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A combined experimental and computational study of wet granulation in a Wurster fluid bed granulator

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ABSTRACT

A methodology combining theoretical and experimental techniques for analyzing the growth of granules in a fluidized bed granulator was developed. The methodology combines several key features of this complicated process: (i) population balancing (PB) of growth of different granules; (ii) hydrodynamic modeling of the gas–solid mixture flow using Computational Flow Dynamics (CFD); (iii) modeling of contact mechanics and granule formation; (iv) the Stokes number analysis for calculation of successful collisions; (v) well-controlled experimental study of the wet granulation. First, a detailed CFD model of the gas–solid flow and agglomeration (Model CFD-PB) within the Wurster type granulator was developed. Second, a simplified PB model of agglomeration in a homogeneous system (Model H-PB) was developed. The quadrature method of moments (QMOM) was used for solution of PB equations in both models. The kinetic theory of granular flow (KTGF) was employed in both models for calculation of the number of collisions between solid particles of different classes. Success factors, based on the Stokes number analysis, were calculated using results of extensive mesoscale simulations of the formation of realistic three-dimensional virtual granules. Comparison of simulation results of CFD-PB vs. H-PB models allowed evaluation of the KTGF kernel functionality to be used in H-PB model. Next, fluid bed granulation experiments were conducted for typical pharmaceutical excipients (microcrystalline cellulose, mannitol and dicalcium phosphate) with 15% HPC binder solution in a pilot plant Wurster granulator. The observed granule growth was a function of the surface roughness of excipients. Finally, the H-PB model was fitted to the experimental data. The only adjustable parameter of the H-PB model was an effective agglomeration rate constant, which we expect to be mostly related to the binder wetness on the surface of colliding granules.

1. Introduction

Wet granulation is a size enlargement process of converting small-diameter solid particles (typically powders) into larger-diameter agglomerates to generate a specific size, improve flowability and to produce a powder with specific properties such as dissolution rates, granule strength and apparent bulk density [1,2]. It is an important powder processing step in the manufacture of tablets, the most common pharmaceutical solid dosage form. Particles of the active pharmaceutical ingredient (API) and an excipient are granulated prior to tabletting in order to improve flowability, compressibility and to ensure composition uniformity. General reviews signifying the interest of wet granulation were published recently [2–5].

Examples of various types of process vessels used in granulation processes include pan, drum and fluidized beds. The main advantage of a fluid bed granulator is that it is a gentle, tunable and robust process during which many steps (pre-blending, granulation, drying) can be performed in the same piece of equipment. Other advantages are usually indicated to be the milder process conditions and product granules with higher porosity and narrower size distribution [5–14]. In recent years several experimental studies were performed to investigate the influence of process variables and physicochemical properties on the granulation mechanisms in fluidized beds [6–15]. Relatively new is to employ the Wurster unit, shown in Fig. 1, frequently used for coating and for granulation [15,16]. The Wurster unit operation has the potential to provide better control of the granulation process, granules with more uniform drug distribution and tighter particle size distribution (PSD).

In the literature, many attempts have been made to describe the process of particle formation in a fluidized bed in terms of population balance (PB) integro-partial differential equation [17–26]. Popular

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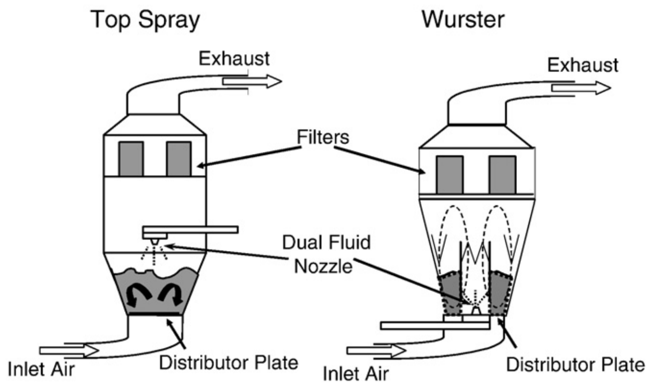

Fig. 1. Comparison of top-spray vs. Wurster bottom-spray fluid bed granulators.

methods for solution of the PB are methods of Monte Carlo (MC), discrete methods (DM) and methods of moments (MOM). A recent review of different MC methods can be found in [18]. At present, the main disadvantage of MC methods is that they cannot be easily interfaced with standard process simulators, which generally implement deterministic integration routines. In the DM, the particle population is discretized into a finite number of size intervals [19–21]. This approach has an advantage of computing the particle size distribution (PSD) directly. The disadvantages of DM (also known as the classes or sectional methods) are that the classes must be defined *a priori* and that a large number of classes may be required. In the MOM [22] the PB equation is transformed into a set of equations for moments of the PSD. Recently developed modifications of the MOM, the quadrature method of moments (QMOM) [23,24] or the direct quadrature method of moments (DQMOM) [25,26] require only a small number of scalars (moments) to track the PSD with very small error. The MOM approaches are useful especially when the entire PSD is not needed and certain average and total quantities are sufficient to represent the PSD.

In development of PB models, the assumption of a spatially homogeneous (well-mixed) system is usually employed. However, since powder characteristics and essential hydrodynamic and kinetic parameters regarding liquid–solid contact and granule agglomeration, particle mixing and segregation are lumped into the kinetic rate constants, population balance models assuming homogeneity cannot be applied for *a priori* design and scale-up of fluid bed granulation process [27]. With the development of high-speed computers, computational fluid dynamics (CFD) has also played an important role in understanding the flow behavior in multiphase fluidized bed systems. Mathematical models [26–28] and commercial software [29] employing the CFD and PB for modeling of fluidized bed spray granulation were recently developed. The models combine the kinetic theory of granular flow (KTGF) [30] for modeling of gas–solid flow with the QMOM [26–29] or with the DM [29] for solution of PB equations.

In recent years various theoretical models were developed to predict coalescence probability from the physical properties of the primary particles, granules and binder [31–33,15]. These models combine size and morphology of the primary particles/granules with physicochemical properties of the binder and collision velocities of the granules and predict whether the granules will stick together or rebound on collision. Criteria for successful collisions have been derived in the form of the critical Stokes number [31–33,15]. It is theoretically and practically attractive to employ KTGF also for derivation expressions for aggregation and breakage kernels in fluidized beds [27,28,34,35]. The number of collisions between particles of different species calculated from the KTGF are then multiplied by a success factor [27] for agglomeration upon collision to obtain the number of successful collisions. It was also shown that the aggregation kernel derived from the KTGF is closely related to the recently developed equi-partition of kinetic energy (EKE) kernel [36].

The success factor for agglomeration is expected to depend on various factors, such as particle surface properties and wettability, particle velocity, binder type and concentration [27,28,35,36,39]. The effect of primary particle morphology on the formation of wet agglomerates and on spatial distribution of binder in wet granules was simulated using the volume of fluid (VOF) method [37–39]. Functional relationships between the volumetric composition of a granule and the fraction of binder accessible on its surface, as well as the average thickness of the binder layer were derived by means of computer simulations [39]. Such relationship can be combined with the Stokes number analysis in order to derive coalescence kernels for PB modeling.

First objective of the present work is to develop mathematical models which combine the QMOM for solution of the PB of growth of different granules with the CFD modeling of the gas–solid mixture flow and collision rate based on the KTGF. Second objective is to use simulation results of the dependence between the granule composition and the binder fraction and thickness for the Stokes number analysis and calculation of the success factors. Third objective is to compare the model predictions with results of experimental study of the wet granulation in a Wurster fluidized bed granulator. A similar methodology for the analogous problem of attrition during pneumatic conveying was reported recently [40].

2. Theoretical

2.1. Balance equations

The population balance (PB) equations for agglomeration of solid particles in non-homogeneous flow systems can be written in terms of the volume fraction of particle size (class) i as

$$\frac{\partial}{\partial t}(f_i\alpha_s\rho_s) + \nabla\cdot\left(f_i\alpha_s\rho_s\,\vec{u}_s\right) = \alpha_s\rho_s(B_i - D_i) \qquad i = 0,1,2,...,M-1 \tag{1}$$

α_s, ρ_s, $\vec{u}_s$ is the total volume fraction, density and velocity vector of solid particles, f_i is the fraction of particles of size i, M is number of classes (number of intervals in the discretized PSD) and B_i, D_i are the particle birth and death rates. In the CFD-PB granular multiphase model the continuity equations for solid phase (1) are solved in each cell of the geometry mesh together with the momentum balance for the solid phase, the continuity equation and momentum balance for the gas phase, the balance equation for the fluctuating kinetic energy (Appendix C) and corresponding boundary conditions [29].

A homogeneous population balance (H-PB) model represents the simplest approximation of the flow and agglomeration in the investigated equipment and can be written as

$$\frac{df_i}{dt} = B_i - D_i \qquad i = 0,1,2,...,M-1 \tag{2}$$

The discrete methods (DM) for solution of the PB models described by Eq. (1) or (2) are based on representing the continuous PSD in terms of a set of discrete classes [19–21]. The disadvantages of DM (also known as the classes or sectional methods) are that the classes must be defined *a priori* and that a large number of classes may be required.

On the other hand the quadrature method of moments (QMOM) [23,24] or the direct quadrature method of moments (DQMOM) [25,26] require only a small number of scalars (moments) to track the PSD with very small error and are computationally affordable for use with CFD codes. The QMOM approach is based on taking the moments