Scale-up of fluid bed granulation of an active formulation with a scale independent parameter and a process model

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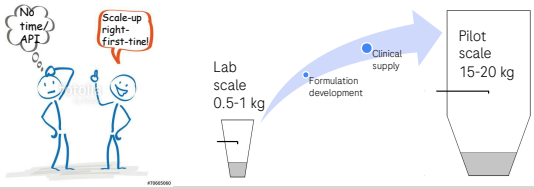
Right-first-time scale-up in accelerated and lean development

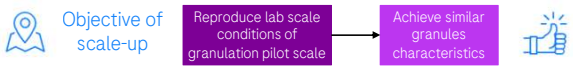
With the current trend of portfolio projects acceleration and the aim to efficient development, often process experience collected with the active formulation at the conclusion of the formulation development phase is little and limited to the laboratory scale [1].

Depending on the clinical needs, it can be required to scale up a process from a laboratory scale (0.5-1 kg batch size) to the pilot scale (15-20 kg).
API for technical experiments aimed at assessing scale-up effects is often not available and therefore scale-up must be done right-first-time.

In this work, an approach based on process engineering and process modelling was applied to scale-up fluid bed granulation for the Phase 2 clinical manufacture of a portfolio project, where limited experience had been collected at laboratory scale during the formulation development.



Fluid bed granulation scale-up



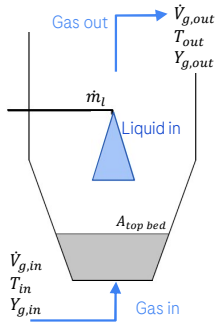
Few key response variables affect more directly the granulation process [2].
Two were used here and kept the same across scales:

- Gas surface velocity to achieve similar bed hydrodynamic behavior

$$\dot{V}_{g,pilot} = \frac{\dot{V}_{g,lab}}{A_{top\ bed,lab}} \cdot A_{top\ bed,pilot} \quad \text{(Eq. 1)}$$

- Evaporation energy to drying capacity ratio to achieve similar product bed moisture

$$\frac{EE}{DC} = \frac{\dot{m}_l \cdot \Delta H_{vap}}{c_{p,g} \rho_g \dot{V}_g (T_{in} - T_{WB})} \cdot 100 \quad \text{(Eq. 2)}$$

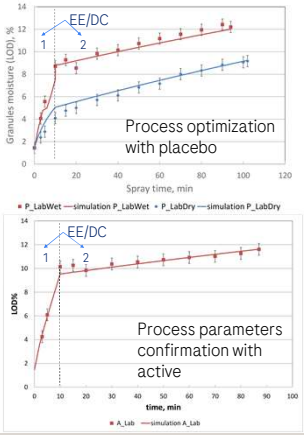


Method

Step	Scale x n. of experiments	Placebo or active formulation	Objective of experiments
Process optimization	Laboratory 1 kg x 3	Placebo	Identify suitable process parameters in view of scale-up.
Process parameters confirmation	Laboratory 1 kg x 1	Active	Confirm process parameters.
Scale-up confirmation	Pilot 15 kg x 2	Placebo	Experiment 1: test scale-up and identify scale differences. Experiment 2: test adjusted process parameters.
Clinical manufacture	Pilot 15 kg x 2 (repeats)	Active	Clinical manufacture.

Scale-up approach to pilot scale:
- Air flow rate calculated with Eq. 1.
- Spray rate $\dot{m}_l$ calculated by keeping constant EE/DC ratio (Eq. 2) across scales.
- A process model (gFormulate, Siemens PSE, London, UK) was used to predict when to switch spraying phase (objective: granules moisture between 10 and 12%).

Results of experiments at laboratory scale



Process optimization experiments were planned by targeting wet and dry conditions by choosing a high and a low EE/DC for the initial granulation phase.

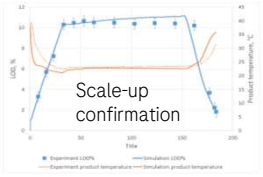
In the second granulation phase an EE/DC close to 100 was chosen and no granules moisture increase was expected: indeed granule moisture increases more slowly.

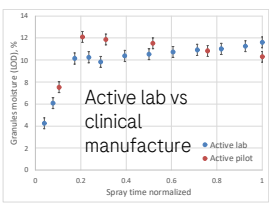
Similar granules moisture was achieved with the active formulation.

Experiment	EE/DC (1)	EE/DC (2)
PLabDry	116	97
PLabWet	174	98
ALab	174	97

A process model was used to simulate granules moisture. The Lyngberg [3] drying model was used at this scale.

Results of scale-up and experiments at pilot scale





At pilot scale the granule moisture tends to decrease with the EE/DC ratio equal to 100% (scale difference).
The process model was improved to better describe the pilot scale process, and the drying model Burgschweiger and Tsotsas [4] with an additional evaporation term was used.

The second placebo trial at pilot scale succeeded in maintaining the desired granules moisture as in laboratory experiments.

These experimental conditions were then applied to perform right-first-time the manufacture of two active batches at pilot scale. Similar granule moisture profiles were achieved at the two scales.

Conclusions

Process engineering and modeling were applied to scale-up right first time the fluid bed granulation process of an active formulation in view of a Phase 2 clinical supply.

- The EE/DC ratio allowed to qualitatively estimate the rate of increase of the granules moisture, and it was used to guide experimentation at laboratory scale.
- The EE/DC, together with the gas surface velocity, were used to predict process parameters at pilot scale.
- This scale-up approach was complemented by the use of a process model to predict the process dynamic behavior and to account for scale differences.

References

1. Gavi and Dischinger, Scale-up of Fluid Bed Granulation Using a Scale-Independent Parameter and a Process Model, AAPS PharmSciTech 22 (4), p. 148.
2. Pharmaceutical process scale up. Levin, M. (2002). Marcel Dekker Inc., New York.
3. Process Simulation and Data Modeling in Solid Oral Drug Development and Manufacture, edited by Marianthi G. Ierapetritou and Rohit Ramachandran (2016). Humana Press, Springer Science+Business Media LLC New York.
4. Burgschweiger , J., Tsotsas, E. (2002). Experimental investigation and modelling of continuous fluidized bed drying under steady-state and dynamic conditions. Chemical Engineering Science, 57: p. 5021-5038.