Modeling of crystallization and granulation processes using the gSOLIDS and gCRYSTAL frameworks.

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Analysis of the Inhibitory Effect of Polymers on API Crystallization Using gCRYSTAL

Motivation

Recently, there has been increased recognition of the solubility advantage of formulations containing an amorphous drug due to their ability to increase effective solubility to levels much higher than their crystalline counterparts and enhance the dissolution rate of the active pharmaceutical ingredient (API). A major challenge associated with these amorphous compounds is their inherent metastable nature. To prevent crystallization, amorphous APIs are often combined with a polymer to form an amorphous solid dispersion. Several studies have shown that solid dispersions yield higher and/or more sustained supersaturation levels in comparison to the pure amorphous API. This has been attributed to the inhibition of drug nucleation and growth from the supersaturated solution by the polymer.
Herein, felodipine crystal growth is decoupled from nucleation by experimental design. The growth kinetics are determined from seeded experimental data and then used as inputs in the mathematical model to extract the nucleation kinetics. Estimation of the crystallization kinetic parameters is implemented in gCRYSTAL.

Modeling Framework

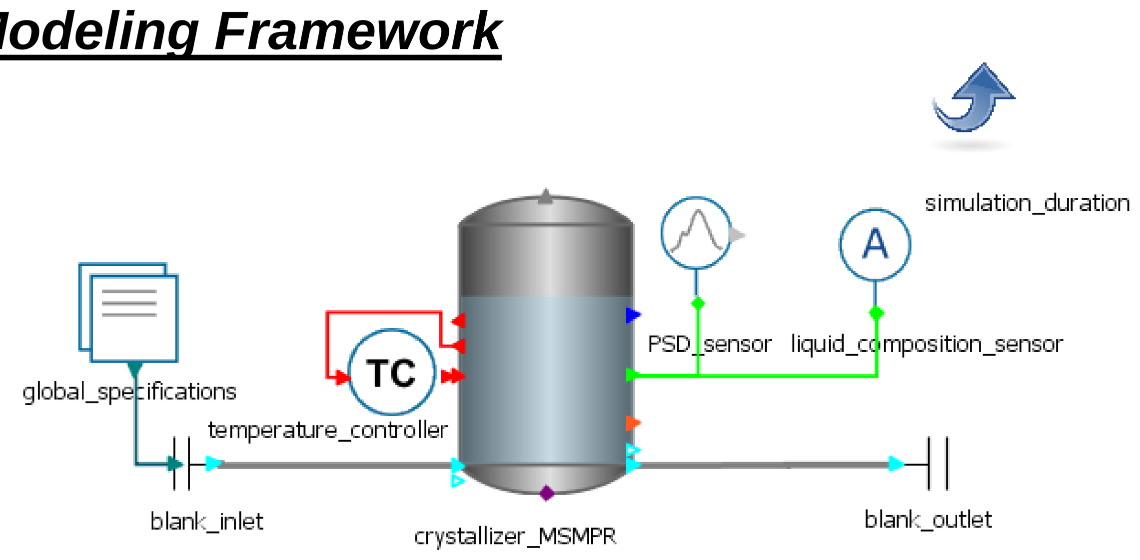

Figure 1. Flowsheet of a crystallization process using an MSMPR in gCRYSTAL

Results

Effect of HPMC on felodipine nucleation:

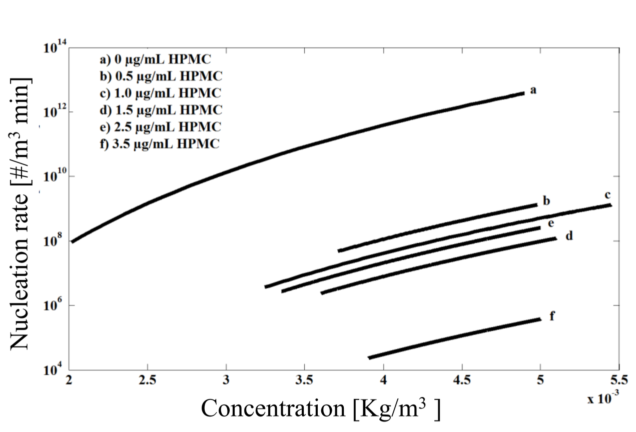

Figure 2. Nucleation rates of felodipine (S of 10) in the absence and presence of HPMC

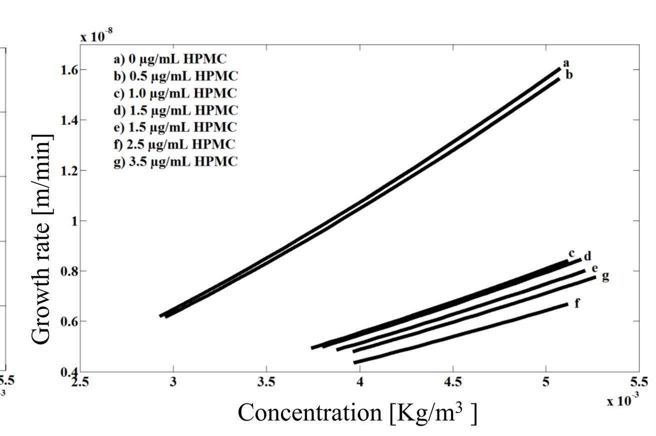

Figure 3. Growth rates of felodipine (S of 10) in the absence and presence of HPMC

Effect of HPMC on felodipine growth:

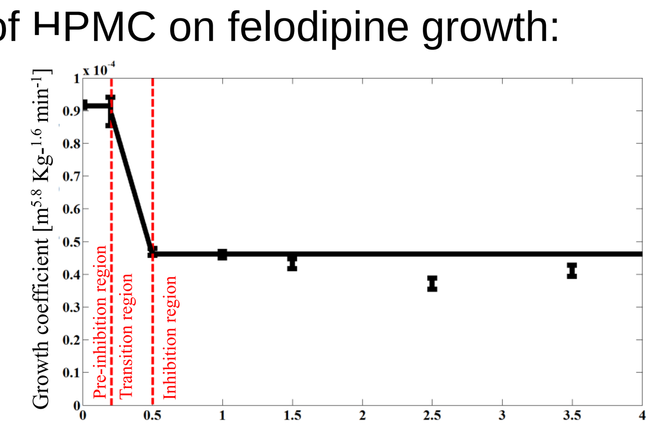

Figure 4. Inhibition regions of HPMC

- HPMC is able to retard both the nucleation and growth rates of felodipine
- Parameter estimation results yielded a growth order of 1.6 indicating a growth regime intermediate between mass diffusion and surface integration controlled growth
- HPMC has a much greater effect on inhibiting nucleation (up to 8 orders of magnitude decrease in nucleation rate) vs. only a decrease by a factor of two for the growth rate

Predicting Granule Properties Using gSOLIDS

Motivation

The objective of this work is to develop a model for the prediction of size distributions and other granule product attributes using gSOLIDS. The model will describe granulation rate processes as a function of formulation properties and process parameters. Heterogeneous flow in the high-shear mixer geometry is a significant modeling challenge and accurate compartmentalization of flow via DEM input to gSOLIDS will help provide better flow modeling between each population balance compartment.

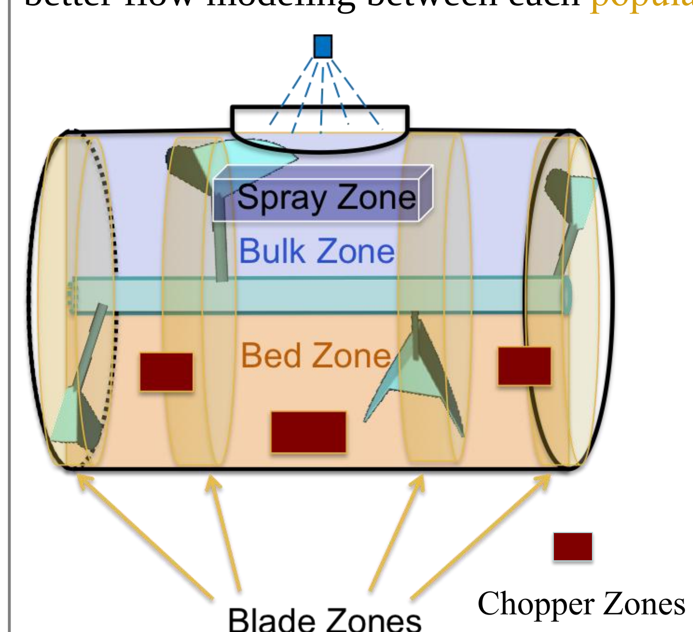

Figure 4. Example of a heuristic approach to compartmentalize flow in a plough mixer.

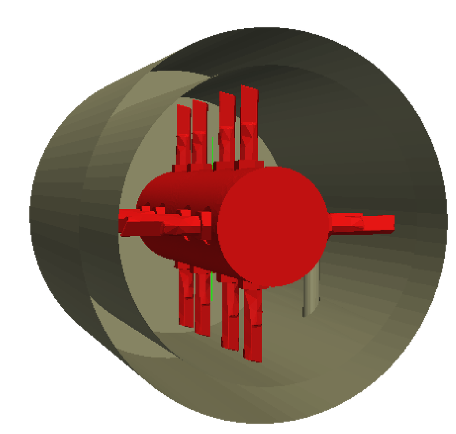

Figure 5. Example DEM environment for simulation using LIGGGHTS of the high-shear pin mixer system.

Modeling Framework - Compartmentalization

The three rate processes that describe the change of granule properties during granulation are wetting and nucleation, consolidation and growth, and attrition and breakage. Population balance models incorporated in gSOLIDS can be used to track particle property distributions of each well mixed compartment based on models for these rate processes.

- The population balance allows for the tracking of granule properties that include liquid saturation, porosity, size, and mass.
- A compartmental model of a ploughshear mixer will be implemented in gSOLIDS.
- DEM simulation information will be used as an input to the compartment model flowsheet via the go:MATLAB tool and LIGGGHTs DEM software.

An example of the heuristic approach to compartmentalization of the flow field in the mixer is shown in Figure 6. For the plough share mixer, flows can transition between a periodic slumping behaviour and a centrifugal roping behaviour at high speeds. The flows shown in this simplified version are modelled as stilled tank rate constants. gSOLIDS will be employed as the compartmentalization tool of choice to determine the flow behaviour between the heuristic compartments using DEM data.

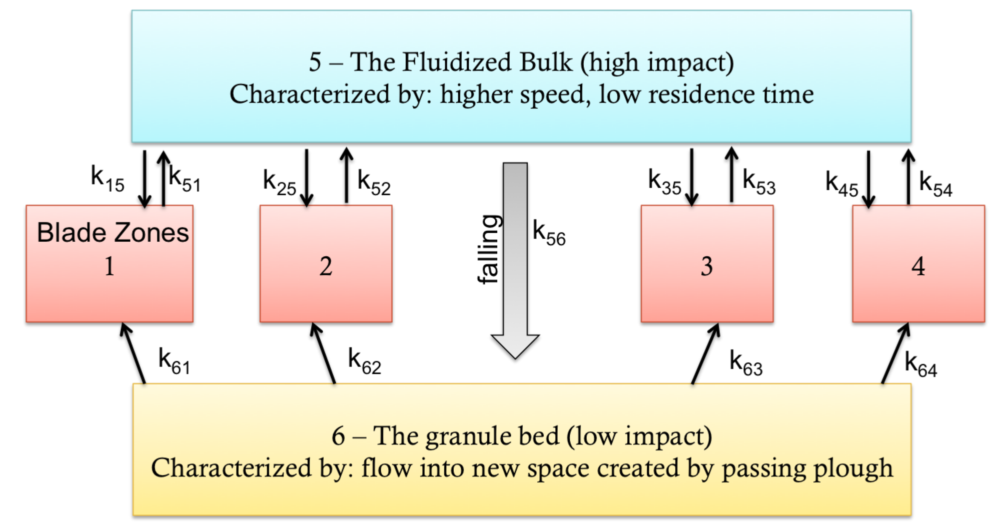

Figure 6. Simplified heuristic model for meso-scale compartment flow in a ploughshare granulator. Each compartment represents separate treatment of the granulation rate processes. Spray and chopper zone are withheld for clarity.

Compartmental Modeling of Detergent Granulation Using gSOLIDS

Motivation

Population balance equations are very useful in modeling the complexity of granulation processes. During granulation, several rate processes occur at varying intensities throughout the different regions of the granulator. Discrete Element Method (DEM) models can be used as a tool to separate the entire granulator space into regions, or compartments, where rate processes are of a similar intensity. Population balance equations can then describe each of the rate processes within the different compartments forming a compartment model. gSOLIDS is ideal for modeling complex processes such as granulation as it already contains many kinetic models for the different phenomena taking place during granulation, namely agglomeration and breakage.
In this work, gSOLIDS flow sheet modeling will be used to make a compartment model for the granulation process using information from both experiments and DEM modeling.

Modeling Framework

The production of dry laundry detergent is carried out using a granulation process. Characterization of the breakage and agglomeration rate process used a model developed by Vogel et al (2005).
This model uses two equations one for the probability of breakage Eq. 1, and the second for calculating the size of the resulting granules, Eq. 2, and is already part of gSOLIDS 2.0 "gSOLIDS Unit Op- Size change models".

$$P_B = 1 - \exp\{-f_{MAT,}xk(W_{m,kin} - W_{m,min})\} \quad \text{[Eq.1]}$$

$$B = \left(\frac{x}{y}\right)^q \frac{1}{2}\left\{1 + tanh\left(\frac{y-y'}{y'}\right)\right\};\ \text{q=cv+d} \quad \text{[Eq.2]}$$

- Experiments are carried out using a modified hammer mill, Figure 7.
- Single granule breakage data are generated by measuring the change in granule size.
- Data are fit to a linearized version of Eq. 1 to determine the material constants fMat and x*Wm,min shown in Figure 8.
- Data are then implemented in gSOLIDS and parameter estimation is used to determine the constants q and y' in the Vogel model.
- The completed model will fit into a larger compartment model for the dry laundry granulation process.

Figure 7. Modified hammer Mill for single impact breakage experiments.

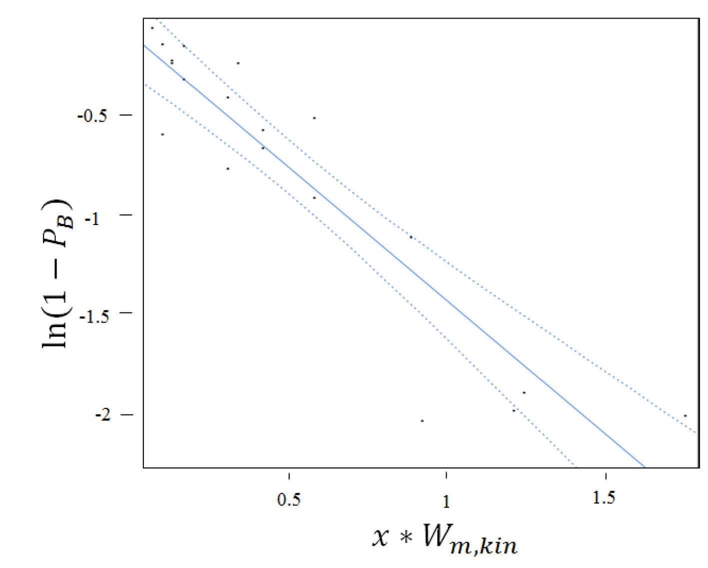

Figure 8. Linearized form of breakage data to determine model constants.