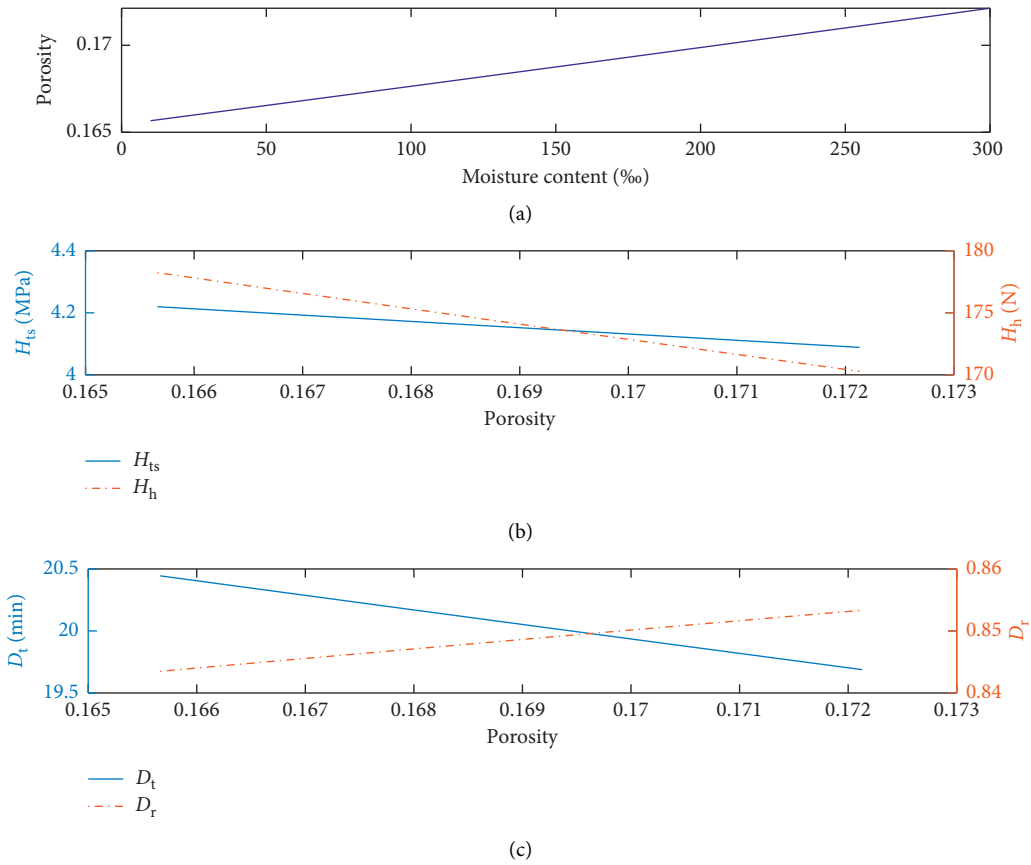

Figure 13: The experimental results for tabletting: the influences of moisture content.

First we discuss the effects of input variables on porosity. As shown in Figure 10, firstly, as the turret speed increases, the dwell time of the tablet will be reduced [3], and the work on the powder column will also be reduced. The degree of compression of the powder column will decrease accordingly, such as the plastic deformation and the crushing and recombination of the fragments will weaken, and then the effect of forming the new contact points between the particles and the interparticle forces will be reduced [60]. Therefore, the degree of elastic recovery will increase after the tablet is completed [61], and so the porosity will increase with the increase of the turret speed. Secondly, the effect of rolling reduction on porosity is like the human foot stepping into loose dust. When other variables are constant, the greater the rolling reduction, the more the work done on the powder column, the smaller the apparent volume of tablet and the greater the bulk density of tablet, so the smaller the porosity [62], as shown in Figure 11. Thirdly, the smaller pressure required to reduce the same powder column volume for the greater sized particles, which is attributed to a smaller surface area, lesser contact points, and a lower cohesion and frictional force [50]. Moreover, the initial porosity is large when the particles are large due to the relatively looser packing arrangement, and a higher elastic recovery is also observed for larger size particles [50, 53]. Therefore, when other variables are constant such as the same rolling reduction, the smaller pressure, the larger initial porosity, and the higher elastic recovery together result in a large porosity in case of larger APS [8, 56], as shown in Figure 12. Lastly, in general, the moisture in the particles acts as an intrinsic lubricant, contributing to the sliding and plastic flow of the powder, and the humidity of powder can affect its mechanical properties, i.e., the strength and hardness are greatly reduced as humidity increases [60]. Because the mechanism of influence of moisture on porosity is very complicated, we carry out simple analysis based on this theory. Powder particles with high moisture content are softer, and the degree of fragmentation is lower when the particles are combined, i.e., less fragment particles are formed [60]. Therefore, the pores in the original powder are preserved relatively intact, resulting in a larger porosity of the final powder column, as shown in Figure 13.

Table 3: The simulation conditions for process quality control.

Material attributes		Desired qualities		Algorithm parameters			
		H_{ts} (MPa)	1.5	γ	0.6	n_p	3
$d_{p,0}$ (μm)	50			r	1	κ	0.01
		H_h (N)	48	q	1	ν	5
ρ_p (kg/m^3)	450			η	0.5	b_1	1×10^{-6}
		D_t (min)	6	μ	5	b_2	0.03
μ_b (Pa·s)	0.0474			$\mathbf{Q}$	$\mathbf{I}_{4\times4}$	α	1×10^{-5}
		D_r	0.9	$\mathbf{G}_0$	$2 \times \mathbf{I}_{4\times4}$	Γ_1	$0.1 \times \mathbf{I}_{4\times4}$

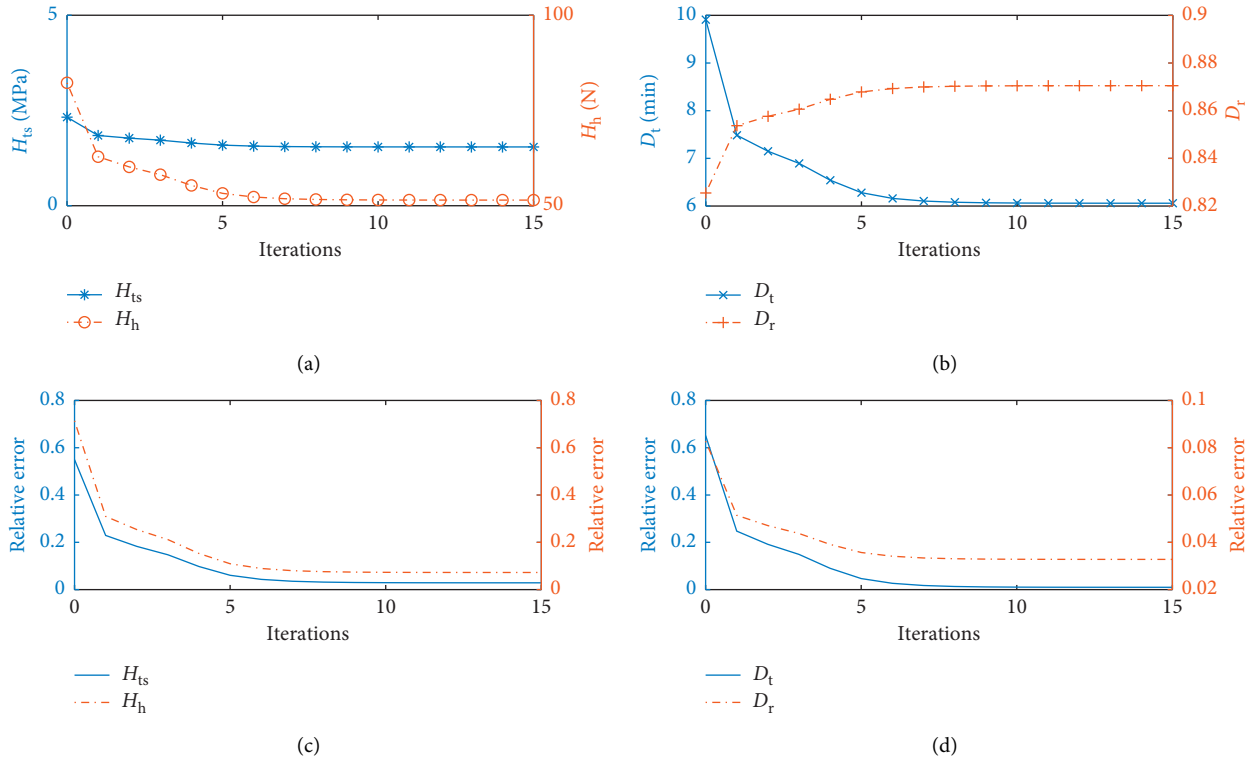

Figure 14: The simulation results of tablet quality indexes for process quality control.

Then the influences of porosity on tablet quality indexes are, respectively, analyzed based on the results shown in Figures 10–13 and compared with the widely accepted conclusions to verify the effectiveness of simulation models for tabletting.

Firstly, the tensile strength and hardness decrease with increasing porosity, which is agreed with the experimental conclusions in [3, 8, 56, 62]. Tensile strength and hardness reflect the degree of bonding between the particles in the tablet [24]. From the point of view of work, the more the work done on the powder column, the greater the degree of compression (such as more plastic deformation and crushing and recombination of the fragments), the greater the interparticle force is formed, the greater the degree of bonding between the particles, and the greater the tensile strength and hardness [60]. So we analyze the effect of turret speed and rolling reduction on tensile strength and hardness from the perspective of work. When the other variables are kept constant, the turret speed increases, the tablet dwell time becomes shorter, and less work for overcoming the elastic rebound is needed [61]. So the interparticle force is small, resulting in smaller tensile strength and hardness. The rolling reduction is directly applied to the powder column. When the other variables are constant, the amount of work is proportional to the rolling reduction. Therefore, the larger the rolling reduction, the greater the tensile strength and hardness of the formed tablet. APS affects the interaction between particles. Reduction in particle size can give an increase in the number of contact points between particles and an increase in interparticulate frictional and cohesive forces [53]. These factors may explain the increase in tablet tensile strength and hardness with decreasing particle size. The increase in moisture content leads to an obvious reduction in Young's modulus that determines the rigidity of the powder [60]. When the moisture content is high, the powder particles are soft and then the tensile strength and hardness of the tablets are small.

Secondly, the disintegration time decreases with increasing porosity, which is consistent with the conclusions in [3, 56]; meanwhile, the dissolution rate increases with the increase of porosity, which is consistent with the results in [63]. The disintegration and dissolution of tablets are somewhat similar in mechanism. The tablet comes into contact with the solution to initiate disintegration or dissolution, whose rate is related to the surface area of the solution in contact with the tablets, i.e., large contact surface area leads to rapid disintegration or dissolution. Porosity can reflect the contact surface area to a certain extent: tablets with large porosity generally have large contact surface areas. So the effect of operations or process variables on disintegration time and dissolution rate is analogous to the effect on porosity. Additionally, from the simulation results, it can also be found that the tensile strength and the dissolution rate show an opposite trend, as described in [8].

Lastly, the operating variables and material attributes of SFBG ultimately affect the tablet quality by affecting intermediate particle quality of APS and moisture content, so these simulation analyses are no longer discussed.

4.3. Computational Experiments on Model Verification in the Level of Process Control. In this subsection, using the developed simulation models to simulate the reality of

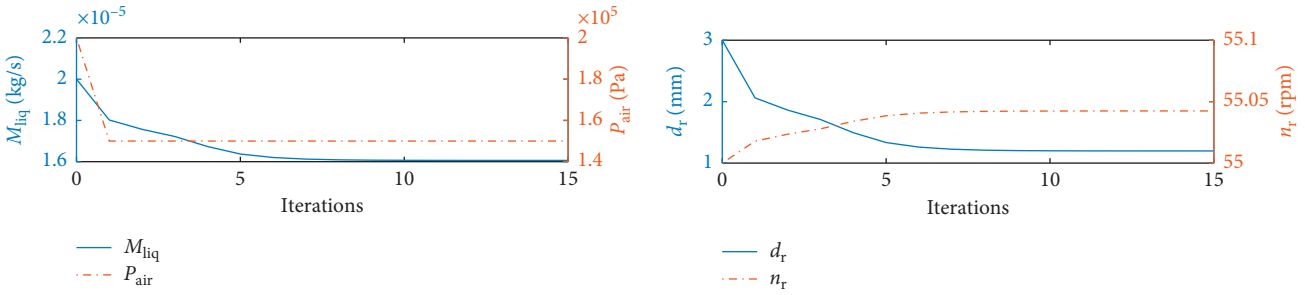

Figure 15: The simulation results of process inputs for quality control.

SFBG-based PTMP, process quality control is performed to further validate the feasibility and effectiveness of simulation models in the level of process control. The SFBG-based PTMP can be described by the following repeatable MIMO nonlinear system:

$$\mathbf{y}(k) = f(\mathbf{u}(k), \mathbf{x}), \tag{32}$$

where k denotes the iteration number, $\mathbf{y}(k)$ and $\mathbf{u}(k)$ are the system outputs (tablet quality indexes) and inputs (all operating variables for SFBG-based PTMP) of the k-th iteration, respectively, $\mathbf{x}$ represents the vector of material attributes, and $f(\cdot)$ is an unknown nonlinear function. Given the material attributes $\mathbf{x}$ and a desired output $\mathbf{y}_d$, the control objective is to find a appropriate control input $\mathbf{u}(k)$ such that the system outputs $\mathbf{y}(k)$ follows the desired one.

A data-driven predictive iterative learning control (DDPILC) method is applied to validate the feasibility of the simulated SFBG-based PTMP in the process quality control. For the specific form of the controller, refer to [64] for details. The simulation conditions are listed in Table 3, and the simulation results are shown in Figures 14 and 15, which indicate that the developed simulation models can be effectively used for the process quality control and further for designing and validating control algorithms.

5. Conclusions

In this work, a simulation modeling framework is developed for a SFBG-based PTMP. Firstly, a simulation model that simultaneously reflects the influences of process operations and material attributes on APS is built using PBM, in which a Hussain's aggregate kernel and a Walzel's model are utilized to, respectively, introduce critical material attributes and important operating variables into modeling framework, and a drying model to determine particle moisture content is then introduced to be coupled with the established PBM predicting APS, so that the simulation model of SFBG is developed. Secondly, because all the tablet quality indexes depend on the porosity, a promoted Heckel equation-based simulation model is developed to describe the changes in porosity with compression time, punch pressure, and initial particle rearrangement, where several empirical models for state variables such as initial porosity and punch pressure are constructed according to the widely accepted analysis and conclusions in the field. After that, several recognized models that are all related to porosity are introduced or constructed to calculate important tablet quality indexes, including tensile strength, hardness, disintegration time, and dissolution rate. Lastly, the feasibility and effectiveness of simulation models are validated by performing a computational experimental study. On the one hand, the scientific process understanding is explored by analyzing the influences of process inputs on intermediate or final quality indexes and the simulation results are consistent with the widely accepted conclusions in the field. On the other hand, a process control algorithm is introduced to study the quality control of simulated PTMP, and the results show that the developed simulation models can be effectively used for the process quality control and further for designing and validating control algorithms.

Data Availability

The data of model parameters supporting the development of simulation models are from previously reported studies and datasets, which have been cited.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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