

# The time-dependent effect of airflow profile on DPI performance

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## Abstract

Dry Powder Inhalers (DPIs) have been traditionally developed based on *in-vitro* testing with a “square-wave” airflow profile, as stipulated by the USP. Our *in-vivo* measurement of the inspiratory flow rate of 16 volunteers shows that this USP flow profile is a poor approximation to reality in some important aspects. For example, a healthy adult will take around half a second to reach their peak inspired air-flow rate, compared to the milliseconds typically achieved using *in-vitro* test apparatus.

In DPIs, the deagglomeration performance is dependent on using the energy in the inhaled airflow to aerosolise the powdered dose. The concern is that, without careful management of this airflow, some of the formulation may be dispensed from the DPI before the peak in airflow energy is reached. Thus a variable and perhaps sub-optimal powder deagglomeration could occur. We present how particle size distribution and flux vary with time when a simulated adult airflow profile is applied to a commercially available DPI.

We constructed a tuneable airflow profile generator consisting of a bespoke air-capacitor and flow-resistance network coupled to the traditional “as-per USP” vacuum pump and solenoid valve. The time constants of this network can be tuned to give an air-flow profile at the DPI mouthpiece that is a good approximation to the expected *in-vivo* profile. A publicly available “Commercial DPI” filled with Salbutamol Sulphate was used as the device. A Malvern Spraytec was used to measure the evolution of particle size distribution and particle flux as a function of time, correlating to the inhalation profile.

We contrast the behaviour of the DPI when exposed to the range of airflow profiles generated by the volunteers, and when exposed to a square-wave in accordance with the USP. We then highlight which aspects of a DPI design could be optimised to give better performance with likely *in-vivo* airflow profiles.

## *In-vivo* Human Lung Power Data

Cambridge Consultants are interested in gaining an in-depth understanding of the nature of lung power of different target therapeutic group, as a prerequisite to achieving a successful DPI design by matching the device to the physiological behaviour of the patient. As part of our previous Human Lung Power investigations, we have measured the temporal pressure and flowrate response of healthy volunteers on a bespoke “air Watts” rig that simulates the resistance characteristics of different types of DPI by use of various resistance orifice plates (*David Harris, Testing inhalers, Pharmaceutical Technology Europe, September 2007*). We found that an orifice of diameter 5.6mm gave a resistance similar to a common medium resistance DPI; namely 60 LPM at 4 kPa. Hence we use our Human Lung Power data from measurements on the 5.6 mm orifice as being indicative of what a patient would achieve using most DPIs.

## In-vitro Human Lung Power Mimic

In order to apply similar *in-vitro* flowrate profiles as observed in the Human Lung Power investigations to real DPIs containing pharmaceutical formulations we constructed a bespoke air-capacitor and flow-resistance network. This network was connected between the Commercial DPI and a standard Copley Critical Flow Controller, as shown in Figure 1. By careful choice of the two capacitances and two resistances we introduced time constants into the system which effectively shaped the square wave airflow profile from the Critical Flow Controller into a form that mimics the first one second of flowrate in the Human Lung Power data. The first one second of data is of most interest, since after that time the Human Lung Power flowrates have reached their peak and decay to zero. It is assumed that the formulation will have exited the device by that time.

The flowrate was quantified by use of a fast response pressure transducer coupled to a PC based data acquisition system. Our knowledge of the resistance of the Commercial DPI allowed us to convert pressure into flowrate.

A Malvern Spraytec laser diffraction instrument was used to measure size and concentration data as a function of time within the first second of airflow. A bespoke reduced volume inhalation cell was developed for use with the Spraytec to minimise both the capacitance and recirculation in the cell.

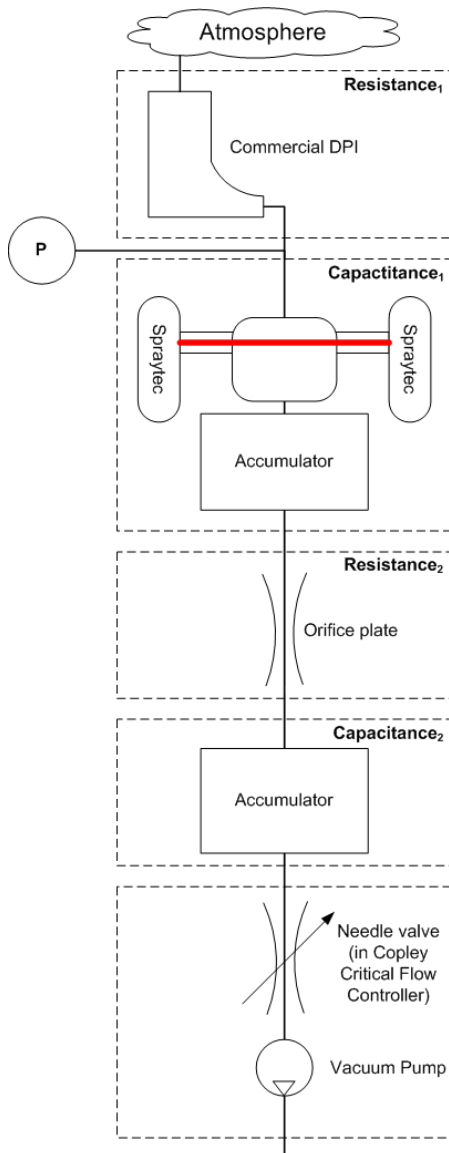
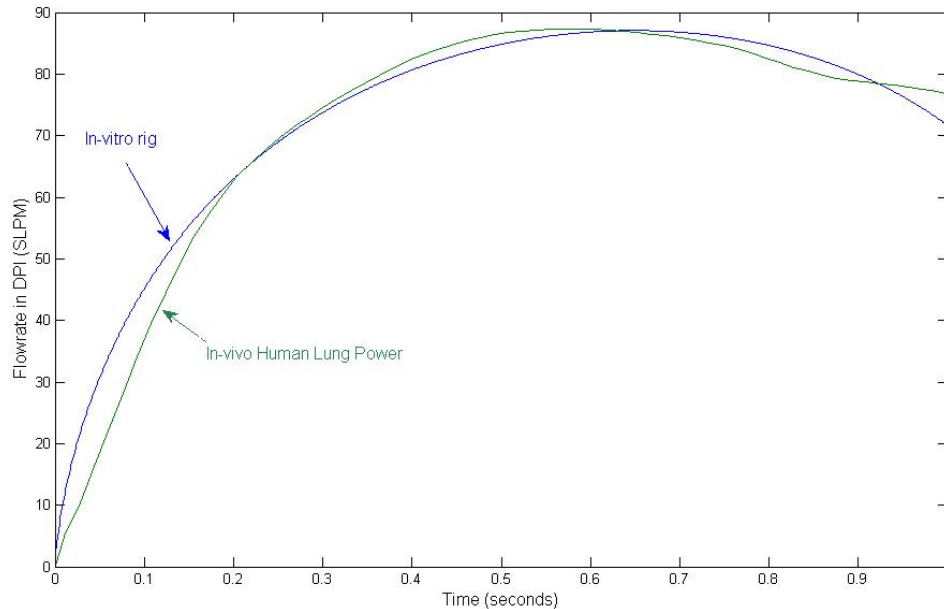


Figure 1: Rig for use as a Human Lung Power mimic

Figure 2 shows a typical comparison of *in-vitro* flowrate through the DPI when connected to the capacitance network of Figure 1, with flowrate measured in the Human Lung Power experiments. The *in-vitro* rig provides a good mimic of the *in-vivo* data.



**Figure 2: Comparison between flowrates in the *in-vitro* rig, and the original Human Lung Power experiments.**

The simpler *in-vitro* flowrate rig specified in the USP (Section 601, United States Pharmacopeia 29) has no appreciable capacitance between the inhaler and the Copley Critical Flow Controller, apart from the presence of a Cascade Impactor if used. We created such a setup by simplifying the rig in such that the Commercial DPI connected into the Spraytec and thence straight into the Copley Critical Flow Controller. Hence the USP apparatus will produce apply what is closer to a square-wave flowrate profile to the DPI. In order to get a reasonable comparison between the square-wave and Human Lung Power mimic configurations, the flowrate for the square-wave was set at 57 SLPM at the Copley Critical Flow Controller to give equivalent airflow energy over 1 second as that from the Human Lung Power profile.

## Results and Conclusions

The experimental work will be completed before the conference. We will present our results and a more quantitative discussion of these at the conference, where copies of this completed work will be available from our poster stand.

We anticipate that our experiments will reveal that, in comparison to a square-wave profile, a time-varying airflow akin to that which is generated *in-vivo* will influence both the emitted particle diameter distribution and the optical density (relating to concentration) of the aerosolised formulation. This effect of airflow profile on aerosolisation performance will have implications for the way DPIs are designed in order to achieve a preferable distribution of drug in the lung and hence optimal therapeutic effect.