A Scrutiny of Scale: Considerations for the Manufacture of Orally Inhaled Drug Products

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Summary

Traditionally, scale considerations for pharmaceutical manufacturing processes have focussed on scale up of the constituent unit operations and generally have been based on empirical approaches. This paradigm is increasingly challenged by regulatory expectations for improved understanding/robustness of manufacturing processes, which drives a need for development of mechanistic models. Other challenges to the scale-up paradigm include the customisation of healthcare through personalised medicines which will demand manufacture of smaller, more frequent, 'on demand' product batches and technological innovations such as continuous manufacturing[1], where scale-up may either be irrelevant or more modest compared to changes in equipment scale within batch processes.

Specific to Orally Inhaled Drug Products (OIDPs), the lack of a 'SUPAC-like' guidance to inform on required *in vitro/in vivo* studies to underwrite changes in manufacturing process scale and, in particular, the absence of a simple bioequivalence measure, drives a product/process 'design freeze' earlier in development than for immediate release solid oral dosage forms, which results in the need to develop the commercial scale manufacturing process ahead of pivotal clinical studies. Additionally as a combination product, considerations of scale must be applied to manufacturing processes for both formulation and inhalation delivery device.

In this paper, scale considerations will be reviewed for typical unit operations that comprise the manufacturing process train for a unit dose inhalation powder, identifying the process variables that impact quality of output product, highlighting key best practices and, where possible, where scale-independent mechanistic models can be used to inform technology selection, technology transfer and scale up.

Introduction

Analogous to the seismic changes in the automotive and electronics industries which today provides us with 'connected cars' and 'wearable' technology, our medicines in the future will be 'smarter'. To deliver on this promise, the pharmaceutical factory of the future will need to change and realise the FDA's goal[2] of "[a] *maximally efficient, agile, flexible manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight*". Common factors contributing to poor product quality can be identified from a review[3] of FDA Inspectional Observation Summaries ('483s') and improving product quality as a contribution to reduce drug shortages and recalls is a key driver for the launch of the FDA's Office of Product Quality [4]. Guidance for industry on process validation[5] describes the expected evolution of product knowledge and process understanding through the process validation lifecycle and that *"...to understand the commercial process sufficiently, the manufacturer will need to consider the effects of scale..."* and "*...activities, such as experiments or demonstrations at laboratory or pilot scale, also assist in... prediction of performance of the commercial process...*". Likewise the FDA Compliance Policy Guide[6] which advises Agency staff on standards and procedures to apply when determining compliance, identifies scale as an important issue "...[readiness for manufacturing assessment includes] *a review of the firm's scale-up studies*...[and] *firm may need to change the submitted proposed commercial process as scale-up studies are completed and knowledge is gained...*". Scale considerations for OIDPs have some clear differences to immediate release (IR) solid oral dosage forms, not least in a typically smaller absolute scale (a consequence of both low therapeutic dose and low formulation unit dose), and the lack of a 'SUPAC-like' guidance to inform on required *in vitro/in vivo* studies to underpin changes to manufacturing process, equipment and scale. The delivery device brings an added complexity as its manufacturing process also needs to be developed, transferred and scaled.

Developing Understanding of the Manufacturing Process

Scherzer[7] described a hierarchical framework of models (Figure 1.), from empirical 'trial and error' experimentation through to mechanistic models based on well understood physical, chemical and engineering principles. Outside the inhaled drug delivery field, a good example demonstrating the evolution from empirical to mechanistic models is provided by Björn *et al*[8] for the high shear wet granulation unit operation.

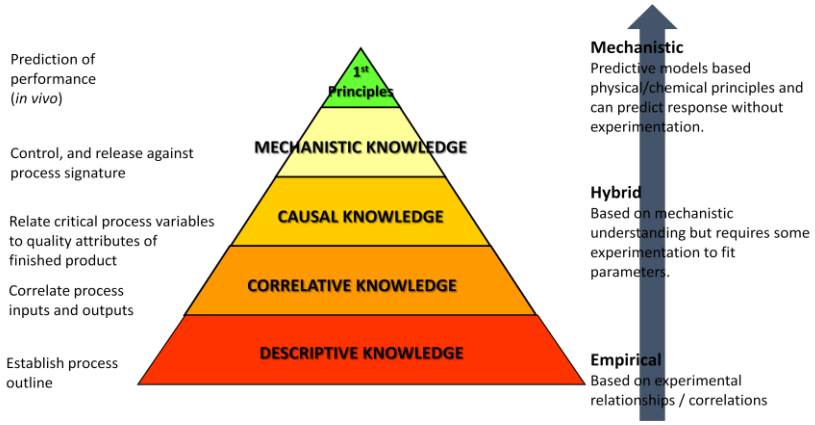


Figure 1. Hierarchical model framework (adapted from[7])

For the purposes of this paper, scale considerations are restricted to the following unit operations of the Drug Product manufacturing process train[i] - API particle forming step, particle size reduction (micronisation), powder blending, powder filling and development of the inhalation delivery device

For each unit operation, a process flow can be created that identifies the input attributes and process parameters that impact the quality attributes of the output material (exemplified in Figure 2. for the micronisation unit operation). In developing the product control strategy for the commercial manufacturing process, the criticality of each process parameter to product critical quality attributes will have been risk assessed (based on scientific understanding and prior knowledge) and controls established commensurate with the risk to product quality. Likewise the impact of scale can be risk assessed under an FMEA type scheme.

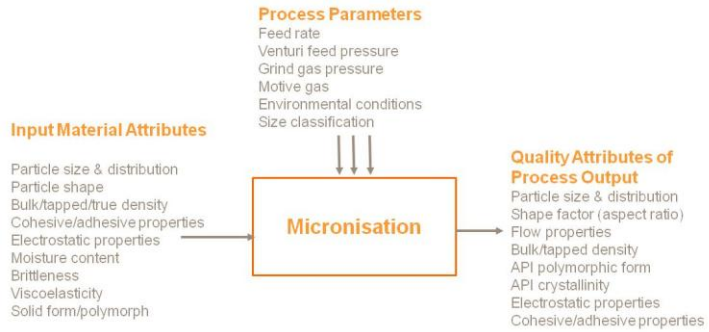


Figure 2. Input/Process/Output diagram for micronisation unit operation

API particle forming step

API material attributes mechanistically linked to downstream Drug Product manufacturability, performance and stability e.g. particle size distribution, particle shape, specific surface area, surface texture moisture content, amorphous content etc., can be impacted by process parameters that may vary with scale e.g. seeding, super saturation & agitation (crystallisation), driving pressure (filtration & washing), temperature, agitation & pressure (drying). During API process design, sensitivity to scale (batch size, equipment scale and equipment type) for unit

[i] Scale-up considerations for API synthesis are considered out of scope as assumed that the final particle forming step imparts to the API those critical material attributes that impact Drug Product Critical quality attributes (the interested reader is referred to the publication of Muller, F.L. and Latimer, J.M., *Anticipation of scale up issues in pharmaceutical development*, Proceedings of European Congress of Chemical Engineering (ECCE-6), Copenhagen, 16-20 September 2007, for an example of a methodology to evaluate risk of scale-up of chemical synthesis). For the Drug Product manufacturing process train, development of a general approach to scale for device assembly and packaging processes is complicated by the bespoke and semi-continuous nature of the operations and has been excluded from consideration. For the purposes of this paper, development of the delivery device is considered a 'unit operation'.

operations comprising the particle forming step covers changes is assessed, focusing on variables most impacted by process timescale and equipment:process scale ratio. Process understanding generated at lab and pilot scale will inform whether design space can be defined by scale independent parameters/scale-up models or whether commercial scale verification is required.

Particle size reduction (micronisation)

Effective size reduction in a spiral jet mill depends on geometry of the mill design (diameter of grinding chamber, shape, number & angle of grinding nozzles) as well as operational parameters (solids feed rate, gas mass flow rate and mechanical properties of material to be micronised). Key parameters to be considered for scale-up are gas mass flow rate and solids feed rate (sometimes combined as specific energy, E_{sp}[9]) and diameter of mill chamber which determines mill capacity[10]. For a target particle size and throughput, control of the solids feed rate and gas mass flow rate assures a consistent output Particle Size Distribution. To minimise use of a high cost API, one approach to scale up is to micronise at least two surrogate materials on a small scale mill and at least one on a large scale mill to determine mill specific parameters, micronise the API of interest on small scale to determine material specific parameters, combine the material specific parameters and mill specific parameters for the large scale mill and identify combination of solids feed rate and gas mass flow rate required to robustly achieve a desired output particle size.

Powder Blending

Unit dose inhalation powder formulations typically contain size reduced API(s), a larger particle size carrier and potentially additional components to assure product performance and/or chemical/physical stability. The dry powder blending step directly impacts the content uniformity of the powder formulation, which will subsequently impact uniformity of the delivered and aerosolised dose. Identification and optimisation of operating conditions at the desired scale is thus critical. Scale factors such as the Froude number have been applied to inform scale-up of powder blending, with the limitation that geometric similarity of equipment is a prerequisite and thus its use in scaling between mixers of different geometries is problematic[11]. Acknowledging the complexity of computational modelling of inter-particulate interactions during mixing to derive a mechanistic model, Barling *et al*[12] have proposed an iron oxide tracer method to assure equivalence of mixing conditions across mixer type, scale and operating conditions and provide a more quantitative approach to blender scale-up. Dispersion of the iron oxide agglomerates and subsequent deagglomeration to primary particles during the blending process is monitored by colorimetric measurement of hue and hue intensity, allowing construction of formulation deagglomeration/dispersion curves to predict equivalent mixing conditions and blend quality when moving to a new mixer. Further development of this methodology to incorporate equipment covering a wider range of operating principles would be advantageous.

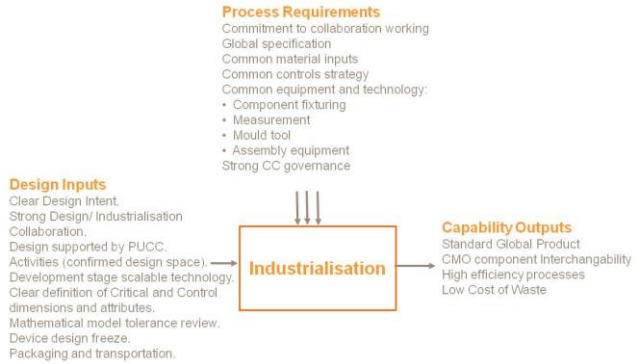
Powder Filling

The powder filling process for unit dose inhalation powders can be considered semi-continuous and scale considerations involve both scale within a given dosing principle (dosator, dosing plate, screw auger, vacuum drum) and also changes between filling principle. Reproducible subdivision of inhalation powders at low dose requires a good understanding of the interaction between input material attributes and filling process parameters and it is important that the selected dosing principle both assures fill weight/content uniformity of unit doses as well as pharmaceutical performance (delivered dose/aerodynamic particle size distribution). Maintaining the dosing principle and expanding the no. of filling stations/dosing bores is a common approach to assure translation of dosing performance across scales. A recent publication[13] describes development of a predictive statistical model for fill weight and fill weight variability for an encapsulation process based on filling parameters (e.g. dosator diameter, dosing chamber length, powder layer depth) and material attributes (e.g. wall friction angle, bulk density, basic flowability energy). Likewise Seyfang et al[14] have demonstrated for a range of dosing principles how dosing performance (fill weight variability) can be predicted from static and dynamic powder properties. Sim *et al*[15] have taken the concept further by establishing a predictive link between powder permeability and drug delivery performance.

Development of the inhalation delivery device

The goal of device development is for a standard global product produced by a high efficiency manufacturing process with low cost of waste and flexibility to interchange components from different CMOs. Key factors in the design phase which contribute to success and bad practices to avoid are summarised in Figure 4. As development progresses, so device tooling evolves to deliver a product commensurate with requirements of the development stage. In progressing from the initial single soft cavity tooling (prototyping) to the low volume industrial tooling (supports clinical, stability and device development), the device developer should make long term technology choices so that there are minimal changes made in transitioning to the high volume industrial tool used to support commercial launch.

a)



b)

Undesirable Practice	Impact
• Incomplete/ unverified design • Manufacturing not engaged early in design development • Multi functional team not engaged • Changes in key technical staff • Fragmented supplier set up (global projects) • Leave metrology strategy for CMO's to manage • Make cost concessions of development technology	• Potential major rework & project delay • May constrain final design • Eases resource constraints but leads to potential project confusion at later stage • Avoid where possible causes project turbulence • Causes divergence in manufacturing requirements and standards • No central understanding of methodology can result in complex discrepancies • Causes knowledge gaps and risks in industrialisation

Figure 3. Inhalation delivery device scale-up, a) considerations for success and b) undesirable practices to avoid

Conclusion

A scrutiny of scale for the constituent unit operations of the batch manufacturing process for a unit dose inhalation powder highlights where scale effects can be anticipated and mitigated during the development process through appropriate risk assessment and better understanding of the fundamental science to aid identification of scale independent descriptors and predictive tools. It is also clear that the product developer also now needs to consider how to deliver products into a future supply chain where customisation of demand (smaller volumes of more products with shorter life-cycles) and implementation of continuous manufacturing will challenge the traditional scale-up model to support the large batch/centralised manufacturing system.

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