From Laboratory to Commercial Scale: Impact of a Dosator-based Capsule Filling Process on a Dry Powder Inhaler Aerodynamic Performance

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Introduction

- The development of a dry powder for inhaler (DPI): complex process integrating **multiple fields of knowledge**.
- The physicochemical properties of the active pharmaceutical ingredient (API), the formulation compositions, the blending and capsule filling process, the device and the environmental conditions can impact the success of a carrier-based DPI.
- When moving from a laboratory to a commercial scale there are several challenges in the different steps of the process:
  - **Blending mechanism** (convection, dispersion and shear) [1];
  - **Capsule filling process** via a dosator filling technology;

The **main goal** of this work was to perform a scale-up of the blending and capsule filling process of a DPI carried-based formulation from a **laboratory to a commercial scale** and to assess the impact on **powder aerodynamic performance**.

Materials & Methods

Blending process

Table 1 – Blending process parameters.

Blend	A	B
Size	500 g	5 kg
Diosna bowl	2 L	25 L
Main impeller speed	450 rpm	200 rpm

Capsule filling

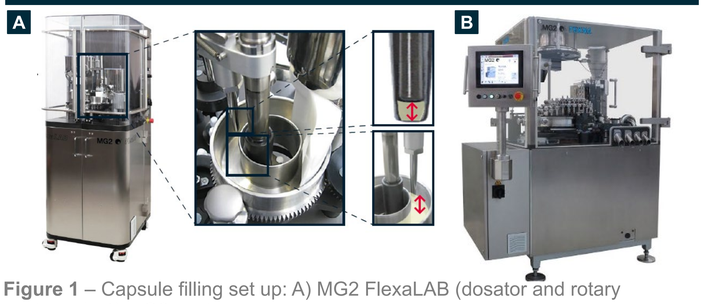


Figure 1 – Capsule filling set up: A) MG2 FlexaLAB (dosator and rotary container); B) MG2 TEKNA.

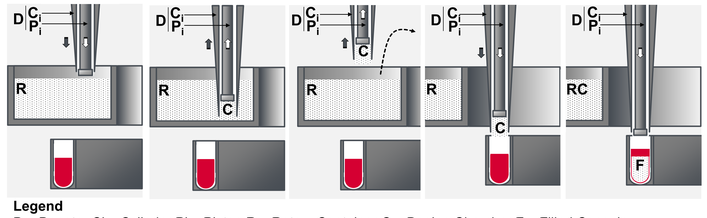


Figure 2 – Schematic representation of a dosator-based filling mechanism.

Analytical characterization

Blend uniformity analysis

5 sampling points (Blend A)

10 sampling points (Blend B)

Rheology by FT4

Basic Flow Energy (BFE)

Specific Energy (SE)

Compressability Index (CPS%)

Aerodynamic Performance

Next Generation Impactor

Plastiape
60 L/min ; Pressure drop of 4 kPa ; N=1

Capsules
HPMC; Size #3; Swedish orange

Results and Discussion

BUA	A	B
Average (% w/w LC)	101.4	101.2
% RDS	3	3
Success factor	% RDS < 5	

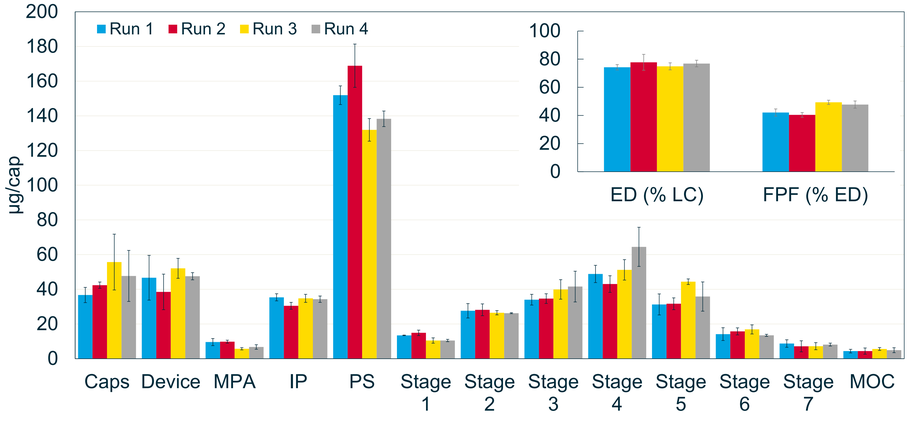
Efficient blending process;
Mixture uniformity independent from blending scale;

FT4	A	B
BFE (mJ)	260	284
SE (mJ/g)	5.8	6.1
CPS (% @ 15 Pa)	11	12

Easy flowing powders[2];
Similar rheological properties;

Table 2 – Capsule filling process parameters.

Run	Technology	Dosator diameter (mm)	Layer depth (mm)	Dosing chamber height (mm)	Chamber / Layer ratio	Speed (caps/h)
1	FlexaLAB	2.8	5.5	4.3	0.9	2000
2	FlexaLAB	2.8	8.0	4.1	0.5	2000
3	TEKNA	2.8	20.0	4.1	0.2	14000
4	TEKNA	2.8	20.0	4.1	0.2	20000



Comparable **ED;**

Slight increase of **FPF** for Run 3 & 4;

The scale-up was successful.

Conclusions

- No impact on the blend properties was observed upon scale-up;
- Overall, a very good aerodynamic performance was maintained when scaling-up the process from a FlexaLAB to a TEKNA unit;

High shear mixing & Dosator-based capsule filler are **reliable and robust technologies** for increasing batch size requirements;

1. WKinnunen H, Hebbink G, Peters H, Shur J, Price R: An Investigation into the Effect of Fine Lactose Particles on the Fluidization Behaviour and Aerosolization Performance of Carrier-Based Dry Powder Inhaler Formulations. *AAPS PharmSciTech* 2014, vol. 15, 4: 898–909.
2. Freeman Tehcnology, W instruction Specific Energy W7031, Issue A (Jan.2008)