Optimising the Design Space of a Dry Powder Inhaler Platform

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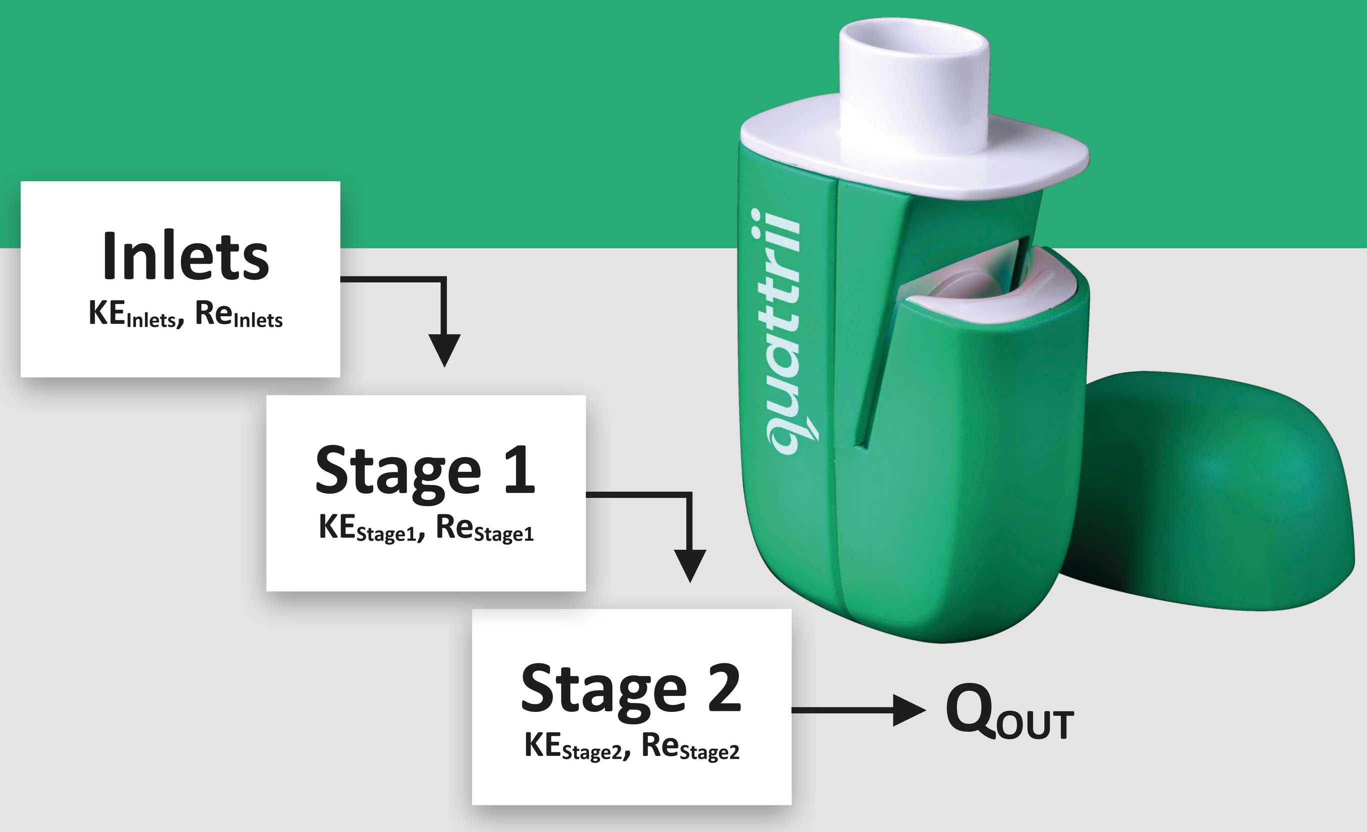

A method to enable precise tuning of a multi-stage Dry Powder Inhaler for diverse formulations, by mapping the design space, revealing key parameters that enhance payload delivery

Figure 1: *A simple schematic (left) and image (right) of the multi-stage Quattrii DPI engine. The total flowrate (Q) and fluid dynamic properties (Re & KE) through each stage can be tuned independently.*

INTRODUCTION

In respiratory medicine there is a growing demand to deliver higher payloads (for example, over 50 mg) to the lung, driven by an increasing number of lower potency molecules for treating conditions beyond asthma and COPD.[1, 2] These higher payloads present significant challenges for the current delivery technology, resulting in variability in the delivered dose, and an undesirably low respirable fraction.[3]

Quattrii™ is a novel, blister-based dry powder inhaler, designed to enable efficient delivery of high powder payloads (e.g. >50 mg) to the lung. The proprietary (patent-pending) deagglomeration engine is comprised of three stages, presented schematically in Figure 1.

STUDY AIMS

We present a methodology to map the design space of the Quattrii DPI. The aims of the study are to:

1. Improve the understanding of the underlying physics of the Quattrii engine by interrogating the design space
2. Provide a method to predict the performance of a particular geometry for a given powder
3. Highlight the optimum region of the design space for a given powder to enhance payload mass and / or delivered lung dose

METHOD

The design space can be mapped in terms of the fluid dynamic properties of the flow through each stage:

1. Kinetic energy flow (KE): energy available for deagglomeration $KE = \frac{1}{2}\rho \dot{Q} v^2$

2. Reynolds number of the flow (Re): level of turbulence $Re = \frac{\rho v D_h}{\mu}$

3. The total flowrate (Q) through the device $\dot{Q}_{Total} = \sqrt{\Delta P}/_{R}$

$\rho = air\ density,\quad \mu = air\ dynamic\ viscosity,\quad v = fluid\ velocity,\quad D_h = hydraulic\ diameter,$
$\dot{Q} = flowrate,\quad \Delta P = pressure\ drop\ across\ device,\quad R = device\ resistance$

For each permutation of the design space, three independent flowrate measurements are taken to determine the resistance of each stage in isolation. The stage fluid dynamic parameters can then be calculated.

Weighted score
The seven parameters (Reynolds number and Kinetic energy flow for each stage and total flowrate) are normalised and combined into a single weighted average to produce a weighted score. Each of the normalised parameters is multiplied by a weighting. The seven weightings can be individually adjusted to indicate the relative importance of the parameter on the DPI performance, where a weighting with large magnitude indicates that the parameter has a strong influence on the device performance. A heat map showing the unweighted scores across the design space under test is presented in Figure 2 (all weightings set to unity).

Aerodynamic Particle Size Distribution Data (APSD)
To explore how the payload delivery performance varies across the design space, Aerodynamic Particle Size Distribution (APSD) measurements were taken for eight geometries. The geometries tested are indicated in bold in Figure 2. Gravimetric APSD measurements were taken using a Next Generation Impactor (NGI). Measurements were made with Owlstone Medical's proprietary spray-dried formulation, with a geometric particle size (D_{50}) of 2.3 µm.

Adjusting the weightings
A non-linear GRG (Generalised Reduced Gradient) solver algorithm[4] is used to maximise the r-squared value of the linear regression best fit between weighted scores and chosen APSD parameter by varying the seven weightings.

Unweighted Heat Map

Inlet Dimension = 1.00

Stage 2 Dimension \ Stage 1 Dimension	0.49	0.56	0.64	0.68	0.72	0.81	0.90	1.00
0.23	**60.0**	**69.4**	68.9	68.4	69.8	70.9	73.6	**71.9**
0.25	61.0	63.4	63.7	66.8	68.6	69.0	72.1	72.1
0.30	58.6	60.8	63.8	68.8	73.1	72.3	77.0	73.5
0.33	59.8	60.7	65.7	64.7	68.1	69.0	72.1	74.6
0.38	55.8	59.9	60.7	61.4	69.1	69.7	74.7	71.9
0.42	59.9	60.3	60.9	63.3	65.7	66.5	70.2	70.2
0.45	55.7	58.0	58.3	60.0	67.3	66.6	70.3	70.6
0.50	56.4	58.4	59.4	62.1	61.8	63.7	66.0	66.4
0.53	54.5	57.1	56.7	57.8	**65.5**	65.3	67.9	67.4
0.58	54.1	56.8	58.5	61.1	63.6	63.4	64.4	66.2
0.60	52.4	53.9	55.1	56.7	62.5	62.2	64.5	63.8
0.67	52.5	54.6	57.2	57.4	58.8	61.2	61.7	63.3
0.75	51.4	53.3	54.1	54.2	57.1	58.1	58.7	59.6
0.83	49.5	51.8	52.1	53.9	55.3	56.2	56.5	58.7
0.92	50.0	51.4	51.2	51.7	52.3	**53.8**	53.6	55.2
1.00	47.2	49.0	49.5	50.0	50.5	50.9	51.5	52.6

Stage 1 Dimension = 0.81

Stage 2 Dimension \ Inlet Dimension	0.59	0.66	0.73	0.81	0.90	1.00
0.58	54.8	59.1	61.4	61.4	61.6	**64.0**
0.60						
0.67	54.2	54.9	57.3	58.5	60.8	61.0
0.75	50.7	51.8	55.3	56.8	**58.7**	58.6
0.83	50.2	50.7	54.0	55.7	56.2	57.0
0.92	**48.2**	49.5	52.2	52.7	53.8	53.9
1.00	46.8	47.5	48.8	50.6	51.4	51.5

Figure 2: *Heat map showing the unweighted scores across the design space under test (all weightings set to unity). The elements in bold indicate geometries for which APSD data was recorded. In the left matrix the blister inlet dimensions were held constant; in the right matrix the stage 1 dimension was held constant, and these measurements were taken with a smaller blister size. The black outline indicates approximately overlapping design space permutations. All dimensions have been normalised.*

Weighted Heat Map

Inlet Dimension = 1.00

Stage 2 Dimension \ Stage 1 Dimension	0.49	0.56	0.64	0.68	0.72	0.81	0.90	1.00
0.23	**39.2**	**49.1**	47.3	46.2	47.4	48.1	50.7	**48.8**
0.25	41.2	42.8	42.4	45.3	47.0	46.9	50.0	50.0
0.30	44.5	45.9	48.2	52.9	57.2	55.9	60.7	57.2
0.33	45.3	45.5	49.8	48.7	51.7	52.5	55.4	58.0
0.38	44.2	47.1	47.6	48.1	54.9	55.3	60.1	57.6
0.42	50.3	50.2	50.6	52.4	54.4	55.1	58.4	58.7
0.45	47.0	48.4	48.6	49.8	55.6	55.0	58.4	59.0
0.50	50.3	51.4	52.2	54.0	53.9	55.4	57.4	58.2
0.53	50.1	51.5	51.5	52.2	**57.3**	57.4	59.7	59.7
0.58	53.7	55.0	56.0	57.5	59.2	59.3	60.4	62.0
0.60	51.4	52.1	52.9	53.7	57.0	57.2	59.0	59.1
0.67	56.8	57.5	58.6	58.9	59.6	61.1	61.9	61.7
0.75	61.5	61.9	62.4	62.7	63.3	63.8	63.4	63.0
0.83	65.8	65.6	66.1	66.1	65.3	64.4	64.2	62.8
0.92	73.5	73.3	73.9	72.8	71.8	**69.4**	69.7	67.7
1.00	67.0	65.6	64.7	63.8	63.1	62.5	61.7	60.5

Stage 1 Dimension = 0.81

Stage 2 Dimension \ Inlet Dimension	0.59	0.66	0.73	0.81	0.90	1.00
0.58	58.5	59.6	59.4	59.4	58.9	**59.7**
0.60						
0.67	61.7	61.2	61.3	61.1	61.4	61.0
0.75	65.8	65.3	65.1	64.8	**64.5**	63.5
0.83	69.4	69.0	68.3	66.9	65.5	63.8
0.92	**77.5**	76.7	74.4	72.7	70.3	69.3
1.00	70.4	69.9	68.2	64.8	62.8	61.8

Figure 3: *Tuned heat map showing the weighted scores across the design space, adjusted to maximise correlation with MMAD for the powder under test. The elements in bold indicate geometries for which APSD data was recorded. In the left matrix the blister inlet dimensions were held constant; in the right matrix the stage 1 dimension was held constant, and these measurements were taken with a smaller blister size. The black outline indicates approximately overlapping design space permutations. All dimensions have been normalised.*

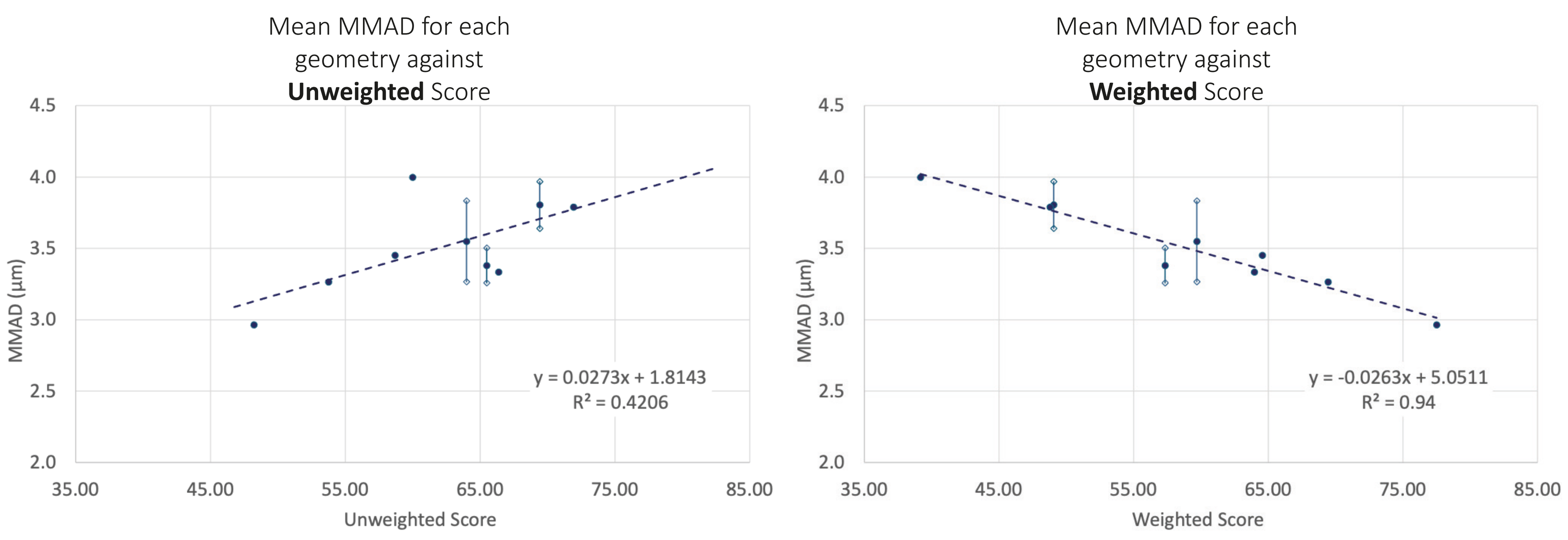

Figure 4: *Mass Median Aerodynamic Diameter (MMAD) from eight geometries, against unweighted (left) and weighted score (right). Where repeat APSD measurements have been recorded for a geometry, the mean is plotted, and the standard deviation is indicated with error bars. A linear regression best fit line is plotted. The unweighted scores have a poor correlation to MMAD, with an r^2 value of less than 0.5. With weighted scores the strength of fit is improved to 0.94.*

DISCUSSION AND CONCLUSIONS

- **The method is demonstrated using Mass Median Aerodynamic Diameter (MMAD), but any APSD performance parameter could be selected**
- **Tuning the weightings of the weighted score increased the strength of fit with MMAD from r^2 <0.5 to 0.94 (Figure 4)**
- **The results demonstrate that the method presented can be used to predict APSD performance data from weighted input parameters**
- **We recommend that this method could be employed for tuning the design of other DPI devices to optimise performance for a particular powder**

References
[1] Claus S, Weiler C, Schiewe J, Friess W, How can we bring high drug doses to the lung?, European journal of pharmaceutics and biopharmaceutics: official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik 86(1) 2013
[2] Hickey A, Why we need to deliver large amounts of powder to the lungs and the concurrent challenges, Drug Delivery to the Lungs, Volume 30, 2019
[3] Sibum I, Hagedoorn P, Boer A H, Frijlink H W, Grasmeijer F: Challenges for pulmonary delivery of high powder doses, International Journal of Pharmaceutics 2018 ;Volume 48, 1: pp 325 – 336.
[4] Microsoft Excel native solver

In collaboration with OWLSTONE MEDICAL

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