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 (FFP), 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

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.
THERE IS NO “TYPICAL” DPI RESISTANCE

DPIs that are commonly prescribed today have a large range of resistances, ranging from Plastiape’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 √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}) of approximately 30 LPM, so its resistance is calculated as follows:

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

The units of resistance are awkward and not particularly memorable, so from this point onward, I will refer to √Pa 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 √\(\Delta P\) 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_{nom}, 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 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-
Specific geometry employed to create excellent independence of flow rate.

Other DPIs that use swirl chambers are 3M’s Conix® device, which employs a reverse-specific geometry employed to create excellent 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:

\[
i = \int F dt = \int t u \frac{df}{dt} dt = \int \left( \frac{\Delta u}{r_e} + \frac{\Delta u^2}{2} + t u \right) dt
\]

- 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:

\[
i' = \int_{S_{in}} \left( \frac{\Delta u}{r_e} + \frac{\Delta u^2}{2} + t u \right) dS_1 + \int_{S_{out}} \left( \frac{\Delta u}{r_e} + \frac{\Delta u^2}{2} + t u \right) dS_2
\]

- 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 momentum is not problematic for the low-resistance design (Figure 7).

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

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

**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.

**REFERENCES**

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