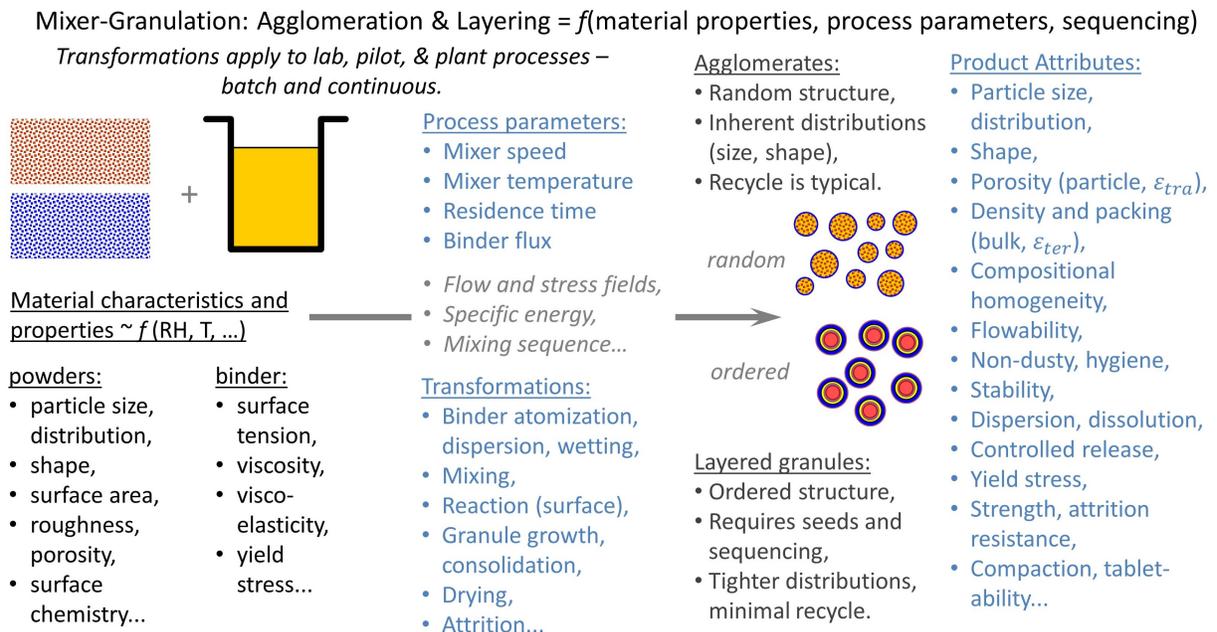


Binder-granulation and coating process scaleup and scale down: Equipment sizing for lab, pilot, and manufacturing.

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November 2025



Objectives

- Review the academic and industrial literature, prioritizing progress since 2000, on the scale-up and scale-down of integrated granulation and coating circuits, where scale up/down requires:
 - similarity of critical product attributes; and
 - sensor/actuator relations used to monitor and control the process.
- Discuss granular product attributes in terms of:
 - granular size and size distributions;
 - granular shape and shape distributions;
 - porosity and structure;
 - ensemble properties including flowability and permeability;
 - consideration of composition including sticky or semi-solid materials.
 - dust, safety, and hygiene.
- Identify “smallest-best” unit operations that can be used to develop a granular product using:
 - mixer granulation and layering (medium-high-shear), with a focus on dense inertial flows with mechanical binder dispersion; and/or
 - fluidized bed granulation and coating, focusing on inertial-collisional flows with binder atomization contacting particles as droplets.
- Discuss scaling relations used in transferring “smallest-best” unit-op data to a pilot or manufacturing scale granulation circuit. The circuit may include powder feeders, binder pumps, granulator, dryer, classifier, mill, and recycle handling.

Approach

This draft covers some of the IFPRI research on granulation as part of the introductory background, including its influence on the author’s former industrial collaboration with several IFPRI associates.

Examples provided in the draft are skewed toward author’s own work, and will be expanded based on feedback.

1. Introduction
 - Foundational concepts: dispersion and coalescence mechanism;
 - Fluidized-bed granulation;
 - Mixer-granulation - agglomeration;
 - Mixer-granulation - layering and ordered mixing.
2. Flow field analysis
 - Dimensionless groups;
 - Practical control.
3. Granular product attributes:
 - Example, ensemble regression model of granular size and size distributions.
4. “Smallest-best” unit operations that can be used to develop a granular product.
 - Proposed survey of commercial options, “what is available”?
 - Option to focus on developmental process prototypes, i.e., “what is needed”?
 - Possibility for smaller-scale powder-binder testing, e.g., drop templating.
5. Systems integration and scale-up:
 - Agnostic model-based systems approach, optional using reduced-order modeling (e.g., machine learning) to simplify multi-scale challenges;
 - Process flowsheet models, capability with bench-scale development data.
 - Focus on prescriptive platforms, e.g., QBD/QBC, applied to regulated industries.

1 Introduction

IFPRI members have asked for a review on granulation scale-up, prioritizing advances since 2000. In 2001, a foundational review on binder granulation, involving three IFPRI associates, set the stage for many of the works that followed [1]. The review by Simon Iveson, Jim Litster, Karen Hapgood, and Bryan Ennis provided a framework for granulation in terms of physical transformations: nucleation, coalescence and growth, and breakage of granules in a wet-granulation process. Their review considered mixer-granulation, fluidized beds, and hybrid agitated fluidized beds. These processes extended across flow regimes and binder-powder flux conditions.

This review emphasizes the importance of flow and stress fields in granulation unit operations, as they apply to the above transformations, importantly that of binder-powder dispersion at the point of contacting powder with the added binder, illustrated in Figure 1. Dispersion has been classified in terms of distribution via droplet wetting, for exemplifying using a finely atomized binder spray in a fluidized bed granulation system, and alternatively in terms of templated immersion of fine powder into a larger binder droplet. A hybrid of the two classifications occurs via contact spreading in a shear field, characteristic of a high-shear mixer-granulation system.

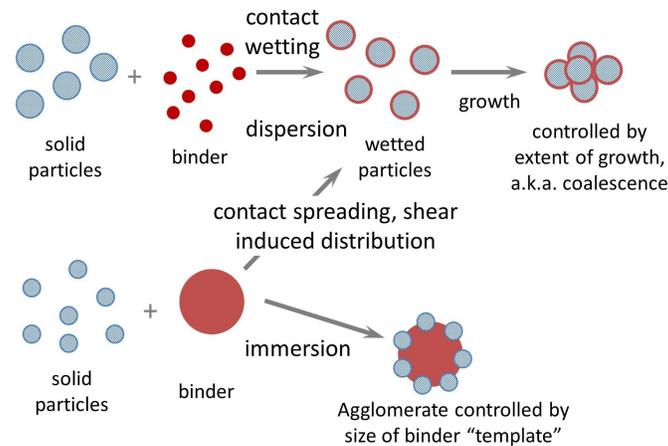


Figure 1: Binder-powder dispersion according to distribution, immersion, and contact-spreading mechanisms.

Sequencing the contact order of binder dispersion and powder immersion onto larger core or seed granules can produce layered structures having ordered compositions or interfaces. In this example, the first step is to wet the seed particle with binder, then contact the wetted seed with fine powder, and then immerse the fine powder into the binder to create a layered granule as illustrated in Figure 2.

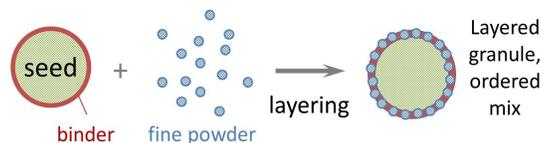


Figure 2: Layering mechanism for ordered growth using a sequential process of binder dispersion to make wetted seeds followed by immersion of fine layering powder.

In binder-granulation processes, wet-granule structure is characterized in terms of saturation, representing binder-filling of the granule’s internal porosity, illustrated in Figure 3. The transformation of wet binder to a solid or semi-solid phase may occur with subsequent drying or reactive phase changes, depending on the formulation design. The degree of saturation can carry over to the final granule structure affecting is porosity, shape, flowability, and other characteristics of potential interest to a range of product functions.

Saturation and liquid bridging structures can change with the amount of binder and/or amount of available porosity:

$$\text{saturation, } S = \frac{(\text{binder volume})}{(\text{unfilled pore volume}) + (\text{filled pore volume})}$$

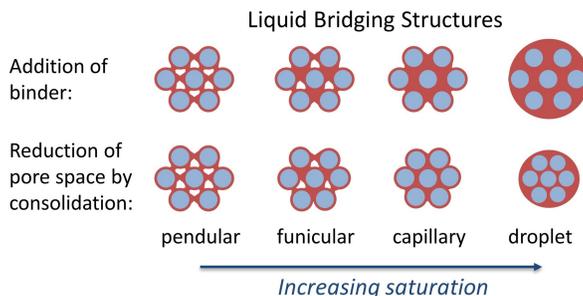


Figure 3: Granule structure characterized in terms of saturation.

An extensive handbook on granulation was produced in 2007 including contributions from many authors associated with IFPRI [2]. The handbook includes 29 chapters on various granulation processes as well as industry-specific applications including pharmaceuticals, enzymes, fertilizer, and detergents. The current author provided a review on the scale-up of batch and continuous mixer-granulation processes based on the in-process transformations that relate process parameters to granular product attributes [3, 4]. This approach was influenced by earlier IFPRI research [5] as well as the author’s collaboration with Gabriel Tardos while representing Procter & Gamble in IFPRI [6, 7]. While the above represents a rich legacy of granulation work related to IFPRI, including reports in the IFPRI archive, there has been little IFPRI work in granulation processing since the granulation control project led by Frank Doyle [8]. Currently, there

is renewed interest in the form of this review and a new project on fluid-bed sensing led by Johannes Khinast.

The prognosis for predictive control and scale up of fluidized bed granulation is reasonably well framed based on predictive enthalpy and fluidization balances [9, 10]. Note that use of fluidization air to induce flow can pose challenges for the processing of fine powder susceptible to elutriation, in which case a hybrid process of mixer-granulation followed by fluidized bed granulation can be an advantage [11]. Spray granulation in a well-fluidized bed has been well adapted to bead coating, where the same physical models apply. In coating, the objective is to wet, coat, and dry a film layer with minimal granulation [12].

Mixer-granulation relies on the physics of wet-mass rheology which has many complex interactions. One approach is to model the granulation process by combining relevant material and machine parameters in a controlling group, illustrated in Figure 4. There are several advantages of constitutive modeling approach: its basis on measurable material properties and process parameters; utility for compensation of seasonal or other raw material variations, e.g., moisture, humidity and temperature; and its direct relationship to process and formulation “handles” used in scale-up and process control. For batch processes, $E/M = \int (\text{power}/\text{mass})dt$; in continuous, $E/M = \text{power}/\text{throughput}$.

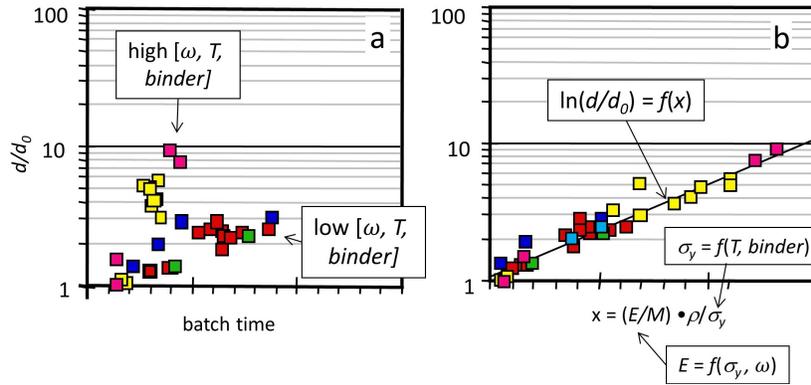


Figure 4: Example of a mixer-granulation growth kernel combining machine and material functions [4]: a) bench-scale trials run using varying binder content, mixer speed, ω , and temperature, T ; b) granule coalescence scaled to yield stress, $\sigma_y = f(\text{binder}, T)$, and specific energy, $E/M = f(\omega, \sigma_y)$.

More recent mixer-granulation reviews have considered aspects of binder granulation in context of machine and product functions [13, 14]. On one hand, the inter-relational aspects of machine and material functions creates possibilities for control and optimization, for example balancing the interaction of binder dispersion and granule consolidation in shearing flow fields inherent to mixer-granulation systems. On the other hand, the many-to-many interactions between adjustable process parameters and affected attributes can compromise

control rules, even to the point of mechanistic ambiguity. This leads to empirical guidance for scale-up, a best case having adjustable parameters to compensate for scale-related differences in attributes [15–18].

Ordered mixing concepts have been applied to reduce complexity and enable more predictive process control strategies and scale-up criteria. Examples include layered growth via staged addition of binders and layering powders building on a coarse core or seed granule [19, 20]. While more recent academic reviews suggest seeded agglomeration as novel, it has a long history in the mining industry where layering has been applied to the large scale production of taconite pellets. Industrial balling systems produce huge tonnages in a comparatively stable operation that can be practiced mechanistically on a small bench scale system [21]. The micro-mechanics of layering are consistent with those of granulation by coating [22], as illustrated in Figure 5.

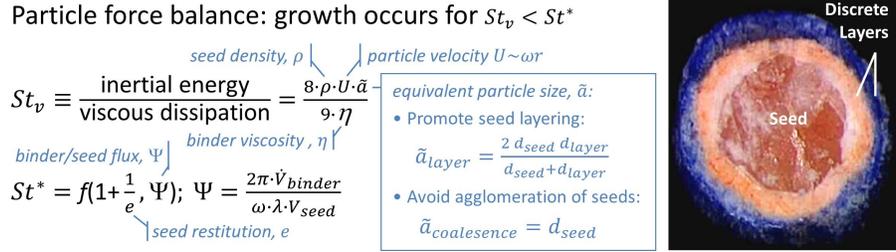


Figure 5: Particle scale layering using modified Stokes criteria applied to a mixer-granulator with angular velocity, ω , dimensionless flux, Ψ , and number of layering loops, λ , in the mixer flow field.

2 Process flow and stress fields

Considering scale-up on the basis of transformations is one way to link the macro-scale equipment decisions with granule-scale product attributes. This approach can be applied to the scale-up of a batch and/or continuous granulation processes as well as transitioning from small batch prototypes to continuous production circuits. Understanding flow and stress fields in the granulation process is a foundational starting point. In context of the regime map shown in Figure 6, we seek an optimal operating regime for granulation, preferably having fluid-like flows that support uniform binder dispersion, consolidating stresses that are consistent with desired product structure, and boundary conditions that avoid build-up or segregation. In context of fluid-bed granulation, efficient gas-solid contact is also needed.

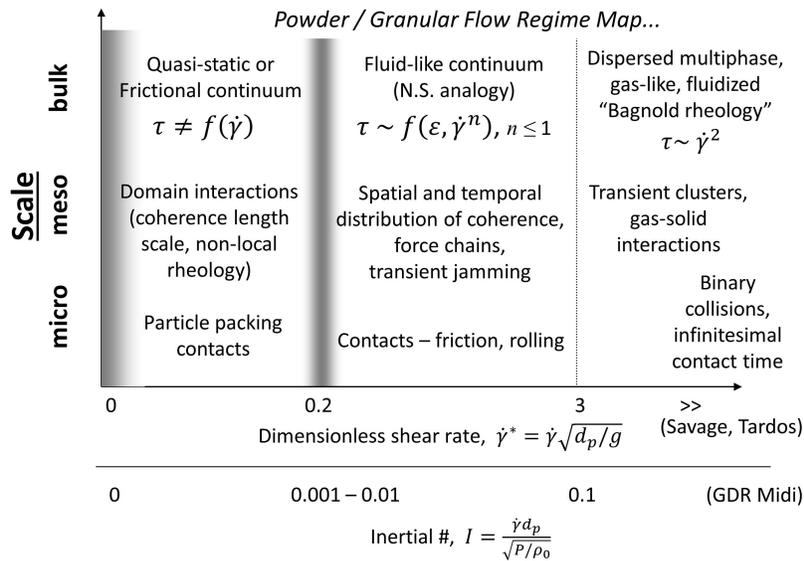


Figure 6: Flow and stress fields relevant to particulate processes in terms of dimensionless shear rate, $\dot{\gamma}^*$ and/or inertial number, I .

While dimensionless groups can be useful toward process understanding and scale-up based on flow and stress fields, it can be difficult to monitor and control them as such. For direct control of flow and stress fields in a mixer-granulator, the rotational speed of impellers or choppers is typically adjustable. In a fluid bed granulator, airflow can be adjusted to control fluidization. For process monitoring, the integral of flow and stress relative to holdup can be expressed as power or energy/mass and can be displayed as a tangible in-process measurement. The control goal is typically consistent with process efficiency - apply the needed specific energy to achieve the desired transformation, and no more, i.e., avoid overworking the product.

In the context of mixer-granulation, both $\dot{\gamma}^*$ and I depend on shear rate, suggesting tip speed scaling. Both also depend on particle size, which changes in the granulation process. At higher Froude numbers, gravity scaling no longer dominates the dimensionless shear rate, suggesting replacement of g by $\omega^2 r$ [4]. Alternatively, the inertial number requires measurement of pressure within the dense inertial flow, which is typically not monitored. From an empirical perspective, both tip speed, $U = \omega r$ and Froude number, $Fr = \sqrt{\omega^2 r/g}$, have been used as control and scaling criteria. In one creative study, [23], seeking to monitor stress fields, stress scaling was found to be intermediate between tip speed and Froude scaling.

While empirical, having a foundational understanding of flow and stress is at the nexus of relating granule product attributes to the equipment design and its operation, outlined in Figure 7.

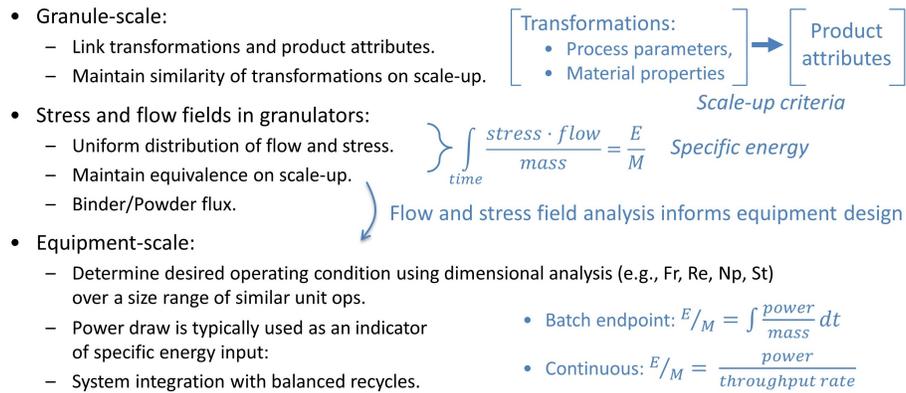


Figure 7: Criteria for scale-up based on transformations, and relation to equipment design and operation via flow and stress field analysis.

3 Granule attributes

An entire review could be devoted to granular characterization. In the context of this review combining product and process functions, we will focus on granule size and shape as independent distributions, with porosity, density, flowability, and permeability as ensemble characteristics.

The primary objective for process scale-up and scale-down is the ability to control and maintain critical product attributes. For granulation, the critical attributes are on the granular scale, which is considerably smaller than the process scale. Attributes include both distributed (i.e., size, shape, porosity, structure) and ensemble (e.g., flowability, dispersibility, permeability, compactability, etc.) granular characteristics.

Broadly, we can categorize granulation processes in terms of product structure, for example in context of porosity or permeability, per Figure 8. Spray drying can produce granules with significant intra-granular porosity, ϵ_{tra} , while high shear granulation produces more consolidated structures. Fluidized bed granules are typically intermediate, with agglomerated structures. Layered granules may have the most rounded morphology.

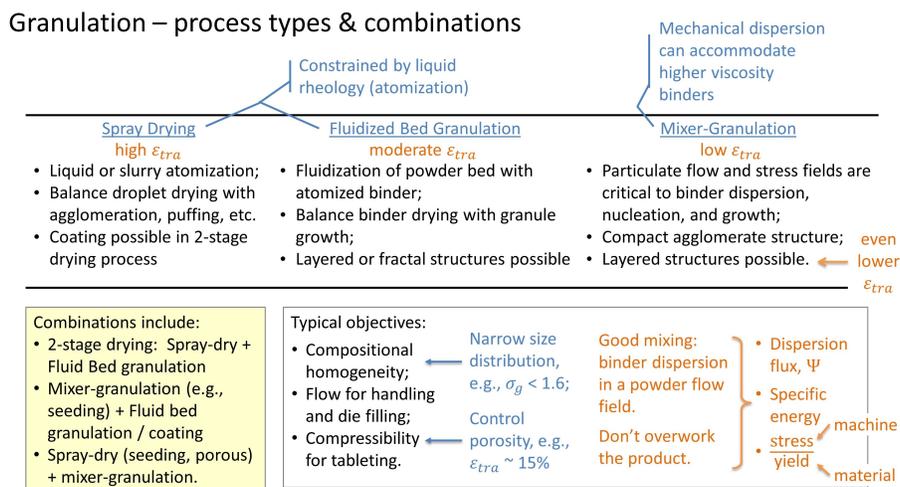


Figure 8: Summary of granular structure by process type.

Relating experimental process data to granule characteristics is challenging without having a robust modeling framework. First principle models in granulation processes are rare. In mixer-granulation, adjustable parameters are typically inter-related with mechanisms and control objectives. For example, coupled flow and stress fields can affect growth, consolidation, and breakage depending on local conditions and material effects. Even population balance models require empirical kernels.

Reliance on empirical models suggests the need for small-scale experimental process equipment that can produce measurable transformations (i.e., power curve related to saturation) or samples having representative characteristics (e.g., size, shape, porosity) that can be measured and applied to a predictive model. It is a lot to expect that small-scale process feasibility will produce products that are truly representative when scaled up. The literature is replete with examples of systematic bias on scale up, for example consolidation stress increasing with scale resulting in higher granule density.

Predictive modeling is tenable in the case of mass, energy, and fluidization balances applied to fluidized bed granulation (FBG). Where there are inter-related effects, for example airflows affecting both fluidization and drying enthalpy, drying and fluidization are both predictable based first-principle models that can be implemented in process control, i.e., based on process sensing and adjustable parameters. For a specific process under a defined set of stable process conditions, ensemble regression can provide details of distributed characteristics. A recent example combines rich characterization data (dynamic image analysis of granule size and shape) with fluidized bed granulation process parameters [24], shown graphically in Figure 9. This is an example of a model-constrained study with sparse process data collected on a pilot scale, providing higher confidence.

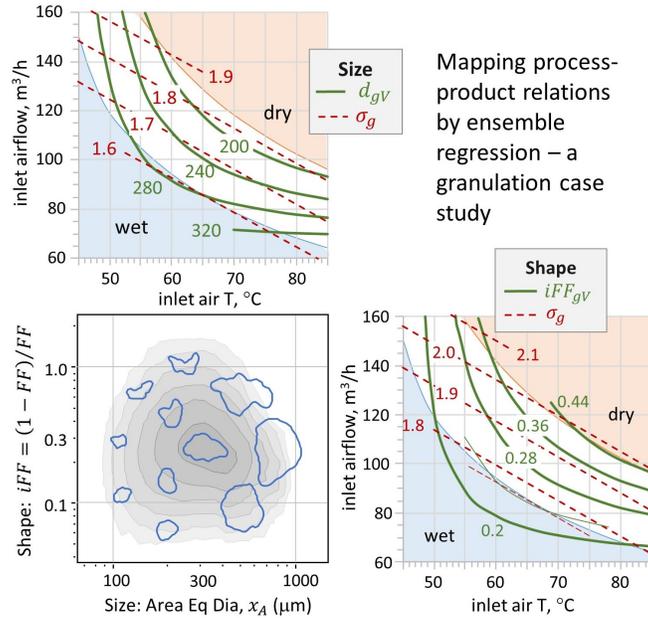


Figure 9: Graphical abstract of ensemble regression used to link volume-based geometric size and shape distributions with FBG parameters; $iFF = P^2/(4\pi A) - 1$; P is granule perimeter, A is area.

4 Bench-scale developments

Equipment manufacturers have developed bench-scale equipment aimed at formulation development with minimal use of raw materials. While these may not be fully scale-able on a process perspective, the intent is to provide preliminary indications of process feasibility together with prototype samples for early-stage product testing.

This section is envisioned as a compilation of process scale data with a priority given to available equipment from commercial suppliers, i.e., bench, pilot, manufacturing scales for mixer-granulators and fluidized bed systems.

Optionally, this can include prototype developments from academic labs including small-scale testing and droplet templating.

5 System-level scale-up

An agnostic systems approach is shown in Figure 10. The model suggests capability to integrate functional models from a granule feature scale all the way to manufacturing systems.

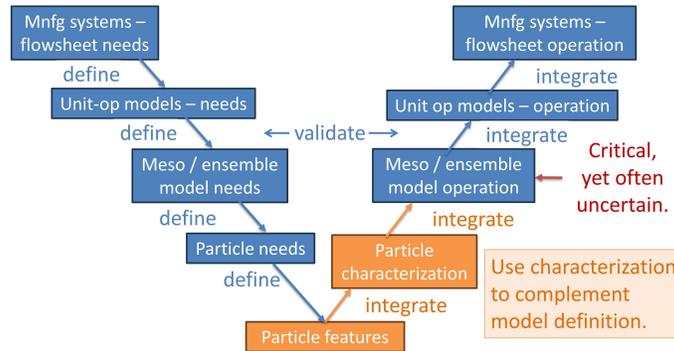


Figure 10: Model-based systems engineering approach using V-model: drill down on multi-scale problem definition; build up with integrated systems approach, validating at each level.

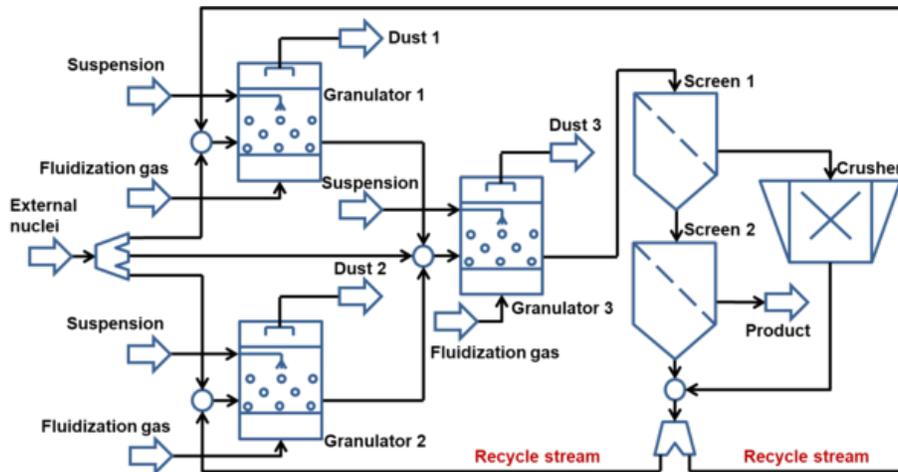


Figure 11: Example of a granulation flowsheet model, from Dyssol DFG SPP 1679.

Critical ensemble attributes (e.g., flow, dispersion, compaction) may depend on meso-scale interactions with distributed populations (i.e., size, shape, composition of granules). Predicting ensemble attributes by building up from particle features and distributed characteristics of said features is truly a grand challenge in and of itself. A reduced-order modeling approach may be reasonably considered at this stage, for example using ensemble regression or machine learning techniques.

Unit-op models in the system-V relate to the “what is needed” equipment discussed in the previous section.

On the manufacturing systems level, available flowsheet modeling options can be discussed, specifically in context of their ability to operate in context of anticipated bench-scale data. Further assessment of flowsheet capability can assess scale-up uncertainties, for example, using sensitivity studies.

Specific to pharmaceutical granulation, regulatory agencies have encouraged the development of small-scale continuous processes based quality-by-design and control (QBD, QBC) concepts incorporating in-process sensing and control with process analytical technologies (PAT), illustrated in Figure 12. The initial focus on continuous has been relaxed to include semi-continuous and small-batch under system-level controls.

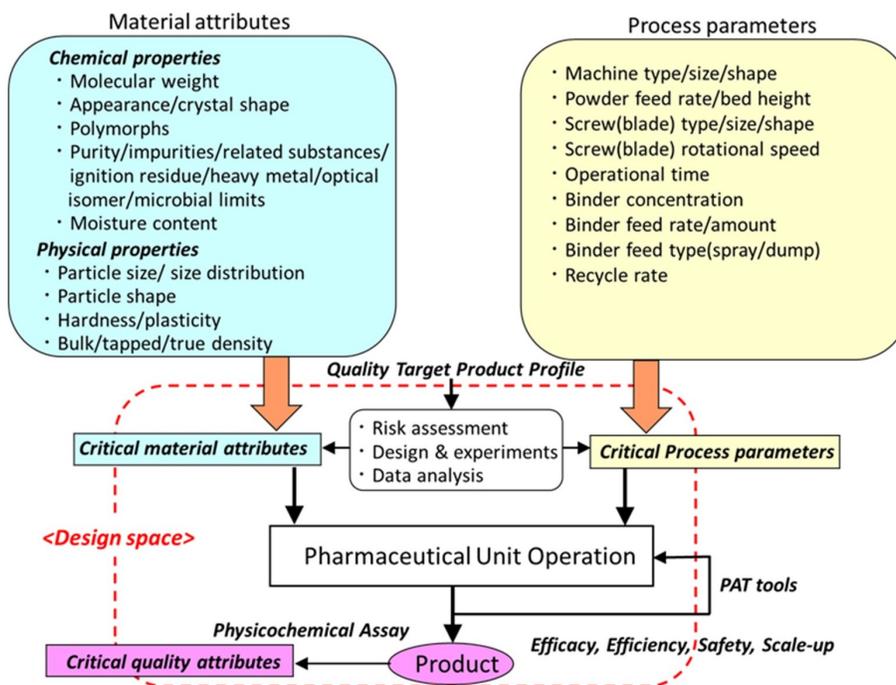


Figure 12: Quality by design approach to development.

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