DEVELOPMENT BY DESIGN

An approach to spray drying process development

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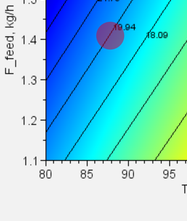
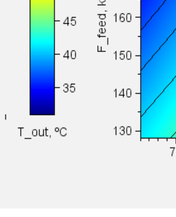
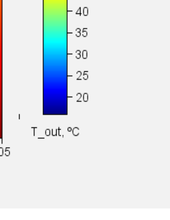
1. Purpose

Spray drying is nowadays a well stablished technology in the pharmaceutical industry. In such a competitive and fast-paced area, the need for robust and lean process development methodologies is critical in order to minimize the consumption of resources, namely time and materials. Moreover the product quantities required in the early stages of the development are usually small but may quickly increase by several orders of magnitude as the drug candidate advances through the clinical phases and reaches the market. CMC development is therefore increasingly on the critical path of drug development, especially for drug candidates with compressed clinical development timelines.

The current work describes a systematic methodology for the development of spray drying processes with minimal expenditure of drug substance. Laboratory tests are used to build scale-independent correlations that are used to support the scale-up to larger units, while the costly experiments such as process intensification and process design space definition are deferred to latter stages of the process development. Concurrently, modelling tools are used to estimate the spray drying conditions required to target specific powder properties.

2. Methodology

- Systematic methodology for scale-up based on scale independent correlations
- Main goal is to reduce the experimental burden of multiple scale-up stages by focusing the resources when really needed – later in the development process

LAB (grams)	CLINICAL SUPPLIES (several kg)		TO COMMERCIAL (hundreds of kg)
Familiarization	**Clinical Supply**	**Intensification**	**Design Space**
Build scale-independent correlations	Scale-up supported by lab-work and simulation tools	Maintain / tune product properties and optimize process throughput and cycle time	Experimental work in commercial scale to define the design space and evaluate process robustness
	*Scale-up under GMP* →  → *Scale-up under GMP*		
Lab trials	Clinical supply (and registration) batches		Research trials, clinical supply and commercial batches

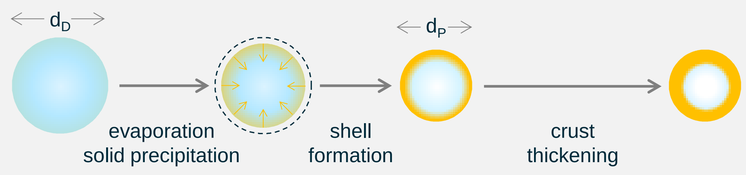
3. Process Development Toolbox

1 - Thermodynamic Modelling

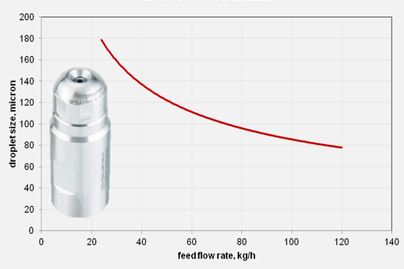
- Mass and energy balance and L-V equilibrium equations
- Accurate knowledge of the thermodynamic space and spray drying conditions estimation
- Anticipation of spray drying conditions impact on ASD stability: *e.g.* RS_out vs SDD T_g

2 - Atomization Modelling

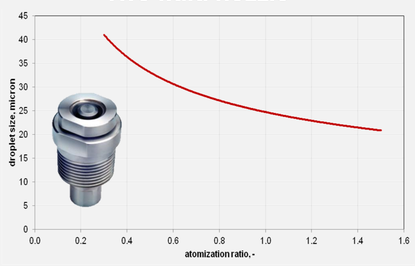
- Droplet size is the main factor affecting particle size and it can be tuned for attaining a specific particle size
- Droplet size = *f* (nozzle, feed pressure / atomization ratio, solution properties)

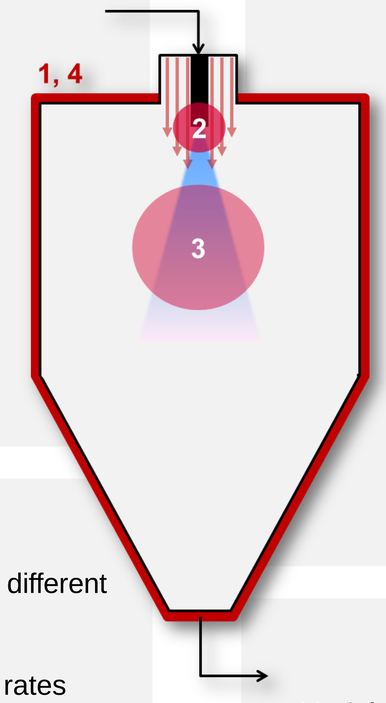


Pressure nozzle



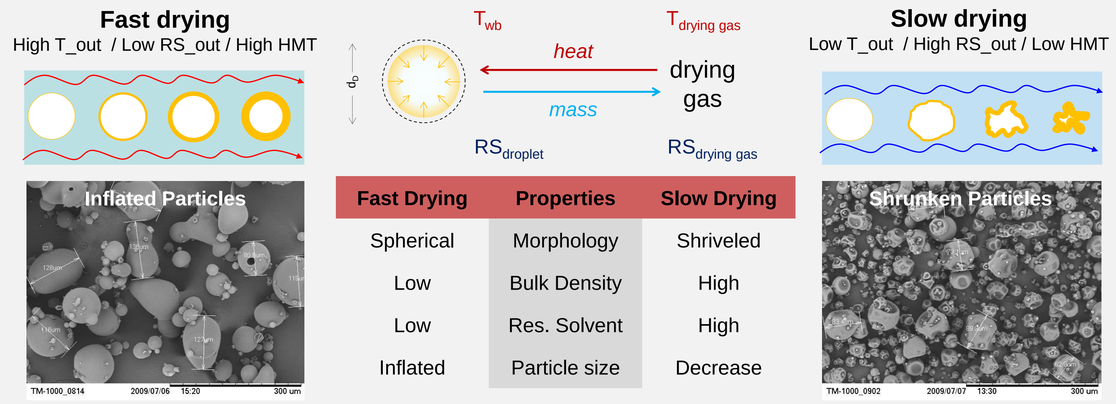
Two fluid nozzle





3 - Drying Kinetics

- Droplet and particle size are intrinsically connected, however particles can follow different formation pathways depending on the drying kinetics and product properties
- Drying kinetics can be controlled by the temperature, relative saturation and flow rates



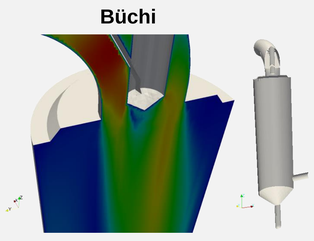
Fast Drying	Properties	Slow Drying
Spherical	Morphology	Shriveled
Low	Bulk Density	High
Low	Res. Solvent	High
Inflated	Particle size	Decrease

4 - CFD Modelling

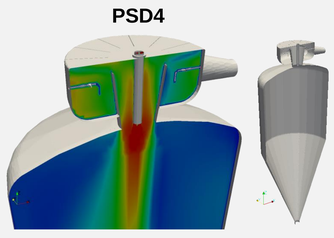
- Models developed for all spray dryers scales provide detailed flow and temperature profiles
- Used to support scale-up and for troubleshooting

Velocity and Temperature Profile (1)

Büchi



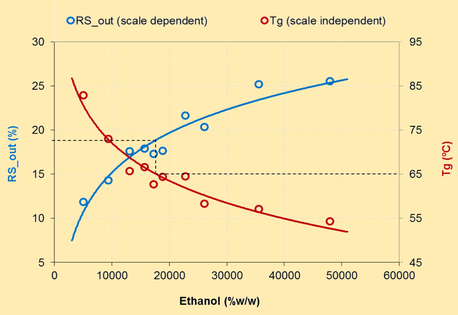
PSD4



4. Illustrative Case-Study

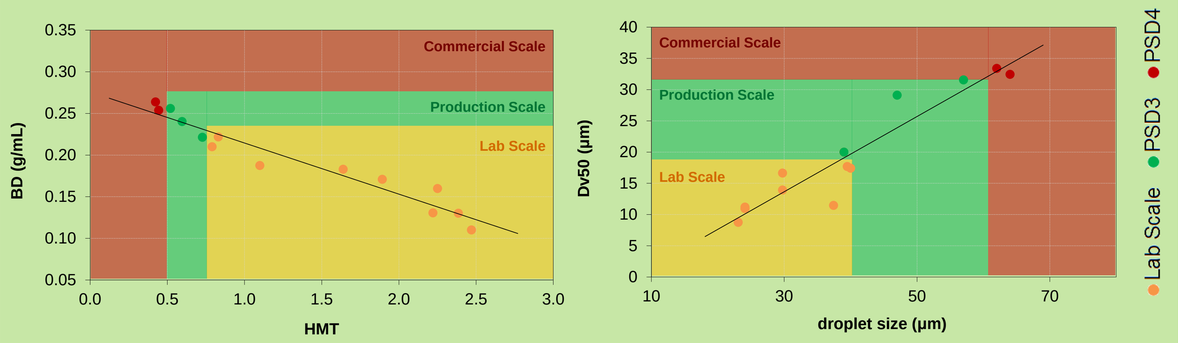
Laboratory Scale

- A stable process is set at lab scale and research trials are performed in order to correlate powder properties with scale independent parameters:
  - Plasticization and drying curves
  - Droplet size *vs* particle size
  - Heat to mass transfer ration (HMT) *vs* bulk density (BD)



Scaling-Up the Process

- Larger units have larger drying chambers and therefore the residence time of the powder is longer.
- The scale-up is based on the scale-independent correlations determined at the lab



Commercial Scale

- **Process Intensification:** The main target is to maintain powder properties (by maintaining droplet size and relative saturation) while increasing process throughput by increasing feed rate and / or feed solution concentration

Nozzle	A	B	C
P_feed (bar)	32	49	68
d_D (mm)	**~70**	**~70**	**~70**
F_feed (kg/h)	25	90	175
RS_out (%)	**19**	**19**	**19**

- **Design Space Definition and Process Robustness**: Research tests are made at the commercial scale (*e.g.* experimental design) to define the design space, NOR and evaluate process robustness

5. Conclusions

An effective knowledge management and a strong scientific understanding of the spray drying process (thermodynamics, atomization, CFD and drying kinetics) make process scale-up across different production scales a straightforward task. A methodology based on such modelling tools and on laboratory data is nowadays used at Hovione to manage process development in a timely and cost effective manner. The advantages are a **leaner process development with minimal resources use**.