

## Influence of material and capsule filling process with Minima® on aerosolization performances by DPIs

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### Summary

Material characteristics and filling process have significant consequences on aerosolization performances of DPIs. Different settings of a bench-capsule filler, Minima®, were compared by means of a design of experiment to identify most significant parameters affecting capsule weight among bed powder height, compression and dosage volume. Four types of lactose were used as coarse fraction in binary mixtures with micronized lactose to simulate low dosage API for inhalation. Mixtures with three dosages of fine lactose, namely 2%, 5% or 10%, were prepared for filling capsules, to study aerosolization behaviour of low-dose DPI products, which are of particular interest for lung administration. Data indicate that Minima® provides consistent results, in terms of weight and repeatability. Compression was identified as the main parameter affecting both final weight and emitted fraction after capsule discharging by DPI RS01. On the other hand, the type of raw material mainly influences the fine particle fraction, with Lacto-Sphere® MM50 showing the best performances, with the 2% of fine lactose.

### Key Message

The effect of capsule filling parameters on emitted dose and fine particle fraction by a DPI was investigated using a table-top device for capsule filling. Compression was the parameter that affected weight and emitted fraction the most, while the type of coarse lactose seems to influence the fine particle fraction.

### Introduction

The delivery of drugs to the lungs by dry powder inhalers (DPIs) is strongly influenced by the characteristics of formulation and process parameters involved in capsule filling [1]. Powder formulations for inhalation products commonly consist of a binary adhesive mixture between a coarse carrier, typically lactose, and the active principle, to provide appropriate aerosolization performance even in the case of very low dosage drugs [2]. Material attributes and filling process parameters may have a critical effect on dosage uniformity and aerosolization performances of powders. In this work we aimed at analysing, on the material side, the contribution of different types of lactose, and, on process side, the effect of instrumental settings on dose uniformity and aerosolization performances of powder mixtures dosed in hard capsules through a bench-capsule filler, Minima®.

### Experimental methods

The first part of this study was devoted to the evaluation of the effects of encapsulation parameters on final capsule weight. Capsules were filled by means of a Minima® table-top volumetric capsule filler (IMA S.p.A., - IMA Active Division, Italy), equipped with a dosator having a diameter of 2.5 mm. The effects of encapsulation parameters on capsule filling were evaluated by means of a full factorial design of experiment 2<sup>3</sup> by considering as factors 1) bed powder height, 2) compression, expressed as chamber height from bottom of the sampling cup, and 3) dosage, expressed as mm with respect to internal length of dosing chamber. Two levels for each factor were explored and coded as reported in Table 1.

Table 1: Coding of levels for variables selected for the 2<sup>3</sup> DoE

| Input parameter        | -1  | +1 |
|------------------------|-----|----|
| Bed powder height (mm) | 15  | 30 |
| Compression (mm)       | 0.4 | 4  |
| Dosage (mm)            | 6   | 10 |

Experiments were performed in random order, including replicates and centre points for model validation. These tests were performed with Pharmatose® 125M (DFE Pharma GmbH, Germany). For each setting, six Coni-Snap® hard gelatin capsules size 3 (Capsugel®, Lonza) were filled with the lactose powder. Average weight of the capsules and relative standard deviation (RSD%) were selected as critical quality attributes (CQAs) to be considered as outputs of the design. Data analysis and model computation were performed with the software Chemometric Agile Tool (CAT).

Then, four types of  $\alpha$ -lactose monohydrate were selected as coarse carriers, namely a fractionate (90-125  $\mu\text{m}$ ) lactose (Chiesi Farmaceutici), Lactohale® 206, Respitose® ML001 (both from DFE Pharma GmbH, Germany) and Lacto-Sphere® MM50 (Micro-Sphere SA, Switzerland). All types of lactose were sieved through a 38  $\mu\text{m}$  sieve for one hour, two times consecutively. Only the fraction retained above this size was used for following experiments: particle size distribution analysis was performed by laser diffraction (Spraytec, Malvern, UK), to check the efficacy of sieving process as well as to estimate the residual percentage of powder with a diameter below 3  $\mu\text{m}$ . These four lactose types were used as coarse fraction for the preparation of binary mixtures in association with micronized lactose (Lacto-Sphere® MM3, Micro-Sphere SA, Switzerland,  $Dv_{50} = 3\mu\text{m}$ ), which was selected to mimic the behaviour of a micronized API [3]. Lacto-Sphere® MM3 was added at a final percentage of 2%, 5% or 10% w/w, respectively. All mixtures were prepared by putting the fine lactose between two layers of coarse lactose in a “sandwich” mode, then samples were blended in a Turbula mixer for 40 minutes.

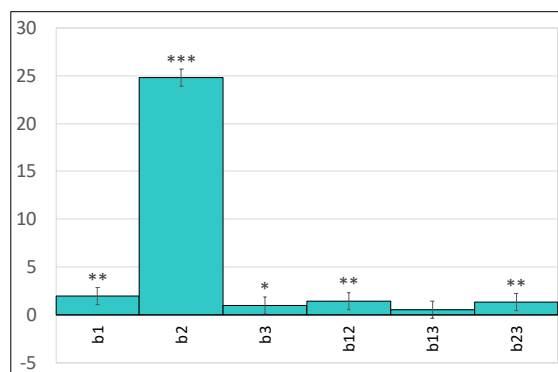
The effect on aerosolization performances was assessed by Fast Screening Impactor (FSI) selecting as outputs emitted fraction and fine particle fraction, while the emitted dose was also determined with a dose unit sampling apparatus (DUSA). Aerosolization was performed using a medium resistance inhaler, RS01® (Plastiap S.p.a., Italy,  $R = 0,033 \text{ kPa}^{1/2} \text{ min L}^{-1}$ ) for 4 seconds at a flow of 60 L/min (Copley scientific, UK, pressure drop of 4 kPa, air volume of 4 L). The emitted dose was determined as a difference between the weight of device + capsule before and after actuation, while fine particle dose was determined by weighing the amount of powder collected on the filter. Emitted fraction % and fine particle fraction % were calculated from emitted dose and fine particle dose, respectively, as a percentage with respect to loaded dose and emitted dose. Data were compared by two-tailed unpaired t-test performed with Microsoft Excel.

## Results

The weight of capsules obtained from each setting was measured and the average of six replicates used to calculate a linear regression model, as reported in equation 1, where  $X_1$  = bed powder height,  $X_2$  = compression  $X_3$  = dosage. The model was validated at central point.

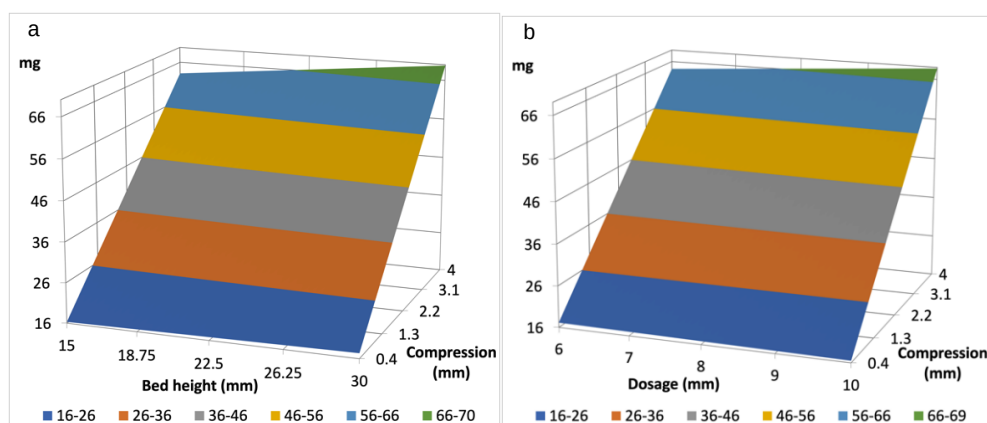
$$\text{Average weight} = 41.61 + 1.94 X_1 + 24.79 X_2 + 0.99 X_3 + 1.45 X_1 X_2 + 0.48 X_1 X_3 + 1.32 X_2 X_3 \quad (1)$$

Coefficients associated to linear terms were highly statistically significant, confirming, as could be expected, that all factors have a critical role on the final weight (Figure 1).



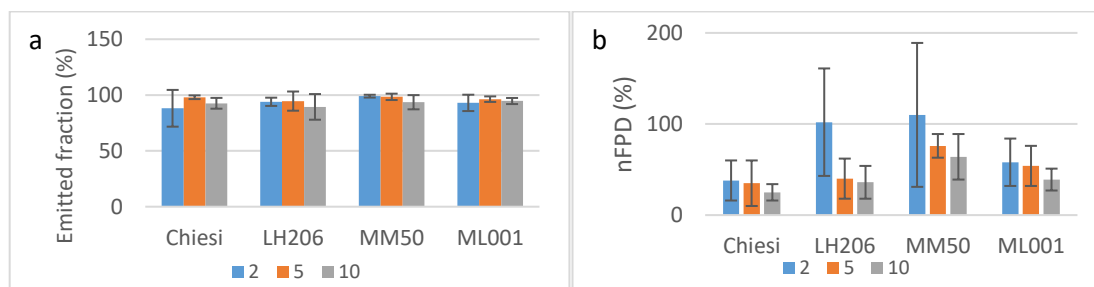
**Figure 1 - Significance of coefficients for the regression model related to average weight of capsules**

As it can be deduced also by coefficient digits, compression is by far the most relevant factor affecting final weight, as also confirmed by significance of interaction terms involving this parameter. This is also evidenced by response surfaces related to interaction between compression and bed powder height (Figure 2a) or between compression and dosage (Figure 2b).



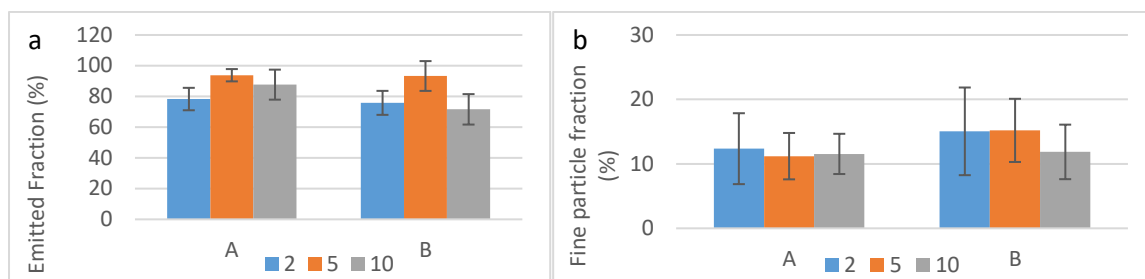
**Figure 2 – Response surfaces related to effect of interaction between compression and bed height (a) or dosage (b) on average weight**

When considering relative standard deviation, this was always below 5% and none of the parameters affected it significantly. This suggested that the filling with Minima<sup>®</sup> provided consistent results independently on settings and that the regression model could be used to predict the average weight of capsules. A further step of the work was focused on the evaluation of the role of material properties on aerosolization performances. Four raw materials were selected and sieved. Particle size analysis by laser diffraction confirmed the effectiveness of sieving in eliminating the fine particle fraction. Respiritose<sup>®</sup> ML001 had the lowest  $Dv_{50}$  (51.97  $\mu\text{m}$ , span 1.73), while the fractionated lactose (115.55  $\mu\text{m}$ , span 1.71), Lactohale<sup>®</sup> 206 (105.12  $\mu\text{m}$ , span 1.12) and Lacto-Sphere<sup>®</sup> MM50 (95.01  $\mu\text{m}$ , span 1.33) had similar  $Dv_{50}$ , close to 100  $\mu\text{m}$ . Fractionated lactose had a wider size distribution, as evidenced by the higher span value. This analysis also allowed the estimation of the amount of residual fraction having diameters below 3  $\mu\text{m}$ : for Respiritose<sup>®</sup> ML001, 7.73%, for fractionated lactose 3.89%, for Lactohale<sup>®</sup> 206 1.92% and for Lacto-Sphere<sup>®</sup> MM50 1.37%. These values were added to the nominal amount of fines in the mixtures and used to normalize the fine particle dose, indicated as nFPD(%). Evaluation of aerosolization performance by FSI allowed the comparison of the effects of different coarse raw materials on emitted fraction and fine particle fraction ( $n=10$ ). No significant differences could be found within different types of lactose as well as within different dosages of fine particles in terms of emitted fraction (Figure 3a). As for nFPD(%), a high variability was observed for all mixtures, independently from the type of lactose or amount of fine fraction (Figure 3b). A common trend was observed for all types of lactose with the value of normalized fine particle dose recovered on the filter decreasing with the increase of the percentage of fine component.



**Figure 3 – Emitted fraction (a) and normalized FPD (%) (b) obtained by FSI analysis of capsules prepared with Minima<sup>®</sup> starting from four different lactose carriers and at three dosage levels, 2, 5 or 10% w/w**

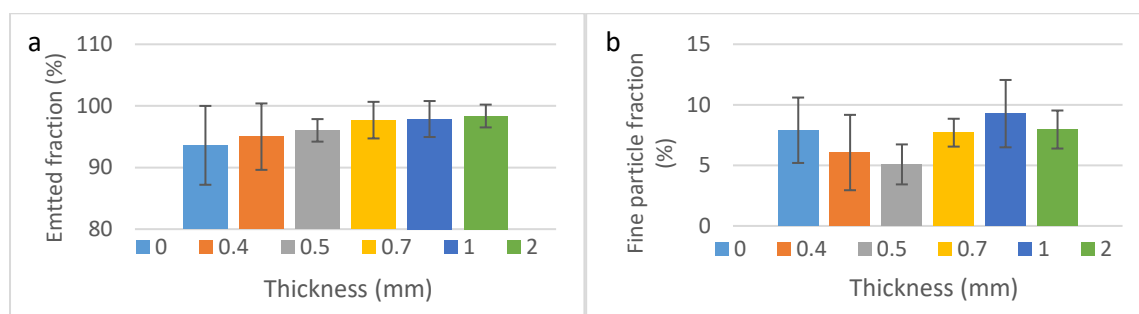
Fractionated lactose was the worst performing in terms of nFPD (%). On the other hand, Lacto-Sphere<sup>®</sup> MM50 was the best performing at all concentration levels and was for this reason selected for the following experiments. The three mixtures were used to fill two Coni-Snap<sup>®</sup> hard gelatin capsules size 3 with Minima<sup>®</sup>: two settings were compared. For setting A, dosage was 20 mm and compression was set at 3 mm; for setting B, dosage was 5 mm and no compression was applied. For each setting, 15 capsules were filled, with a target weight of 15 mg. Taking into consideration the emitted fraction, no significant differences could be detected between filling setting A and B for mixtures containing 2% or 5% of fine fraction, while a significantly lower amount of powder was emitted for the mixture with 10% fines filled with method B ( $p = 0.001$ ) (Figure 4a).



**Figure 4 – Emitted fraction (a) and fine particle fraction (%) (b) obtained by FSI analysis of capsules prepared with Minima® with filling method A or B**

As for FPF% (Figure 4b), no significant differences could be observed among all types of mixtures, independently from the filling method, which could be ascribable to a high variability in results. Nevertheless, filling method A seems to provide more consistent results within different types of mixtures, both in terms of FPF% and variability.

A further parameter that was investigated with Minima® was the cup height that was varied by inserting thicknesses of 0.4 mm, 0.5 mm, 0.7 mm, 1 mm or 2 mm below the cap. Dosage was set at 20 mm and compression at 3 mm, as in method A described above. Five capsules were filled with the binary mixture of Lacto-Sphere® MM50 with 10 % of Lacto-Sphere® MM3 at all thicknesses and the relevant aerosolization performance was tested. An increasing trend in emitted fraction was observed with increasing thicknesses (Figure 5a), while no specific pattern could be observed with respect to fine particle fraction (Figure 5b).



**Figure 5 - Emitted fraction (a) and fine particle fraction (%) (b) obtained by FSI analysis of capsules prepared with Minima® with different cup height**

## Discussion and conclusions

The obtained results suggest the reliability of the used table-top device for capsule filling in terms of accuracy and repeatability, even at very low dosing, comparable to those reported in literature for other type of equipment [4]. Compression was identified as the main parameter affecting both final weight and emitted fraction after capsule discharging with RS01. On the other hand, the type of raw material affects the fine particle fraction, with Lacto-Sphere® MM50 showing better performances with the 2% of micronized powders, that is particularly interesting as surrogate low-dose API formulation.

## References

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