Model-Assisted Design of Granular products for High Shear and Fluid Bed Wet Granulation

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1. Executive Summary

The overall aim of this proposal is to develop validated and predictive process and product models for high-shear granulation (HSG) and fluid-bed granulation (FBG) for both batch and continuous process configurations. The models will be multi-scale and multi-dimensional and will be able to describe the dynamics and evolution of important granule properties as a function of key process parameters, formulation/material properties and design attributes. The granule properties we propose to describe are distributions w.r.t. to 1. particle size, 2. liquid/binder, 3. porosity and 4. active ingredient (active). Efficient numerical and model reduction strategies will be implemented to ensure that these complex process models are able to be accurate/predictive while being computationally efficient for practical implementation and use. In terms of primary mechanisms and basic mathematical structure, the different HSG and FBG configurations are similar. To capture secondary mechanistic features and differences, particle/granule-scale experiments will be performed to ensure accurate sub-physics are captured. To test the robustness and predictive capabilities of models and kernels, DOEs will be performed for a range of diverse formulations at lab-scale. A scale-up methodology will also be proposed and implemented to ensure that key granule properties can be predicted from lab-to-pilot-to-manufacturing scale.

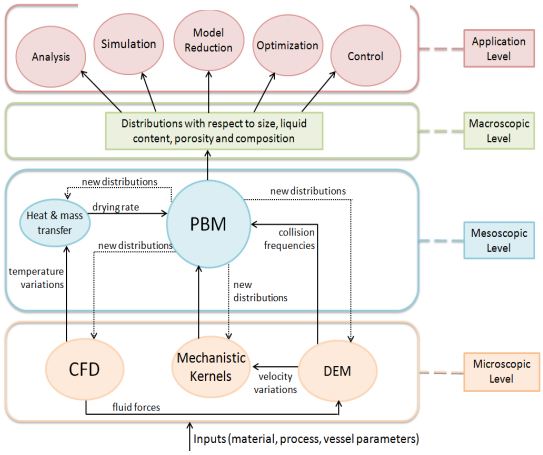
2. Proposed Approach

The following sub-sections describe the details of the proposed approach undertaken in this proposal. The work proposed leverages and builds upon the PI's previous/current work in the same area as can be evidenced by his numerous publications in the areas of 1) multi-scale model development, 2) mechanistic kernel development, 3) experimental studies and particle/granule-scale analyses, 4) computationally efficient numerical solution, model reduction and high-performance computing. See link for papers published by the PI (http://www.pslrutgers.com/publications).

2.1 Identification of best modeling methodologies and framework

There exist several modeling methodologies in the literature to describe the different aspects of the multi-scale dynamics of granulation processes spanning from the micro- to meso- to macro-scale and its relation to product performance. These range from population balance models (PBM), discrete element method models (DEM), volume of fluid methods (VoF), computational fluid dynamics models (CFD), residence time distribution models (RTD) and reduced order models (ROM) such as Artificial Neural Networks (ANN) or partial least squares (PLS). However, much of the work in the literature has focused on only particle size as the sole indicator of product performance with limited extensions to other performance indicators. In cases where more than one property has been described, models have often been limited to either being (semi)-empirical, with the need for significant experimental effort for model calibration that then translates to limited ranges of predictions. Often, there has also been a lack of rigorous coupling between model forms to enable effective predictive capabilities as a function of key process, formulation and design inputs.

Fig 1: multi-scale framework



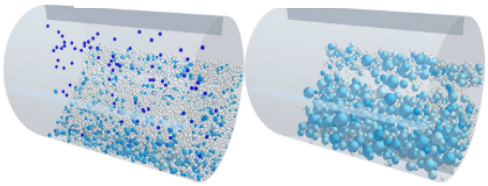
To this effect, we propose a flexible multi-scale model framework (**Figure 1**) to capture the effect of critical inputs (process, formulation, design) on key granule properties (distributions w.r.t. to size, liquid/binder, porosity and active). The basis of the framework will be the multi-dimensional PBM (**Figure 2**) which in its full form will consist of four internal coordinates to describe two solid components (e.g. for active,

excipient), one liquid component (for liquid/binder) and one gas component (for porosity). The rate terms that will be described are layering, liquid distribution, consolidation, nucleation, aggregation and breakage. Based on this framework, we will first elucidate the integrated model for the batch HSG process. We expect this to be a coupled compartment-based PBM-DEM model where the DEM incorporates the equipment geometry, initial particle size distribution and formulation properties and provides as output micro-scale information such as collision properties (e.g. particle-particle, liquid-particle), shear forces, bulk particle velocities and heterogeneities w.r.t to velocity, and liquid distribution (**Figure 3**). In **Figure 3**, it can be seen that between the two sub-figures, as time progresses, there is homogenizing (and growth) of liquid (dark blue) and particles (grey) to form light blue larger particles. Much of this and related information will be received by the PBM along with other kernel inputs to describe the evolution of the distributed properties for the identified compartment(s). Depending on the sensitivity of the micro-scale properties, PBM outputs can be periodically coupled back into the DEM for updated propagation of dynamics. For the continuous HSG, we expect to utilize the same framework with the addition of inflow and outflow terms in the PBM as well as the axial velocity term whose information will be obtained from the DEM. For batch FBG, we will utilize this developed model in addition to the incorporation of CFD, to determine the effect of the fluid flow term on DEM as well as the micro-scale information previously identified. An energy balance term to account for heat/mass transfer will also be incorporated into the PBM to account for simultaneous heat exchange, drying and (re)-wetting. Inflow, outflow terms will then be added along with axial, radial velocity terms for the continuous FBG. It should be noted that the incorporation of DEM and CFD is important in the model formulation. For instance, in the calculation of aggregation rates; PBM and related criteria (e.g. Stokes criteria) is able to provide information on the collision efficiency but not on the collision frequency. Therefore, a multi-scale model formulation is needed to capture the essential physics-based dynamics.

$$\overbrace{\frac{\partial F(s_1,s_2,l,g,t)}{\partial t}}^{Temporal} + \overbrace{\frac{\partial}{\partial g}\left[F(s_1,s_2,l,g)\frac{dg}{dt}\right]}^{consolidation} + \overbrace{\frac{\partial}{\partial s_1}\left[F(s_1,s_2,l,g)\frac{ds_1}{dt}\right] + \frac{\partial}{\partial s_2}\left[F(s_1,s_2,l,g)\frac{ds_2}{dt}\right]}^{layering} + \overbrace{\frac{\partial}{\partial l}\left[F(s_1,s_2,l,g)\frac{dl}{dt}\right]}^{drying/rewetting} = R_{nuc}(s_1,s_2,l,g) + R_{agg}(s_1,s_2,l,g) + R_{break}(s_1,s_2,l,g)$$

Fig 2: PBM formulation

Fig 3: DEM analysis of liquid distribution



2.2 Identification of critical inputs, granulation regimes, kernels and sub-models

The above section (#2.1) represents the proposed model framework for batch and continuous HSG and FBG processes. In this section, we propose to develop the knowledge to distinguish between the mechanistic details and secondary features of HSG and FBG so that only the necessary and applicable physics are implemented into the model framework. We will first perform a risk and criticality analyses to ensure key process inputs, formulation properties and design/equipment attributes are captured in model formulations for both HSG and FBG. This will be performed via a combination of literature review, prior knowledge from the PI's research and interaction/consultation with IFPRI member companies and other companies in the PI's network. For instance, for batch HSG, this could translate to: 1. Process parameters (e.g. L/S ratio, liquid addition time, impeller speed, wet massing time), 2. formulation properties (e.g. system viscosity, solubility and hydrophobicity and 3. design attributes (e.g. vessel and impeller geometry and material type). The next step will be to identify formulation specific regimes and its boundaries for HSG and FBG. This is because, even for the same formulation and similar process parameters, a different balance of rate processes could exist between a HSG and FBG system due to differences in shear rates, differences in particle/droplet size ratio etc. As an example, in the case of a formulation with differing contact angles, where the liquid droplet is larger

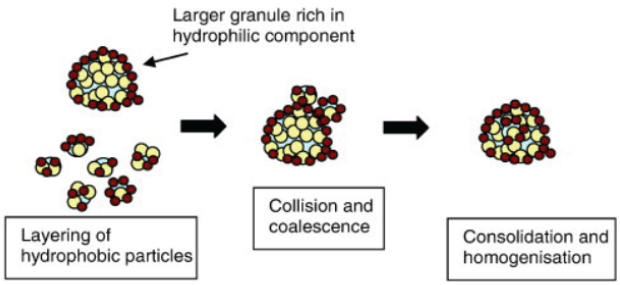


Fig 4: proposed growth scheme (Hounslow, Salman et al. 2013)

than the primary particle (e.g. in HSG), the literature postulates that the hydrophilic component is preferentially nucleated while the hydrophobic component remains mostly unnucleated. This in turn leads to initial aggregation whereby the granule is rich in the hydrophilic component where layering then takes place via the adhering of hydrophobic particles onto the granule (**Figure 4**). This is followed by further aggregation and consolidation to eventually form homogeneous granules. Similar theory, postulations and/or studies exit for different formulation scenarios and granulation systems (e.g. FBG, TSG, drum etc.)

We will first study and discern these differences via regime map approaches (nucleation, growth, peak flow stress vs. capillary number). Subsequently, for the same granulation process, we will study regime differences and boundaries for a variety of selected formulation types (see #2.4) to understand mechanistic differences between formulation characteristics. While the regime map approaches provide a reasonable static understanding of these mechanistic differences, additional effort is required to understand the time-dependencies of these mechanisms and eventually translate them to mathematical kernels (rate equations) for the purpose of model-based simulation and analyses. Via dynamic image analyses and quantification of particle microstructure (initial result obtained in **Figure 5**), we will begin to understand not only the time dependency of different granule mechanisms but also their magnitude as a function of process parameters, formulation properties and granulation type. Via this integrated approach, we can articulate the important rate processes in the PBM for both HSG and FBG and also deconvolute their coupled effects during the granulation process. This can then be further broken down to be formulation type specific. We will limit our analyses to develop mechanistic understanding for layering and aggregation. This is primarily because layering is not well described in the literature but is evidently important to account for when certain formulation types are used. Aggregation, while prominent in the literature is often developed as a generic sub-model with missing physics and is not suitable for certain granulation types and/or formulation characteristics. Nucleation has been previously studied in the literature by several groups (Litster, Hapgood, Poon, Emady, Smith etc.) and we will leverage much of that work into this proposal. Breakage on the other hand can be extremely complex to understand and for the purpose of this proposal, we will use a previously developed mechanistic kernel (Ramachandran et al. 2009 in http://www.pslrutgers.com/publications) developed by the PI that is able to sufficiently describe breakage kinetics as a function of key process, formulation and design properties. Consolidation and liquid addition/distribution are described via standard rate equations that have proven to work well. Moreover, much of their mechanistic details will come from the DEM simulations and not from their explicit kernel forms.

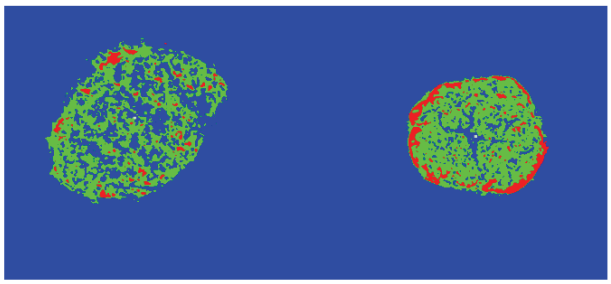


Fig 5: Left: uniform distribution via aggregation.
Right: one component in the periphery via layering

The next step is to translate the developed mechanistic aggregation and layering knowledge into granulation kernels (rate equations). The kernels essentially form the sub-models that are incorporated into the PBM to be able to fully describe granule properties as a function of its inputs. We envision that the process of layering is similar in both HSG and FBG. Finer particles layer on larger granules primarily as a result of capillary forces and to a lesser degree solid cohesion. We will perform a DEM based analysis to model these effects and to understand how layering arises as a result of these forces for different formulation properties. Qualitative comparisons will be made with actual images obtained from granules. Layering correlations will be formulated to be able to describe the layering kinetics as a function of critical inputs. The process of aggregation is inherently different for HSG and FBG processes. In FBG, the liquid droplet is smaller than the primary particle and much of the literature on aggregation is suited for this application. This is essentially based on the Stokes' criteria (e.g. Type 1, Type 2 and rebound) first postulated by the groups of Ennis, Litster and Liu. Criteria has also been established (Stepanek, Hapgood) where aggregation is seen as a function of collision efficiency and frequency where efficiency is a function of surface coverage and liquid layer thickness and is governed first by a successful contact of a dry particle on wet area followed by the balance of kinetic energy and viscous forces to determine a successful aggregation event. Much of

this previous work and theory can be leveraged in our proposal to develop FBG specific aggregation kernels for bi-component systems with further considerations to hydrophobicity, viscosity and solubility. For HSG, where the liquid droplet is larger than the primary particle, there exists much less theory compared to the case for FBG. Mostly, two different growth behavior types are explained by the Stokes deformation number which attempts to separate the induction growth regime from the steady growth regime. While this provides qualitative understanding of the evolution of aggregation, there is limited quantitative detail in terms of robust rate equations. Furthermore, much of the existing high shear aggregation kernels are limited in terms of incorporating salient process and formulation inputs and cannot account for multiple components and/or formulation differences in terms of solubility, viscosity and hydrophobicity. Via a combination of regime map approaches and granule-scale experimental analyses we will begin to formulate rate equations for aggregation as applicable to HSG. This will elucidate the dependency of the aggregation rate on key process inputs and formulation properties. We will then perform small-scale DEM simulations to understand the effect of forces (e.g. viscous, capillary, cohesive) as a function of deformable area and contact angle to determine the strength of liquid bridges. This will enable us to formulate constitutive rate equations specific for high shear systems.

At the end of this task, we envision a robust and flexible model framework that is able to incorporate the necessary physics and mechanisms specific to HSG and FBG as a function of different formulation types, to predict key distributions of multiple important granule properties.

2.3 Identification of an efficient solution strategy

The work proposed in sections 2.1 and 2.2 while leading to a more accurate and physics-based model that is much needed to describe granule dynamics, can also lead to computationally intensive simulations. This is mainly due to the large processing requirements for the DEM and CFD models and to a lesser extent the numerical solution of the multi-dimensional PBM. We propose a multi-pronged approach to ensure these simulations are computationally efficient and this is also based on the PI's on-going work in this area. Firstly, the PBM to describe size, liquid content, porosity and active content need not be formulated as a full 4-dimensional problem. This is because much of the experimental data is inherently lumped when measured. For instance, although particle size is generally reported as a function of mass frequency vs. size, other attributes such as porosity (bulk density), active content and liquid content are measured as an average value across different size classes. Therefore, this enables us to re-formulate the 4-D PBM as a 1-D distributed PBM w.r.t to size with lumped equations for other attributes as a function of size. In previous work, we have shown such an approach to be computationally efficient while minimizing loss of accuracy. We also propose the use of reduced order models (e.g. ANN) to replace portions of DEM and CFD calculations. This is because, we have shown in previous work that we are able to utilize DEM and CFD to perform a small but important portion of the micro-scale calculations needed for the PBM, rather than using DEM and CFD to perform the entire simulation. This enables the efficient isolation of the CFD and DEM and with off-line training of the ANN, the ANN is able to fully replace these intensive models and maintain accuracy of information passed to the PBM. We will also utilize our previous work and knowledge on efficient numerical solutions and parameter estimation methods to ensure accurate and computationally efficient model calibration and validation.

2.4 Design of experiments, material property identification, model calibration, experimental validation

In combination with PI's ongoing work and member company input, we will formulate optimal design of experiments for testing of our models and methods. The primary focus will be on varying the formulation space for a system with two solid components. The formulation space we expect to take into consideration is hydrophobicity (i.e. components with similar contact angles and differing contact angles), viscosity (e.g. different binder grades) and solubility (both solid components insoluble, one component soluble). Other formulation characteristics (e.g. drug loading) can be designed into the experiment as required. We will work with the member companies to arrive at the right material selection which can incorporate pharmaceutical, non-pharmaceutical or model compounds. The secondary focus will be on

varying the process parameter space and similar to above, we will work with the companies to identify and vary parameters of interest. We envision much of the experimental work to be performed at Rutgers with some experiments at member companies depending on interest. For selected formulations, material property testing, and calibration of model inputs (e.g. those in DEM) will be subsequently performed. In terms of output properties, we will measure size distributions, liquid content, porosity (also bulk density) and active content. The PI has access to key facilities required for these testing methods. As needed, additional tests can be performed in member companies. The models built for HSG and FBG will be tested against these lab-scale data. We envision that some level of iterations and kernel/model update will be needed to ensure experimental sensitivities are captured and that experimental data is validated. Statistical metrics will be used to quantify parameter confidence intervals and ranges of validity.

2.5 Scale-up methodology

Specifically, for batch HSG and FBG, we propose a scale-up methodology to be able to identify optimal operating conditions so as to achieve similar granule properties across scale. Currently for scale-up prediction, dimensional groups (e.g. constant tip speed, constant Froude number) are used with limited success. Even in the successful cases, this can result in additional tedious trial and error experimentation and/or the matching of only one granule attribute (e.g. d_{50}) with mis-match in other attributes such as porosity or content uniformity. The dimensionless number and scale-up approaches currently existing in literature capture only some of these rate mechanisms. In order to develop a holistic scale-up approach it is required to have a more mechanistic framework where each of these rate mechanisms could be evaluated and correlated with different scales of operation. For instance, recent work has shown that for a HSG process, when a constant Froude number was used to determine optimal conditions at the next scale, this shifted the growth regime toward 'nucleation only' resulting in weaker and more porous granules. We will use a combination of dimensional groups, regime maps and model-based analyses to design scale up criteria. First, the dimensional group will provide a starting point for operating conditions. Subsequent regime map analyses will be used to fine-tune these conditions to ensure similar regimes are captured across scales. This will then be the next starting point for the model-based analyses which also captures the associated equipment differences. We will then use the model to optimize the set of operating conditions to ensure granule properties across scales match. The coupled model can also be used to maintain shear rates and hydrodynamics across scales that otherwise dimensional groups and regime maps cannot account for, but nevertheless are important to match up across scales. This integrated approach will be first tested from lab to pilot scale and subsequently from pilot to manufacturing. With sufficient training and model updates, we envision a scenario where only one manufacturing scale data set would be needed with other scenarios being able to be predicted from the scale-up methodology. We will work with member companies to identify scales of interest. Data at pilot and/or manufacturing scale would be requested from member companies.

3. Identification of critical unknowns and effect on project direction/outcome

We do not anticipate any critical unknowns that would adversely affect project direction/outcome. One potential unknown could be the timely availability of granulation data at larger-scales for the different formulation types (e.g. manufacturing scale). However, there is sufficient time for planning to ensure this is minimized. Another unknown could be re-prioritization of some of the tasks (based on member company input) which perhaps would change the order of which the outcomes are achieved.

4. Project timeline

Year 1 will focus on developing and identifying the integrated process modeling frameworks for 1. Batch HSG, 2. Continuous HSG, 3. Batch FBG and 4. Continuous FBG. We will also develop and implement efficient numerical solution and model reduction techniques to ensure these integrated models have the right balance between capturing accurate physics and being computationally efficient. DOEs will be performed for batch HSG and FBG for the baseline formulation. Model and experimental risk and

sensitivity analyses will also be performed to ensure key experimental trends and sensitivities are captured and that critical formulation, process and design parameters are reflected in model formulations. We will also establish the design space and important boundaries to understand which regimes/kernels are important for different granulation processes and formulations. Experimental validation as benchmarking will be performed using the baseline formulation for batch HSG and FBG. **Year 2** will focus on developing/updating granulation kernels (from the literature and from PI's previous work) to reflect specific granulation and formulation types. Additional DOEs will be performed as a function of formulation type (e.g. soluble, insoluble, hydrophilic, hydrophobic). Particle/granule-scale experiments will also be performed to extract physics and knowledge for kernel development. Experimental validation and model/kernel iteration/update (as needed) for different formulations will be performed for batch HSG and FBG. **Year 3** will focus on batch scale-up of HSG and FBG and extensions to continuous HSG and FBG. For continuous granulation, DOEs will be performed for the different formulations and used for experimental validation. We expect much of the previously built knowledge to be transferrable but with still some additional process/model development. We will also develop the methodology to predict granule properties at scale-up conditions. DOE and data will be requested from companies for the different formulation types for the purpose of experimental validation. Although some of the tasks are sequential and iterative, several tasks are mutually exclusive and can be re-ordered (e.g. starting with which formulation types and with which granulation processes) based on priority, as determined by IFPRI member companies.

5. Synergy between proposed project and existing research programs in my group

The PI and his team are working on research programs that were/are funded by both federal/non-profit (e.g. NSF, DOE, U.S. FDA, NIPTE) and industrial (e.g. BMS, BASF, Evonik, Syngenta, Janssen, GSK, CNH Industrial, Handok Pharmaceuticals, Bosch) sources (http://www.pslrutgers.com/partners) in three specific areas that are highly synergistic to this proposed IFPRI project (http://www.pslrutgers.com/research-areas). These are 1. Multi-scale model development and validation of granulation processes, 2. Development of efficient numerical techniques and high-performance computing strategies and 3. Experimental studies and analysis of particle/granule microstructure. These areas form a solid foundation for the work proposed in the current IFPRI proposal and the PI has been working in these areas for more than 10 years and published more than 80 journal papers (http://www.pslrutgers.com/publications) in the areas of batch and continuous wet granulation (high-shear, fluid-bed and twin-screw), multi-scale modeling, numerical solution, granulation kernel development, experimental analyses, etc. Furthermore, continued research activities from existing projects add further value to the IFPRI project. Similarly, new learnings and findings from the IFPRI proposal will strengthen the PI's existing projects.

6. Interaction framework with IFPRI members and technology transfer

The PI and his team have substantial experience working with industry either individually or through consortiums such as the Rutgers Pharmaceutical Engineering Research Center (www.csops.org) and Rutgers Catalyst Manufacturing consortium (https://cbe.rutgers.edu/catalyst-manufacturing-center). In a similar capacity, we envision working closely with IFPRI members/companies via the following ways: 1. Receiving additional non-proprietary materials/formulations for testing, 2. Using different test methods available to the company(ies), 3. Updating project direction through industrial member guidance and mentorship, 4. Receiving data at different granulator scales and 5. Technology transfer. We expect to successfully transfer technology developed and know-how via the following methods: 1. Documentation of all codes (e.g. Matlab, EDEM, Fluent), test methods and protocols. 2. GUI development for code (E.g. Excel-based interface) for ease-of-use. 3. Periodic training at Rutgers and/or IFPRI meeting(s), 4. Hosting company personnel from member companies at Rutgers. As required, we will work closely with IFPRI members to continuously improve ways to collaborate and to transfer technology/know-how to ensure maximum benefit.