Population Balance Model Based Multi-Objective Optimization and Robustness Analysis of a Continuous Plug Flow Antisolvent Crystallizer

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Abstract—Crystallization is a major separation process in the pharmaceutical industry. Most crystallizations are performed batchwise, but there is great incentive for switching to continuous operation. We have investigated the modeling, simulation, optimization, and robustness of a multi-segmented, multi-addition plug-flow crystallizer (MSMA-PFC). The design accepts multiple antisolvent flows along its length, permitting localized control of supersaturation. A mass balance equation was used to track the depletion of dissolved solute (flufenamic acid), and a population balance equation for tracking the crystal size distribution. Multiobjective optimization was done using the antisolvent flows into each segment as decision variables. The genetic algorithm was used to calculate the Pareto frontiers for the two competing objectives of maximizing average crystal size ($L_{43}$), and minimizing coefficient of variation ($CV$). The sensitivity of the Pareto frontier to variation in the growth and nucleation kinetic parameters was investigated. The robustness of a single solution was examined as well with respect to error in the kinetic parameters, as well as to errors in antisolvent flowrate.

I. INTRODUCTION

The pharmaceutical industry is pursuing new, lower-cost manufacturing technologies [1]–[7]. Crystallization is a major separation unit operation in fine chemical and pharmaceutical manufacture. Over 90% of drugs are crystallized from solution [8]–[10]. Batch operation is predominant, despite the economic advantages of continuous manufacturing [11].

Continuous crystallization has been of recent interest in the literature [9], [11]–[15]. A design of interest in this work is the plug-flow crystallizer (PFC), which is a tube through which saturated liquor flows, and crystallization occurs. Advantages of the PFC include potentially lower capital cost, smaller equipment size due to intensified processing, and less crystal breakage due to gentler agitation [11].

An optimization problem involving this design has been indirectly suggested in the literature by Alvarez and Myerson [9], and similarly by Nguyen et al [14]. These investigators attempted to improve the crystal output properties by manipulation of injection configuration and/or antisolvent flowrates using trial-and-error. By use of rigorous modeling and optimization, we solve this optimization problem to find better operating conditions for the MSMA-PFC. The model drug is the anti-inflammatory agent flufenamic acid [9], [16]. In previous work on batch crystallization, the goal is to manipulate supersaturation with respect to time to achieve an optimal set of crystal properties at the conclusion of the batch [17]–[19]. Analogously in this work, we manipulate supersaturation with respect to length order to optimize the crystal properties at the outlet.

In the modeled crystallizer, an unseeded intake stream flows into the first baffled tube, where it mixes perfectly with the first input side stream of antisolvent. Crystallization occurs, and this mixture is then fed into the next tube section with a new antisolvent stream. This process continues recursively until the exit of the crystallizer ($x_{end}$) is reached, where the final product crystal size distribution (CSD) is achieved. By altering the antisolvent flowrates in the various sections, the supersaturation can be controlled locally along the length of the crystallizer. The supersaturation within a segment strongly affects the nucleation and growth kinetics therein, and thus gives us a method for manipulating the product CSD at the outlet. The process is modeled using a steady-state population balance model (PBM), and is solved using either the method of moments (MOM), or a high-resolution finite volume scheme [10], [20].

Frequently in engineering, it is desirable to optimize two or more conflicting quantities simultaneously; some applications have tens, or even hundreds of objectives [21]. We utilized a multi-objective optimization framework (MOO), which is useful for fully investigating the capabilities of particular design. The solution of MOO problems are cast in terms of finding the “non-dominated set” of possible solutions, e.g., the solutions for which it is impossible to improve one objective without degrading another. This non-dominated set is referred to as the “Pareto frontier” [21]–[23]. MOO has been applied previously to batch crystallization [24], [25]. The objective functions used here were maximizing the mass-mean crystal size ($L_{43}$) and minimizing the coefficient of variation ($CV$). We solved the MOO problem using MATLAB’s non-dominated sorting genetic algorithm (NSGA-II) [23]. The results are Pareto frontiers for CV vs $L_{43}$. The Pareto frontier demonstrates some sensitivity to kinetic parameters.

We have additionally investigated the robustness of obtained solutions to uncertainty in empirical growth and nucleation kinetic parameters, as well as uncertainty in antisolvent flowrate.
II. MODELING OF THE MSMA-PFC

A. MSMA-PFC Diagram

Figure 1: Diagram of multi-segmented, multi-addition plug-flow crystallizer (MSMA-PFC) system.

The MSMA-PFC is based on the setup in Alvarez and Myerson [9]. It is modeled as a series of ideal plug flow elements, and antisolvent is added at the beginning of each segment (Figure 1 above). Each of the $N$ segments is a separate PFC, running with steady-state, isothermal operation. $A_i$ is the antisolvent flowrate added to the $i^{th}$ mixing point. The solvent and antisolvent streams are assumed to mix together perfectly, and attain plug-flow. The inlet stream at the far left feeds mother liquor at flowrate $V_i$, with an initial concentration of solute, $C_0$, and a seed CSD, $n_0$. In this work, we consider only the unseeded case ($n_0 = 0$). The population and mass balance equations are solved for each segment, and the output of one segment recursively becomes the input to the next segment. The procedure begins anew, with fresh antisolvent flowing into the main flow stream. $n$ and $C$ are adjusted for the dilution induced by addition of antisolvent at each mixing point. The final CSD, $n_N$, is used for formulating the multi-objective problem, which are then solved by manipulating the $A_i$'s.

B. Model Equations

The MSMA-PFC model equations consist of a PBM that tracks the evolution of the CSD, coupled with a mass balance equation that tracks the depletion of solute concentration due to crystal growth and nucleation. The PBM framework is a key tool in the model-based control of crystallizers [26]–[29]. The energy balance equation has been neglected due to the assumption of isothermal operation. The steady-state population balance equation is:

$$u_x \frac{\partial n}{\partial x} + \frac{\partial (nC)}{\partial L} = 0 \quad (1)$$

Where $u_x$ is the average velocity of the fluid (m/s), $n$ is the crystal size distribution ($#/m^3$), $x$ (m) is the length along the crystallizer, and $L$ (m or μm) is the characteristic crystal length, and $G$ (m/s) is the linear crystal growth rate. $L$ is referred to as the "external coordinate," and $x$ as the "internal coordinate." Average velocity is computed by adding up the total volumetric flowrate of solvent and antisolvent in a given PFC segment, and dividing by the cross-sectional tube area. Our boundary conditions are $n(0,x) = B_0/G$ [9], [30], and $n(L,0) = 0$ (unseeded). $B_0$ is the nucleation rate ($#/m^3.s$). Equation 1 tracks the CSD as solution passes through the PFC array.

The solute mass is tracked with the integro-differential mass balance equation:

$$u_x \frac{dC}{dx} = -3\rho_c \kappa_c G \int_0^\infty L^2 n \, dL \quad (2)$$

Where $C$ is the solute concentration in the liquid phase, $\rho_c$ is the solid crystal density, and $\kappa_c$ is the crystal shape factor.

The boundary condition is $C(x = 0) = C_0$.

The growth and nucleation rate expressions:

$$G(S) = k_g S^a, B_0(S) = k_b S^b \quad (3)$$

The percent antisolvent ratio, supersaturation, and solubility curve expressions for the $j^{th}$ PFC segment are:

$$X_A^{(j)} = 100 \times \frac{\sum_{i=1}^{N_j} A_i}{V_0 + \sum_{i=1}^{N_j} A_i}$$

$$S^{(j)} = C^{(j)} - C_{sat}^{(j)}$$

$$C_{sat}^{(j)} = A_{fit} \exp\left(-B_{fit} X_A^{(j)}\right) \quad (4)$$

Where $S$ is the supersaturation, $k_g$, $g$, $k_b$, and $b$ are growth and nucleation rate law parameters, $X_A^{(j)}$ is the antisolvent volume percentage, $C_{sat}^{(j)}$ is the solubility concentration, and $A_{fit}$ and $B_{fit}$ are fitted parameters for the solubility curve. The solubility, rate-law, and geometry parameters used in this work are from Alvarez and Myerson for the case of flufenamic acid [9]. The values are summarized in Table 1 below.

$C$ decreases along the length of the array via growth, nucleation, and also dilution. At the entrance of each segment, $n$ and $C$ were adjusted by multiplying with a factor which corrects for dilution [9]:

$$\gamma_j = \frac{V_0 + \sum_{i=1}^{N_j-1} A_i}{V_0 + \sum_{i=1}^{N_j} A_i} \quad (5)$$

This factor is derived by performing a mass balance around all PFC segments and mixing points up to and including the $j^{th}$ PFC segment ($A_0 = 0$, and $j = 1$ for the first PFC segment, and always $j \geq 1$).

C. Solution of Model Equations

Depending on the application or desired information, some solution methods are more appropriate than others. A fast solution method is the method of moments (MOM). In MOM, the $k^{th}$-moment of (1) is taken, reducing the coupled ODE-PDE system to a system of $k + 1$ ODE’s ($k$ moment equations, plus the mass balance (2)). “Moment” is defined in equation 9 below.

The moment transformation of (1) is (for $i = 0, 1, ..., 5$):

$$\frac{d\mu_i}{dx} = \frac{\partial \mu_{i-1}}{u_x} + \frac{\partial \mu_0}{u_x} b_0 \quad (6)$$

\begin{table}[h]
\centering
\caption{Parameters for Crystallization Optimization}
\begin{tabular}{|c|c|}
\hline
Parameter & Value \\
\hline
Inner diameter, m & 1.27 x 10^{-3} \\
Initial concentration, $C_0$, mg/m$^3$ & 1.24 x 10^{-3} \\
Solubility parameter, $A_{fit}$, mg/m$^3$ & 3.36 x 10^{-3} \\
Solubility parameter, $B_{fit}$, dimensionless & 0.108 \\
Shape factor, $\kappa_c$, dimensionless & $\pi/6$ \\
Crystal density, $\rho_c$, mg/m$^3$ & 1.47 x 10^{-3} \\
Mother liquor flowrate, $V_0$, mL/min & 100 \\
Segment length, m & 0.6 \\
Growth rate constant $k_g$, m/s & 9.9 x 10^{-4} \\
Growth law exponent, $g$, dimensionless & 1.1 \\
Nucleation rate constant $k_b$,#/m$^3.s$ & 1.5 x 10^{-3} \\
Nucleation law exponent, $b$, dimensionless & 2.1 \\
\hline
\end{tabular}
\end{table}
Physically, the first few moments can be interpreted as follows:

- \( \mu_0 \) – The total number of crystals (per unit solution volume).
- \( \mu_1, \mu_2, \) and \( \mu_3 \) – The total length, surface area, and solid volume of crystals (per unit solution volume).

With the MOM approach, full information about the CSD is lost. However, it is useful to observe the CSD from the results of our optimizations. To do this, the model equations were also solved using a high resolution finite volume (FV) technique, which is the combination of the semi-discrete finite volume technique with the van Leer flux limiter [20], and provides \( O(h^2) \) accuracy where the solution is smooth. The method discretizes (1) into \( K \) ordinary differential equations, where \( K \) is the number of crystal size bins. The discretization started at 2 \( \mu \text{m} \), and marched upward in 4 \( \mu \text{m} \) increments, up to the maximum bin size of 998 \( \mu \text{m} \), for a total of 250 bins. Equation (2) is solved simultaneously, as shown in the bottom equation in (6).

To summarize, the MOM method entails solving \( 6 + 1 \) simultaneous ODE’s, while the FV method requires solving \( 250 + 1 \). Since MOM requires only \( 1/16^{th} \) of the wall-clock time of FV, it is more efficient for solving the optimization problems discussed ahead. The MOM equations were solved using MATLAB’s ode23 solver, while the FV equations were solved using ode45. The idea is to use the fast MOM method with the genetic algorithm to find the optimal antisolvent profiles and crystallizer design, but use the FV method to observe the full CSD at points of interest. Theoretically, the FV could still have been solely used since real-time control was not performed here, but it was more efficacious to use the MOM method for hastening calculation.

III. OPTIMIZATION OF THE MSMA-PFC

A. Multi-objective Problem Formulation

A general formulation for an MOO problem is posed as:

\[
\begin{align*}
\min_{u} \quad & F = [f_1 f_2 \ldots f_M]^T \\
\text{subject to} \quad & g(u) = 0, \quad h(u) \leq 0
\end{align*}
\]

(7)

(8)

Where \( F \) is a vector of objective functions, \( u \) is a vector of decision variables, and \( g \) and \( h \) are vectors of equality and inequality constraints. MOO is somewhat more complicated than single-objective optimization, and generally no single \( u \) can feasibly minimize each objective simultaneously [31].

The objective functions, \( L_{43} \) and \( CV \), for \( n(L_{x_{\text{end}}}) \) were calculated with:

\[
\mu_k = \int_{0}^{L} L^k n(L_{x_{\text{end}}}) dL
\]

(9)

\[
L_{43} = \frac{\mu_4}{\mu_3}, \quad CV = \sqrt{\frac{\mu_2}{\mu_3^2} - 1}
\]

(10)

\[
F = \left[1/L_{43} \quad CV\right]^T
\]

(11)

We generally desire a narrow CSD (low \( CV \)) with a large \( L_{43} \). Optimization was done using MATLAB’s version of NSGA-II, gamultiobj, to search over \( A \) for the non-dominated set. For each \( A \), the model equations in section II.B were solved. The final result from the last crystallizer segment was used to calculate the objective function values. We have used \( 1/L_{43} \) because gamultiobj seeks to minimize functions.

For ease of implementation, the actual decision variables were fractions of a required total antisolvent flowrate:

\[
A_l = u_l A_{\text{total}}
\]

(12)

Where \( u_l \) is the decision variable for the \( l^{th} \) crystallizer segment, and \( A_{\text{total}} \) is the total required antisolvent flowrate. An equality constraint forced these percentages to sum to 1:

\[
\sum u_l = 1
\]

(13)

Each decision variable was also bounded by:

\[
0 \leq u_l \leq 1
\]

(14)

IV. RESULTS AND DISCUSSIONS

A. Multiobjective Optimization and Kinetic Parameter Sensitivity Results

Figure 2 below shows Pareto frontiers calculated by NSGA-II for different sets of growth and nucleation rate constants used in (3). The system is the four-segment MSMA-PFC delineated in [9]. Total antisolvent flowrate was constrained to be 200 ml/min. The \( \gamma \)’s in the legend correspond to multipliers of the base case, e.g. \( \gamma_b = k_b' / k_b \). The base case, shown in red, corresponds to \( \gamma_y = 1 \) and \( \gamma_y = 1 \), with \( k_b = 1.3 \times 10^8 \text{ #/(m}^3 \text{s}) \), and \( k_y = 9.9 \times 10^{-7} \text{ m/s} \).

NSGA-II used a population size of 100, and was permitted to run for a maximum of 500 generations, though on average finished after about 165 generations. For \( \pm 50\% \) variance in the kinetic parameters, little change was seen in \( CV \), and \( L_{43} \) varies by about \( \pm 2.5 \mu \text{m} \). We refer to the point at the red arrow (\( L_{43} = 89.98 \mu \text{m}, CV = 0.20 \)) in subsequent results.

A. Comparison between Heuristic Antisolvent Profiles and Rigorous Optimization

![Figure 2](image-url)

Figure 2 Pareto frontier plots for four injections (\( CV \) vs. \( L_{43} \)) and different sets of kinetic rate parameters, \( k_b \) and \( k_y \). For clarity, only the final 25 generations of each parameter set are plotted. The point at the tip of the red arrow referred to in the text as a “representative point.”
Alvarez and Myerson [9] experimented with splitting 200 ml/min antisolvent equally over 1, 2, 3, and 4 injection points in the PFC array, and observed the effect on the volume size distribution. We show that rigorous optimization of antisolvent profile predicts a better result. Referring to the red arrow in Figure 2 above, we have selected a representative point from the red front (\( L_{43} = 89.98 \mu m, CV = 0.20 \)), which uses the original set of kinetic parameters (\( k_b = 1.3 \times 10^6 \#/(m^3 \cdot s), \) and \( k_g = 9.9 \times 10^{-7} \) m/s). In the 1, 2, 3, and 4 injection plots, 200 mL/min of antisolvent is split in the manner described in Table II below. The optimal result uses the flow profile taken from the representative point in Figure 2. Numerical values of these flowrates for each of these cases are given in Table II below.

Plugging these profiles into the FV solver generates the volume fraction distributions shown in Figure 3 below. The red curve, produced by the optimal profile, has a larger mean size than the previous results – though the spread of the distributions appear relatively equal. The 4-injection case performs worse that the 3-injection case due to negative supersaturation generated in the first stage.

The properties calculated for our representative optimal do not exactly match what they originally were on the Pareto frontier; \( L_{43} = 89.98 \mu m, CV = 0.20 \) at the red arrow, versus \( L_{42} = 92.05 \mu m, CV = 0.21 \) calculated in Table II. The difference is due to a small difference in accuracy between the MOM and FV methods. The equation of the volume fraction distribution, \( f_v \), is given in (15) in the Appendix.

B. Robustness Analyses with Respect to Uncertainty in Kinetic Parameters

Optimal solutions are often sensitive to uncertainty. We investigated the sensitivity of the previous optimal profile to uncertainty in kinetic parameters, \( k_b \) and \( k_g \), and uncertainty in the flow profile. To avoid confusion with our Pareto frontier results in Figure 2, we explain further. In the Pareto frontier results, a set of kinetic parameters were chosen and then optimization was performed. The previous results indicate how sensitive the optimization is to error in the kinetic parameters.

**TABLE II. ANTSOLVENT FLOW PROFILES USED TO GENERATE CRYSTAL VOLUME SIZE DISTRIBUTIONS**

<table>
<thead>
<tr>
<th>Flow in Injection Port (ml/min)</th>
<th>Separate Cases</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Optimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>200</td>
<td>100</td>
<td>66.7</td>
<td>50</td>
<td>59.9</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>x</td>
<td>100</td>
<td>66.7</td>
<td>50</td>
<td>1.22</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>x</td>
<td>x</td>
<td>66.7</td>
<td>50</td>
<td>57.72</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>50</td>
<td>81.02</td>
<td></td>
</tr>
</tbody>
</table>

Converting these profiles into the MOM solver generates the volume fraction distributions shown in Figure 3 below. The red curve, produced by the optimal profile, has a larger mean size than the previous results – though the spread of the distributions appear relatively equal. The 4-injection case performs worse that the 3-injection case due to negative supersaturation generated in the first stage.

The properties calculated for our representative optimal do not exactly match what they originally were on the Pareto frontier; \( L_{43} = 89.98 \mu m, CV = 0.20 \) at the red arrow, versus \( L_{42} = 92.05 \mu m, CV = 0.21 \) calculated in Table II. The difference is due to a small difference in accuracy between the MOM and FV methods. The equation of the volume fraction distribution, \( f_v \), is given in (15) in the Appendix.

The results in this section, using the same representative point from Figure 2, indicate sensitivity of a final obtained result. At the point represented by the red arrow, we permitted \( k_b \) and \( k_g \) to vary by ±50%, and examined the effect on \( L_{43} \) and \( CV \). The results are plotted in Figure 4 below. The base case, \( k_b = 1.3 \times 10^6 \#/(m^3 \cdot s) \), and \( k_g = 9.9 \times 10^{-7} \) m/s lies at the center of the axes of these plots. In both plots, we see significant change in crystal properties with respect changes in \( k_g \), but much less with respect to \( k_b \).

Some trends match intuition. \( L_{43} \) increases with increasing \( k_g \) due to larger crystals being grown in shorter time, and decreases with increasing \( k_b \) due to excessive nucleation. \( CV \) decreases as well with \( k_g \). A counterintuitive result is that \( CV \) also decreases slightly with \( k_b \), it is anticipated that \( CV \) would increase with \( k_b \) due to greater fines production. Plotting the corresponding volume-size distributions using the finite-volume solver (data not shown due to space limitations) showed that increasing \( k_b \) eliminated a smaller-sized mode in the CSD, thus decreasing \( CV \).

C. Robustness Analyses with Respect to Antisolvent Flowrates

Error was simulated in the flow profile by a simple Monte-Carlo simulation. Using the same optimal flow profile from Table II, \( 10^4 \) random samples were taken over a range of ±50% for each of the four flowrates. After a random flow vector was chosen, the MOM solver was used to solve for \( L_{43} \) and \( CV \), and the results are presented as scatterplots. The impact of flowrate error in multiple stages was examined by varying the flows cumulatively.

Figure 5 below shows these results for \( 10^4 \) trials in each case. The red dot corresponds to the nominal (zero-error) case. Stage II imparts only mild change in the response, which is likely due to the small flowrate. However, significant variation is observed when stage III is reached.
Figure 4 Variation in $L_{43}$ and $CV$ for the representative chosen point. Significant sensitivity is observed with respect to $k_{g_2}$.

The first stage, where primary nucleation occurs, is by far the most sensitive segment. It appears that proper control of nucleation will have significant process impact, and that uncertainty in antisolvent flowrate will drastically affect performance wherever nucleation predominates over crystal growth. We also conclude that error is best treated by considering the flow profile as a whole, since there appears to be significant interaction between how the upstream stage impacts the downstream performance – a known issue in continuous pharmaceutical manufacture and process design in general.

V. CONCLUSION

In summary, we have presented a framework for identification of the Pareto frontier of crystal properties produced by an MSMA-PFC. Sensitivity analyses show that error in kinetic parameters and antisolvent flowrate can impart wide variation in the output crystal properties.

Concerning real systems, the methodology discussed herein is useful in the early stages of design, where one must determine immediately whether a given design can satisfy all critical quality attributes and production constraints. In this case, critical attributes would be minimum permissible values of $L_{43}$ and solid yield, and maximum permissible $CV$. Once a satisfactory set of designs are found, further information can help judge which design from this “short list” is best suited for the task at hand.

There are other important considerations that are neglected in this work. Global economic optimization of the flowsheet would likely change the optimal operation due to upstream-downstream interaction effects. We placed no importance on the solids concentration within the liquid phase, but this may be an important parameter for downstream washing and drying processes. Furthermore, the process dynamics are an open research question. The general dynamical behavior the MSMA-PFC is also unknown, e.g. fast- or slow-equilibration, limit cycles, or bifurcation behavior. This knowledge is important not only for design purposes, but also dynamical control.

APPENDIX

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Name</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A$</td>
<td>Antisolvent flowrate vector</td>
<td>m$^3$/s</td>
</tr>
<tr>
<td>$A_{fit}$</td>
<td>Fitted solubility curve parameter</td>
<td>mg/m$^3$</td>
</tr>
<tr>
<td>$B_{fit}$</td>
<td>Fitted solubility curve parameter</td>
<td>n/a</td>
</tr>
<tr>
<td>$B_0$</td>
<td>Nucleation rate</td>
<td>#/ s·m$^3$</td>
</tr>
<tr>
<td>$C_V$</td>
<td>Mass coefficient of variation</td>
<td>n/a</td>
</tr>
<tr>
<td>$C_s$</td>
<td>Solute concentration</td>
<td>mg/m$^3$</td>
</tr>
<tr>
<td>$C_{sat}$</td>
<td>Saturation concentration</td>
<td>mg/m$^3$</td>
</tr>
<tr>
<td>$F$</td>
<td>Vector of objective functions</td>
<td>n/a</td>
</tr>
<tr>
<td>$f_0$</td>
<td>Volume fraction distribution</td>
<td>m$^1$</td>
</tr>
<tr>
<td>$f_1, f_2 \ldots f_M$</td>
<td>Individual objective functions</td>
<td>n/a</td>
</tr>
<tr>
<td>$G$</td>
<td>Crystal growth rate</td>
<td>m/s</td>
</tr>
<tr>
<td>$g,b$</td>
<td>Growth and nucleation exponents</td>
<td>n/a</td>
</tr>
<tr>
<td>$g(x), h(x)$</td>
<td>Equality and inequality constraints</td>
<td>n/a</td>
</tr>
<tr>
<td>$k_g$</td>
<td>Nucleation rate constant</td>
<td>#/(m$^3$·s)</td>
</tr>
<tr>
<td>$k_G$</td>
<td>Growth rate constant</td>
<td>m/s</td>
</tr>
<tr>
<td>$k_G$</td>
<td>Crystal shape factor, π/6</td>
<td>n/a</td>
</tr>
<tr>
<td>$L$</td>
<td>Crystal size (internal coordinate)</td>
<td>μm</td>
</tr>
<tr>
<td>$L_{43}$</td>
<td>Mass-mean crystal size</td>
<td>μm</td>
</tr>
</tbody>
</table>
\( n(L, x) \) Crystal size distribution #/\mu m^4
\( \rho_s \) Crystal material density mg/m^3
\( S \) Supersaturation mg/m^3
\( u \) Vector of decision variables varies
\( \mu_k \) \( k^{th} \) moment of size distribution varies
\( u_x \) Average velocity m/s
\( V_0 \) Mother liquor flowrate m^3/s
\( x \) (external coordinate) m
\( x_{end} \) Length of the entire MSMA-PFC m
\( X_{ABS} \) Volume percentage of antisolvent %
\( \gamma_f \) Dilution correct for \( f^{th} \) stream n/a

Calculation of \( f_v \):
We have presented several results in terms of the volume-fraction distribution, as opposed to the crystal size distribution. The equation for calculating \( f_v \) from \( n \) is:

\[
 f_v(L) = \frac{L^3n(L)}{\int_0^\infty L^3n(L)\,dL} \quad (15)
\]

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