HOVIONE

SCALE-UP & QBD APPROACHES FOR SPRAY-DRIED INHALATION FORMULATIONS

Here, Eunice Costa, PhD, Scientist, Drug Product Development; Filipe Neves, PhD, Senior Scientist, Group Leader, Drug Product Development; Gonçalo Andrade, PhD, Business Development Manager; and Conrad Winters, PhD, Director, Drug Product Development, all of Hovione, describe the strong position of inhalable products in preclinical and clinical pipelines and make the case for formulation-based approaches to enable and enhance pulmonary product development. Spray-drying technology in particular is highlighted as a highly favourable, scalable manufacturing technique for inhalable composite particles.

INHALED DRUG DELIVERY

Inhaled drug delivery is a growing niche market within the pharmaceutical industry. Pulmonary drug delivery accounted for US$19.6 billion (£11.6 billion) in revenues in 2010[1] and represented approximately 15% of the drug delivery market.[2] Inhalation is emerging as an alternate drug delivery route, expected to reach $44 billion by 2016 [1] and representing approximately 20% of the drug delivery market by 2017.[2] This growth will be driven by new drug product launches for unmet clinical needs, novel drug product combinations and products for improving patient compliance, where pressurised metered-dose inhalers (pMDIs) and dry-powder inhalers (DPIs) are expected to be the major contributors (15.7% CAGR and 12.3% CAGR, respectively).[1]

MARKET TRENDS

Pulmonary drug delivery can offer significant advantages over other administration routes. Compared with parenteral administration, it is a convenient and less intrusive alternative, reducing the need for medically trained staff during administration. Also, compared with parenteral formulations, DPIs may not require the refrigeration often necessary for vaccines and, when compared with the oral route, lower doses can be used with the potential for reduced side effects.

For drug molecules that have a pronounced food effect, extensive first-pass metabolism, or are subject to efflux or low aqueous solubility, pulmonary delivery offers a viable route where oral delivery would be extremely challenging.

This high number of projects presently in clinical development (Figure 1) reflects different development strategies, ranging from lifecycle management strategies related to inhaler redesign, such as AstraZeneca's ongoing Symbicort (budesonide + formoterol) programme, to new chemical entities for inhaled delivery (e.g. Aesica's development programmes). The majority of these clinical programmes are aimed at treating respiratory based illnesses such as asthma and chronic obstructive pulmonary disease (COPD), cystic fibrosis and pneumonia. However, there have been an

	Preclinical	Phase I	Phase II	Phase III
Number of projects	196	28	2	1

Figure 1: Dry-powder inhalation products in clinical development (Source: PharmaCircle, May 2013).

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increasing number of DPI products in clinical development that target non-respiratory indications. For example, in Type II diabetes, MannKind Corporation has filed a US NDA for Afrezza (inhalable insulin).

One other major driver for DPI formulation development is compliance with the Montreal Protocol, which establishes a control over ozone-depleting gases and led to the replacement of the original CFCs in metered dose inhalers for HFAs (and HFCs).[3,4] But the latter still constitute an environmental threat since both HFAs and HFCs are greenhouse gases and environmental concerns may lead to a phase down/phaseout in pMDIs [4] and drive their conversion to DPI formulations, also contributing to the results of Figure 1.

TECHNOLOGY TRENDS

Innovation in inhalation drug delivery has primarily been focused on two parallel pathways: the development of novel inhaler devices, and the improvement of powder formulations.[5] Although pulmonary delivery can be enhanced by designing more sophisticated inhalers (e.g. electronic synchronisation), such devices tend to be complex and costly, and their practicality has been questioned. On the other hand, superior delivery efficiency may be achieved more cost-effectively by developing optimised formulations, in physical blends with carriers or as composite particles, for use with simple and user-friendly inhalers.[6] The latter is broadly known as particle engineering.

Among several attributes of a DPI formulation, particle size is one of the most important design variables; particle size relates to the aerodynamic diameter and this, for most inhalation drugs, needs to be in the 1–5 µm aerodynamic range.[7] Jet milling is still the most common size-reduction method in the pharmaceutical industry. However, and in spite of being cost-effective and of easy operation, there may be disadvantages such as lack of control over size, amorphous content and surface properties of the milled particles.[8] In order to overcome some of these challenges, methods that consider the active ingredient suspended in a liquid media have been gaining significant momentum.[9] However, the use of an anti-solvent system, and the potential for residual solubilisation, may pose challenges from a chemical and physical stability perspective, whereas the need of a final isolation step may also be considered a drawback.

	Strengths	Limitations
Carrier-based	• Established • Crystalline material • Easy to develop (Innovators)	• Variability (except high dosage) • Homogeneity (except high dosage) • Delivery efficiency
Composite	• Formulation in single step • Uniformity • Improved delivery efficiencies • Biologics / innovators	• Complexity in formulation / process development • Stability for amorphous material • Not applicable to generics

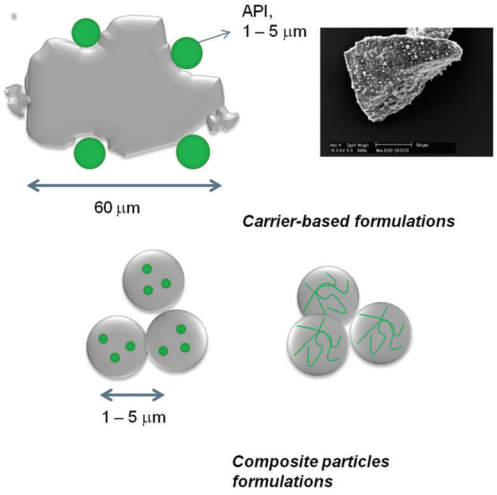


Figure 2: Carrier-based versus composite particle approaches: strengths and limitations.

Other techniques for making micron-sized particles involve direct particle formation from solution. In this field, spray drying (SD) has emerged as a noteworthy approach for achieving the desired aerodynamic size, morphology and, ultimately, powder flow.[10] This technique is distinctly different from milling, as particles are built up by spraying the drug and excipients from a solution or emulsion into fine droplets that are afterwards dried in a chamber. Compared with milling, SD can produce more spherical particles that tend to be amorphous, conferring enhanced solubility of poorly soluble drugs.

Spray drying has been extensively used for the generation of inhaled composite platforms, namely Pulmosol (Pfizer), Pulmospheres (Novartis) or iSperse (Pulmatrix). This technology has been applied to a diverse array of molecules, from small molecules for respiratory disease treatment to biomacromolecules for systemic delivery. For example, insulin was engineered in order to yield particles with a corrugated surface that improved dispersibility (Exubera DPI from Pfizer). More recently, Pulmospheres, based on solid foam particles prepared by SD of an emulsion, have been employed for a DPI formulation of tobramycin (TOBI Podhaler).

As summarised in Figure 2, these platforms are challenging to develop given the simultaneous requirements of physical stability and optimal aerodynamic performance. Conversely, the particle engineering and formulation are done in a single step, overcoming potential uniformity issues of traditional lactose-based DPI approaches and enabling the delivery of higher fine-particle fractions (FPFs).[10]

The following paragraphs address spray-drying technology as a manufacturing technique for inhalable composite particles, starting by focusing on the scale-up procedure, typical challenges and ways to overcome them, and finishing by showing how systematic methodologies and scientific understanding can be used to conduct the process development based on QbD principles.[11]

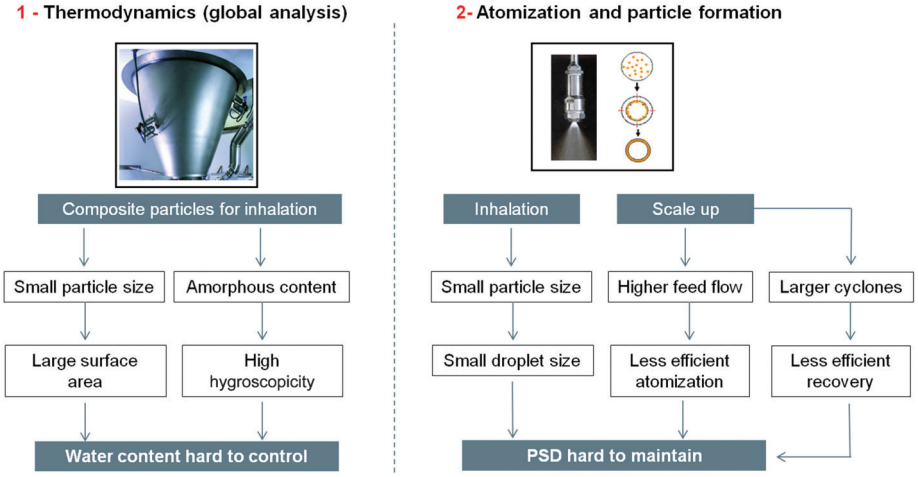


Figure 3: Main difficulties during development and scale-up of spray-dried inhalation products.

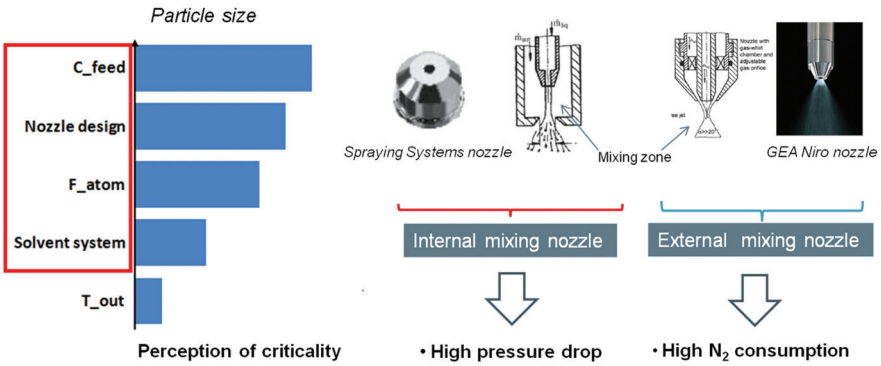


Figure 4: Main critical parameters and challenges during the atomisation step. C_feed = solids feed concentration, F_atom = flowrate of atomisation gas, and T_out = outlet drying gas temperature (Nozzle schemes adapted from Hede et al, 2008.)

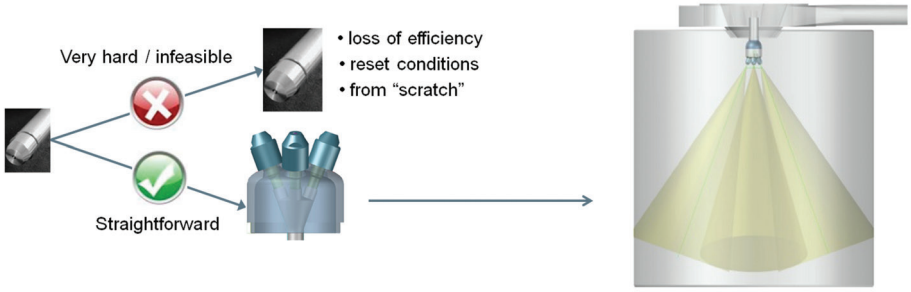


Figure 5: Multi-nozzle approach for expediting scale-up of atomisation (Hovione's apparatus).[12]

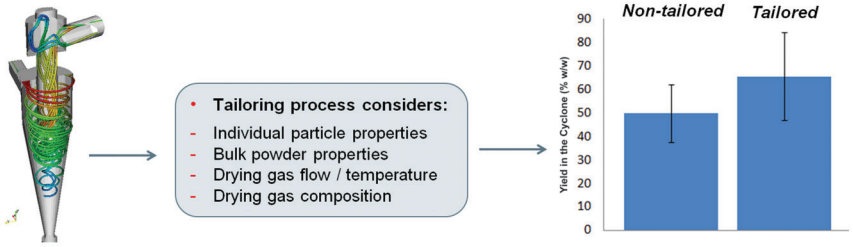


Figure 6: Tailoring process of cyclones for improved recovery of inhalation powders during scale-up.

SPRAY DRYING SCALE-UP APPROACH

The manufacturing of spray-dried inhalation powders involves two main challenges: particle size and residual moisture control (Figure 3). Firstly, a very small particle size is required, and this should not increase during process scale-up. By itself, this poses significant problems during the droplet formation (atomisation efficiency decreases for higher feed flow-rates) and particle recovery (cyclone efficiency decreases in larger units) steps. Secondly, due to the small size of the particles, the total surface area of the bulk powder is significantly high which, when combined with the increased hygroscopicity of amorphous phases, leads to challenges in moisture control.

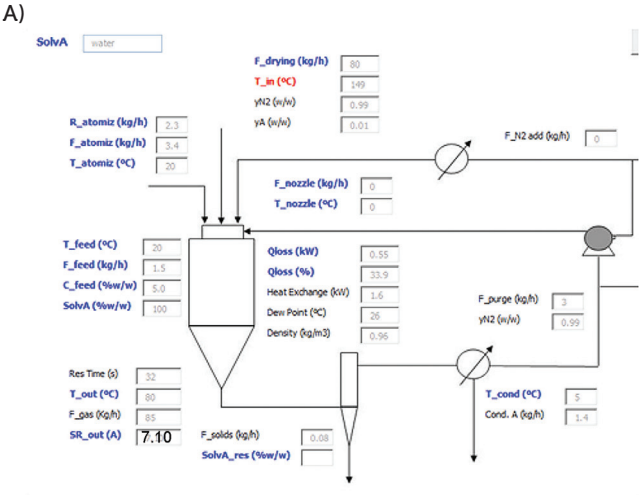
With regards to particle size control, as introduced before, most of the difficulties during development result from the loss of efficiency of current off-the-shelf atomisation systems, when managing increased throughputs during scale-up.

Such loss of efficiency is translated by a higher demand of atomisation gas flow and this will lead to different bottlenecks depending on the type of atomisation systems (Figure 4):

a) For external two-fluid nozzles (high consumers of atomisation gas at low pressures), the flow of atomisation gas may increase so much that the drying chamber will be incapable of dealing with it (atomisation gas flow can grow to a demand of 30-50% of the drying gas flow).

b) For internal two-fluid nozzles (lower consumers of atomisation gas but at higher pressures), the increase of atomisation gas may promote such a high pressure

A)



B)

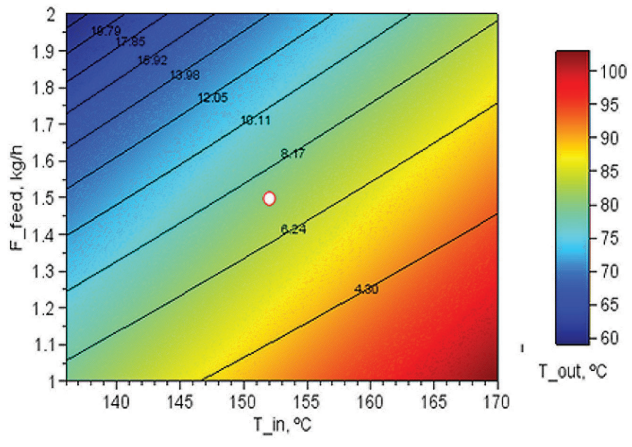


Figure 7: Use of thermodynamic simulations for relative humidity / saturation space mapping: (A) operating parameters and (B) design space.

drop on the nozzle that the pressure of the gas-feed lines may often require very complex / expensive upgrades.

In this constraining reality, as shown in Figure 4, nozzle design and atomisation gas flow are the main process parameters that can typically be used to control particle size. Solids concentration is another one, but minimising particle size via C_feed decrease is not recommended, given the corresponding penalty on process throughput.

Regardless, even when these constraints can be overcome, it is not guaranteed that droplet size can be maintained during scale-up. During this process, nozzle operating ranges are often exceeded and time-consuming testing needs to take place in order to select a new nozzle. As there are physical limitations on the atomisation of large liquid flow rates into very small droplets, this is not always successful.

Under the above scenario, the use of multi-nozzle apparatuses comprising several low-throughput nozzles (as opposed to a single high-throughput nozzle) becomes appealing. By using this approach, the ratios between liquid and atomisation gas flow can be maintained (in each nozzle), avoiding some of the constraints described earlier and enabling a smooth scale-up (as operating conditions do not need to be changed, since each nozzle is always performing the same "work").[13]

However, this approach requires some special care during the engineering of the SD units, as: i) distribution of the liquid feed and atomisation gas flows needs to be homogeneous, ii) apparatus size / positioning cannot impact the drying gas flow pattern, and, iii) the apparatus needs to enable spray-drying angles in a way that no overlapping occurs nor spray shape is impacted by the drying gas flow (in order to avoid secondary atomisation).

Nonetheless, when successfully accomplished, the only scale-up action (during product development) will be the increase of the number of nozzles used, proportionally to the scale of the unit (see Figure 5).

Regardless of the many advantages of a multi-nozzle apparatus, its use – by itself – does not guarantee successful particle size control during scale-up. The reason is the typical loss of recovery efficiency when moving to larger cyclones. As smaller particles tend to escape to a greater extent (when compared with larger particles), if significant losses are experienced this will impact on the particle size distribution (PSD) of the recovered product. One successful way of overcoming this serious hurdle is tailoring the cyclone to the product's characteristics (Figure 6).

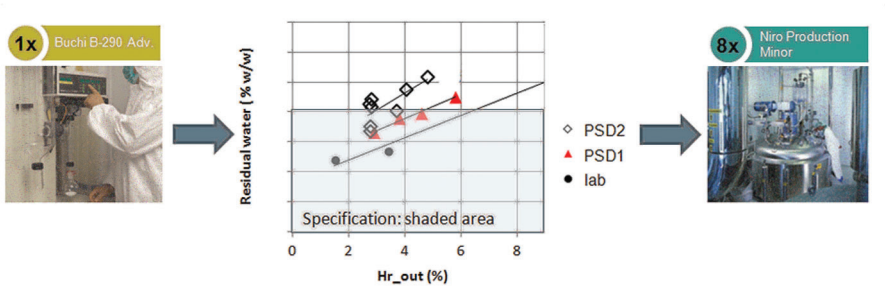


Figure 8: Typical challenges of moisture control during scale-up of spray drying processes: lab scale (black circles); pilot scale (red triangles); and manufacturing scale (open diamonds).

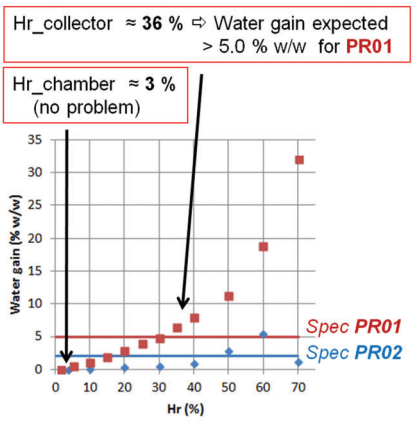
This tailoring process considers the specific attributes of the particles and of the SD process (e.g. particle density and drying gas composition) in order to yield a product-specific design, capable of maximising recovery. The costs involved in tailoring a new cyclone are typically low and quickly recovered, considering the high value of the products and the advantages of a superior control.

Another critical point for SD process development and scale-up is controlling the residual moisture levels to control microbiological and physiochemical stability, considering that aqueous feed solutions are usually employed and that (partially) amorphous materials are obtained. In addition, materials are sticky in a glassy state, so it is important to process them at temperatures and relative humidity (RH) below the glass transition. Hence, in order to obtain material compliant with the target moisture content, while ensuring a good process yield, understanding thermodynamics is key.

The SD scale-up methodology should integrate mechanistic modelling (e.g. heat and mass balances) in order to determine a thermodynamic design space for a given process and scale. Typically the RH inside the SD chamber is critical in determining the moisture content of the product. Additional knowledge, such as dynamic vapour sorption behaviour, is also important to determine product sensitivity to RH. Given the product specification, an operating range is obtained for key process parameters – such as temperature profile (T_in / T_out) and feed flow (F_feed) – that determine the target RH (Figure 7).

Usually, during SD process scale-up, operating parameters are selected so that RH is maintained across scales and hence the resulting product moisture content is kept constant. This can be referred as a conservative scale-up approach, since increased residence time in a larger dryer should favour a reduction in product moisture content. However, for some products, an increase in water content is observed upon scale-up even when pursuing this conservative approach, as shown in Figure 8. These deviations are often due to water uptake at the cyclone discharge, given the typical high hygroscopicity of the material produced by spray drying.

Indeed, the collector at the cyclone discharge is at a lower temperature than the outlet of the SD chamber which, for a constant absolute humidity, results in



	Pros	Cons
Heated vessels	- Predictability - Control	- Lack of scalability - Thermal degradation - Crystalization for amorphous compounds
Nitrogen sweep	- Scalable - Enables lower Hr	- Controlability - Potential back flow of fine material

Figure 9: Challenges with moisture uptake (left) and ways to prevent these (right).

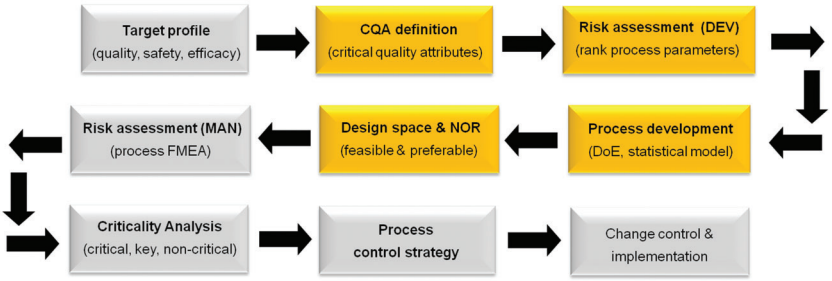


Figure 10: Overview (main steps) of the general QbD approach followed at Hovione.

an increased RH inside the collector (see Figure 9). For preventing water uptake during collection of highly hygroscopic materials, two different engineering strategies can be followed; namely either heating the collectors or introducing a nitrogen stream. The first approach enables more control with a predictable impact on the final properties. However, it is not a scalable approach and cannot be adopted for all molecules. Conversely, a nitrogen sweep, preventing the "wet" drying gas to contact with the collected product, enables lower RH levels and is readily scalable, thus addressing some of the challenges of the former strategy.

Despite the overall challenges in establishing and scaling-up a spray drying process for manufacturing an inhalation drug product, the issues are well-known and can be overcome through an integrated process understanding and implementation of science-based solutions, thus ultimately enabling a development under QbD principles.

SPRAY DRYING DEVELOPMENT UNDER QBD

The QbD approach followed at Hovione is shown in Figure 10, while its application to the spray drying process of an inhalation powder is illustrated in Figure 11.

The critical quality attributes (CQAs) are defined based on the target product profile. These translate the properties of the drug that need to be kept within an appropriate limit or range in order to assure the desired product quality, for example, purity, solid state and particle size. For the sake of simplicity, only particle size is considered in Figure 11.

During the first risk assessment, and for each CQA, an analysis of the potential critical process parameters (pCPPs) and potential critical material attributes (pCMAs) is conducted. The aim is to evaluate, in each process step, which operating parameters / raw materials have the potential to impact a CQA (within the known ranges) and, therefore, should be monitored or controlled. Since the number of parameters is usually high, this risk-assessment (based on prior knowledge of product/process) is used to rank the parameters in terms of perception of criticality. The ultimate goal is to keep the development process as lean as possible, by focusing the studies on those parameters with higher likelihood of being critical (atomisation ratio, feed concentration and drying temperature, in Figure 11).

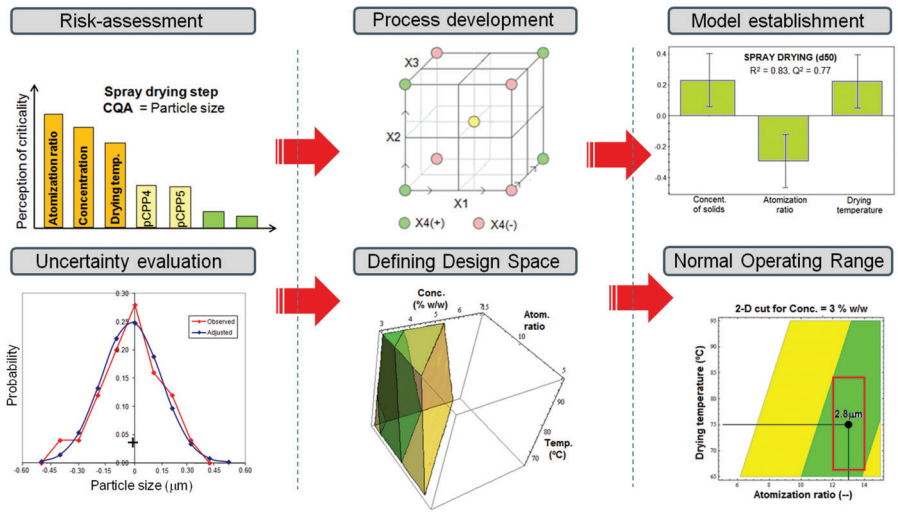


Figure 11: Application (main steps) of the general QbD approach to a spray drying process of an inhalation powder.

The output of the previous risk assessment is a qualitative match between CQAs and pCPPs and pCMAs. To confirm the dependences and quantify the effects, a process development stage is conducted. Often a statistical approach is followed through a sequence of Designs of Experiment (DoE) with different objectives such as screening/optimisation and robustness studies. This development stage constitutes the core of the QbD methodology since most of the process knowledge is generated here and, although not mandatory, a statistical and/or mechanistic model is a usual outcome of this step.

Once the impact of the pCPPs/pCMAs is quantified on the CQAs, a feasible operating space can be defined. This space, also known as design space, will consider the interactions between operating parameters and material attributes and will often be a multi-dimensional space (see Figure 11). Within the design space, the normal operating range (NOR) is established. This is the part of the design space where the process typically operates. When setting both these spaces, the error distributions that are associated to each prediction model should be considered in order to define statistical confidence levels. So, in Figure 11, the yellow shaded regions consider 90% of the error distribution, while green shaded ones correspond to 95%, the latter being more constrained but also more reliable.

The remaining steps of the methodology are not illustrated in Figure 11, but will be briefly described given their importance. After defining the design space and NOR, an exhaustive analysis of the process is conducted at the manufacturing scale. In this study – a Failure Mode Effect Analysis – all manufacturing aspects are reviewed, evaluating the equipment characteristics and the operating procedures against the process knowledge that was gathered to date.

The purpose of this study is to understand and quantify the risk and to define actions to minimise failures. By knowing the feasible operating regions (the design space) and after evaluating the equipment/procedures at the manufacturing scale (directly linked to the practical NORs), a final criticality analysis takes place in order to identify CPPs/CMAs that will require tighter monitoring or control, for example, all those for which the corresponding NORs are close to the boundaries of the design space. Finally, once the criticality around a process parameter and/or raw material attribute is confirmed, appropriate control

strategies will be set in place. The ultimate goal is to assure that operation is taking place within the design space, therefore assuring product quality.

CONCLUSIONS

Although carrier-based formulations still represent the vast majority of the products on the market and under development, approaches based on composite particles are gaining momentum due to a number of important advantages. Spray drying is a key technology for the manufacturing of such particles and, although some challenges can be recognised during scale-up, these can be overcome through an integrated process understanding and implementation of science-based principles, ultimately resulting in highly capable manufacturing processes.

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EVERYTHING FOR INHALATION

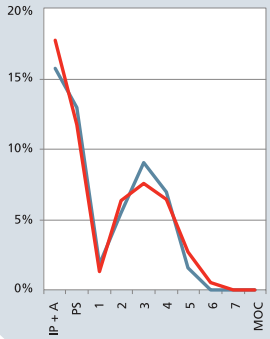
API PARTICLE REDUCTION

- Jet milling
- Wet polishing
- Composite particles
- Nanocoating
- Microencapsulation
- Spray drying

FORMULATION

- Pure API
- Carrier based
  - Lactose based
  - Leucine based
  - Mannitol based
  - Custom excipients

MATCHING INNOVATOR DEPOSITION PROFILES



CAPSULE FILLING

- Phase I clinical trials (Fill gun)
- Phase II clinical trials up to low volume commercial - automated capsule filling (100% net weight unit verification)
- Blistering and packaging

Integrated Development and API Supply

Budesonide, fluticasone, formoterol, mometasone, salmeterol, tiotropium

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