Modern Modelling Tools for Small Molecule Solid Dose Manufacturing

Mathematical and computerized modelling tools can improve scale-up and efficiency of continuous manufacturing of oral solid dosage drugs.

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OVERVIEW

Rising costs, evolving regulations, and technological advancements are all impacting the manufacture of pharmaceutical oral solid dosage forms (OSDs). To remain competitive, companies must adopt efficient manufacturing practices that drive product innovation. As the pharmaceutical industry continues moving from batch towards continuous manufacturing, model-based approaches to process design and development, rather than empirical experimentation, offer the necessary insight to achieve product efficacy and manufacturing efficiency. This article explores current trends for OSD manufacturing and references real-world case studies to examine how mathematical and computerized modelling tools can improve scale-up and efficiency.

INTRODUCTION TO OSD MANUFACTURING PROCESSES

Typically, OSD manufacturing involves a sequence of unit operations that begins with feeding in the purified drug substance and any excipients and ends with encapsulation or tablet compaction-coating route. While the exact choice of manufacturing route depends upon the individual formulation, processing conditions, and any practical equipment considerations, those most widely employed as upstream pharmaceutical manufacturing processes are direct compaction, dry granulation, wet granulation and spray drying.

Process models are utilized to support the determination of design space, formulation and process optimization, scale-up, release-testing, and control strategy development. They provide the basis for establishing a risk-based framework to understand the functional relationships between important inputs, such as material attributes (MAs), process parameters (PPs), and design properties (DPs), and their effects on quality attributes (QAs), some of which will be Critical Quality Attributes (CQAs) that must be maintained within specified limits.

PRINCIPLES OF MODELLING

In regulatory terms, process models can be categorized as:

- **Low Impact** - used to support process or product development, e.g., formulation optimization models.
- **Medium Impact** - aid in assuring product quality but are not the sole or significant indicator of product quality, e.g., design space models.
- **High Impact** – can be used as the sole or significant indicator of product quality, e.g., surrogate models for dissolution.

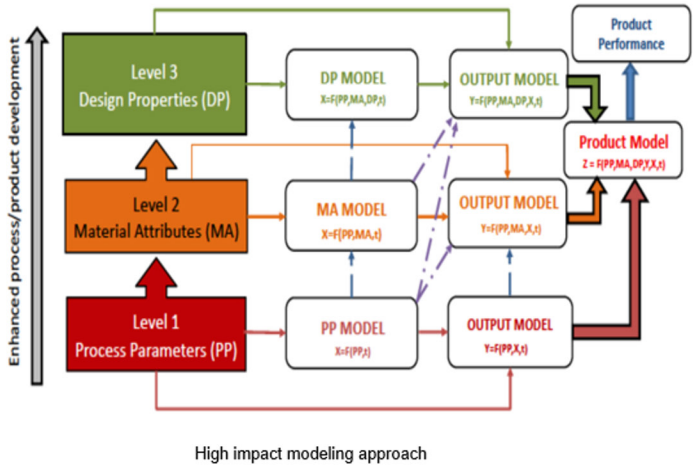
While there is no direct correlation between model impact and the degree to which a model or simulation reproduces the state and behaviour of a real-world object, there is a direct correlation between model impact and model physics. Models that contain increasing degrees of physics understanding via the incorporation of PPs (Level 1), MAs (Level 2), and DPs (Level 3) to quantify effects on QAs, are considered to trend toward higher impact. (**FIGURE 1**) outlines the development framework for a high-impact model intended to predict product performance, the most desirable attribute to understand, control and optimize.

(**FIGURE 2**) shows the types of model fidelities common in particulate pharmaceutical processes and underpin the construction of models for different purposes. At one end of the spectrum are models derived from first principles, balances, or theoretical properties. An example would be the computational fluid dynamics–discrete element model (CFD–DEM) used to investigate the translational and rotational dynamics of polydispersed particles in a pseudo-two-dimensional spouted bed. Next are empirical/data-driven models, derived primarily by fitting data to certain estimated parameters. Next are the hybrid models that combine both first principles and data-driven attributes. These are especially useful for processes where the physics is well understood in some parts but not in all. Finally, there are more recent physics-informed/constrained data-driven models. As shown, each model has its specific advantages and drawbacks.

MODELLING TECHNIQUES AT DIFFERENT SCALES

Model-based solutions can help identify optimal design spaces, a fundamental requirement for Quality by Design (QbD). At the microscopic level, models are typically first-principles based or hybrid and can properly account for

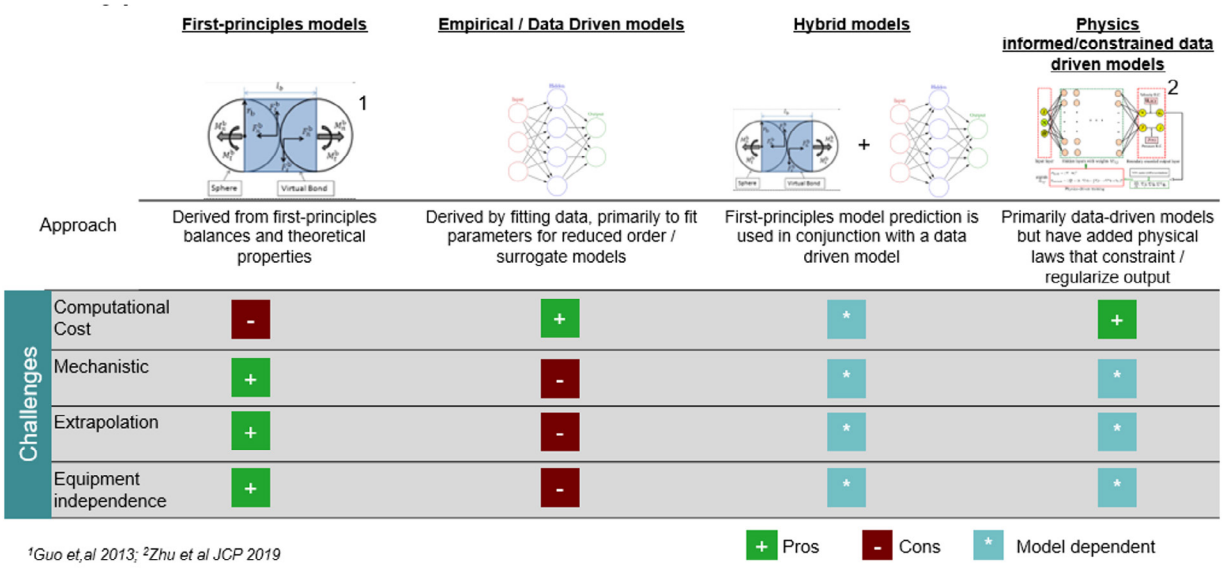
FIGURE 1: High-impact mode development framework.



High impact modeling approach

- Higher level incorporation of model physics typically enhance the use of the model for process/product development
- Intermediate models are model representations that provide a quick estimation of output that usually is not measured and is not a descriptor of product quality.
- Output models are model representations that take input from intermediate models and predict process output that can be measured but are not a descriptor of product quality.
- Product models are model representations that take input from output models are predict metrics that are direct indicators of product quality.

FIGURE 2: Types of process model fidelities.



[1]Guo et,al 2013; [2]Zhu et al JCP 2019

the physics at these levels. Models at the mesoscopic level are usually semi-mechanistic, equation-based models. Macroscopic level models are generally data-driven or empirical and can be used for rapid analysis, simulation optimization, and control. All these models can be incorporated when examining the particulate processes integral to pharmaceutical manufacturing. Model building starts from the microscopic level and brings in all the important material properties, equipment properties, and process parameters. Building then moves seamlessly, right through to the application level. Such modelling supports greater understanding, improvement, and optimization of all the processes involved (**FIGURE 3**).

Process modelling transforms pharmaceutical manufacturing by providing the scientific insight that ensures a process is designed for its intended outcomes. Greater process visibility means less trial and error, improved compliance, and continuous improvement. And by characterizing the design and response spaces, modelling helps reduce R&D cost and time.

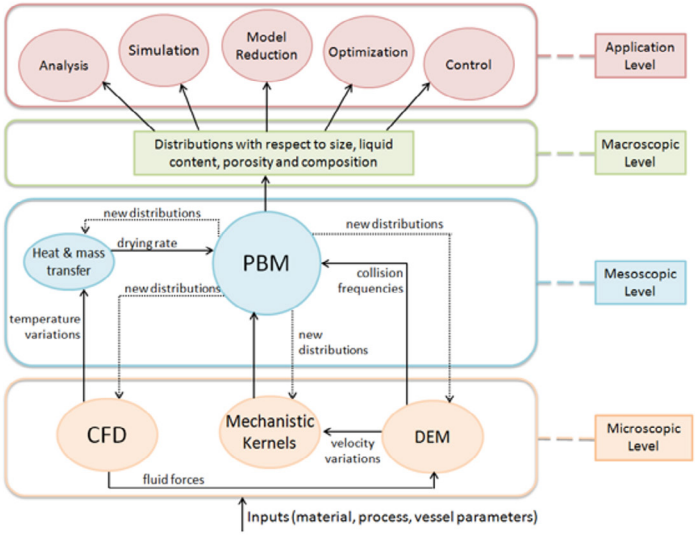
CASE STUDY 1: APPLYING MODELLING TO WET GRANULATION AT RUTGERS

Wet granulation is a particle enlargement process whereby fine powder is converted into granules through the addition of a liquid binder, improving a material's flow and compression properties and reducing segregation. It is widely applied in OSD manufacturing. Understanding wet granulation requires the categorization of the key inputs (process parameters, material attributes, design properties) and key outputs (particle/granule size distributions, liquid content and distribution, porosity/bulk density, content uniformity, friability, flow, dissolution kinetics). Process parameters include rotational rate and liquid/solid ratio, while key material attributes include viscosity, solubility, and wettability. Design properties are equipment-dependent characteristics, for example, geometry and the type of blade and screws used. The outputs are all the QAs, many of which will translate to the final CQAs requiring quantification.

Wet granulation modelling strategies and their application are explained in (**FIGURE 4**), which references the different

levels of model and approaches discussed earlier. Primarily, a first principles DEM is combined with a mesoscopic population balance model (PBM) approach. This gives a Level 1-3 model that is computationally highly intensive, which makes it applicable for process design simulation but impractical for process optimization and control. Moving to the next level requires the DEM to become a reduced order model (ROM), achieved using an artificial neural network (ANN). The idea behind using a PBM and ROM is that the model is just as accurate as the previous PBM-DEM but is computationally much more efficient, the caveat being that the ROM must be well-trained using input and output data from the full model.

FIGURE 3: Modelling techniques at different scales.



- Model-based solutions can aid in identifying optimal design spaces necessary for QbD.
- Models at the microscopic level are typically first-principles based or hybrid.
- Models the mesoscopic level are typically semi-mechanistic (e.g., PDE based models).
- Models at the macroscopic are typically data-driven or empirical.

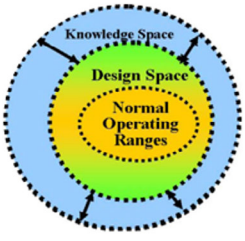
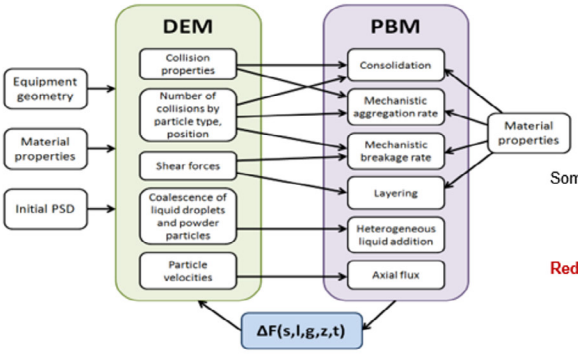
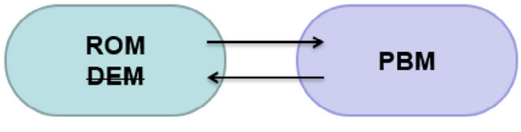


FIGURE 4: Wet granulation modelling strategies.

Particle distributions within DEM are updated from PBM at specified time intervals. Data transfer occurs in real time. **Process parameters** can be inputted in both DEM and PBM.

- **Level 1-2:** Multi-dimensional population balance model (PBM) + model verification. Often does not incorporate most material properties. Cannot account for design properties.
- **Level 1-3:** PBM + DEM (Discrete element method) coupling. Includes relevant material and design properties. Computationally intensive.
- **Level 1-3:** PBM + ROM (reduced order model) coupling. Computationally efficient and accurate if trained well.





Some calculations require much faster solutions

- Optimization, parameter estimation, flowsheet modeling, model-based control
- Ideally, one iteration should be solved in minutes or seconds.
- Parallel computing is unlikely to meet these needs

Reduced order modeling (ROM)

- Simpler model is "trained" based on input and output data from full model
- Response surface methodology, Kriging, artificial neural networks
- Some loss of accuracy expected depending on model training.

Experimental work involving a twin-screw granulator first explored making changes (seven levels) to one of the process parameters (the liquid-to-solid (LS) ratio) while keeping all other parameters constant. As expected, increasing the LS ratio resulted in larger granules, narrower size distribution, and lower porosity. The challenge was to use a model calibrated with experimental data to predict outcomes.

When a model is not fully physics or first principle based, it is often hybrid or empirical, containing parameters that do not necessarily correlate with the physics but are important in accounting for any error or model uncertainty. These parameters must be tuned with a limited set of experiments to predict data under different conditions.

In its first version, the Level 1 PBM developed in this experiment was designed to predict three different types of particle size distribution: the D25, D50, and D75. In practice, the measured and simulated product sizes versus LS ratio proved to be in close agreement. This basic model does a good job but there are many ways to improve it, one of which is to incorporate material attributes. Here, as in many other instances, the goal is to improve the physics of the model. This is often achieved by combining it with other model forms. It is important not only to include material attributes but also to reduce the number of empirical parameters, to make the model more flexible and more versatile.

One way of achieving this is to incorporate a DEM, and it is instructive to see where this will fit. In wet granulation systems, aggregation rate is important and is a function of collision frequency and collision efficiency (the likelihood that a collision will result in granulation). Collision frequency is usually determined empirically with the assumption that every particle can collide with every other. Often, however, this is false and can lead to over-estimation of the aggregation rate. Collision rate can be more accurately determined directly from a DEM in which particle interactions are tracked from the outset. Collision efficiency has also to be factored into the granulation model. Here empirical terms remain in use in the literature, but there is a growing trend towards the development of more mechanistic, or first principle-based terms, incorporating a variety of materials properties. Essentially, as models advance, each one incorporates a higher level of understanding, enabling their use for many purposes.

CASE STUDY 2: MODEL-BASED PROCESS DEVELOPMENT OF FLUID BED GRANULATION AT CATALENT

In a typical fluid bed granulation sequence, raw materials are first fluidized by heated inlet air volume. The binder solution is then sprayed onto the fluidized solid particles. As the binder droplets collide with the solid particles, these begin to agglomerate and eventually enlarge in size. A drying stage follows to reduce the moisture content of the granules to a predetermined value.

The typical and traditional way of managing fluid bed granulation is through temperature control. Once temperature ranges are set, the equipment PID loop then maintains control. However, modelling from a thermodynamic perspective has shown that the relative humidity (RH) of the fluid bed plays a significant role in the agglomeration process and that collision mechanisms between droplets and solid particles also govern the way agglomerations are formed.

The main CQAs for the granules are granulation density, particle size distribution, and moisture content. The major critical processing parameters (CPPs) include product and exhaust temperature, atomization air pressure and volume, spray rate, nozzle geometry, and binder solution properties. Establishing a bridge between the CPPs and the CQAs enables the process to move towards delivering the expected results in terms of granulation properties.

(**FIGURE 5**) describes how the CPPs influence the granulation process and, therefore the CQAs of the granules. Clearly, the inlet air humidity and the spray rate affect the aggregate moisture content of the bed. The more moisture, the

larger the particle size distribution. Looking at this from the fluidization viewpoint, insufficient airflow will lead to a stalled bed that fails to fluidize. At the other extreme, too much inlet air would result in very lean fluidization in which binder solution droplets evaporate before having the chance to collide with the solid particles and thus trigger agglomeration. Inlet airflow also affects the rate at which moisture is removed from the system, while the droplet particle collision mechanism, droplet size, and droplet particle relative velocity all impact the wetting mechanism.

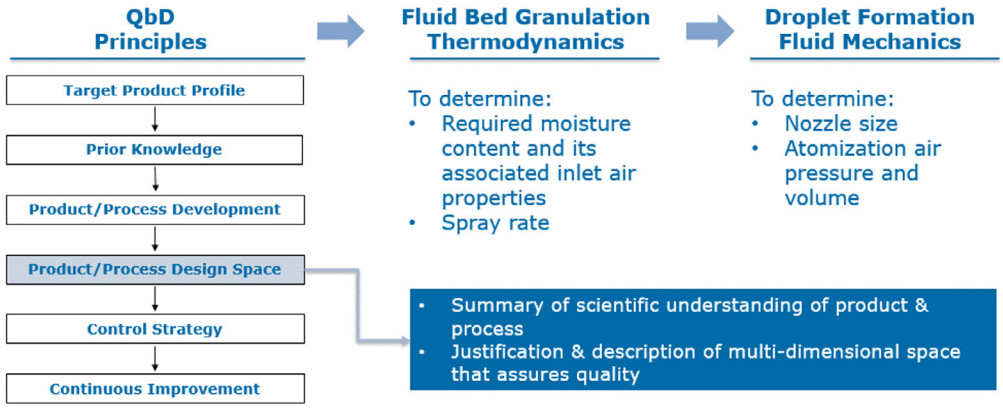
In pharmaceutical manufacturing, fluidized bed granulation scale-up is often performed empirically. The traditional approach is to increase the spray rate proportionally with the cross-sectional area of the air distributor plate. However, this is a very simplistic approach, given that the most important factors driving granulation are the fluidized bed moisture level and the collision mechanism. Other disadvantages of the traditional approach are that it requires feasibility batches that increase R&D time and costs, and it is not possible to quantify the scale basis for regulatory and filing purposes.

As shown in (**FIGURE 5**), which looks at applying QbD principles to model-based process development of fluid bed granulation, the model-based manufacturing processes normally occur where product and process design spaces are being defined. Following QbD principles, the main goal is to provide a summary of the scientific understanding of the product and process, together with a justification and description of the multidimensional space that assures the final quality of the product.

As already touched upon, the two main aspects of fluid bed granulation are the thermodynamics of the granulation and the fluid mechanics of the droplet formation. From a thermodynamics perspective, the fluid bed moisture level must be optimal for the intended particle size distribution. Knowing the moisture level enables the determination of the required spray rate. Once the spray rate is known, decisions about the droplet formation mechanism must take account of droplet size distribution and droplet pattern. These eventually boil down to nozzle size, atomization, air pressure, and volume. Traditional approaches do not deliver scientific or risk-based justifications for many of these parameters.

At Catalent, model-based process development can draw upon large amounts of historical data and experience, and this is used to train and modify the process models. System inputs comprise all the historical data for raw materials and equipment at different scales, which informs the models' outputs.

FIGURE 5: Implementing QbD principles to model-based process development of fluid bed granulation.



To make this approach applicable to a variety of users, models are being integrated into a software developed using QbD principles. This will streamline information flow across different organizational entities, from supply chain and testing laboratories, for example, through process and product development and eventually to quality control. Ultimately, it will be a simple task to upload information, or download it from the supply chain and go straight to the models.

FIGURE 6 exemplifies the process development of a fluid bed granulation using a model and compares it with the same process developed empirically. As the empirical process (left) is temperature oriented, the PID loop tries to maintain product temperature and has to make frequent changes to both the process airflow and process air temperature. Such changes impact the RH of the fluid bed. In the redesigned, model-developed process (right), control was maintained with only minor variations in inlet air temperature or flow and, thus minimal disruption to the RH of the bed.

Optimizing the process using the model also enabled a narrowing of the particle size distribution with enhanced flowability of the material, minimizing the risk of segregation, improving content uniformity, and achieving greater compressibility of the granules. This also translates into an improved capability to meet tablet thickness specifications, with lower compression forces and reduced dwell time required to achieve the same level of tablet hardness. Overall, this enables manufacturing at higher production speeds, resulting in increased system efficiency and productivity.

MODELLING IS INSTRUMENTAL IN DRIVING CHANGE

As the pharmaceutical industry works towards Pharma 4.0, process modelling is transforming manufacturing processes. The regulatory expectation is that the industry will apply scientific and risk management approaches to developing a product and the associated manufacturing processes. Compared with empirical approaches, process models offer the scientific insight needed to ensure a process is designed specifically to deliver the intended outcomes. There is greater process visibility, less trial and error, greater compliance, and continuous improvement. Furthermore, modelling can significantly reduce the R&D cost and time by characterizing the design and response spaces.

FIGURE 6: Modelling validation by comparing process designs on quality and processing impact - process control.