  

# The role of the Hydraulic Lung in comparing the performance of dry powder inhalers

***Simulating human inhalation at fixed levels of inspiratory effort, it allows flow rates through DPIs to vary with device resistivity and enables rapid, fair DPI testing and comparison.***

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## Introduction

The GlaxoSmithKline Hydraulic Lung (GSK, Ware, Hertfordshire, UK) was developed to simulate human inhalation to allow comparative *in vitro* testing of dry powder inhalers (DPIs) at a consistent level of inspiratory effort, rather than a single flow rate or pressure drop. It has also been used to explore the relationship between inspiratory effort, device resistance and flow rate or pressure drop, to provide a means of calculating relative flow rates appropriate for testing different DPIs. This article describes the development of the hydraulic lung and illustrates its use.

## Background

Dry powder inhaler devices are highly varied in their design. Almost all DPIs, however, rely on the patient's inhalation to draw the dose from the device and provide the energy for deaggregation of the powder formulation to provide respirable particles of drug. Not surprisingly, given the variety in design, DPIs also vary greatly in the resistance they offer to airflow.

In any DPI, pressure drop is expected to increase at higher flow rates. However, a high resistivity DPI may generate a pressure drop more than ten times higher than that generated by a low resistivity inhaler at the same flow rate.[1] The term "resistivity" here refers to the specific resistance obtained by plotting the square root of pressure drop against flow rate, which typically results in a linear relationship.[2] The slope of the line represents resistivity.

The problem for an analyst wishing to compare the *in vitro* performance of two DPIs of different resistivity is the choice of flow rate for testing each device. Two approaches have been commonly used: testing both devices at the same flow rate (e.g., 60 liters/minute) or testing both devices at the same pressure drop (e.g., 4 kPa).[3,4] In order to be a fair comparison, however, the tests should use the relative flow conditions that a patient would be expected to achieve through the two devices, which is not achieved by either of these methods. The obvious way to approach this question is to study the inhalation characteristics of volunteers or patients inhaling through devices (or model devices) of varying resistivity. Two key studies, both reported in the mid-1990s, took this approach and attempted to establish a relationship that could be used to select relative flow rates for testing different DPIs.

A study by Clark and Hollingworth[5] used healthy volunteers, eight model devices of varying resistivity and commercial DPIs. Plotting peak pressure drop against resistivity for their healthy volunteers led them to conclude that, for all but low resistivity devices, the peak pressure drop achieved reached a plateau at approximately 80 cm $H_2O$ (~7.8 kPa), which they hypothesized might be the maximum pressure drop that the respiratory muscles could achieve.

Olsson and Asking[6] took a similar and entirely empirical approach with the intention of finding a relationship between device resistivity, flow rate and inspiratory effort. They plotted pressure drop against flow rate for seven DPIs and fitted an equation (1) to the resulting curves.

$$\Delta P = C.Q^{1.9} \tag{1}$$

Where $\Delta P$ = pressure drop *(Pa)*, $Q$ = flow rate (liters/minute) and $C$ = proportionality coefficient *(Pa* $s^{1.9}$ $L^{-1.9}$*)*

They then plotted the inspiratory flow rate achieved by healthy volunteers against the resistance coefficient for a series of model devices and found that each patient had a fairly consistent value for $K$ (Equation 2), which they termed the "inspiratory force," though it is not a force in the strict sense, as it does not have the correct units.

$$K = C.PIF^{2.4} \tag{2}$$

Where $K$ is inspiratory force *(Pa* $s^{-0.5}$ $L^{0.5}$*)*

The result was a useful system, which provided the ability to calculate appropriate flow rates based on inspiratory force, though it was not widely adopted by other researchers.

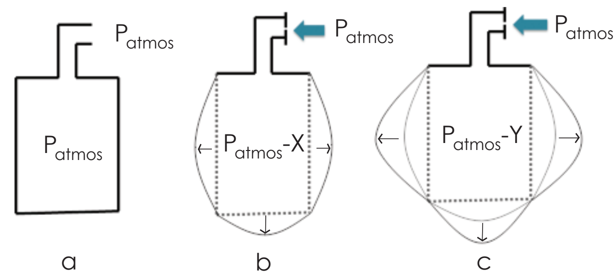
The difficulty in establishing an exact relationship between inspiratory effort, device resistivity and the resultant flow rate or pressure drop achieved during an inhalation may be due to the levels of variability inherent in human-based studies. The objective in developing the hydraulic lung was to design a mechanical system that would provide both a means of investigating the relationship between these parameters without the associated issue of patient variability and an apparatus for practical/comparative *in vitro* performance testing under conditions representative of human inhalation without the need for measuring and recording profiles from patients.

## Development of the hydraulic lung

The starting point for developing a non-human system was to consider inhalation as a very simple process. Figure 1a shows a simplistic diagram of the lungs, throat and mouth. The pressure in this open system is the same inside and out: atmospheric pressure.

**Figure 1**

**A simplified model of inhalation**




At the beginning of an inhalation, the chest and diaphragm muscles expand the lung volume by a small amount. The expansion creates a momentary drop in the pressure inside the lungs (Figure 1b). Almost instantaneously, the external atmospheric pressure forces air into the lungs and the pressure is equalized. If a restriction is introduced at the mouth which slows the flow of air into the lungs, the resultant pressure drop will be greater and will have longer duration. As the pressure drop is equalized, the force exerted by the muscles is able to expand the chest further (Figure 1c) which, in turn, creates more pressure drop and atmospheric pressure forces in more air, and so the process continues. Of course, this is not a stepwise procedure; it is a constant and dynamic process. As the chest approaches the limit of its expansion, the pressure drop returns to zero and the inflow of air stops.

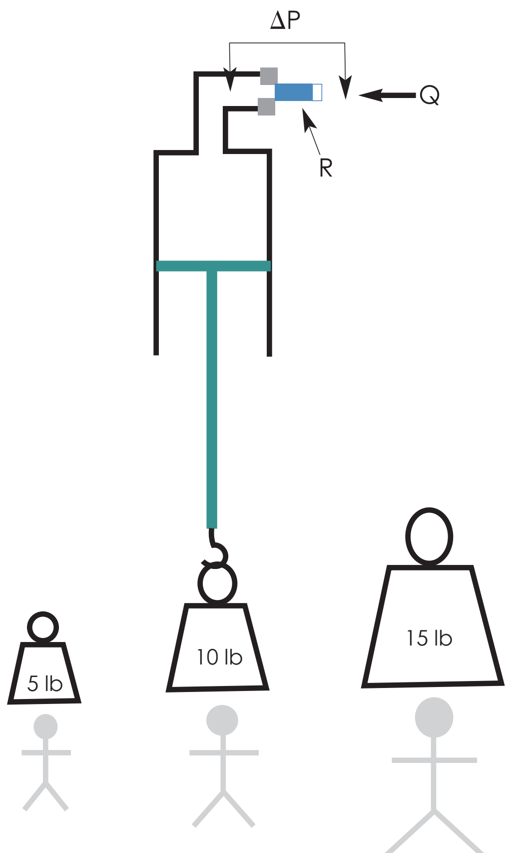
Figure 2 illustrates the first concept for modeling such an inhalation system in which the lung "chamber" is represented by the inside of a giant syringe. The "lungs" expand as the syringe plunger moves down. This is driven by mass and gravity rather than by chest muscles.

The inspiratory effort can be modified by changing the mass. Although this model is useful theoretically, it is not entirely practical because a giant syringe would be likely to exhibit poor reproducibility of the friction between the plunger and the syringe walls.

A practical approach taken was to replace the syringe plunger by a column of falling water. The chosen design employs a "U" shaped tube (Figure 3) in which the water level is raised on one side to a

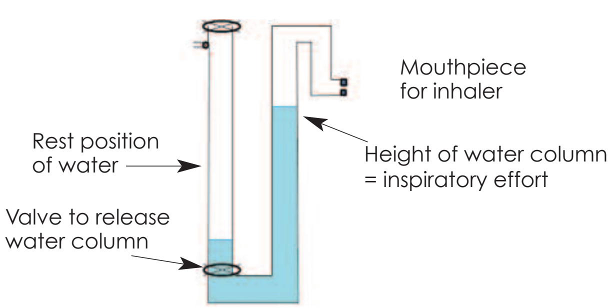
## Figure 2

**Initial concept for an inhalation apparatus**




## Figure 3

**Schematic of the hydraulic lung**

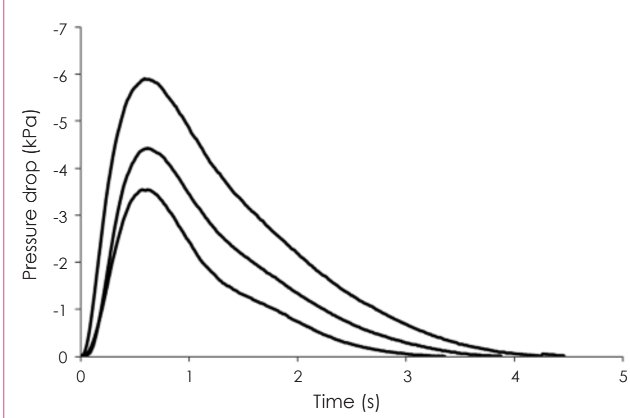



height selected to represent a given inspiratory effort and then allowed to fall back to the equilibrium position. The falling water level generates a partial vacuum that draws air through a resistance (such as a DPI) placed at the "mouth" of the tube. The other side of the tube, where the water rises, is open to the atmosphere during the inhalation manoeuvre. Appropriate valves were added to allow compressed air to raise the water level when required and to initiate the fall of the water column.

Real patient inhalation profiles naturally show considerable variation in shape and other characteristics, but typical examples have a rapid acceleration to a peak flow (or pressure drop) value followed by a slower decline back to zero. The resultant inhalation profiles generated by the hydraulic lung are "human-like," displaying comparable shape to a typical human profile (Figure 4), with flow acceleration and volume increasing at higher inspiratory efforts. Pressure drop vs. time inhalation profiles were recorded through measurement of the pressure difference across the test resistance, i.e., between atmosphere and the "lips" of the throat using a differential pressure transducer attached to the throat and an inhalation profile recorder (GSK, Ware, Hertfordshire, UK). The pressure drop profiles may be converted to flow rate vs. time profiles according to Equation 3, discussed in more detail below.

## Figure 4

**Typical inhalation profiles from the hydraulic lung at three levels of inspiratory effort**




## Clinical evaluation

In order to examine the inspiratory effort/resistivity/flow rate relationship using the hydraulic lung, and to validate the results against human inhalation characteristics, a study was designed employing a series of model device resistances and, for the hydraulic lung, a range of different effort levels or water column heights. A model device was constructed that could be fitted with resistor discs containing accurately-drilled holes of varying diameter. Orifice diameters of 3.0, 4.5, 5.0, 6.0 and 7.0 mm were used to represent the resistivity expected from a wide range of commercial DPIs.

Inhalation profiles were recorded as pressure drop/time profiles using the inhalation profile recorder. These profiles were converted to flow/time using Equation 3.[7]

$$Q = \sqrt{\Delta P}/R \qquad (3)$$

Where $Q$ = flow rate (liters/minute), $\Delta P$ = pressure drop (kPa) and $R$ = resistivity or specific resistance ($kPa^{0.5}.liters^{-1}.minute$).

Inhalation profile characteristics of peak pressure drop, peak inspiratory flow and inhaled volume were determined for all profiles.

In order to make a comparison between the hydraulic lung and human inhalation in terms of the peak pressure drop/flow rate resulting from a given resistivity, it is necessary to equate hydraulic lung inspiratory effort levels to human inspiratory effort levels. This was achieved by determining the maximum inspiratory pressure (MIP) generated when inhaling against an infinite, or near infinite, resistance in each case.

MIP is a particularly useful definition of inspiratory effort as it is a standard measurement in plethysmography and published values are available for various patient groups.[8]

Inspiratory effort levels generated by water column heights of 15, 20, 25, 30, 35, 40, 45 and 50 cm were applied for the hydraulic lung for each of the five resistors. The MIP value for each effort level was also determined.

Ethics approval was obtained to conduct a clinical study in which 20 volunteers, both male and female, aged 25 to 53 years were included. This was a single-center, single-blinded, 5-way crossover study conducted in two sessions. In the first session, the subjects were trained to inhale through a model device with moderate resistivity. Once satisfactory technique had been established, the MIP achievable by each volunteer was measured. The second session was conducted one week after the first where, for each volunteer, duplicate profiles were recorded through each of the resistance levels in a randomized order.

The effort levels (MIP values) for both the hydraulic lung and the human subjects were 3.5–9.7 kPa and 5.0–14.9 kPa, respectively. There is not complete overlap for the two sets of effort levels, but there is a reasonable range of overlap. The hydraulic lung could not reach high enough inspiratory efforts levels to cover the range achieved by all human subjects. This was one of the reasons for designing a MK II apparatus, which is discussed below. It was also evident that the peak pressure drop achieved by human subjects continued to increase with increasing resistivity, rather than reaching a plateau at ~8 kPa as reported by Clark and Hollingworth.

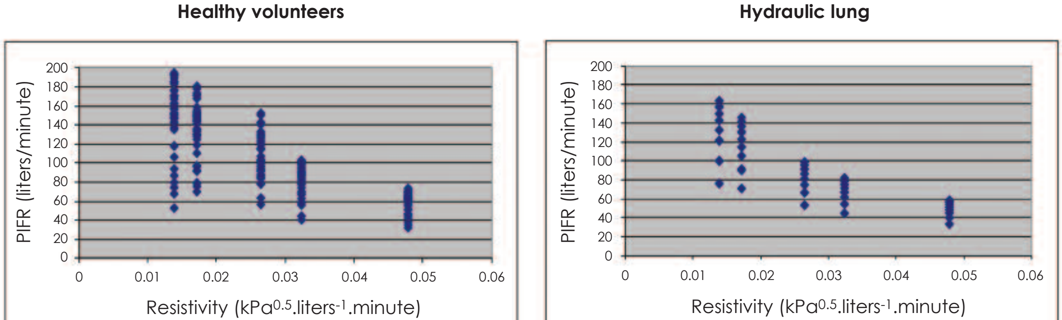
As expected, the hydraulic lung produced far more reproducible results than the human subjects, though using maximal inhalation and allowing subjects sufficient recovery time between inhalations allowed quite good reproducibility for peak pressure drop. Flow acceleration, which may be an important factor for performance of some DPIs,[9] was found to be highly variable.

A comparison of the peak inspiratory flow rate (PIFR) achieved at each resistivity by healthy volunteers and the hydraulic lung (Figure 5) confirmed that the behavior of the hydraulic lung followed the same pattern as the human subjects, though a few volunteers achieved higher values of PIFR because they had a higher MIP. The human data also appears to have some unexpectedly high values for central resistance.

The simplest relationship that could be established between inspiratory effort, resistivity and peak pressure drop (Equation 4) was the linear relationship found by plotting the square root of ΔP against *1/R* (which allows the inclusion of the MIP

**Figure 5**

**PIFR values with varying resistivity for healthy volunteers and the hydraulic lung**



value where $R$ = infinity or $1/R = 0$). This can be expressed alternatively in terms of a flow rate (Equation 5).

$$\sqrt{\Delta P} = \sqrt{MIP} - k/R \; kPa^{0.5} \qquad (4)$$

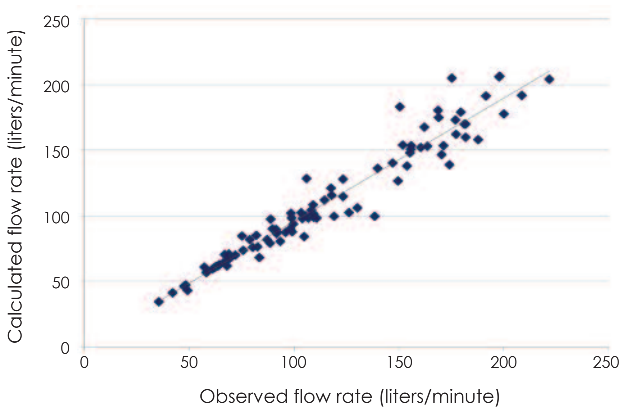
Where $k = 0.011$

$$Q = \sqrt{MIP}/R - 0.011/R^2 \text{ liters/minute} \qquad (5)$$

The equation fails at the extreme of low resistivity, but fits the data well across the range of resistivities encountered with commercial DPIs. Equation 5, derived from the hydraulic lung, was used to predict the peak flow rates achieved by the healthy volunteers based on their MIP values. Comparison with the observed values is shown in Figure 6.

**Figure 6**

**Comparison of calculated and observed flow rates for healthy volunteers**




The flow acceleration achieved by the hydraulic lung for each resistivity and MIP value fell within the range of values recorded for the human subjects, but was typically lower, at approximately 80% of the mean human value.

## Practical *in vitro* performance testing

The relationships derived from the hydraulic lung have been widely applied at GSK, but the hydraulic lung has found as much, if not more, utility as a practical laboratory tool for testing DPIs. In general, it is used to determine the dose that is able to pass beyond the throat (ex-throat dose) and which therefore constitutes the potential "lung dose."

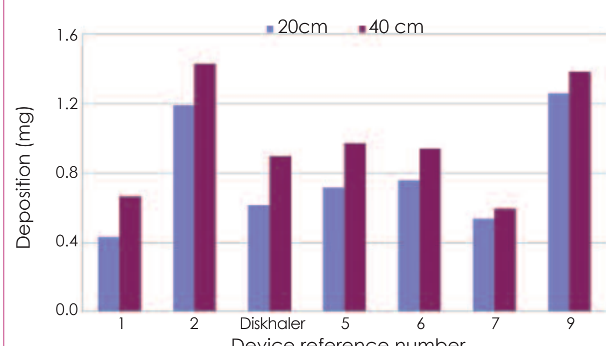
Ex-throat dose testing is performed by connecting the device being tested into the "mouth" of a coated anatomical throat model and total trap filter connected to the hydraulic lung.

The practical application of the hydraulic lung is illustrated by a study conducted during the influenza pandemic threat of 2009, when projected demand for commercial Relenza Rotadisk/Diskhaler (GSK, Brentford, Middlesex, UK) was expected to outstrip supply. An alternative Rotacap/Rotahaler delivery system was proposed in order to meet demand. In addition, a range of alternative (DPI) devices, originating from GSK and external companies, were screened to evaluate their performance with the Relenza formulation to establish if any could closely match the performance of the Rotadisk/Diskhaler product, such that unprecedented demand might be met by collaboration between companies. The study also provided an opportunity to explore the impact of widely-varying device design on product performance with a single formulation.[10]

The throat deposition and ex-throat dose were determined on the hydraulic lung using a coated, average-sized, adult anatomical throat model[11] at two levels of inspiratory effort (20 and 40 cm columns of water). The devices varied widely in resistivity, such that the higher effort level (equivalent to 4 kPa pressure drop across the Diskhaler) resulted in peak flow rates ranging from approximately 50 to 150 liters/minute. The ex-throat doses at the two inspiratory effort levels for seven DPIs are shown in Figure 7. Sensitivity of ex-throat dose to throat size was also examined by further testing with both small- and large-sized adult anatomical throat models (Figure 8).[11]

**Figure 7**

**Ex-throat doses at two inspiratory effort levels for seven DPIs**

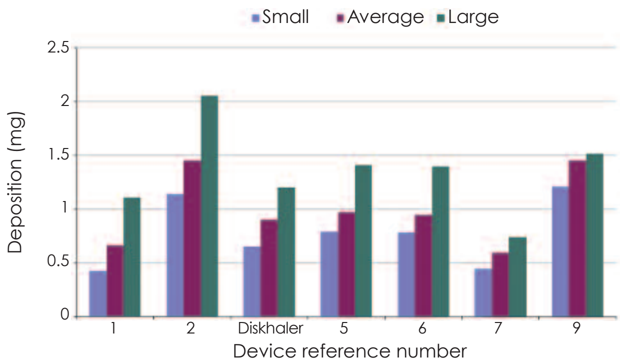



For the majority of the devices, halving the inspiratory effort had significant impact on the resultant ex-throat dose. Devices 7 and 9 were found to be least affected by change in inspiratory effort and throat size. Devices 5 and 6 were most similar in performance to the Diskhaler product.

The results highlighted the ways differences in device design, including resistivity and aerosolization principle, have a profound effect on product performance with this formulation. Further work would be required to establish whether alternative formulations demonstrate a similar behavior. The

Figure 8

Sensitivity of ex-throat dose to throat size with small- and large-sized adult anatomical throat models




value of this type of ex-throat dose testing on inhaled devices, and employing a representative range of flow rates and throat sizes, have also been highlighted by Olsson et al.[12]

## Advantages and limitations of the hydraulic lung; Further developments

The hydraulic lung can successfully simulate human inhalation at fixed levels of inspiratory effort, allowing the flow rate achieved through a DPI to vary according to the device resistivity. This has allowed determination of a formula that can be used to calculate the relative flow rates for comparative testing of multiple DPIs. The hydraulic lung has also proven to be a useful *in vitro* apparatus to enable rapid and fair comparison of a number of devices where collection and use of real patient inhalation profiles is impractical.

Some shortcomings in the design of the original hydraulic lung have been noted and an MK II hydraulic lung has now been designed and built to address these. In addition to ergonomic improvements, the MK II instrument can achieve the full range of human MIP values (>14 kPa), match human flow acceleration, accommodate additional equipment and flexibly vary characteristics such as inhaled volume, while maintaining the same inspiratory effort level.

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