MECHANISTIC MODELLING OF AGGREGATION PHENOMENA IN POPULATION BALANCES OF GRANULATION

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Abstract: This paper addresses the development of population balance models for granulation processes. The novelty in the present approach is two fold: firstly, the employment of a multi-dimensional population balance; and secondly, the exploitation of advancements in the underlying science to develop mechanistic models for the various rate processes.

Keywords: Keyworks: Granulation, population balances, aggregation, mechanistic modelling

1. INTRODUCTION

Granulation processes find application in a wide range of industries spanning pharmaceuticals, fertilisers, detergents, food processing, etc. In these processes, granulation is employed to improve such properties as handling, flow properties, controlled dissolution and delivery rates, uniformity in the distribution of multiple solid components, and taste and aesthetics. At present, granulation processes are operated in a highly inefficient manner, with large recycle ratios within the process (3-4:1, recycle:product) (Mort et al. (2001)). This is because of the need to maintain specified size ranges for the granules. Granules that are either smaller or larger than the allowable range are recycled to the process for reprocessing. Such inefficient operation with recycle ratio of about four is attributed to an improper understanding of the process, with operation being based on prevalent practice than on strong scientific considerations. Also, in batch processing such as in the pharmaceutical industry, it is very important to ensure homogeneity in the granules in terms of the main ingredient and the excepients. Further, advanced control objectives on the granulation process include the control of granule Particle Size Distribution (PSD), in order to enable an inferential control of different granule properties including delivery rates of drugs and taste of food products. These various factors advocate the need for good mechanistic models of the granulation process, taking advantage of the recent advances in the science of granulation.

The rate processes in granulation

Granulation process is categorised under the general class of particulate processes or population balance systems. Thus, the underlying process mechanisms can be broadly classified into birth, growth and death processes. Birth or particle nucleation accounts for the formation of new granule particles. This occurs by the wetting of the dry powdery feed material with the binder liquid, and the subsequent formation of loosely-held solid grains. Growth of the granules occurs mainly by the aggregation process, which accounts for the combination of two granules in the presence of the binder liquid to form a single larger granule. A pre-requisite to aggregation in wet granulation is the availability of binder liquid in the granules that participate in the aggregation process. Thus, the granules that collide with each other as a result of the mixing and tumbling within the granulator will aggregate if there is enough binder liquid in either of the granules, either at the surface to cause sticking or within the granules to cause a viscous dissipation of their kinetic energy. The aggregation process is aided by the consolidation

process, which accounts for the compaction of the granules (reduction of the pore volume) and the associated increase in the fractional binder content of the granules. The particles might also be involved in fragmentation, again due to collision with the walls or with the other particles, or due to the mixing action. Thus, the granule size distribution is mainly determined by the phenomena of granule nucleation, consolidation and aggregation, and granule breakage (Iveson et al. (2001)). In addition to the above processes, there could be simultaneous crystallisation from solution and an associated layering of the granules with the solids, perhaps due to a supersaturation induced by chemical reactions. Layering can also occur through physical processes, by the interaction of smaller granules or the feed powder with larger and wet granules. Also, the granulation process might involve simultaneous drying of the binder (undesirable), depending upon the temperature of operation. Thus, the process offers a rich blend of unit operations and processes.

State-of-the-art in granulation modelling

In view of the particulate nature of the granulation process and the characteristic of the underlying rate processes, the population balance modelling framework provides the best methodology for the granulation processes. Several successful applications of population balances to granulation processes have been reported in the literature. While a majority of these studies have focussed on a one-dimensional population balance to model the particle size distribution, some of the recent attempts have been on a multi-dimensional approach to model the particle size distribution. This is clearly warranted by the mechanism of the process, as explained below.

In addition to this shift in the approach to the structure of the population balance, there has also been a noteworthy shift in the approach to the modelling of the underlying rate processes. While some of the early modelling studies employed an empirical framework to model the underlying aggregation, consolidation and breakage phenomena, the more recent approaches shift to physically-based models and even further into first principle mechanistic models.

The focus of the present contribution is to develop a mechanistic model for the aggregation phenomenon, to be employed in a three-dimensional model of the granulation process. In developing this mechanistic model, advances and ideas from the models of other particulate processes are exploited.

2. POPULATION BALANCE MODEL

As indicated above, a suitable methodology for modeling the granulation process is through population balances, which account for the nucleation, consolidation, aggregation and breakage phenomena. The consolidation process essentially causes the compaction of the granules, reducing the granule porosity and thereby increasing the surface binder content of the granules. The aggregation of the granules constitutes the merging of two granules, perhaps subsequent to their collision. In addition to its dependence on the size of the granules, the sticking capability of the colliding granules also depends on the binder content of these granules, in particular, the availability of binder on the granule surface. Thus, a realistic characterization of the aggregation rate has to account for the granule size (or solid volume), the binder content, and the porosity, thereby necessitating three internal coordinates to obtain an accurate representation of the process (Verkoeijen et al. (2002)). These three variables can be recast as the volume of solid, liquid, and gas in the granules. The advantages with this choice of internal coordinates are:

(1) the decoupling of the individual mesoscopic processes (aggregation, consolidation, layering, drying, *etc.*), and
(2) the mutually exclusive character of the internal coordinates that substantially improves the solution of the aggregation model.

The corresponding population balance equation with this choice of internal coordinates is given by:

$$\frac{\partial}{\partial t}F(s,l,g,t) + \frac{\partial}{\partial s}(F(s,l,g,t)\frac{ds}{dt}) + \frac{\partial}{\partial l}(F(s,l,g,t)\frac{dl}{dt}) + \frac{\partial}{\partial g}(F(s,l,g,t)\frac{dg}{dt}) = \Re_{aggre} + \Re_{break} + \Re_{nuc} \quad (1)$$

where $F(s,l,g,t)$ is the population density function, defined such that $F(s,l,g,t)dsdldg$ is the moles of granules of solid volume between s and $s+ds$, liquid volume between l and $l+dl$, and gas volume between g and $g+dg$. $\Re_{nuc}(s,l,g,t)$ accounts for the rate of nucleation of new granules. $\Re_{aggre}(s,l,g,t)$ account for the gain/loss of granules due to the aggregation process, while $\Re_{break}(s,l,g,t)$ comprises similar terms due to granule breakage. The partial derivative with respect to g on the left hand side accounts for the consolidation phenomenon, wherein $\frac{dg}{dt}$ is negative (there is a continuous decrease in the pore volume of the granules as they compact, while the solid and liquid content of each granule is left unaltered). Likewise, the partial derivative term with respect to s accounts for simultaneous crystallization and the layering of the granule surface with the solid, while the term with respect to l accounts for drying effects. These latter two terms are usually restricted to a few special cases. Thus, it is

easy to see the decoupling of the individual unit operations and its advantage in the development of population balance models.

Two different types of the nucleation phenomena have been identified, subject to the conditions (or regime) of operation of the process (Adetayo et al. (1995); Iveson et al. (2001)). These depend upon the powder wetting characteristics, the binder spray rate, and the bed mixing rate, and are termed the droplet-controlled regime and the mechanical dispersion regime. In the former regime, each binder droplet results in a separate well-formed granule nuclei, while in the latter case, multiple droplets coalesce onto the dry powder that then gets broken into smaller nuclei due to mechanical dispersion forces. A mechanistic kernel can be developed for the former process (in terms of the binder spray rate, the powder turn-over rate, the nozzle characteristics, and the penetration time of the binder fluid into the dry powder). The latter case is similar to the breakage process, and very limited information is available to develop a first principles model for this case.

The consolidation phenomenon accounts for the compaction of the granules and the associated decrease in the particle porosity. The particle porosity ε is defined as $\varepsilon = \frac{l+g}{s+l+g}$, which is modelled using heuristic information as shown below Verkoeijen et al. (2002). In this equation, the constant c has been found to be dependent upon the mixing rate or tumbling rate in the granulator although no clear correlations have been established.

$$\begin{aligned} \frac{d\varepsilon}{dt} &= -c(\varepsilon - \varepsilon_{min}) \\ \frac{dg}{dt} &= -c\frac{s+l+g}{s(1-\varepsilon_{min})}\left[l - \frac{\varepsilon_{min}s}{1-\varepsilon_{min}} + g\right] \end{aligned} \quad (2)$$

The formation and depletion terms associated with the aggregation phenomenon are defined in Equations (3)-(5) (Ramkrishna (2000)). In these equations, s_{nuc} is the solid volume of nucleii (assumed fixed), and $\beta(s_1, s_2, l_1, l_2, g_1, g_2)$ is the size-dependent aggregation kernel that signifies the rate constant for aggregation of different granules of internal coordinates (s_1, l_1, g_1) and (s_2, l_2, g_2).

$$\Re_{aggre}(s,l,g,t) = \Re_{aggre}^{formation} - \Re_{aggre}^{depletion} \quad (3)$$

where

$$\begin{aligned} \Re_{aggre}^{formation} = \tfrac{1}{2}\int_{s'=s_{nuc}}^{s-s_{nuc}}\int_{l'=0}^{l}\int_{g'=0}^{g} \\ \beta(s', s-s', l', l-l', g', g-g')F(s', l', g', t) \\ F(s-s', l-l', g-g', t)ds'dl'dg' \end{aligned} \quad (4)$$

$$\begin{aligned} \Re_{aggre}^{depletion} = F(s,l,g,t)\int_{s'=s_{nuc}}^{s_{max}}\int_{l'=0}^{l_{max}}\int_{g'=0}^{g_{max}} \\ \beta(s', s, l', l, g', g)F(s', l', g', t)ds'dl'dg' \end{aligned} \quad (5)$$

As is common in the previous granulation modeling studies, the turn-over or mixing rate in the granulator is assumed to be high enough to justify the application of the law of mass action in modeling the collision rate in Equations (4) and (5).

Aggregation phenomenon and its modelling

The primary growth processes in granulation is the aggregation phenomenon. Aggregation is the process in which two (or more) primary granules combine in the presence of a binding agent. A good model of the aggregation phenomena should account for the various factors that determine the same, so as to provide the model with predictive capabilities. Such a predictive model will be the best suited for an analysis of the effect of different operating factors on the granule size distribution, and hence to develop a more robust operating strategy for the process, minimising the recycle ratios and also satisfying advanced objectives on distribution control.

Different forms of empirical kernels have been employed in the 1-D population balance modelling of the granulation process. While some of these kernels are purely empirical, others have considered physically-based kernels. However, in order to further improve the predictive capabilities of these models and to extend their region of validity, one has to directly incorporate the mechanistic details of the process and develop a kernel based purely on first principles. Such an approach is bound to be expensive and complex in form, and would also result in several more parameters than an empirical model. These parameters will need special experimentation for estimation. But it is these additional parameters that will render the models developed more universally-valid and predictive. The mechanistic understanding of the process has reached a stage wherein such a modelling venture is warranted. This paper presents a methodology for developing these first-principle aggregation kernels. The details of this mechanistic model of the aggregation process will be discussed in the next section.

3. PROPOSED MECHANISTIC AGGREGATION KERNEL

As indicated earlier, a primary challenge in the development of detailed process models is the understanding of the mechanisms underlying the process, and the development of appropriate mathematical representation for the same. This challenge is particularly pronounced in the development of the kernels required in the population balance models. While the development of a multi-dimensional population model is warranted by the physics of the problem, it is a bigger challenge to obtain the required three-dimensional kernels,

accounting for the dependence of the rates of the different phenomena on both the particle size and the binder content. However, very good progress has been made in this regard for various systems. For instance, for the emulsion polymerization process, detailed fundamental models of the coagulation process have been developed (see for instance Immanuel et al. (2003)). Usually, such fundamental models involve a number of parameters that are either unknown or uncertain. These parameters are fitted to macroscopic experimental data (on, say, the particle size distribution) employing the full population balance model. This approach serves as the best alternative to the determination of the model parameters based on detailed experiments at the mesoscopic levels, which are either expensive or not well developed. The modelling

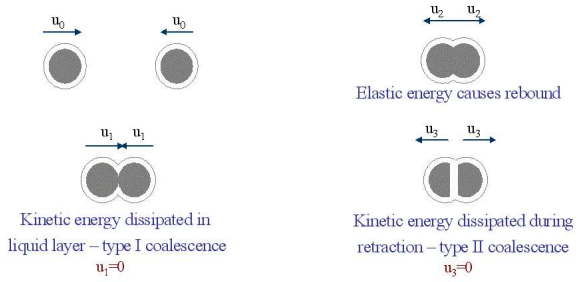

Fig. 1. Schematic representation of the two types of aggregation phenomena (Liu et al. (2000); Iveson et al. (2001)). u_0 is the approach velocity at infinite separation; u_1 is the velocity at impact; u_2 is the initial rebound velocity; u_3 is the velocity at the separation of binder layers.

of the kernels requires the identification of the net attraction potentials (energies) between the different particle pairs. Figure 1 shows a schematic representation of the aggregation phenomenon for a typical wet granulation process. In the granulation process, the kinetic energy of the particles constitutes the major potential of attraction between the granules ($mu_0^2/2$) (Ennis et al. (1991); Liu et al. (2000); Iveson et al. (2001)). The dissipation of the kinetic energy of the granules is primarily attributed to the viscous forces in the liquid binder film. Other forces that contribute to the dissipation are the collision energy and the elastic energy of the granules, which come into play only when the particles are involved in an actual collision by overcoming the viscous dissipation. Different forces become important in different regimes of particle sizes, binder content and operating conditions (mixing rates). The capillary repulsive forces between the particles are usually neglected in relation to the stronger viscous forces.

The particles that approach each other as a result of their kinetic energy will either coalesce or rebound. Coalescence is classified into two types - type I and type II. Type I coalescence occurs when the viscous force is able to overcome the kinetic energy, causing the particles to coalesce before the occurrence of a collision (through the liquid bridge). Type II coalescence occurs when the particles actually collide with each other. The collision causes particle deformation, which in turn results in the release of the elastic energy of the particles thereby causing the particles to retract. If the released elastic energy is dissipated in the viscous layer, then type II coalescence occurs. On the other hand, if the elastic energy is not completely dissipated in the viscous layer, then the particles rebound.

Net attractive potential for type I coalescence (balancing the kinetic energy with the viscous repulsion) is given by Equation (6), where p_1 and p_2 are the two particles, m is the reduced mass of the particles, h is the separation distance between the particles, and u is the varying relative velocity of the particles as they approach each other (Liu et al. (2000); Iveson et al. (2001)). The velocity u is given by Equation (7), wherein h_0 is the depth of the liquid binder film on the surface, u_0 is the initial approach velocity of the particles (based on the mixing rates in the granulator), and St_v is the viscous Stokes' number.

$$\psi(p1, p2, h) = \tfrac{1}{2} m (2u(h))^2 \tag{6}$$

$$u = u_0, h > h_0$$
$$u = u_0 \left[1 - \tfrac{1}{St_v} ln(\tfrac{h_0}{h})\right], h < h_0 \tag{7}$$

For type II coalescence, two different sequential processes are involved - the forward and the reverse paths. The process with the higher energetic is the rate-determining process. The net attractive potential for the two processes are given in Equations (8) and (9), where E_c is the energy lost during impact and deformation, given in Equation (10), u_1 being the velocity at impact calculated from Equation (7). The net rebound velocity u' is defined in Equations (11) and (12), δ'' being the permanent plastic deformation in the granules (Liu et al. (2000); Iveson et al. (2001)).

$$\psi_{forward}(p1, p2, h) = \tfrac{1}{2} m (2u(h))^2 - E_c \tag{8}$$
$$\psi_{reverse}(p1, p2, h) = -\tfrac{1}{2} m (2u')^2 \tag{9}$$
$$E_c = \tfrac{1}{2} m (2u_1)^2 \tag{10}$$

$$u'(h) = u_2 - \tfrac{3\pi\mu\tilde{D}^2}{16\tilde{m}h^2}$$
$$\left[(\delta'')^2 \left(\frac{h^2}{h_a^2} - 1\right) + 2h\delta'' \left(\frac{h}{h_a} - 1\right) + 2h^2 ln(\tfrac{h}{h_a})\right], \quad 0 < h < h_0$$
$$u'(h) = u'(h_0), \quad h > h_0 \tag{11}$$

$$\delta'' = \left(\frac{8}{3\pi}\right)^{\frac{1}{2}} (St_{def})^{\frac{1}{2}} \tilde{D} \left[1 - \frac{1}{St_v} ln(\frac{h_0}{h_a})\right] \left[1 - 7.36 \frac{Y_d}{E*} (St_{def})^{-\frac{1}{4}} \left[1 - \frac{1}{St_v} ln(\frac{h_0}{h_a})\right]^{-\frac{1}{2}}\right] \quad (12)$$

These steady state forces can be incorporated into a dynamic calculation of the aggregation rates and the aggregation kernel, as described in the emulsion polymerization literature (Immanuel et al. (2003)). These net attractive potential information can be employed in the Smoluchowski formulation as shown in Equation (13). The Fuch Stability ratio W is defined in Equations (14) and (15) for type I and type II aggregation, respectively. In these equations, r_i is the radius of particle p_i, k is the Boltzmann constant, T is the temperature, and c_1 is an adjustable constant.

$$\beta(p_1, p_2) = c_1 \frac{4\pi u_0 (r_1 + r_2)^2}{W} \quad (13)$$

$$W(p_1, p_2) = (r_1 + r_2) \int_{D=(r_1+r_2)}^{\infty} \frac{exp(\frac{\psi(p_1, p_2, D)}{kT})}{D^2} d(D) \quad (14)$$

$$\frac{W(p_1, p_2)}{r_1 + r_2} = max(\int_{D=(r_1+r_2)}^{\infty} \frac{exp(\frac{-\psi_{forward}(p_1, p_2, D - r_1 - r_2)}{kT})}{D^2} d(D), \int_{D=(r_1+r_2)}^{\infty} \frac{exp(\frac{-\psi_{reverse}(p_1, p_2, D - r_1 - r_2)}{kT})}{D^2} d(D)) \quad (15)$$

4. SIMULATION RESULTS

In solving the three-dimensional population balance model, a hierarchical solution strategy is employed that explicitly casts the population balances in terms of the underlying rate processes (aggregation, consolidation, nucleation etc. as appropriate) (Immanuel and Doyle III (2003, 2004)).

Typical simulation results are shown in Figures 2 and 3. The aggregation phenomenon is modelled employing the mechanistic aggregation kernel developed in this study. Consolidation phenomenon is modelled employing the empirical equations shown in section 2. Although the population balance itself is formulated in terms of the volume of solid, the volume of liquid and the volume of gas as the three internal coordinates, the results are presented in terms of the more physically meaningful internal coordinates, *viz.* the total particle radius and the fractional binder content (and the porosity where appropriate). These quantities are defined as follows: particle radius is defined as $\left[\frac{3}{4\pi}(s + l + g)\right]^{\frac{1}{3}}$ and the particle fractional binder content is defined as $\frac{l}{s+l+g}$. The particle porosity was defined previously.

The simulation is of a seeded batch granulation process. The initial seed is unimodal and narrow, with an average size of 38 μ m, and a small fractional binder content of 0.02. In view of the low binder content, there is little growth at the initial times as seen in Figure 2. Starting from 1 minute, binder liquid is being sprayed into the granulator vessel at the rate of 1×10^{-6} $\frac{m^3}{s}$ for a duration of 4 minutes. This binder is assumed to be uniformly distributed into the granules. Figure 2 records a rapid growth during this period. The growth rate begins to slacken after 5 minutes, when the binder addition is discontinued. The final average particle size is about 85 μ m.

Figure 3 shows the evolution of the distribution in two-dimensions at different times during the batch. The initial period records an increase in both the particle size and the binder content, with an associated spreading of the distribution. Subsequently, there is a shifting of the distribution along the particle size axis, resulting in a bimodal distribution. These simulation results, particular those of the distributed variables, prove valuable in the validation of the mechanisms and the models. They will also provide useful information regarding model reduction approaches. For example, the possibility of representing the three-dimensional distribution (along size, binder content, and porosity) in terms of two one-dimensional distributions (one along particle size, and the other along binder content) can be examined through these results. Such studies will be pursued, along with suitable experimentation for quantitative model validation.

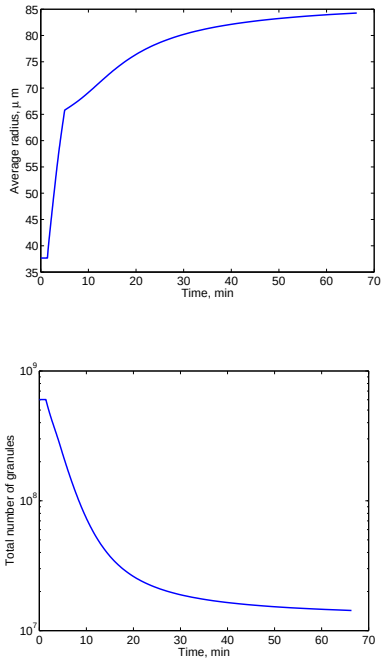

Fig. 2. Time profiles of average particle size and total particles.

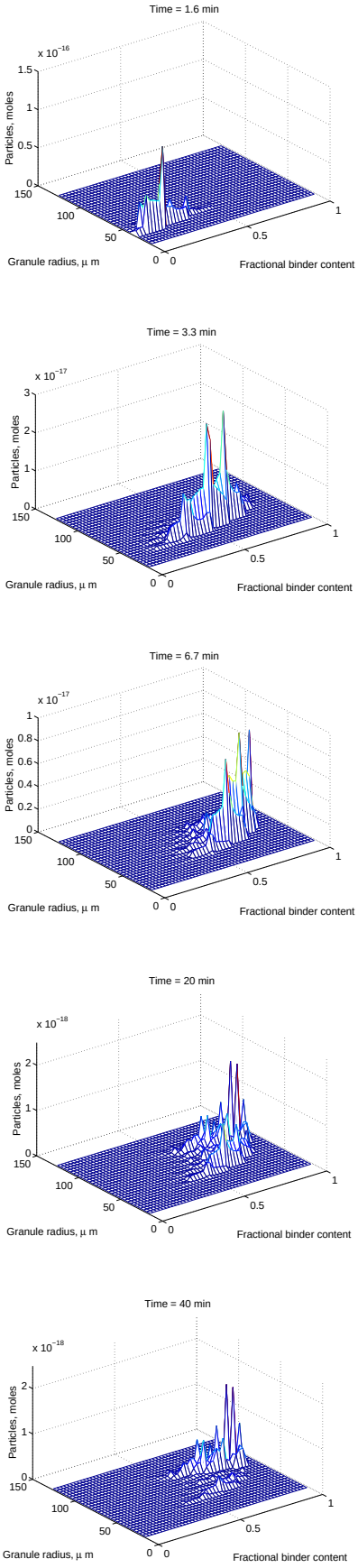

Fig. 3. Two-dimensional representations of the evolution of the granule PSD.

5. CONCLUSION

In this paper, the important problem of the development of a realistic model for granulation processes was addressed. The operation and control of granulation processes, like those of most solid handling processes, is currently primarily based on operator experience and is more an "art rather than a science". With advancements in the understanding of the underlying science, a crucial next step is to systematise these scientific developments into a mathematical model that will in turn find application in rigorous optimisation and control of these processes. The paper addressed the population balance-based modelling of the granulation process. Further, it presents a mechanistic model for the aggregation phenomenon that constitutes a major growth mechanism in the granulation processes. The mechanistic aggregation kernel is embedded into the population balance model. This is a novel approach compared to previous models that employ empirical models for the kernels, based on macroscopic experimental observations. The preliminary results capture experimental trends in a qualitative manner. The advantage in the present mechanistic formulation is its applicability to much broader range of conditions than its empirical counterpart.

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