Applying QbD principles in early DPI development: designing for robustness through Design Space exploration

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Summary

A major benefit of performing Design Space exploration as early as possible during Dry Powder Inhaler (DPI) development is the identification of optimal design parameters as well as the quantification of the robustness of such optimal design points. Design Space exploration is a cornerstone of Quality by Design (QbD) based approaches to pharmaceutical product development and its application to inhalation device development has been proposed.

Within the context of the development of an enhanced version of the currently marketed TwinCaps® DPI with an enlarged powder cavity targeting effective high dosage drug delivery to the lungs, the current work reports an exploration of the Design Space considering the interactions of device, particle engineering and formulation design variables on key inhalation drug product performance attributes, such as Emitted Mass (EM) and Fine Particle Fraction ($FPF_{5\mu m/EM}$). For that purpose, an experimental characterization of the Design Space defined by the i) device powder cavity outlet blockage σ, defined as the ratio between obstruction and total channel area (design parameter), ii) model drug particle size and iii) formulation fill weight, was performed using rapid prototyping technologies together with fast screening analytical methods.

Results from the current Design Space exploration revealed that the selection of a device powder outlet blockage between 0.7 and 0.85 delivers a robust EM and $FPF_{5\mu m/EM}$ performance across the interval of particle size and formulation fill weight values evaluated.

Introduction

Quality by design (QbD) approaches to pharmaceutical product development [1] aim to demonstrate safety and efficacy of a drug product through characterization of its Design Space. Previous work [2] has proposed the extension of the QbD approach to drug delivery devices through a systematic characterization of the effects of multidimensional interactions of device and formulation design input variables on the overall critical quality attributes (CQAs) of the drug product. The characterization of such multidimensional Design Space ultimately aims to provide a scientific understanding about the impact of design inputs on the drug product's CQAs and drive the establishment of device specifications which ensure confidence of an overall robustness.

Moreover, Design Space exploration during the early stages of DPI development is becoming increasingly feasible due to the quality of prototypes produced using 3D printing technologies [3] and the reduction in analytical lead times achieved through the use of fast screening techniques [4], which in conjunction allow the experimental characterization of an increasing number of alterative device designs during early development phases in a cost effective manner.

Within this context, previous work [5] reported the development of an enhanced version of the currently marketed TwinCaps® DPI, a single use disposable inhaler for acute treatments, which comprised an enlarged powder cavity and targeted effective high dose drug delivery to the lungs, here designated as TwinMax™. Previous work [5] considered the selection of device design parameters for optimal particle aerosolisation considering flow rate effects. It showed that the blockage, σ, created by a sudden geometric obstruction in the air flow path at the exit of the powder cavity – defined as ratio of the obstruction's area, $A_{obstruction}$, to the total channel cross sectional area, $A_{channel}$ – was a key device design variable influencing shear forces and particle deagglomeration through the obstruction which ultimately affected the emitted mass (EM), fine particle mass ($FPM_{5\mu m}$) and fine particle fraction ($FPF_{5\mu m/EM}$).

The current work aims to explore and characterize the Design Space considering the interactions of device, particle engineering and formulation variables. The particle size strongly influences the cohesive-adhesive behaviour of the powder in drug alone products and the fill weight influences particle aggregation and the cavity space available for turbulence to take effect. Both thus influence the dispersion and deagglomeration forces required from the device for effective aerosolisation. Design space exploration was then carried out with the goal of investigating the robustness of device design parameter selection in the presence of variations in particle size and formulation fill weight.

Materials and methods

For the purpose of Design Space exploration and associated characterization studies, five TwinMax™ prototypes were produced using a stereolithography (SLA) rapid prototyping process using Accura® Xtreme polymer supplied by 3D Systems Corporation comprising a built-in obstruction at the powder cavity outlet corresponding, respectively, to geometric blockage ratios of σ = {0.5, 0.7, 0.85, 0.95, 0.98} (Table 1). Prototypes were tested with three batches of inhalable amorphous composite particles comprising 80% trehalose and 20% leucine produced by spray drying with a median particle size by volume (Dv50) respectively of 1.03, 1.13 and 1.49 µm (Table 1). These particles were used in the current work as model drug particles considering their challenging cohesion-adhesion behaviour, which is representative of the inhalable powders normally found in high dosage applications. Two fill weights of 20 and 40 mg/cavity were respectively tested with the different prototypes and composite particle batches (Table1). Prototypes were hand filled with the composite powders under controlled temperature and relative humidity.

For each of the experimental conditions defined (Table 1), the emitted mass (EM), fine particle mass ($FPM_{5\mu m}$) and fine particle fraction ($FPF_{5\mu m/EM}$) were determined at 35 L/min using the gravimetric Fast Screening Impactor (FSI) supplied by MSP Corporation. The FSI apparatus was set to draw 4L of air through each inhaler in a single actuation.

Table 1 – Experimental conditions used for the Design Space exploration studies.

Device design parameter σ	Composite particles Dv10 (SD) (µm)*	Composite particles Dv50 (SD) (µm)*	Composite particles Dv90 (SD) (µm)*	Fill weight / cavity (mg)
0.5 0.7 0.8 0.95 0.98	0.43 (0.01) 0.45 (0.01) 0.49 (0.00)	1.03 (0.01) 1.13 (0.01) 1.49 (0.01)	2.27 (0.01) 2.67 (0.02) 3.97 (0.01)	20 40

*** Average of N=3 determinations**

Results and discussion

The impact of i) device powder cavity outlet blockage, ii) median particle size of the composite particles and iii) product fill weight in the device cavity on the i) EM and ii) $FPF_{5\mu m/EM}$ are shown in Figures 1 and 2, respectively. Referring to Figure 1, at both of the fill weights investigated, the EM showed mean values decreasing with increasing blockage for σ = [0.5; 0.95] and a steep mean EM value drop for σ > 0.95. For instance, it was observed a variation from 84% to 72% for σ = [0.5; 0.95] and a mean EM drop to about 26% for σ > 0.95 for the composite particle batch characterized by a Dv50 = 1.13 µm and for a 40 mg/cavity fill weight.

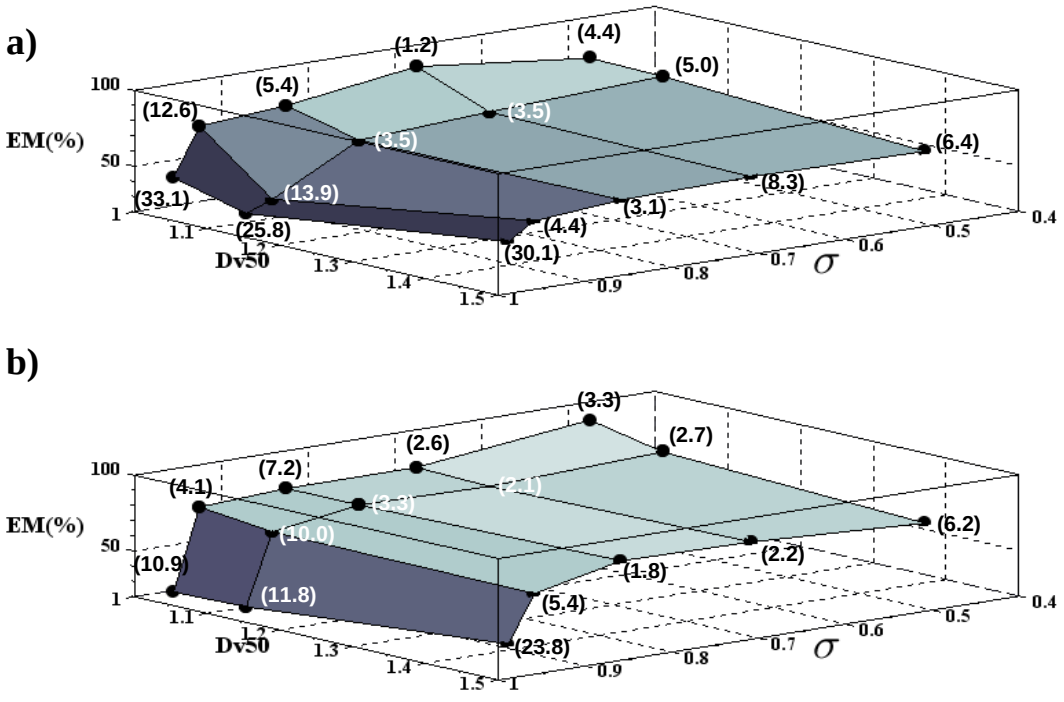

Figure 1. Impact of changes on i) device blockage and ii) size of composite particles in the EM attribute: a) Fill weight of 20 mg/cavity; b) Fill weight of 40 mg/cavity. Data points represented are the mean value of N=3 replicates and values in brackets denote one standard deviation.

Interestingly, it was also observed a trend of increasing mean EM with decreasing Dv50 at both fill weights within the mean particle size (of composite particles) interval investigated. For instance, for σ = 0.5 and 40 mg/ cavity, mean EM values of 94%, 84% and 76% were found for Dv50 values of 1.03, 1.13 and 1.49 µm, respectively (Figure 1 b). Within this Dv50 interval, it may be that lower Dv50 values promote stronger cohesion between particles leading to the formation of agglomerates with larger mean size, which may explain the trend of increasing mean EM with decreasing Dv50, as observed in Figure 1.

Regarding the impact of the studied variables on the $FPF_{5\mu m/EM}$, a weak dependency was found towards the device blockage design parameter σ and composite particles Dv50 at the fill weight of 20 mg/cavity, as shown in Figure 2 a). In fact, a $FPF_{5\mu m/EM}$ of approximately 50% was observed across σ = [0.5; 0.98] and Dv50 = [1.03; 1.49] µm.

However, at the fill weight of 40 mg/ cavity, it was found that $FPF_{5\mu m/EM}$ increased with increasing blockage for σ = [0.5; 0.98] within the Dv50 interval investigated, as shown in Figure 2 b). For instance, a $FPF_{5\mu m/EM}$ variation from about 40% to 75% was observed for σ = [0.5; 0.98] and for the composite particle batch characterized by a Dv50 = 1.13 µm. This trend was noticeably strong for the particle batch with Dv50 = 1.49 µm, where the $FPF_{5\mu m/EM}$ reached approximately 90% at the device blockage parameter of σ = 0.98, as observed in Figure 2 b). These results show that the device blockage design parameter is a driver of particle break-up and deagglomeration performance but its influence is significantly stronger at higher fill weights, with such findings complementing previous work [5].

In addition, exploration of the Trade Space, defined as the space of trade-off, between the EM and $FPF_{5\mu m/EM}$ is shown in Figure 3 for the fill weight of 40 mg/cavity. This analysis allows the identification of the optimal product performance space considering the impact of the variables investigated. At 40 mg/cavity, the Trade Space represented in Figure 3 shows that selection of a device blockage corresponding to approximately σ = 0.95 leads to an optimal compromise between mean EM and mean $FPF_{5\mu m/EM}$, which leads to an optimal value of $FPM_{5\mu m}$. However, an analysis of the robustness of this optimal value reveals that the design space between σ = [0.9; 0.95] is characterized by increasing variability across the Dv50 interval and formulation fill weight investigated. As shown in both Figure 1a) and Figure 1b), this range of device blockage σ is characterized by increasing values of standard deviation associated to the mean EM. Conversely, observation of Figures 1 and 2 reveals that the selection of a device blockage σ = [0.7; 0.85] delivers a robust EM and $FPM_{5\mu m}$ within the interval of particle size and fill weight evaluated.

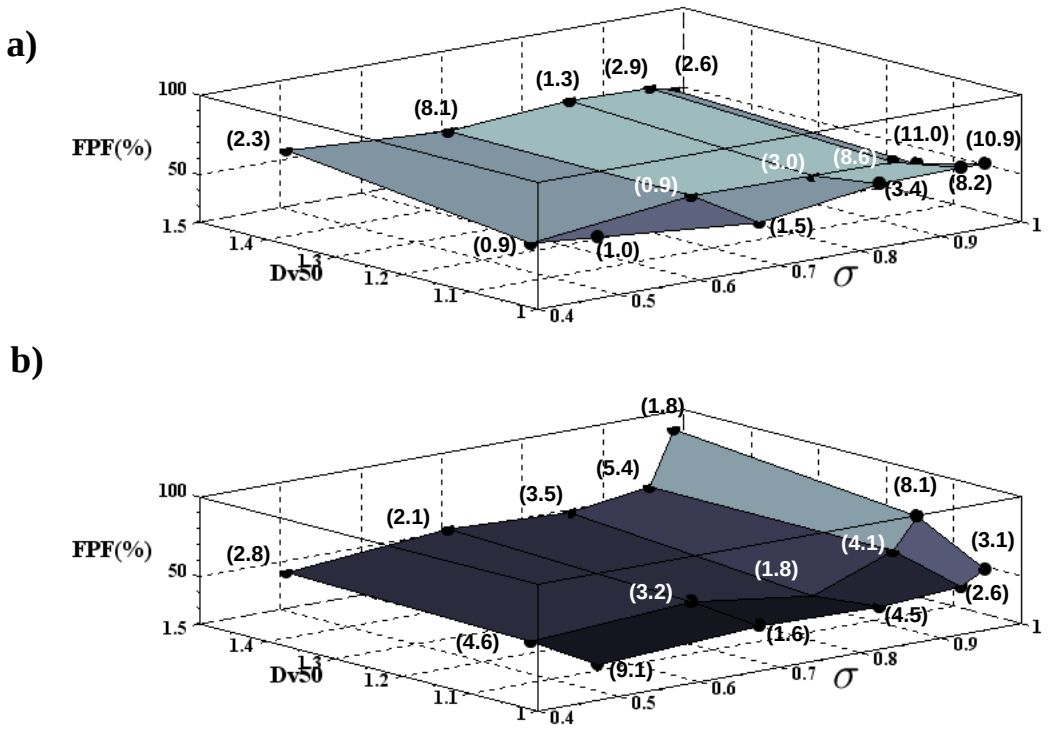

Figure 2. Impact of i) device blockage and ii) size of composite particles in the FPF attribute: a) Fill weight of 20 mg/cavity; b) Fill weight of 40 mg/cavity. Data points represented are the mean value of N=3 replicates and values in brackets denote one standard deviation.

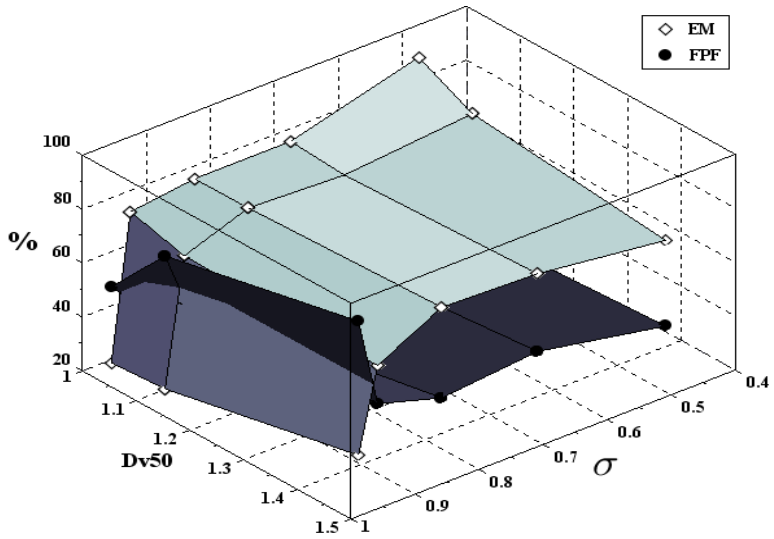

Figure 3. Exploration of the trade-off space between EM and FPF as a function of i) device blockage and ii) size of composite particles at the fill weight of 40 mg/cavity. Data points represented are the mean value of N=3 replicates. Standard deviation values corresponding to each EM and FPF data point are respectively presented in Figures 1b and 2b.

Conclusions

Through the application of QbD principles during early DPI development, the current work explored the Design Space of a novel TwinCaps® DPI targeting high dosage drug delivery to the lungs. In particular, the selection of device blockage was investigated considering the effects of particle size and fill weight. Results demonstrated that a careful selection of the device design parameters is key to deliver both an optimal and robust EM and $FPF_{5\mu m/EM}$ performance.

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