Agglomeration Modeling of Small and Large Particles by a Diffusion Theory Approach

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The interaction particle-binder during the wet granulation process plays a major role in the agglomeration of particles. This interaction has been modeled by a force balance acting on the particle where the binder's viscous force increases the strength of liquid bridge and facilitates the particle agglomeration. In this work, agglomeration kernels based on Brownian movement approach of small particles in the binder layer, the size ratio between particles (monodispersed and polydispersed), and binder's viscous forces were considered to model the wet granulation process of pharmaceutical powders in a laboratory-scale high shear mixer. The assumptions of no-stationary and pseudostationary behavior were suitable to describe the growth kinetics of the two stages (fast and slow) observed. A volume ratio of 150 between large and small particles produces the most effective granulation growth. The developed kernels were tested simulating experimental data (Realpe and Velázquez, Chem Eng Sci. *2008;63:1602–1611) obtained from a high shear mixer.* © 2009 American Institute of Chemical Engineers *AIChE J,* 55: 1127–1134, 2009

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Introduction

Wet granulation is the process of particle size growth by means of addition of liquid or solid binder.[1] It is widely used in many chemical industries including pharmaceutical, food, detergents, and agricultural. The change in particle size as a function of time during the wet granulation process can be modeled by the population balance equation (PBE) as established by Randolph and Larson[2]:

$$\frac{\partial n}{\partial t} + \nabla(vn) - B + D = \frac{1}{V}\left(\sum Q_{\text{in}} \times n_{\text{in}} - \sum Q \times n\right) \quad (1)$$

where n is the number density function, t is the time, v is the particle velocity, B and D are the birth and death rate respectively, V is the mixer volume, and Q_{in} and Q are the inlet and outlet flow rates, respectively. For the case of agglomeration alone in a well-mixed batch granulator with

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Table 1. Size-Dependent Kernels Obtained Empirically, Semi-Empirically, or from Semi-Theoretical Concepts

Kernel Structure	Reference
1	Size independent
$\beta_0(t)(l+\varepsilon)^3$	Smoluchowski[5]
$\beta_0(t)(l+\varepsilon)$	Golovin[6]
$\beta_0(t)(l\times\varepsilon)$	Golovin variation[6]
$\beta_0(t)\dfrac{(l+\varepsilon)^a}{(l\times\varepsilon)^b}$	Kapur and Fuerstenau[7]*
$\begin{cases}\beta_0(t) & t<t_1\\ \beta_0(t)(1+\varepsilon) & t>t_1\end{cases}$	Adetayo et al.[8]*
$\beta_0(t)(l^{1/3}+\varepsilon^{1/3})\times\sqrt{\left(\dfrac{1}{l}+\dfrac{1}{\varepsilon}\right)}$	EKE: Kinetic theory of gases-equipartition of kinetic energy[9]
$\beta_0(t)(l+\varepsilon)^2\times\sqrt{\left(\dfrac{1}{l^3}+\dfrac{1}{\varepsilon^3}\right)}$	Equipartition of kinetic energy[1]

*a, b are parameters, and t_1 was calculated experimentally.

the birth and death terms given by Hulburt and Katz,[3] the PBE reduces to

$$\frac{\partial n(l)}{\partial t}=\frac{1}{2}\int_0^l \beta(l-\varepsilon,\varepsilon)\times n(l-\varepsilon)\times n(\varepsilon)\times d\varepsilon - n(l)\int_0^\infty \beta(l,\varepsilon)\times n(\varepsilon)\times d\varepsilon \quad (2)$$

where $\beta(l, \varepsilon)$ is the coalescence kernel for agglomeration between particles of size l and ε. The $1/2$ in the first term avoids the duplication in the number of collisions. The coalescence kernel can be decomposed into two terms as[4]:

$$\beta(l,\varepsilon,t)=\beta_0(t)\beta'(l,\varepsilon) \quad (3)$$

where $\beta_0(t)$ is the aggregation rate constant, which is a function of factors such as binder viscosity and amount, and impeller velocity, and $\beta'(l, \varepsilon)$ expresses the effect of size on the rate of aggregation between particles of size l and ε.

The current challenge in modeling growth kinetics has to do primarily with incorporation of physical phenomena in the coalescence kernels and its computation. Table 1 shows a list of size-dependent kernels $\beta'(l, \varepsilon)$ obtained empirically, semi-empirically, or from semi-theoretical concepts. In these cases, parameters of the size-dependent kernel and the aggregation rate constant ($\beta_0(t)$) are all calculated by fitting of experimental data. The lack of fundamental understanding to model particle agglomeration causes for example that wet granulation in a high shear mixer is generally controlled by monitoring the impeller torque.[10,11]

The main objective of this article is to develop an agglomeration kernel of wet granulation based on the random motion theory approach[12,13] and considering the viscous force of the liquid bridge between two particles. The goodness of fit of this phenomenon-based kernel is demonstrated with experimental data.[14]

Development of Agglomeration Kernel: Theoretical Analysis

Agglomeration of particles

The process of monodispersed aerosol coagulation (Figure 1a) as established by Smoluchowski[5] is equivalent to the process of agglomeration between small and large particles as shown in Figure 1b. The agglomeration of large and small particles in the presence of binder on their surfaces has been considered previously.[1,9,15,16] These works have proposed a preferred layering mechanism dominated by small-large particle interaction over the agglomeration of similar size particles, and a size-dependent agglomeration kernel[1,9] preferring the agglomeration of large and small particles (see Table 1).

This preferential agglomeration of small and large particles (volume ratio = 150) was also observed by Realpe and Velazquez[14] especially in the first stage of the wet granulation of pharmaceutical powders with initial bimodal particle size distribution (PSD). A less promoted agglomeration, however, was also observed for initial monodispersed unimodal PSD. In the latter, the first stage of granule growth is slow, due to the high concentration of similar sized particles and a weaker liquid bridge between particles. In this case, particles slowly enlarge over the first 8 min transforming the distribution from monodispersed unimodal PSD to polydispersed unimodal PSD. As the new polydispersed volume ratio reaches a value of 150, the growth rate speeds up.[14]

In addition, it is assumed that the local agglomeration process is governed by the diffusion of a particle population of radius r_{p2} through the binder layer to a stationary particle of radius r_{p1}, independently of the high particle transfer by the convection mechanism in a high particle concentration volume. In the case of preferred agglomeration of small and large particles, it is assumed that this diffusion follows the Brownian movement.[12,13,17] This theory is used to describe the physical phenomenon of random movement that minute particles immersed in a fluid go about.

The system shown in Figure 1b could then be represented mathematically by the following diffusion equation[18,19]:

$$\frac{\partial N_2(r,t)}{\partial t}=D_{12}\left(\frac{\partial^2 N_2(r,t)}{\partial r^2}+\frac{2}{r}\frac{\partial N_2(r,t)}{\partial r}\right) \quad (4)$$

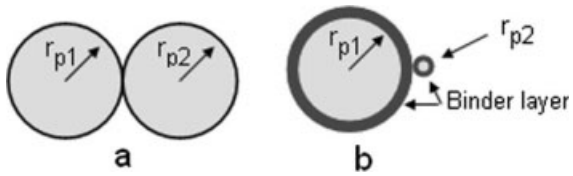

Figure 1. Schematic of aggregation of (a) equal-size particles and (b) different-size particles.

where N is the concentration number of particles, r is the distance from the center of the stationary particle to the center of the diffusing particles, D_{12} is the Brownian diffusion constant of particles through the binder layer. The initial and boundary conditions for the problem are: $N_2(r,0) = N_{2,0}$, $N_2(\infty,t) = N_{2,0}$, and $N_2(r_{p1} + r_{p2}, t) = 0$.

Combining the analytical solution of Eq. 4 and the total collision rate per volume between particles of radius r_{p1} with concentration number $N_{1,0}$ and particles of radius r_{p2}, one obtains

$$r_{\text{col}-r_{p1}\cdot r_{p2}} = 4\pi(r_{p1} + r_{p2})D_{12}N_{2,0}N_{1,0} \tag{5}$$

where the size-dependent kernel can be expressed as

$$\beta(r_{p1}, r_{p2}) = 4\pi(r_{p1} + r_{p2})(D_1 + D_2) \tag{6}$$

Einstein[12,13] related the diffusion constant (D_i) to the average square displacement given by Eq. 7. The mean square displacement is a measure of the average distance a particle travels suspended in air or liquid. In this case, as assumed earlier, the particles are diffusing through the binder layer.

$$D_i = \frac{\langle x^2 \rangle}{2t} \tag{7}$$

The average square displacement can be obtained by analyzing the effect of viscous forces on the motion of particles through viscous liquid layer as presented in the sections below.

Agglomeration mechanism based on Brownian movement and viscous forces

Two-stage granule growth has been observed in wet granulation of wide PSD.[14,8,20] The first stage of wet granulation is a noninertial regime of fast granule random coalescence[7,20] controlled primarily by binder amount. The second stage is characterized by slow agglomeration and described by a pseudostationary coalescence.[20]

Modeling the first stage of fast granule growth of wet granulation

The interaction of particles with the binder layer during the first stage can be described by a force balance acting on the particle[20,21] where a viscous force favors particle motion and the stochastic Brownian force[22] X. This force is randomly positive and negative, since it represents the random force exerted by other particles in the wet granulation process. It maintains the motion of particle through the binder layer and this motion can be modeled as:

$$m_p \frac{d^2x}{dt^2} = \frac{3\pi \times \mu \times r_p^2}{2x}\frac{dx}{dt} + X \tag{8}$$

where μ is the binder viscosity, m_p is the particle mass, r_p is the particle radius, and $2x$ is the separation distance between colliding granules. The initial conditions are:

$$x(0) = h_0 \tag{9}$$

$$\frac{dx}{dt}(0) = v_0 \tag{10}$$

where h_0 is the thickness of the liquid layer on the surface of the particle and v_0 is the relative velocity between the two particles. Multiplying Eq. 8 by x, one obtains:

$$m_p(x)\frac{d^2x}{dt^2} = \frac{3\pi \times \mu \times r_p^2}{2}\frac{dx}{dt} + Xx \tag{11}$$

Considering a large number of particles, then the average of the term Xx is zero by irregularity of direction of forces X.[22,23] Hence, the equation may be rewritten as:

$$\frac{d^2x^2}{dt^2} = 2\left(\frac{dx}{dt}\right)^2 + \frac{6\pi \times \mu \times r_p^2}{2m_p}\left(\frac{dx}{dt}\right) \tag{12}$$

Assuming validity of the equipartition of kinetic energy principle during wet granulation,[1] where the collision velocity, v, is inversely proportional to the particle mass, m, one obtains

$$m_p v^2 = C \Rightarrow v^2 = \frac{C}{m_p} \Rightarrow v = \sqrt{\frac{C}{m_p}} \tag{13}$$

where C is a constant in energy unit.

Replacing Eq. 13 into 12 and $m_p = 4/3\pi r^3$, one obtains

$$\frac{d^2x^2}{dt^2} = \frac{6C}{4\pi\rho\, r_p^3} + \frac{9\mu}{8\rho\, r_p}\sqrt{\frac{3C}{4\pi\rho\, r_p^3}} \tag{14}$$

The analytical solution using the initial conditions (Eqs. 9 and 10) is:

$$x^2 = \left[\left(\frac{3c}{4\pi\rho\, r_p^3}\right) + \frac{9\mu}{16\rho\, r_p}\sqrt{\frac{3c}{4\pi\rho\, r_p^3}}\right]t^2 + 2h_0v_0t + h_0^2 \tag{15}$$

Replacing the mean square displacement (x^2) of Eq. 7, one obtains the diffusion coefficient for each particle.

$$D_i = \left[\left(\frac{3c}{8\pi\rho\, r_{pi}^3}\right) + \frac{9\mu}{32\rho\, r_{pi}}\sqrt{\frac{3c}{4\pi\rho\, r_{pi}^3}}\right]t + h_0v_0 + \frac{h_0^2}{2t} \tag{16}$$

Modeling the stage of slow granule growth

The second stage is characterized by slow agglomeration and described by a pseudostationary coalescence.[20,24] The interaction of particles with the binder layer during the second stage of wet granulation process can be modeled again by a force balance acting on the particle. In this case, the viscous liquid force acts as a resistance to the motion of particle.[22,23] The motion of particles through the binder layer can be modeled as

$$m_p \frac{d^2x}{dt^2} = -6\pi\,\mu\, r_p \frac{dx}{dt} + X \tag{17}$$

Multiplying Eq. 17 by x, Eq. 18 is obtained

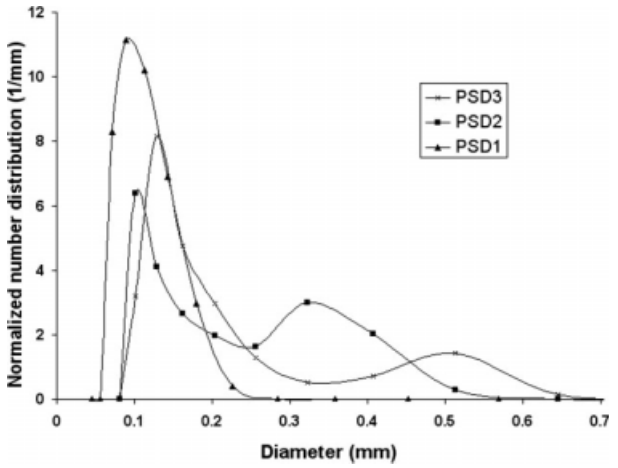

Figure 2. Initial particle size distributions for wet granulation.

$$\frac{m_p}{2}\frac{d^2x^2}{dt^2} - m_p v^2 = -3\pi\,\mu r_p \frac{dx^2}{dt} + Xx \tag{18}$$

Applying again the equipartition of kinetic energy (Eq. 13), the average over a large number of particles of $Xx = 0$ and with the following change in variable $z = dx^2/dt$, the equation becomes

$$\frac{dz}{dt} + \frac{6\pi\,\mu\, r_p}{m_p} z = \frac{2C}{m_p} \tag{19}$$

The general solution using the integrating factor technique is:

$$z = \frac{C}{3\pi\,\mu\, r_p} + C_1 e^{-(6\pi\,\mu\, r_p/m_p)t} \tag{20}$$

For $t \gg 6\pi\mu r_p/m_p$, the particle velocity enter to a pseudostationary state. In this case the exponential is dropped and integrating for time again, it is obtained.

$$x^2 = \frac{C}{3\pi\mu r_p} t \tag{21}$$

Replacing the mean square displacement (x^2) of Eq. 7, the diffusion coefficient for each particle is

$$D_i = \frac{C}{6\pi\mu r_{pi}} \tag{22}$$

Replacing the diffusion coefficient (Eq. 22) into Eq. 6, the coalescence kernel becomes

$$\beta(r_{p1}, r_{p2}) = \frac{C}{\mu}\frac{(r_{p1} + r_{p2})^2}{(r_{p1} \times r_{p2})} \tag{23}$$

Solution of the PBE

Since the PBE is an integrodifferential equation difficult to solve analytically for real cases, a numerical solution was implemented using PARSIVAL, a commercial software to solve a large class of integrodifferential equations using a discretization technique.[25] The algorithm uses a finite-element type Galerkin h-p-method and applies an adaptive Rothe method for a time discretization. Then in each time step a linear time independent partial differential equation system is solved using the Gaussian quadrature method. The next time-step is calculated based on the accuracy that is demanded for the overall time-dependent solution.

Results and Discussion

Comparison of model simulation to experimental data

Simulation results with the kernel developed for the agglomeration process were compared to the granulation experimental data.[14] In the experiments, the pharmaceutical powders used were lactose anhydrous, and monohydrate with unimodal and bimodal PSD. Figure 2 depicts the three PSDs used designated as PSD1 (fine size powders), PSD2 (medium size powders), and PSD3 (coarse size powders). The binder viscosity and amount were also changed in three levels as shown by the factorial experimental design[26] in Table 2.

First stage of wet granulation

A complex coalescence kernel for the first fast stage is obtained by replacing Eq. 16 into Eq. 6. This kernel structure cannot be separated into two terms as suggested,[4] thus it incorporates the effect of liquid viscosity, particle density, liquid amount, particle size, and time. Hounslow et al.[9] founded independently, using a numerical technique, a small dependence of this size-independent kernel ($\beta_0(t)$) with time. As can be seen, the coalescence kernel obtained for the first stage of wet granulation has two parameters (C and h_0). The parameter C has energy unit and is related to the kinetic energy that maintain the local motion of particles, and h_0 is the thickness of a binder layer, which change accordingly to binder amount. Since h_0 is very difficult to measure experimentally, it is typically estimated numerically.[20]

The coalescence kernel predicts the trend of fast growth, which is controlled by the binder amount added during the first 30 s and the high probability of collision between small and large particles. The values of $C = 9.902 \times 10^{-17}$ m^2 kg min^{-2}, $v_0 = 0.005$ m/min, and $h_0 = 6.25 \times 10^{-5}$ m were obtained by trial and error since the amount of data collected during the first stage did not allow for least square estimation.

It would be necessary to obtain more samples during the first 2 min of wet granulation to calculate more accurate parameters by fitting the experimental data. However, the value

Table 2. Experimental Design

Factors	Particle Size (mm), Figure 2.1			Binder Viscosity (cp)			Amount of Binder (% v_{Liquid}/w_{Solid})		
Levels	PSD1	PSD2	PSD3	1	2.49	4.85	9.9	11.7	13.6

Table 3. Fitting the Coalescence Kernels to the Experimental Data

Kernel Structure	Residual: Bimodal PSD
$\beta_0(t)(l+\varepsilon)^3$	4.0120×10^{-1}
$\beta_0(t)(l+\varepsilon)^2 \times \sqrt{\left(\frac{1}{l^3}+\frac{1}{\varepsilon^2}\right)}$	1.7822×10^{-1}
$\frac{C}{\mu}\frac{(l+\varepsilon)^2}{(l\times\varepsilon)}$*	1.2482×10^{-1}

*Equation 23.

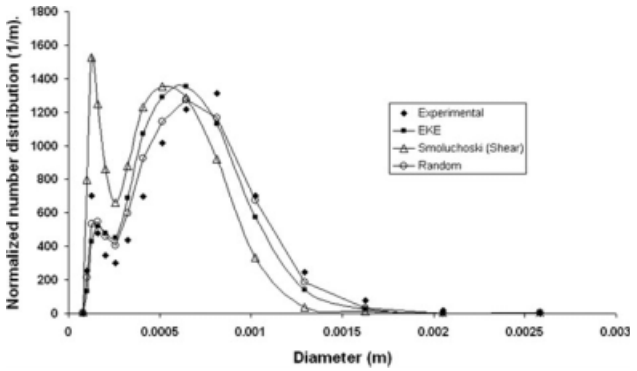

Figure 3. Fitting the coalescence kernels to the experimental data of wet granulation of coarse size powders (PSD3) at 13.6% v/w of binder with 1 cp viscosity.

Simulated (line) and experimental (rhombus). The end of experiment (12 min).

obtained for C is smaller than the value obtained for the second stage using a numerical technique. This agrees with the fact that the particles are smaller at the beginning and therefore its kinetic energy. The h_0 value agrees with values reported in the literature, and v_0 is in the scale of actual blade speed.

A parametric study of the effect of the parameters (particle size, binder characteristics, material properties, equipment design, and others) on the values of C, h_0, and v_0 would provide better insight of the interdependence and the final structure of the kernel and the population balance that

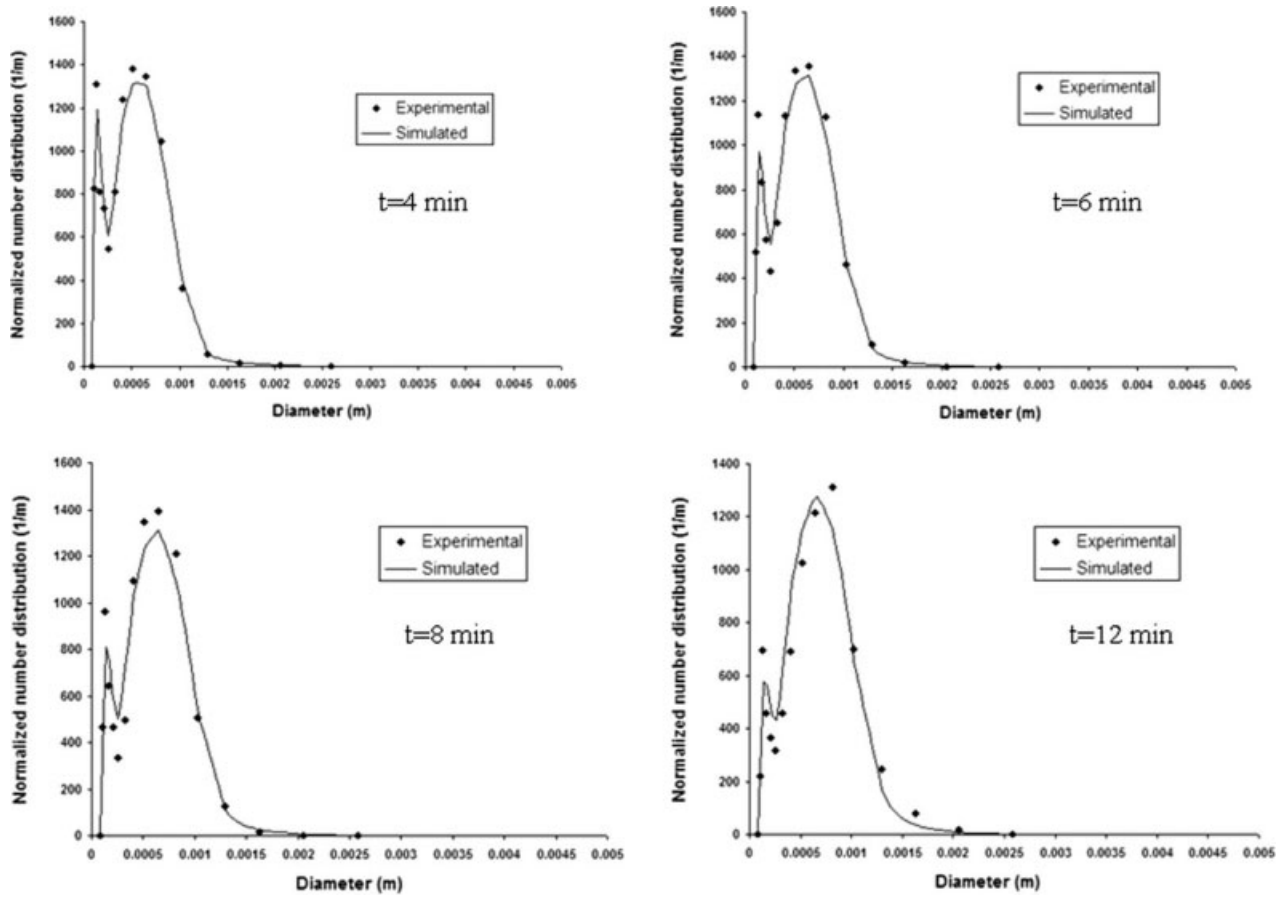

Figure 4. Prediction of the growth kinetics of wet granulation of coarse size powders (PSD3) at 13.6% v/w of binder with 1 cp viscosity.

Simulated (line) and experimental (rhombus).

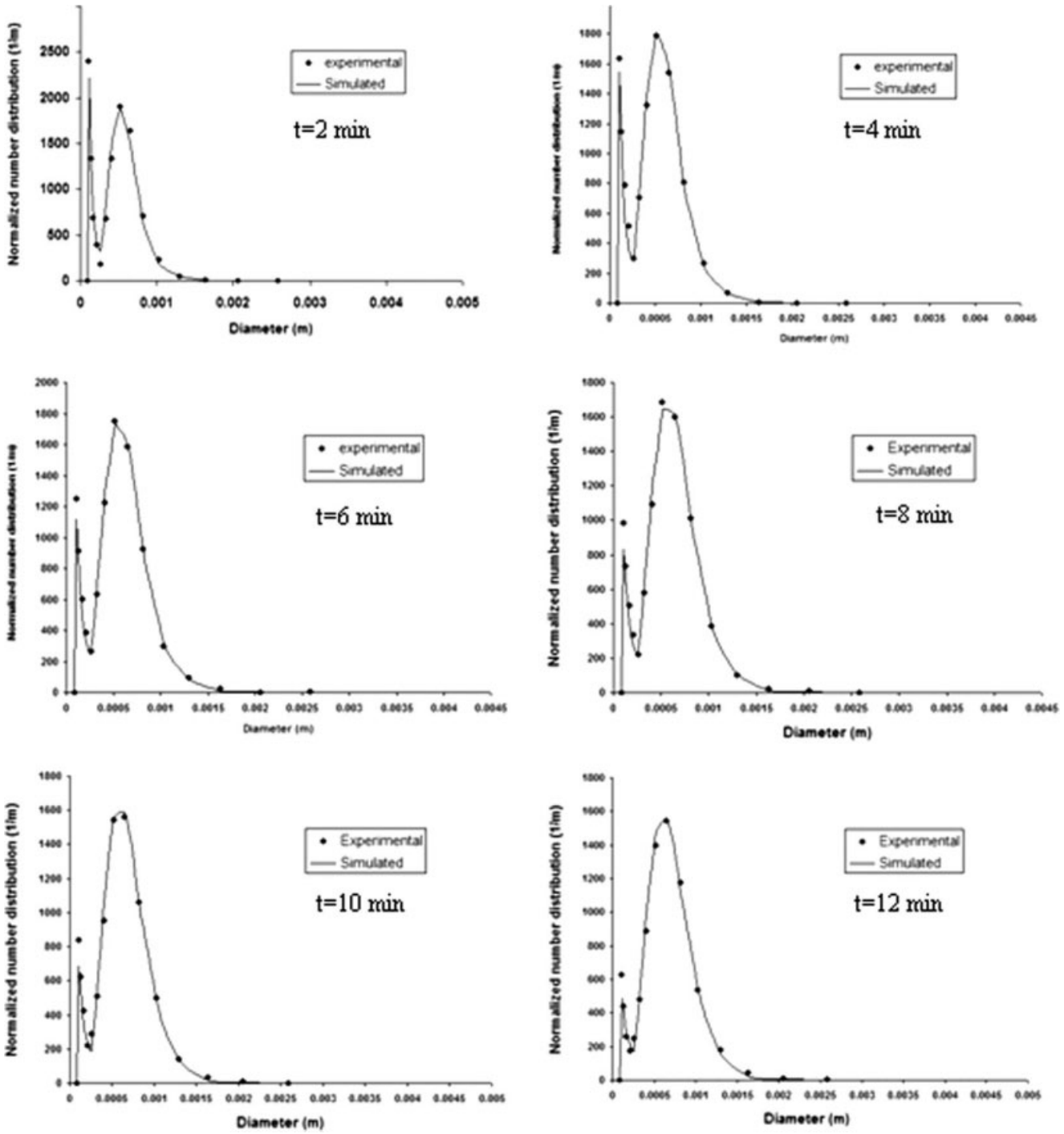

Figure 5. Prediction of the growth kinetics of wet granulation of medium size powders (PSD2) at 13.6% v/w of binder with 1 cp viscosity.

Simulated (line) and experimental (rhombus).

can be established. However, such experiments would require inline measurements of PSD (vision, light diffraction) to generate more data during this short period first stage for a more robust estimation. Another possibility is the automatic withdrawal of samples to avoid stopping the granulator to reduce perturbations in the granulation process.

Second stage of wet granulation

The coalescence kernel of wet granulation of powders with bimodal PSD for second stage of slow growth rate is similar to the kernel obtained by Smoluchowski,[5] but in this case the particle transfer mechanism by diffusion through

binder layer was considered. The kernel can be separated in two terms,[4] β_0 is the aggregation rate constant, which is a function of binder viscosity and the C parameter as defined earlier, and $\beta'(r_{p1},r_{p2})$ expresses the effect of size on the rate of aggregation between particles of size r_{p1} and r_{p2}.

A value of 3.6915×10^{-13} m^2 kg min^{-2} for C was obtained by fitting the coalescence kernel to PSD experimental data using the integral technique of the Parsival software.[25] This value is higher than in the first stage due to the larger mass of the particles in the second stage that increases the kinetic energy. Table 3 shows two kernel structures proposed in literature and the new one based on random movement theory (Eq. 23). The table includes also a quantitative comparison of the goodness of fit of the kernels to experimental data. Figure 3 depicts qualitatively the prediction of the kernels in Table 3 to experimental data obtained from wet granulation of coarse size powders (PSD3) at 13.6% v/w of binder and 1 cp. As can be seen, the random kernel (Eq. 23) gives the best description of the experimental data.

Next, the parameter value was tested by predicting data collected from replica of the experiments (Figure 4). The simulation results match the PSD experimental data during the first 8 min, but tend to diverge a little toward the end of the experiment. The robustness of the kernels in predicting growth rate was tested by simulating, using the previously adjusted parameters, the growth kinetics of wet granulation of medium size powders (PSD2) at 13.6% v/w of binder and 1 cp, as shown in Figure 5. This result indicates that the effect of initial particle size was incorporated into the coalescence kernel by assuming preferential collision between small and large particles.

Wet granulation in a high shear mixer is a complex process, in which these two mechanisms, breakage and agglomeration, could occur separately, simultaneously, or sequentially, depending upon the variation of one or more factors such as initial particle size, initial PSD shape (unimodal vs. bimodal), mixer velocity, and viscosity and amount of the binder. This intricate relationship with so many factors explains why the wet granulation process after many years of research is still not completely understood. Thus, the parameter C in the coalescence kernel still has an unknown dependence on the operating conditions (mixer velocity, binder addition rate, binder amount) and physical properties of the particle and binder such as morphology and surface tension.

In this work, a fundamental understanding of the effect of initial PSD shape (unimodal or bimodal) on agglomeration mechanism in wet granulation was developed. However, it is recommended to extract mathematically from parameter C, based on experimental data, the physical properties of particle and binder, and operating conditions. It is also recommended to study the breakage mechanism to develop in a similar fashion a suitable breakage kernel for the PBE.

Conclusion

A sequential mechanism consisting of two stages (fast and low) was once more observed for the wet granulation of powders with bimodal PSD. The volume ratio of about 150 between small and large particles promotes the faster growth. The agglomeration between small and large particles was considered as a diffusion process of small particles through the binder layer on the particle's surface to reach the surface of the large one. Kernels based on this assumption, i.e., the physical phenomena occurring during the coalescence, have been developed for each stage to predict the growth kinetics of wet granulation from initial properties of powder and binder such as particle size and binder viscosity. The simulation of the first stage predicts the trend of fast growth; however, additional inline measurements are necessary to collect sufficient data to analyze this complex mechanism and at the same time reducing perturbations in the wet granulation process during the first minute. The agreement between experimental and simulated data confirms that the agglomeration process occurs preferably between small and large particles and that the approach of the small particles through the binder to the large one is governed by a diffusive random movement.

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