



THE ADVANTAGES OF DESIGNING HIGH-RESISTANCE SWIRL CHAMBERS FOR USE IN DRY-POWDER INHALERS

In this article, David Harris, Head of Respiratory Drug Delivery, Team Consulting, taps into a powerful combination of detailed anatomical and functional understanding of the human respiratory system, pulmonary drug delivery technology and formulation expertise, and mathematical modelling techniques, in order to put forward the case for high-resistance swirl chambers in dry-powder inhalers, and a rational strategy for optimising the design and thus maximising therapeutic efficacy.

WHY IS HIGH RESISTANCE GOOD FROM A PATIENT'S PERSPECTIVE?

A question dry-powder inhaler (DPI) device developers always face is: "What airflow resistance should I make the device?" Many studies have been conducted and the results often published, but there still appears to be no commonly agreed answer about what is best. The airflow resistance of the pressurised metered dose inhaler (pMDI) is rather arbitrary, as pMDIs produce a respirable aerosol completely independently of how the user inhales. DPIs, on the other hand, rely solely upon the energy available in the user's inspiratory manoeuvre – some of which is transferred into the bulk powder to transform it into a respirable aerosol.

There are several performance factors that are directly affected by the resistance of a DPI...

1. Pressure Drop

All inhaler users will achieve a higher pressure drop across the device when inhaling through a higher-resistance DPI. This is because users achieve their highest inspiratory flowrate under no load (zero resistance); and their highest inspiratory pressure drop under maximum load (infinite resistance). And there is a reasonably linear response between these two extreme scenarios. Achieving a high pressure drop is key to creating an efficient aerosolisation engine, and to producing a high fine particle fraction (FPF), as it is the inspiratory pressure drop that provides the force necessary to create high-velocity airflows within the inhaler.

2. Consistency

The lungs of children and COPD patients are powered by muscles that are more or less as strong as a healthy adult's. This means that, on average, all three patient groups converge toward a common peak maximal inspiratory mouth pressure, which is the maximum pressure drop they can achieve across an infinite resistance device (i.e. zero flow). However, their maximal inspiratory capacity is significantly less than a healthy adult's; a child's because their lungs are not yet fully grown, and a COPD patient's because some proportion of their lungs no longer function normally. Data shows that as the device resistance decreases, users with higher usable lung capacity can achieve higher inspiratory flowrates, and the pressure flow curves of children and adults (for example) diverge (Figure 1).¹

3. Duration of Inhalation

As users achieve lower flowrates through higher-resistance inhalers, it takes more time to fill their lungs and so the duration of inhalation is increased.

4. Lung Deposition

The air velocities within their oropharynx, upper airways and bronchioles within the lungs will be lower when inhaling through a high-resistance device due to the limited maximum inspiratory flowrate that can be achieved. These lower airflow velocities are less likely to cause inertial impaction of respirable particles, which results in an aerosol of a given particle size distribution penetrating deeper into the lungs, and a greater overall therapeutic effect.²



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THERE IS NO "TYPICAL" DPI RESISTANCE

DPIs that are commonly prescribed today have a large range of resistances, ranging from Plastiapi's low-resistance Cyclohaler® to Boehringer Ingelheim's high-resistance HandiHaler®. The airflow resistance of an inhaler is defined as the square-root of the pressure drop divided by the flowrate, assuming turbulent flow. Various units are used, but a sensible approach is to use $\sqrt{\text{Pa}}$ for pressure drop and litres per minute (LPM) for flowrate, as this produces numbers of a reasonable magnitude for the resistance. For example, the HandiHaler has a flowrate at 4 kPa (Q_{out})³ of approximately 30 LPM, so its resistance is calculated as follows:

$$R = \frac{\sqrt{\Delta P}}{Q} = \frac{\sqrt{4000}}{30} = 2.11 \sqrt{\text{Pa}} \text{ min L}^{-1}$$

The units of resistance are awkward and not particularly memorable, so from this point onward, I will refer to $\sqrt{\text{Pa}} \text{ min L}^{-1}$ as "Flohms", or FΩ – a combination of "flow" and "ohms", and a lot easier to write (and pronounce). The Cyclohaler has a much lower resistance, with a Q_{out} of approximately 110 LPM, so a resistance of 0.57 FΩ.

It should be noted that a better method to determine the airflow resistance of an inhaler is to create a pressure-map, i.e. record the steady-state flowrate through the device for a range of pressure drops up to approximately 10 kPa, as this corresponds to the likely range in real use. A graph is then plotted of $\sqrt{\Delta P}$ against Q (the pressure map), and a linear regression calculated (forced through the origin); and the gradient of this line is the airflow resistance of the device.

WHAT FLOWRATES ARE ACHIEVED THROUGH DPIS IN REAL USE?

The US Pharmacopeia (USP) instructs *in vitro* tests to be carried out at a nominal flowrate, Q_{out} , which corresponds to a 4 kPa pressure drop across the device. In reality, however, it is a little more complicated – in that the pressure drop achieved by the user is highly dependent upon the airflow resistance of the device. Most users following typical DPI instructions for use (IFUs) will achieve higher inspiratory pressure drops than the 4 kPa test point prescribed in the USP – particularly for high-resistance devices.

The pressure-flow curves of the three example DPIs have been overlaid on the data in Figure 1, and the average operating points for healthy adults and children can be

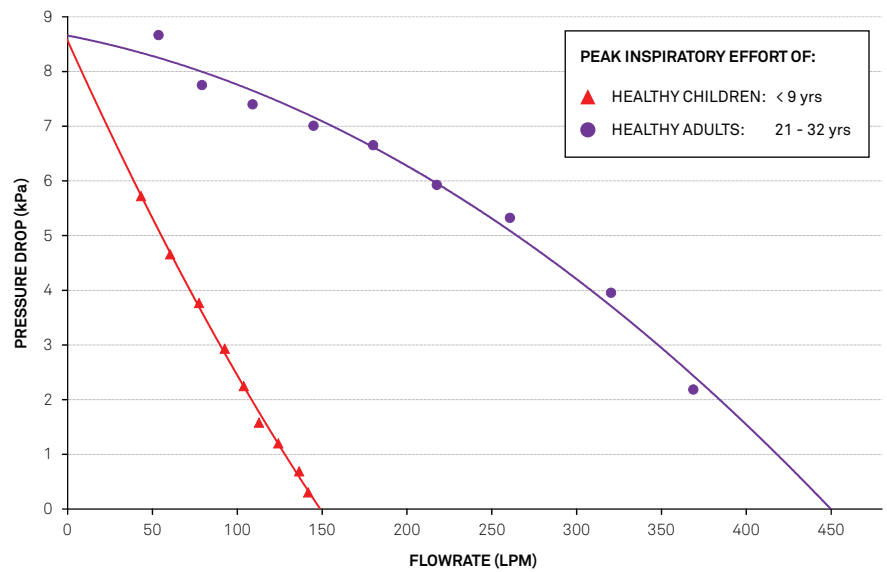


Figure 1: Effect of age on inspiratory flow characteristics.

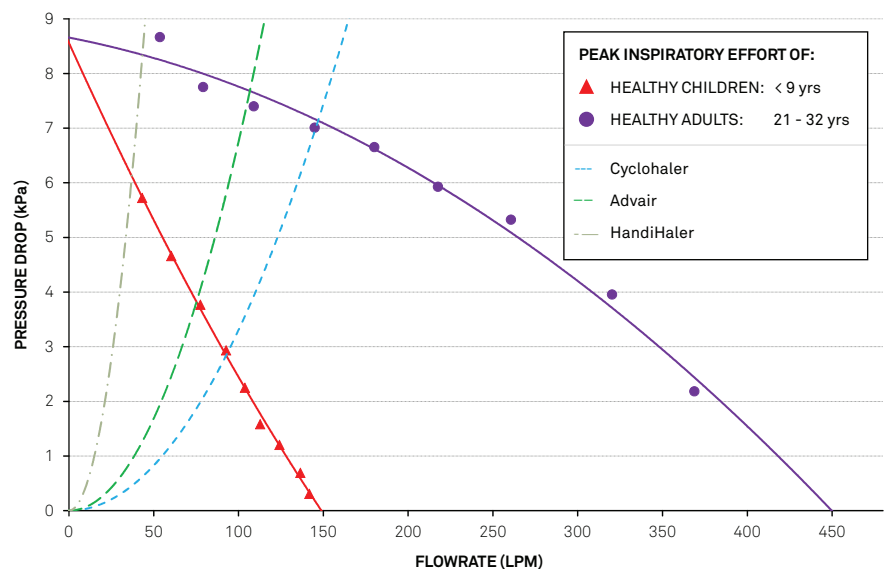


Figure 2: Estimated operating points of DPIs when used by healthy adults & children.

estimated from the intersections of the curves (Figure 2).

Healthy adults are able to achieve very high pressure drops even across the lowest-resistance DPIs when instructed to inhale with maximum effort. Even the low-resistance Cyclohaler is likely to see a pressure drop of approximately 7 kPa in real use; significantly higher than the nominal 4 kPa test point. The high-resistance HandiHaler is likely to see over 8 kPa when used by healthy adults, and ~6 kPa when used by healthy children.

It is also interesting to note that inhaler resistance has a greater effect on the likely operating pressures for children than for adults (Figure 2).

So whilst there is currently no common agreement about the optimal airflow

resistance for DPIs, in terms of reaching maximum performance and greatest consistency between users, high resistance is most likely to achieve this, because users achieve higher pressure drops across higher-resistance devices; and the difference in the pressure drop achieved across a high-resistance device is minimised between user groups.

HOW IS THIS APPLICABLE TO SWIRL CHAMBER DESIGN?

Swirl chambers have been successfully utilised in numerous DPIs to de-agglomerate fine API particles from the much coarser lactose "carrier" fraction. Almiral's Novolizer® DPI uses a powerful multi-inlet swirl chamber; a similar design was later optimised for use in Sun Pharma's Starhaler®, with a spe-

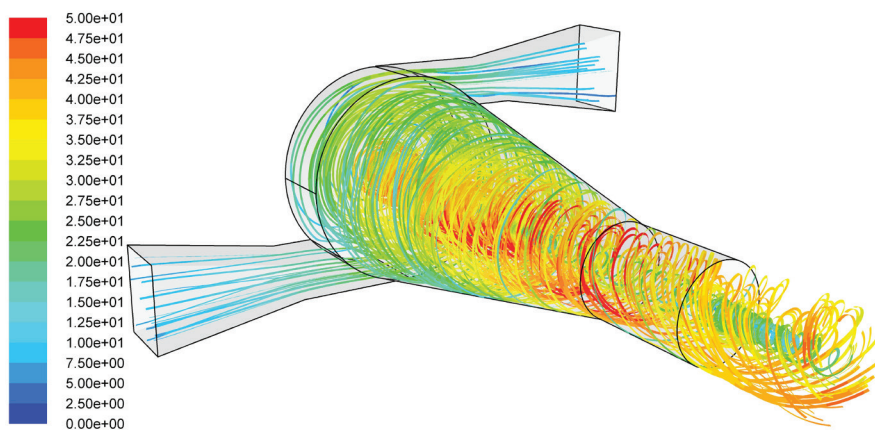


Figure 3: CFD plot showing flow streamlines coloured by velocity magnitude, m/s, in a high-efficiency swirl chamber (CFD work conducted by Stuart Abercrombie, Team Consulting).

cific geometry employed to create excellent independence of flowrate.

Other DPIs that use swirl chambers are 3M’s Conix® device, which employs a reverse-flow cyclone to achieve high de-agglomeration efficiency, and the Twincer® DPI, that uses a pair of swirl chambers that are flat in order to minimise the thickness of the device.

Swirl chambers have many advantages over other de-agglomeration methods:

- With good design they can be self-cleaning – in that the lactose scours the boundary layer and prevents API build up in it, minimising the likelihood of dose “spikes”.
- They create multiple impacts, which results in a high frequency of collisions and more opportunities for API detachment – and consequently better aerosolisation and a higher fine particle fraction (FPF).
- The conservation of angular momentum in a conical converging section creates a highly swirling flow regime, which imparts energy into the formulation efficiently.

The computational fluid dynamics (CFD) plot (Figure 3) shows flow streamlines coloured by velocity magnitude through a twin-inlet, high-efficiency swirl chamber, and illustrates the gains that can be achieved due to the conservation of angular momentum, with peak tangential velocities occurring towards the narrow outlet of the chamber.

We set about a hypothetical challenge of creating a high-performance swirl chamber

to promote good de-agglomeration efficiency of a reference lactose-based formulation. We chose a number of realistic design constraints then mathematically modelled the airflow through the swirl chamber in order to create optimised geometries that would have the properties summarised in Figure 4.

DESIGN CONSTRAINTS

As there will always be limited space for a de-agglomeration engine within a reasonably sized DPI we chose to use the space envelope as the primary design constraint for our mathematical model:

- Fixed space envelope – cylinder of diameter 14 mm and length 33 mm
- Two square, tangential air inlets
- Throat (outlet) area = 1.25x total inlet area
- Parallel section of throat fixed at 5.00 mm.

SWIRL CHAMBER GEOMETRIES

To a skilled cyclone engineer it is clear that increasing the device resistance, whilst abiding by the above design constraints, creates a more “normal” looking swirl chamber, in terms of cone angle and inlet / outlet size in relation to the swirl chamber body (Figures 5-7). A good swirl chamber will maximise swirl velocity in the throat (the most constricted region) through conservation of angular momentum. To achieve this the out-

let diameter must be substantially smaller than the body diameter – which is not possible for the low-resistance design (Figure 7).

WHAT IS “IMPULSE HISTORY”, AND HOW IS IT INFLUENCED BY SWIRL CHAMBER GEOMETRY?

The parameter “Impulse History”, *I*, has been used successfully as a proxy for aerosolisation performance in previous studies.⁴ In a swirl chamber the momentary impulse for a single lactose particle passing through the region of high swirl has been defined according to the following integral over time:

$$I = \int F dt \propto \int |u|^2 dt \propto \int \left(\frac{\Delta u_{ax}^2 + \Delta u_{\theta}^2}{r} + |u|^2 \right) dt$$

- Equation 1

The centrifugal force acting upon the lactose particle is represented by the first term, with the second representing the aerodynamic drag force. Rearranging for path length *S* gives the Impulse History as:

$$I' \propto \int_{Cone} \left(\frac{\Delta u_{ax}^2}{r|u|} + |u| \right) dS_1 + \int_{Cone} \left(\frac{\Delta u_{\theta}^2}{r|u|} + |u| \right) dS_2$$

- Equation 2

The Impulse History is a quantity that is proportional to the actual impulse, and serves as a useful proxy for the aerosolisation performance of the swirl chamber.

In simple terms, why does increasing resistance increase the Impulse History?

- Like in Dyson (Malmesbury, UK) vacuum cleaners, reducing the size of the swirl chamber (cyclone) increases the pressure drop required to achieve a given flowrate – i.e. its resistance increases, which is why Dyson uses multiple cyclones configured in a parallel array.
- For a given pressure drop the net inlet and outlet velocities will be very similar between geometries as the swirl chamber reduces in size. As the outlet diameter reduces, the centripetal acceleration acting on particles in this region increases, as the acceleration is proportional to the square of the (tangential) velocity over the radius. So for the same operating pressure, smaller, higher-resistance swirl chambers create higher centripetal accelerations.
- In a given space envelope and as the resistance increases, the designers can afford a greater difference between the swirl chamber body diameter and the outlet diameter, and due to this, conservation of angular

Resistance →	High	Medium	Low
Example device →	HandiHaler	Advair®	Cyclohaler
Q _{out} →	30 LPM	77 LPM	110 LPM
R →	2.11 FΩ	0.82 FΩ	0.57 FΩ

Figure 4: Summary of example high-, medium- and low-resistance devices.

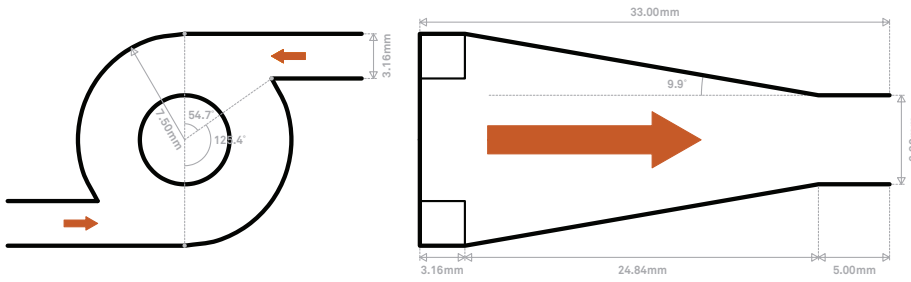


Figure 5: Optimised twin-inlet swirl chamber: High resistance, e.g. HandiHaler.

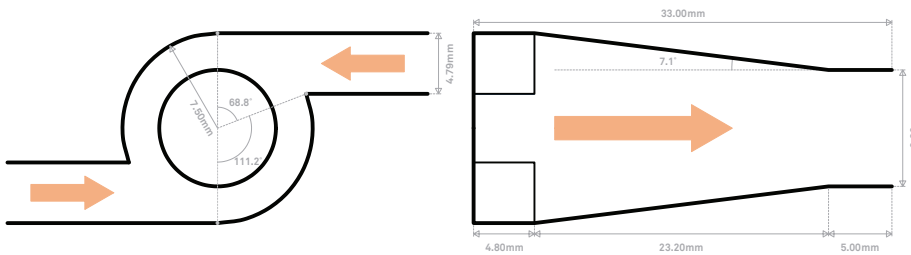


Figure 6: Optimised twin-inlet swirl chamber: Medium resistance, e.g. Advair.

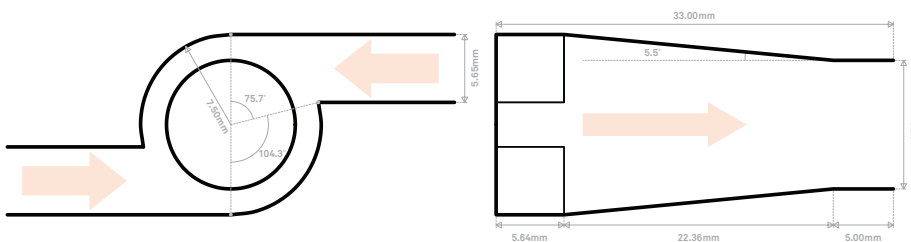


Figure 7: Optimised twin-inlet swirl chamber: Low resistance, e.g. Cyclohaler.

CONCLUSION

It is anticipated that the order of magnitude increase in Impulse History – that can be achieved by designing a high-resistance swirl chamber – is likely to result in a significant improvement in de-agglomeration performance and associated therapeutic effect.

In order to explore this hypothesis, it is proposed to prototype three different swirl chamber geometries for *in vitro* evaluative testing. This will enable an assessment for correlation between the performance predicted by the mathematical model and empirical data to be made.

Assuming that, as with previous studies, the predictions prove to be sufficiently accurate, this could represent a very worthwhile opportunity for improving DPI performance and the therapeutic effect for patients.

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momentum leads to increased swirl velocities in the most constricted region. As the centripetal force acting upon the lactose particles is proportional to the square of the tangential (dominant) component of the swirl velocity, this also increases, leading to a greater Impulse History.

PREDICTED RESULTS

At an operating pressure of 4 kPa an eight-fold increase in the Impulse History

is predicted by the model, from the low- to the high-resistance geometry (Figure 8). As discussed earlier, it’s likely that even children are able to create higher driving pressure drops when instructed to inhale with maximum effort. Predicting the Impulse History at typical healthy adult and child operating pressure drops leads to an even greater difference, with the high-resistance geometry achieving an order of magnitude improvement over the low-resistance design (Figures 9 and 10).

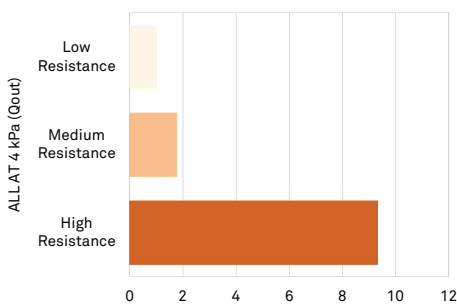


Figure 8: Average Impulse History predicted at 4 kPa for the three different resistance swirl chambers.

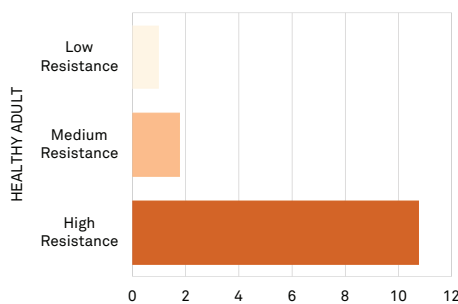


Figure 9: Average Impulse History predicted at healthy adult operating points, for the three different resistance swirl chambers.

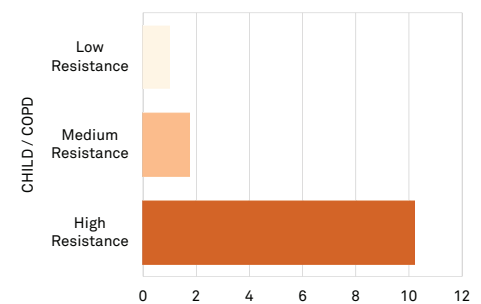


Figure 10: Average Impulse History predicted at healthy child operating points, for the three different resistance swirl chambers.

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