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# DPI carrier-based formulation scale-up: a statistical analysis approach

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## PURPOSE

A dry powder carrier-based formulation including a coarse and a fine lactose is under development for the administration of a model active pharmaceutical ingredient (API).

Proof of concept was initially performed at a small scale using a low shear mixer. A scale-up of the blending process was necessary to support clinical trials.

**In development stages of a carrier-based formulation, a structured DoE approach allows the definition of a design space for the formulation parameters in order to balance an appropriate delivery to the lungs with manufacturability.**

## OBJECTIVE

(1) Blending process scale-up and optimization, following a structured design of experiments considering the following variables:

- Particle size distribution (PSD) of micronized API
- Blending time
- API concentration
- Percentage of fine lactose

(2) Quantify the impact of input parameters on the outputs emitted dose (ED) and fine particle dose (FPD);

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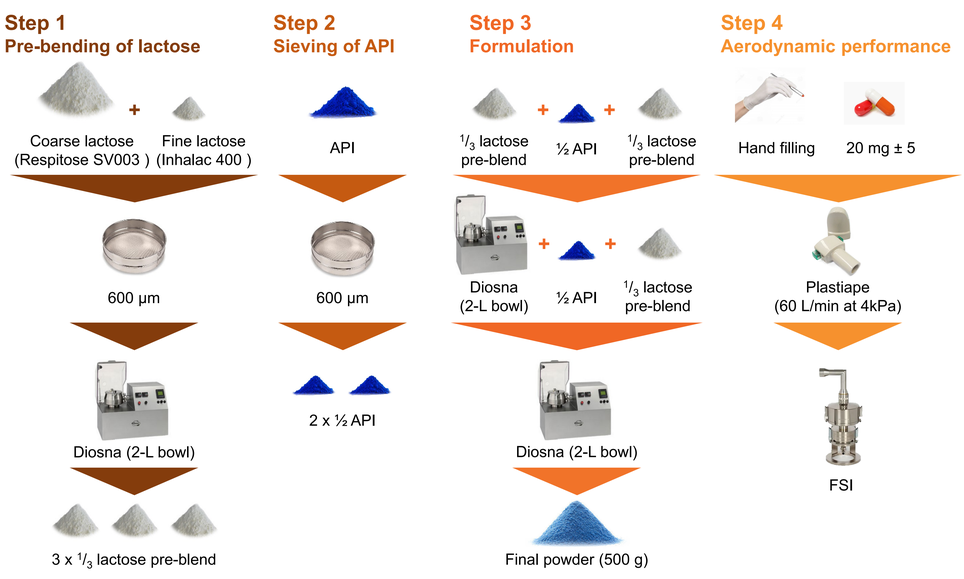
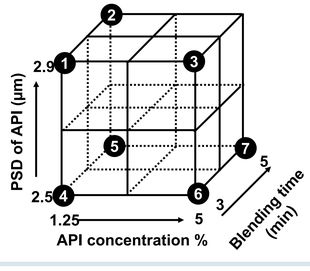
## METHODS

### Experimental procedure




### DoE (% Fine lactose: 2.5%)




### 2 Additional trials

**Table 1 –** Blend composition and mixing conditions for the different experiments.

| Trial # | % fine lactose | API (%) | PSD of API (µm) | Blending time (min) |
|---|---|---|---|---|
| 8 | 5.0 | 0.25 | 2.9 | 3.0 |
| 9 | 10.0 | 0.25 | 2.9 | 3.0 |

### Statistical analysis

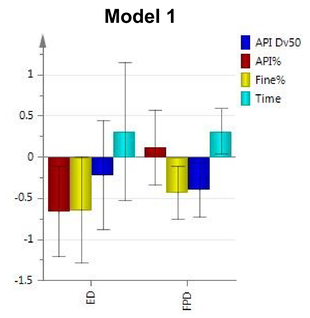
- Software: SIMCA v13.0.3.0 by Umetrics
- Means of partial least squares (PLS)
- Input variables:

| Model 1 | Model 2 | Model 3 |
|---|---|---|
| API Dv50 | API Dv50 | Total fines % |
| API % | Fine lactose % | API Dv50 |
| Fine lactose % | Blending time | Blending time |
| Blending time | | |

## RESULTS

Blend uniformity and aerodynamic performance results demonstrated an efficient blending process;

**Model 1**



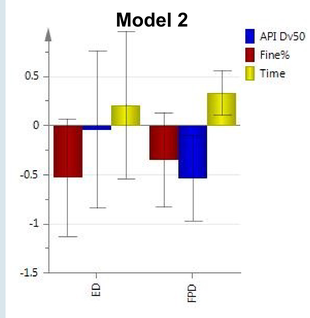

↑ API Dv50
- ED: no impact
- FPD: negative impact

↑ API %
- ED: negative impact
- FPD: no impact

↑ Fine lactose %
- ED & FPD: negative impact

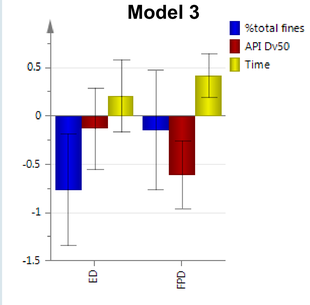
↑ Blending time
- ED & FPD: positive impact

**Model 2**




**The model correlates poorly the experimental data, with lower $R^2$ and $X^2$.**

**Model 3**




↑ Total fines %
- ED: no impact
- FPD: negative impact

↑ API Dv50
ED: negative impact
FPD: no impact

↑ Blending time
- ED: no impact
- FPD: positive impact

**Table 2 –** Statistical results of the partial least squares regressions applied to the experimental data.

| Model # | 1 | 2 | 3 |
|---|---|---|---|
| $R^2$ | 0.80 | 0.65 | 0.78 |
| $X^2$ | 0.39 | 0.39 | 0.61 |
| $r^2$ of ED | 0.73 | 0.42 | 0.77 |
| $r^2$ of FPD | 0.86 | 0.87 | 0.78 |

## CONCLUSIONS

Extensive multivariate statistical analysis demonstrated that blending time is favorable to the FPF. A lower Dv50 of the API also leads to of total fines has a detrimental effect on the ED but it does not affect the FPF. This study shows the need to carefully analyze the obtained statistical models to be able to obtain physically meaningful results. higher FPF. Additionally, percentage of total fines has a detrimental effect on the ED but it does not affect the FPF. **This study shows the need to carefully analyze the obtained statistical models to be able to obtain physically meaningful results.**