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

Ramon Peña [a], Christopher L. Burcham [b], Daniel J. Jarmer [b], Doraiswami Ramkrishna [a], Zoltan K. Nagy [a,*]

[a] School of Chemical Engineering, Purdue University, West Lafayette, IN 47907, United States
[b] Eli Lilly and Company, Indianapolis, IN 46285, United States

HIGHLIGHTS

- 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.

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ABSTRACT

The population balance model is the common approach to simulation and prediction of the size distribution and other properties of particulate systems. Population balance models include any nucleation, growth, breakage and agglomeration mechanisms that are relevant to all industrial particulate processes. However, there are some limitations to many of the previous population balance model formulations for systems with agglomeration. Limitations include physically irrelevant and/or empirically based agglomeration kernels, difficulties in assessing the influence of process conditions (e.g. hydrodynamics, particulate physical properties), solution method efficiency for optimization and control applications, and loss of information on constituent particles. These limitations have prevented the use of population balance models to accurately predict and simulate agglomeration in suspension techniques such as spherical crystallization. To overcome these limitations, an extension of the concept of a coupled population balance model is presented for application in the simulation and optimization of a spherical crystallization system. A coupled population balance model formulation has been developed for a semi-batch, reverse addition, anti-solvent crystallization system with agglomeration. The system includes nucleation and growth of the primary crystals and subsequent agglomeration. The advantages presented by a coupled population balance model formulation include the ability to optimize for specific primary and agglomerate sizes. This presents an opportunity to find optimal operating conditions that meet both bioavailability and manufacturability demands.

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

* Corresponding author.
E-mail address: zknagy@purdue.edu (Z.K. Nagy).

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Nomenclature

$n_{tc}(x,t)$	number density (no. m^{-4}) representing the primary crystals
$n_{cs}(x,t)$	number density (no. m^{-4}) representing the un-agglomerated crystals
$n_a(x,t)$	number density (no. m^{-4}) representing the agglomerates
$n_{ca}(\lambda,t)$	number density (no. m^{-4}) representing the un-agglomerated crystals and agglomerates
G	growth rate (m s^{-1})
B	nucleation rate (no. m^{-3} s^{-1})
$\delta(x)$	dirac delta function (m^{-1})
$\beta(x,\lambda)$	agglomeration rate (m^3 no. $^{-1}$ s^{-1})
$D_{cs,agg}(x)$	death (disappearance) of crystals in suspension due to agglomeration (no. m^{-1} s^{-1})
$B_{a,agg}(x)$	birth of agglomerates from crystal and agglomerate interactions (no. m^{-1} s^{-1})
$D_{a,agg}(x)$	death of agglomerates from crystal and agglomerate interactions (no. m^{-1} s^{-1})
$V(t)$	suspension volume (m^3)
x, λ	characteristic length (m)
t	batch time
$\tilde{n}(x,t) = V(t)n(x,t)$	redefined (non-volumetric) number density
w_i	weights
L_i	abscissas
F_s	solution flow rate (mL/min)
C_S	solute (benzoic acid) concentration (g mL^{-1})
C_{in}	solution concentration (g mL^{-1})
x_{SASR}	solution to anti-solvent ratio
ρ_c	crystal density
k_v	shape factor
S	supersaturation
$\mathcal{SASR}$	solution to anti-solvent ratio
$\mathcal{N}$	agitation rate
k_g, g, k_b, b	growth and nucleation rate constants
ε	energy dissipation (W kg^{-1})
N_p	stirrer power number
d_s	diameter of the stirrer (m)
$\mathcal{AE}$	agglomeration efficiency
$\mathcal{P}$	porosity
$\mathcal{C}_{final}$	final concentration of solute (g mL^{-1})
C_{max}	maximum concentration
$\beth_i$	optimization weights
$\mathcal{B}_T$	bioavailability target
$\mathcal{M}_T$	manufacturability target
$\mathcal{L}_{tc,10}$, $\mathcal{L}_{a,10}$	first moment based mean size
$\mathcal{V}_{tc,30}, \mathcal{V}_{cs,30}, \mathcal{V}_{a,30}$	third moment based mean volume

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 multilayer 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