Modeling and optimization of spherical agglomeration in suspension through a coupled population balance model

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A coupled population balance model for spherical agglomeration systems is proposed. The model enables simulation of crystals and agglomerate particles independently. First principles based process parameters (i.e. agglomeration efficiency, porosity). Optimization framework for both bioavailability and manufacturability targeting. The proposed model can lead to improved parameter estimation and kinetic studies.

1. Introduction

Since its introduction, the population balance model (PBM) has been widely used and accepted as the model formulation method for simulation and prediction of the size distribution and other properties of particulate systems (Randolph and Larson, 1971; Ramkrishna, 2000). PBMs allow for systems that include any or all of the following mechanisms: nucleation, growth, breakage and agglomeration. Following the initial work by Smoluchowski (Smoluchowski, 1917) on the rate of aggregation for spherical particles, there have been many contributions for systems that exhibit agglomeration including dispersion (bubble) coalescence (Coulaloglou and Tavlarides, 1977; Prince and Blanch, 1990), granulation (Iveson, 2002; Liu and Litster, 2002) and particle aggregation during crystallization (Marchal et al., 1988; David et al., 1990; Kumar and Ramkrishna, 1997). The shared limitation in the models between many of the previous studies is the loss of information of constituent particles. This limitation presents obstacles in the estimation of the kinetic parameters (nucleation and agglomeration. Following the initial work by Smoluchowski (Smoluchowski, 1917) on the rate of aggregation for spherical particles, there have been many contributions for systems that exhibit agglomeration including dispersion (bubble) coalescence (Coulaloglou and Tavlarides, 1977; Prince and Blanch, 1990), granulation (Iveson, 2002; Liu and Litster, 2002) and particle aggregation during crystallization (Marchal et al., 1988; David et al., 1990; Kumar and Ramkrishna, 1997). The shared limitation in the models between many of the previous studies is the loss of information of constituent particles. This limitation presents obstacles in the estimation of the kinetic parameters (nucleation and
growth rate vs agglomeration rate) and in developing an understanding of the influence of process conditions on each in population (constituent particles vs agglomerates). Having information regarding the constituent particles would allow for improved particle design through more accurate parameter estimation, simulation, optimization, and control; particularly for the increasingly popular technique of agglomeration in suspension.

Agglomerating fine particles in suspension, through the use of a bridging liquid, to improve particle properties and downstream process efficiency has been known since the late 1960s. Initially, the technique was used mostly in bulk chemical industries, e.g. coal beneficiation (Petela, 1991). Since then agglomeration in suspension techniques have been geared towards application in the pharmaceutical industry to improve filtration and downstream processing of active pharmaceutical ingredient (API) during crystallization by eliminating granulation and milling unit operations (Kawashima, 1984; Kawashima et al., 2003; Amaro-González and Biscans, 2002). In this respect the technique is often referred to as spherical crystallization. Interest in the application of spherical crystallization in pharmaceutical processes has increased through the continued development and understanding of the operating conditions (Kawashima et al., 1982a, 1982b; Kawashima, 1995), choice of binding agent (Katta and Rasmuson, 2008), kinetics (Kawashima and Capes, 1974) and mechanisms (Kawashima et al., 2003; Rasmuson and Thati, 2011; Thati and Rasmuson, 2012; Blandin et al., 2003) that govern experimental outcomes. Peña and Nagy (2015) studied and showed the benefits of spherical crystallization as a process intensification technique, whereby both internal (primary crystals) and external (agglomerates) properties can be controlled experimentally through a decoupled continuous spherical crystallization (CSC) approach; providing the means by which both biopharmaceutical (bioavailability, dissolution) and manufacturing (flowability, filtration, drying) properties can be simultaneously adapted to meet desired quality specifications. This technique opens the door for combined experimental and modeling approaches for the optimization and control of both the primary crystal and agglomerate properties in spherical crystallization processes. However, many of the PBMs currently in literature would fail to accomplish this because of the aforementioned limitations and loss of constituent particle information.

The limitations in previously developed PBMs are related to the complex crystallization phenomena occurring during spherical crystallization processes. For previous models, agglomeration was either an incidental process occurring along with nucleation and growth during crystallization or the main process occurring in seeded or seed-fed systems with negligible nucleation and growth. This allowed for empirical agglomeration models often independent of system properties and solely dependent on fitting to experimental data (Seyssiecq et al., 2000). The accuracy of those models are limited, are very system dependent and have difficulty capturing all the influencing process parameters on the system. Moreover, they only take into consideration the evolution of the agglomerates and not that of the constituent primary crystals. As previously mentioned, from the mechanistic point of view there are numerous studies in the literature that propose agglomeration mechanisms. However, there has yet to be a comprehensive correlation between the proposed mechanisms of spherical crystallization, which include nucleation, growth and agglomeration, and the appropriate agglomeration kernel. This has largely been influenced by the inherit loss of information in the PBMs and the lack of process analytical technology (PAT) tools to help determine and validate proposed mechanisms (Nagy et al., 2013).

Bemer (1979) was one of the first to study agglomeration in suspension from both an experimental and modeling approach. His work led to further implementations of combined experimental and modeling studies. David et al. (2003) developed a multi-layer agglomeration model that considers the efficiency of agglomeration based on the collision mechanism (i.e. Brownian, laminar, or turbulent). As particles change in size their collision mechanism or flow field can change from Brownian to laminar to turbulent, as particle size increases. In their model, the kernel accounted for changes in the collision mechanism and was also a function of the supersaturation and temperature through the growth rate which was used as the efficiency term. It is known that
agglomeration is enhanced by inter-particle growth or agglomerative bond formation; when supersaturation increases the subsequent inter-particle growth between two particles that come in contact increases allowing for higher agglomeration efficiency (Brunsteiner et al., 2005). Madec et al. (2003) simplified the agglomeration model by incorporating a more relevant process parameter into the kernel, specifically their work accounted for the composition of bridging liquid in an agglomerate. It has been shown that there is a critically optimal range for the ratio of bridging liquid to solute volume (BSR); below or above this critically optimal range would produce loosely compacted agglomerates or paste-like amorphous agglomerates, respectively (Petela, 1991; Thati and Rasmuson, 2012; Peña and Nagy, 2015). This unique incorporation of the bridging liquid composition served as the efficiency term by which the process would reach equilibrium.

The most comprehensive study in this area is that of Blandin et al. (2005). In this combined experimental and modeling study, key aspects of agglomeration in suspension are noted:

1. The agglomeration mechanism is a three-step process; (i) bridging liquid droplets capture solid particles and form agglomerate nuclei, (ii) compaction of the agglomerate nuclei due to collisions with other particles causes a rapid decrease in the mean diameter, (iii) growth and consolidation then occur due to the hydrodynamics and process conditions of the system (i.e. collisions, BSR).

2. Agglomeration is only efficient in the critical BSR range: the agglomerate size increases with a strong dependence on BSR, weak dependence on solids concentration and inverse dependence on agitation rate.

3. Porosity decreases as mean diameter reaches equilibrium.

4. Agglomeration stops as mean diameter reaches equilibrium.

Based on these fundamental experimental observations an agglomeration model considering the size and concentration of the agglomerating particles, with the agglomeration kernel expressed as a function of the meeting probability and agglomeration efficiency of the process, was developed. The meeting probability was described by a function of the target efficiency, agglomerate sizes, and collision velocity (Kuboi et al., 1984). The simulations from this work were in agreement with experimental data when the necessary parameters were fit to the data. By identifying the critical experimental mechanisms, Blandin et al. was able to develop a comprehensive model that accounted for both the mechanistic phenomena (e.g. deformability, collision efficiency, and compaction) and process conditions (e.g. energy dissipation, BSR, primary particle size). Although this model showed significant superiority over many others observed in the literature, it still has the limitation of losing the information of the constituent particles. Moreover, the model relies on the assumption that the initial particles participating in the agglomeration are monodispersed. Table 1 summarizes various kernels found in the literature used for agglomeration in suspension modeling with \( r \) defined as the radius of the particle and is interchangeable with the characteristic length.

To overcome the issues of loss of information a coupled PBM formulation is required. A coupled PBM formulation could simultaneously tracks the evolution of the primary crystals and the evolution of the agglomerates. The relationship between primary crystal properties and their effect on final agglomerate properties would thereby be more explicit and more efficient than in traditional approaches. To the best of our knowledge, the only previous work that presented this approach is that of Ochsenbein et al. (2015). In their study, Ochsenbein et al. focused on the agglomeration of needle-like crystals in suspension. Through a coupled PBM framework Ochsenbein et al. were able to develop a population balance equation (PBE) to describe the evolution of the primary crystals by a two-dimensional growth rate to represent the needle like structure of the crystal. Then another PBE was used to describe the evolution of the agglomerates as a function of the primary crystals. For the agglomeration kernel, they derived their own modified kernel that included both characteristic lengths of the primary crystals participating in the agglomeration. The new PBM formulation also allowed for the development of new parameters that add value to the simulations due to their experimental relevance. However, the work of Ochsenbein et al. neglected nucleation, something common to previously developed PBMs with agglomeration. The coupled population balance model framework will be extended herein.

The contribution of this work is the extension of the coupled PBM framework for application in the simulation and optimization of an agglomeration in suspension system. A coupled PBM framework has been developed for a semi-batch, reverse addition, anti-solvent crystallization system with agglomeration. Reverse addition anti-solvent crystallization techniques entail the addition of solution to the anti-solvent. The technique is carried out for low solution to anti-solvent ratios to produce very fine crystals due to very high supersaturation generation. The system includes nucleation and growth of primary crystals and subsequent agglomeration. The purpose of the work is to exploit the advantages presented by a coupled PBM framework; for example, the ability to optimize for specific primary and agglomerate properties. This presents an opportunity to find optimal operating conditions that meet both bioavailability and manufacturability demands. It also allows for the ability to develop a first principles based parameter for agglomeration efficiency and a first principles based estimate for porosity. Additionally, through the retention of the information of the primary particles, the interplay between the effects of operating conditions on the properties of the primary crystals versus the agglomerates will be clear.

### 2. Model development for agglomeration in suspension

Table 1 Common agglomeration kernels.

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<tbody>
<tr>
<td>( K_a )</td>
<td>( K_a(t_i)^3 )</td>
<td>( K_a(r_i + r_j)^3 )</td>
<td>( K_a(r_i + r_j)^3 )</td>
<td>( K_a(r_i + r_j)^3 )</td>
<td>( 5.431 \times 10^{-11}(1 + 2.29d - 2.429d^{0.15}) )</td>
<td>( K_a(r_i + r_j)^3 \left( \frac{c_i + c_j}{100 - \frac{c_i + c_j}{d}} \right)^4 )</td>
<td>( K_a = f(t_i, t, t_{eff}, t_i, t_j) )</td>
</tr>
</tbody>
</table>
the crystal is part of an agglomerate or not (total crystals).

However, since all the other mechanisms are generation rate. It is important to note that traditionally the agglomerate characteristic size is denoted by the volumetric number density ncs and the suspension volume. x (m) represents the characteristic length and t is the batch time.

$$\frac{\partial}{\partial t} \left[ V(t) n_c(x, t) \right] = - \frac{\partial}{\partial x} \left( G(x) V(t) n_c(x, t) \right) + \delta(x) V(t) B - D_{\text{agg}}(x)$$

(1)

In Eq. (1), n_c(x, t) is the volumetric number density (no. m^-3) representing the primary crystals in the system; regardless of whether the crystal is part of an agglomerate or not (total crystals). G (m s^-1) is the growth rate, B (no. m^-3 s^-1) is the nucleation rate, \(\delta(x)\) (m^-3) is the Dirac delta function, and V(t) (m^3) is the suspension volume. x (m) represents the characteristic length and t is the batch time.

$$\frac{\partial}{\partial t} \left[ V(t) n_{c}(x, t) \right] = - \frac{\partial}{\partial x} \left( G(x) V(t) n_{c}(x, t) \right) + \delta(x) V(t) B - D_{\text{agg}}(x)$$

(2)

$$D_{\text{agg}}(x) = V(t) n_{c}(x, t) \int_{0}^{\infty} \beta(x, \lambda) n_{c}(\lambda, t) d\lambda.$$  

(3)

In Eq. (2), n_{c}(x, t) is the volumetric number density (no. m^-3) representing the un-agglomerated crystals (crystals in suspension). This equation differs from the first equation by the third term \(D_{\text{agg}}(x)\) (no. m^-3 s^-1) which represents the death (disappearance) of crystals due to agglomeration (Eq. (3)). The death of crystals can occur through crystal agglomeration with other crystals or agglomerates. This is denoted by the volumetric number density n_{c}(\lambda, t) (no. m^-3) which represents both crystals and agglomerates of a characteristic size \(\lambda\). In Eq. (3), \(\beta(x, \lambda)\) represents the agglomeration rate (m^3 - no. m^-3 s^-1) of a particle of characteristic size x with a particle of characteristic size \(\lambda\).

$$\frac{\partial}{\partial t} \left[ V(t) n_{c}(x, t) \right] = - \frac{\partial}{\partial x} \left( G(x) V(t) n_{c}(x, t) \right) + B_{\text{agg}}(x) - D_{\text{agg}}(x)$$

(4)

$$B_{\text{agg}}(x) = \frac{x^2}{2} \int_{0}^{\infty} \beta(x^3 - x^3) \frac{3}{3} n_{c}(x^3 - x^3, t) V(t) n_{c}(\lambda, t) d\lambda.$$  

(5)

$$D_{\text{agg}}(x) = V(t) n_{c}(x, t) \int_{0}^{\infty} \beta(x, \lambda) n_{c}(\lambda, t) d\lambda.$$  

(6)

In Eq. (4), n_{c}(x, t) is the volumetric number density (no. m^-3) representing the agglomerates produced from the birth \(B_{\text{agg}}(x)\) (no. m^-3 s^-1) and death \(D_{\text{agg}}(x)\) (no. m^-3 s^-1) of agglomerates from crystal-agglomerate and agglomerate-agglomerate agglomeration. \(\beta(x, \lambda)\) is the same as the term in Eq. (3) and represents the agglomeration rate. It is important to note that traditionally the agglomeration birth and death terms are expressed with volume as the internal coordinate. However, since all the other mechanisms are expressed with respect to characteristic length a modification is made to express this in terms with respect to characteristic length following modification steps from the literature (Marchisio et al., 2003a, 2003b; Costa et al., 2007). Eqs. (2) and (4) are coupled through Eq. (7).

$$n_{c}(x, t) = n_{c}(x, t) + n_{d}(x, t)$$

(7)

Eq. (7) is simply the addition of the un-agglomerated crystals and the agglomerates denoted by the number density function \(n_{c}(x, t)\) (no. m^-3). This combined population is used to account for crystal-crystal and crystal-agglomerate interactions and reduce the number of terms in the birth and death terms in Eqs. (1)–(6). Eq. (1) is intentionally made to stand alone based on the assumption of uniform kinetics for all populations tracked in the system. The set of equations will all be coupled by the mass balance which will ultimately determine nucleation and growth kinetics.

3. Solution method

Most of the spherical crystallization systems in literature are semi-batch with limited modeling work. For this reason, a semi-batch system with combined cooling and reverse addition anti-solvent is modeled. To account for the volume change in a semi-batch system the number density functions are expressed as a redefined number density \(n(x, t) = V(t)n(x, t)\) (Nagy et al., 2008; Yang and Nagy, 2014). The modified PBM will be as follow:

$$\frac{\partial}{\partial t} \left[ V(t) n_{c}(x, t) \right] = - \frac{\partial}{\partial x} \left( G(x) V(t) n_{c}(x, t) \right) + \delta(x) V(t) B - D_{\text{agg}}(x)$$

(8)

$$\frac{\partial}{\partial t} \left[ V(t) n_{c}(x, t) \right] = - \frac{\partial}{\partial x} \left( G(x) V(t) n_{c}(x, t) \right) + \delta(x) V(t) B - D_{\text{agg}}(x)$$

(9)

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(10)

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(11)

$$\frac{\partial}{\partial t} \left[ V(t) n_{c}(x, t) \right] = - \frac{\partial}{\partial x} \left( G(x) V(t) n_{c}(x, t) \right) + \delta(x) V(t) B - D_{\text{agg}}(x)$$

(12)

$$\frac{\partial}{\partial t} \left[ V(t) n_{c}(x, t) \right] = - \frac{\partial}{\partial x} \left( G(x) V(t) n_{c}(x, t) \right) + \delta(x) V(t) B - D_{\text{agg}}(x)$$

(13)

$$\frac{\partial}{\partial t} \left[ V(t) n_{c}(x, t) \right] = - \frac{\partial}{\partial x} \left( G(x) V(t) n_{c}(x, t) \right) + \delta(x) V(t) B - D_{\text{agg}}(x)$$

(14)

The above set of PBEs can be solved using the quadrature method of moments (QOMOM) approximation for the redefined moments (Marchisio et al., 2003a, 2003b; Costa et al., 2007; Gimbun et al., 2009).

$$\mu_k = \int_{0}^{\infty} x^k n(x, t) dx \approx \sum_{i=1}^{N} w_i l_i^k$$

(15)

The quadrature approximation transformed set of PBEs can be written as:

$$\frac{d\mu_{k,c}}{dt} = k \sum_{i=1}^{N} w_i l_i^{k-1} G(L_{c,i}) + \delta(k) V(t) B$$

(16)

$$\frac{d\mu_{k,c}}{dt} = k \sum_{i=1}^{N} w_i l_i^{k-1} G(L_{c,i}) + \delta(k) V(t) B$$

(17)

$$\frac{d\mu_{k,c}}{dt} = k \sum_{i=1}^{N} w_i l_i^{k-1} G(L_{c,i}) + \delta(k) V(t) B$$

(18)
The nucleation and growth rate kinetics for traditional anti-solvent crystallization of benzoic acid were used for this study, O’Grady carried out various solubility experiments for benzoic acid at different temperatures and ethanol-water mixtures. The data from his work is taken and fit to a third-order polynomial with respect to both temperature and solution to anti-solvent ratio (SASR) using the Matlab function fit. In Fig. 1, the y-axis (left) and z-axis (right) are read as the concentration of benzoic acid in ethanol expressed in g per mL.

The agglomeration kernel used for this study is a homogeneous kernel derived from the combination of the Brownian diffusion kernel and the Zauner and Jones (2000) and will be referred to as the Brownian + kernel. It is expressed as:

\[
\beta(l_i, l_j) = a(b + c\beta^2 - d\varepsilon)S^3 \frac{k_0(l_i + l_j)^2}{L_d}\varepsilon
\]

The first portion of the agglomeration kernel is composed of the parameters and process conditions defined by Zauner and Jones (2000) where \(a, b, c, d\) and \(\varepsilon\) are constants, \(\varepsilon\) is the energy dissipation and \(S\) is the supersaturation. The energy dissipation is defined as follows:

\[
\varepsilon = \frac{N_d d^3 N^3}{V}
\]

where \(N_d\) is the stirrer power number, \(d\) (m) is the diameter of the stirrer and \(N\) is the agitation rate over \(V\), the volume of the slurry (Subero-Courroy et al., 2006). The second part of the kernel is the Brownian portion that takes into account the surface area effect of the two particles partaking in the agglomeration and is divided by the product of the two particles which allows for a determination effect; as the particles get larger the effect of the Brownian portion of the kernel is reduced. This is appropriate as this model allows the agglomeration rate to decreases as the particles get larger, a common behavior seen in agglomeration in suspension techniques like spherical crystallization.

5. Agglomeration efficiency and porosity

As pointed out by Ochsenein et al. (2015), one of the advantages of the coupled population balance model is that it allows for the development of physically relevant parameters. One parameter is the agglomeration efficiency. The coupled PBM framework allows for the population of all primary crystals, un-agglomerated crystals and agglomerates to be tracked, allowing for the determination of the efficiency of the agglomeration process with regards to the total number of crystals contained in the agglomerates.

Fig. 2 is a schematic representation of the three populations being tracked by the coupled PBM framework. As the figure depicts, the primary crystals population consist of each individual crystal outlined in green within the green dashed box, the individual crystals left in suspension consist of those crystals circled in blue dotted lines and lastly the agglomerates consist of those particles circled in red solid lines. Expressed in terms of volume, Fig. 2 illustrates that the ratio of the volume of agglomerates to the volume of total primary crystals is a measure of the extent of agglomeration:

\[
\text{% of agglomerated crystals} = 100\left(\frac{V_a}{V_{ic}}\right)
\]

There are limited complete studies of the solubility of benzoic acid in ethanol-water mixtures for various concentrations and temperatures except for O’Grady’s PhD thesis (O’Grady, 2007). In his study, O’Grady carried out various solubility experiments for benzoic acid at different temperatures and ethanol-water mixtures. The data from his work is taken and fit to a third-order polynomial with respect to both temperature and solution to anti-solvent ratio (SASR) using the Matlab function fit. In Fig. 1, the y-axis (left) and z-axis (right) are read as the concentration of benzoic acid in ethanol expressed in g per mL.

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\[
\text{% of agglomerated crystals} = 100\left(\frac{V_a}{V_{ic}}\right)
\]

For interpretation of color in Fig. 2, the reader is referred to the web version of this article.
Table 2
Empirical kinetic constants retrieved from Ramisetty (2013).

<table>
<thead>
<tr>
<th>$N'$ - agitation rate (rpm)</th>
<th>$k_a$ ($10^{-6}$)</th>
<th>$g$</th>
<th>$k_b$ ($10^{-3}$)</th>
<th>$b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>1.5</td>
<td>3.1</td>
<td>1.2</td>
<td>1.6</td>
</tr>
<tr>
<td>600</td>
<td>2.6</td>
<td>3.5</td>
<td>3.2</td>
<td>1.9</td>
</tr>
<tr>
<td>800</td>
<td>3.2</td>
<td>3.8</td>
<td>3.6</td>
<td>2.3</td>
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Porosity is a property of interest in agglomeration and granulation due to the effects it can have on other properties like dissolution and compressibility. Many times a final desired porosity can determine the experimental conditions.

Fig. 3 illustrates how the porosity of an agglomerate decreases as subsequent agglomeration continues over time. Due to the one-dimensional PBE, reconstructing the size of the agglomerate from the characteristic length makes the assumption that the particle produced from an agglomeration event is a sphere. This assumption causes high porosity initially (see agglomerate on left in Fig. 3) which is similar to what occurs experimentally. As subsequent agglomeration continues the assumption of a sphere becomes more reasonable and the porosity decreases in the very same manner seen experimentally (left to right in Fig. 3). Expressed in terms of volume Fig. 3 states that volume of the pore ($V_p$) is equal to the volume of agglomerates minus the difference between the volume of primary crystals and volume of un-agglomerated crystals. The porosity determined by dividing this difference by the volume of agglomerates.

\[
V_p = V_a - (V_{ic} - V_{cs})
\]

\[
\varepsilon_p = 1 - \frac{(V_{ic} - V_{cs})}{V_a}
\]

Similar to the agglomeration efficiency the porosity can be calculated with respect to the moments of the coupled PBM ($\tilde{\mu}_{0,c}, \tilde{\mu}_{1,c}, \tilde{\mu}_{2,c}$).

\[
P = 1 - \frac{\tilde{\mu}_3 - \tilde{\mu}_0}{\tilde{\mu}_3/\tilde{\mu}_0} = 1 - \frac{V_{ic,30} - V_{cs,30}}{V_{a,30}}
\]

The aforementioned set of coupled population balance equations and defined parameters are to be used in an optimization framework where internal properties like crystal mean size and external properties like agglomerate mean size can be optimized for subject to constraints on agglomeration efficient and yield, and other quality attributes or process constraints.

6. Optimization framework

Three optimization scenarios were analyzed: (i) minimizing primary crystal size, (ii) maximizing primary crystal size, and (iii) attaining bioavailability and manufacturability targets. For simplicity the total particle mean size using the first and zeroth moment of the respective populations were used, $\mathcal{C}_{t,10}$ and $\mathcal{C}_{t,0}$. The batch time is fixed at 300 min (~5 h) which is typical for agglomeration in suspension systems like benzoic acid spherical crystallization. The optimization variables are the dynamic operating profiles for temperature ($T(t)$), agitation rate ($N'(t)$) and solution flow rate ($F(t)$). The level of discretization for the optimization variables is 10. All the scenarios were subject to the same variable bounds and constraints. The bounds were chosen based on the range of the available solubility and kinetic data. The framework includes constraints on cooling/heating rate, $\mathcal{A}E$; solution addition ($SASR$), agglomeration efficiency, $\varepsilon_p$, yield, ($\mathcal{C}_{final}$) and initial flow rate, ($F(0)$). Due to the fact that a reverse addition anti-solvent crystallization system was chosen for this study the constraint on the initial flow rate assures that a certain crystal mass will be generated otherwise the optimizer may try to crystalize one large particle towards the end of the batch. The optimization problem for the first two scenarios can be written as:

\[
\min_{T(t), N'(t), F(t)} - \mathcal{L}_{t,10} \text{ or } \mathcal{L}_{t,10}
\]
s.t.
\[
16 \leq T(L) \leq 28 \, ^\circ \text{C} \\
400 \leq N(L) \leq 800 \, \text{RPM} \\
0 \leq F_r(L) \leq 2.5 \, \text{mL/min} \\
-0.4 \leq \frac{\partial T}{\partial L} \leq 0.4 \, ^\circ \text{C/min} \\
0.25 \leq SASR \leq 0.40 \\
\Delta \xi \geq 50\% \\
C_{\text{final}} \leq 0.75C_{\text{max}} \\
F_s(0) \geq 1.0 \, \text{mL/min}
\] (38) (39) (40) (41) (42) (43) (44) (45)

The new variable $C_{\text{final}}$ is the final concentration of solute in solution while $C_{\text{max}}$ is the maximum concentration if all the solution is added to the system and no crystallization occurred. As written the constraint requires a 25% yield. The optimization problem is solved using the “interior point” method of $fmincon$ in Matlab. The objective function of the optimization problem for the last scenario can be written as:
\[
\min_{T(0),N(0),F_r(0)} \left( B_t - L_{\text{cr},10} \right)^2 + \left( M_t - L_{a,10} \right)^2
\] (46)

$B_t$ and $M_t$ represent bioavailability and manufacturability targets. For this scenario the optimization problem is a multi-objective framework with $\geq 1$ and $\geq 2$ being the weights for each objective. The weights in Eq. (46) are shown as a generalization for situations in which bioavailability or manufacturability is more heavily weighted than the other. In this work, $\geq 1$ and $\geq 2$ each have values of one. This scenario is restricted to the same constraints previously described.

7. Results and discussion

7.1. Minimizing primary particle mean size

The first scenario of interest is the minimization of the particle size. Minimization of primary crystal mean size is relevant in many industrial scenarios and helps with micromeritic properties in pharmaceutical applications like bioavailability and dissolution. This scenario will also serve to illustrate the capabilities of the coupled population balance model approach. The moments of this scenario illustrate the ability to keep track of all the populations in the PBE set. Fig. 4 shows the zeroth moment for the three populations. The zeroth moment is representative of the total particle count. In Fig. 4, the total particle count for the primary crystals in the system increases as solution is fed and the system becomes supersaturated. For this scenario, an inflection point occurs (at 105) indicating a significant increase in nucleation and a plateau is reached (at 220 min) indicative of zero supersaturation (zero nucleation).

Focusing on the zeroth moment of the un-agglomerated crystals and the agglomerates it can be seen that there is an initial increase in un-agglomerated crystals that correlates with that of the primary crystals when the system first nucleates. There is a delayed increase in the agglomerate counts since agglomeration cannot begin until there are crystals present. At 38 min, the un-agglomerated crystals count begins to spike but is then quickly reduced due to agglomeration. Since agglomerate formation can occur from crystal-crystal, crystal-agglomerate and agglomerate-agglomerate interactions, the zeroth moment of the agglomerates decreases further; even though there is no longer nucleation (zeroth moment of primary crystals plateaus). The difference in magnitude of the primary crystals and un-agglomerated crystals in the beginning is also an indication of agglomeration.

Fig. 5 shows the third moment for the three populations. As the system begins to nucleate and grow the volume of the primary crystals increases steadily until the supersaturation is depleted. Comparing both Figs. 4 and 5 suggests that most of the particle volume is created at the onset with low total counts followed by secondary nucleation shown by the jump in the total counts but only a slight increase in total volume. The volume of un-agglomerated crystals is significantly smaller than the volume of primary crystals and agglomerates suggesting that most of the agglomeration happens at after the inflection (increase in nucleation) in primary crystals counts. The third moment of the three populations shows the same trend for all optimization scenarios investigated and hence will not be shown for other scenarios.

Comparing Figs. 4 and 5 can be misleading given that in Fig. 4 the total count of un-agglomerated crystals is increasing along with that of primary crystals, while in Fig. 5 the total volume of un-agglomerated crystals rapidly decreases and is significantly smaller than that of the primary crystals. This can be clarified by looking at the mean sizes of the three populations.

The mean size optimization profiles of the three populations for this scenario are shown in Fig. 6. The mean size is expressed as the
first moment divided by the zeroth, $L_{tc,10}$. The minimum primary particle size achievable in this scenario is 2.5 μm. While the crystals left in suspension have a mean size of 0.1 μm and the agglomerates are of a mean size of 28.8 μm. The small size of the un-agglomerated crystals again suggests that the increase seen in the total counts relates to secondary nucleation, which in turn corresponds to a small particle size and very small/negligible volume. The agglomerate mean size and the primary crystal mean size follow the trend observed from the zeroth moment. When the primary crystal mean size plateaus the agglomerate mean size increases otherwise they follow the same pattern as the primary crystal mean size increases and vice versa.

Fig. 7 shows the optimal flowrate, temperature and agitation rate profiles for the minimization of the primary crystals mean size. Flowrate is initialized at its upper bound, the temperature profile starts near its lower bound and the agitation rate is initialized at its upper bound. High nucleation or crashing out is characteristic of reverse addition anti-solvent crystallization. As a result, the optimizer begins the process by nucleating from the addition of solution to the anti-solvent, at lower temperatures and high agitation rate to promote nucleation and generate small crystals. This period lasts the first 15 min and allows for the system to reach a supersaturated state quickly.

Immediately following the initial period, the flow rate of solution is decreased to its lower bound, the temperature begins to decrease further and the agitation rate is decreased to 600 RPM. These changes allow the system to decouple the effects of solution addition, temperature and agitation on nucleation. Whenever solution addition is increased, temperature is slightly increased and whenever solution addition is decreased, temperature is slightly decreased allowing for nucleation to be controlled by flowrate or temperature. This keeps the system supersaturated and in a nucleation phase, evident by the continued decrease in the primary crystals mean size, until the plateau in primary crystals is reached at 220 min. Nucleation is reduced in this period by an increase in temperature and solution addition. This period is continued until the end of the batch. This final addition of solution satisfies the solution to anti-solvent ratio constraint and decreases supersaturation. Fig. 8 shows the operating curve along the solubility surface for this scenario.

7.2. Maximizing primary particle mean size

Maximizing particle size also has industrial relevance in that some systems exhibit low downstream processing efficiency when the particle size is too small. For this scenario, Fig. 9 shows the primary crystal count very quickly reaching a plateau (100th min) indicative of the system avoiding secondary nucleation. A similar behavior in the zeroth moment of un-agglomerated crystals and agglomerate population is observed. The initial spike in the number of un-agglomerated crystals increases similarly to the primary crystals, however once the primary crystal counts plateau the counts of un-agglomerated crystals decreases sharply. This is followed by an increase and then a decrease in the agglomerate counts as the system transitions from crystal-crystal agglomeration to agglomerate-crystal and agglomerate-agglomerate agglomeration.

Fig. 10 shows the optimization results for the maximization of the primary particle size. The maximum achievable primary particle size is 41.8 μm. While the un-agglomerated crystals left in
suspension have a mean size of 61.6 μm and the agglomerates are of a mean size of 117.8 μm. With regards to the growth of the primary crystals and agglomerates the trends are very similar to that of the first scenario. The mean size of the primary crystals remains constant after the 100th min which aligns with the plateau in primary crystals counts indicative of little supersaturation or growth beyond this point. As in the previous scenario, the agglomerate mean size increases when the primary crystal mean size is constant or when increasing. Interestingly, the un-agglomerated crystal mean size continues to increase even after the 100th min point. This is due to the agglomeration kernel used to describe the system. The Brownian + kernel favors the agglomeration of smaller particles. Hence, once the system plateaus with regards to counts and has depleted supersaturation; agglomeration will favor smaller particles, which is the reason for the increase in mean size of un-agglomerated crystals, due to the removal of fine crystals from this distribution. This is also the reason why the increase in the mean size of un-agglomerated crystals increases with a higher order trend versus the agglomerate mean size which increases with a linear trend. Every small crystal that leaves the un-agglomerated crystals population increases the percentage of large crystals left behind while only marginally increasing the size of the agglomerate they attach to.

Fig. 9. The zeroth moment for each population in the PBE set for the maximization of \(L_{tc,10}\).

Fig. 10. Primary crystal mean size \(L_{tc,10}\), un-agglomerated crystals mean size \(L_{cs,10}\) and agglomerate mean size \(L_{a,10}\) for Scenario 2.

Fig. 11. Optimal flowrate, temperature and agitation rate profiles for the maximization of \(L_{tc,10}\).

Fig. 12. Operating curve along the solubility surface for the maximization of primary crystal size.

Optimizing for both bioavailability and manufacturability targets is the unique scenario that is made feasible by the proposed coupled population balance model framework. Prior to evaluating the attainability of bioavailability and manufacturability targets, the maximization of agglomerate particles is evaluated to understand the range and limitation to the maximum agglomerate size; although the optimal profiles are not shown here. The maximum attainable agglomerate size for the fixed batch time and operating conditions used here is 154.4 μm. The minimum and maximum size for the primary crystal were 2.5 and 41.8 μm, respectively. Given these results, the bioavailability target, \(B_T\), for the mean size is set to 10 μm and the manufacturability target, \(M_T\), is set to 50 μm.

Fig. 13 shows the results of the mean sizes for the bioavailability and manufacturability targets. Both the bioavailability and manufacturability target sizes were attained within 1 μm. \(B_T = 10.1\) and \(M_T = 49.9\) μm. The trends of mean size profiles
described for the previous scenario is similar in this scenario. When the primary crystals mean size is increasing or constant the agglomerate mean size increases. While the primary crystal mean size is constant the un-agglomerated crystal mean size increases because agglomeration favors smaller particles due to the agglomeration kernel used in this case. All the mean sizes decrease when nucleation occurs due to the increase in smaller counts for all populations.

Fig. 14 shows the optimal process profiles for the solution flow rate, temperature and agitation and Fig. 15 shows the operating line along the solubility surface. Analyzing these figures together, it is obvious that the optimal profile is a combination or interpolation of the previous two scenarios. One apparent difference is the number of temperature cycles observed in this scenario driven by the need to balance both nucleation and growth of the primary crystals so to attain both targets. From a solution flow rate perspective, the system is initiated and carried in the same manner as the previous scenario of maximizing primary particle size. The solution flow rate is initiated at 1.0 mL/min and then increased to the upper bound while the temperature is increased linearly to the upper bound (30°C). As in the previous scenario, the system is undersaturated until the solution flow rate is increased (Fig. 15). A temperature cycling phase then commences at a very low solution addition. This temperature cycles and low solution addition balance nucleation and growth allowing for both the bioavailability and manufacturability targets to be reached. The agitation rate follows the same trend as both previous scenarios.

The agitation profile is fairly similar for all three scenarios indicating that agitation rate is impacting the nucleation and growth kinetics more than the agglomeration kinetics. Overall the trend in agglomerate size with respect to changes in agitation rate did not match those reported in the literature (Kawashima, 1984, 1995; Katta and Rasmuson, 2008). This is most likely due to the set of nucleation and growth kinetic models used as both have an agitation rate dependence. The influence temperature profiles also had an impact on this results since most spherical agglomeration experiments had previously been conducted at constant temperature.

Table 3 summarizes the optimization results. All scenarios met the agglomeration efficiency (larger than 50%), yield (25% or greater) and SASR constraints (between 0.25 and 0.40). The bioavailability and manufacturing target scenario required the lowest amount of solution to the system but produced the highest yield. This is most likely due to the greater number of temperature cycles. The scenario to minimize primary crystal mean size had lowest yield most likely due to prevention of growth in the system. This scenario also had the highest agglomeration efficiency which is also related to the high amount of nucleation in this scenario and the fact that agglomeration favors smaller particles.
The results from shown in Table 4 show that a lower $i$ value results in a significantly larger achievable minimum and maximum primary crystal mean size. Modulating $i$ varies the extent of secondary nucleation in the system. A lower $i$ value decreases the extent of secondary nucleation which in return allows more supersaturation to be consumed by growth.

Fig. 17 shows the mean size profiles for both the minimization and maximization of primary crystal size. The mean size profiles show a significant difference from that of the system with a higher value for $i$. Most notably, changes in the mean size for the agglomerate follow more closely the changes in mean size of the primary crystals. The agglomerate mean size stays relatively constant, increases and decreases with the same trend as primary crystal mean size. This shows the impact that secondary nucleation can have on the final agglomerated size. The trends observed with lower values for $i$ are more reasonable when compared to the experiments in the literature (Rasmuson and Thati, 2011; Thati and Rasmuson, 2012), but will need to be fit to experimental data to attain a system specific value.

8. Conclusions

In this work, a coupled population balance model with nucleation, growth and agglomeration was developed. Three populations of interest are tracked: primary crystals, un-agglomerated crystals and agglomerate populations. Tracking these populations separately gives access to otherwise unattainable information in traditional population balance models. This allows for optimization frameworks and process design efforts tailored to the property specifications for each population.

An optimization framework has been developed to achieve optimal flowrate, temperature and agitation rate profiles for a reverse addition, anti-solvent crystallization system of benzoic acid with agglomeration. The results of this work show that operating parameters can be optimized to achieve the desired primary and/or agglomerate properties. The framework allows for bioavailability (primary crystal size) and manufacturability (agglomerate particle size) optimization. Moving forward this model formulation will allow for the development of better, more relevant kinetic and agglomeration parameters. Given that each population is tracked separately, kinetic parameters can be fit separately without having to lump all the kinetics into one population; thereby increasing accuracy of the parameter fit. Agglomeration kernel identification would greatly improve with this model formulation, and can begin the shift from purely empirical kernels to combination kernels that relate the physical mechanisms and operating conditions more accurately. Moving forward the proposed model formulation will be fit to data from various agglomeration in suspension systems to assess its capability to predict product properties.

Acknowledgements

Eli Lilly & Co. for their advice and funding support through the Lilly Research Award Program. Special thanks Omar José Guerra Fernández and Francesco Rossi from Dr. Reklaitis’s research group at Purdue University.

References


