System to perform flow profile measurements with inhalation devices while used by human volunteers

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Summary
Flow profile studies are not explicitly mentioned in the OIP guideline[1], although most clinical development plans for generic dry powder inhalers (DPI) carefully enquire this aspect and its results. The reason is that the guideline implies the need for a study measuring inspiratory flow profiles.
For the lack of a commercially available measuring device, Inamed developed a system according to several criteria.
The system was set up from components, which are commercially available and calibrated in a way that it allows to measure the pressure drop at the mouth piece of an inhaler as a function of time. The data had to be collected and converted into a flow rate as a subject inhales through a dry powder inhaler. The modification of the DPI does not alter the airflow resistance of the inhaler. The data is analysed for typical parameters like peak inspiratory flow rate or inhaled volume to generate output parameters for characterisation and comparison of the inhalation.
Based on a thorough validation and qualification our system has proven to be reliable in 4 clinical trials, with more than 400 patients. It has been used with various DPIs amongst them were Turbohaler and Diskus as well as one breath triggered device.
The system can be used for both drug free studies with focus on the device and the handling itself or for studies with a drug delivery to the patient. Additionally this can be in combination with pk and scintigraphic deposition studies.

Introduction
Even though, they are not explicitly mentioned in the OIP guideline[1], flow profile studies are part of most clinical development plans for generic dry powder inhalers. The guideline states on page 3: Scope of guideline:
"*Further to clinical performance in respect of the clinical efficacy and safety of the product administered via the inhaler device, knowledge of the in vitro performance, and particularly the flow-dependent particle size distribution of the product, is important and will have some influence on the clinical development program."*

It further states in section 4.4: Dry Powder Inhalers:
"*In contrast to pressurized and non-pressurized MDIs dry powder inhalers (DPIs) often show a high flow dependency in their deposition characteristics. Therefore characterisation of flow rate dependency in the patient populations in whom the DPI is to be used must be presented (see also section 5.2 below)...."*
Section 5.2:
"Data from the complete particle size distribution profile of individual stages of a validated multistage impactor/impinger method should be provided. Unless justified otherwise, comparative in vitro data on flow rate dependence should be obtained with a range of flow rates. This range should be justified in relation to the intended patient population. The minimum (e.g. 10th percentile), median and maximum (e.g. 90th percentile) achievable flow rate in this patient population(s) should be investigated."

This implies the need to measure the inspiratory flow profile representing the patient population covered by the authorisation of the reference product and therefore the need for a clinical trial measuring inspiratory flow profiles.
Since it is vital to measure those flow profiles while the patient is inhaling from the respective device, and no commercial method is available to be used with different DPIs, Inamed developed its own method. Several options are available to measure the flow through a dry powder inhaler and the selection of the most appropriate way is complex. The criteria that influenced our chosen principle were following:

- Accurate measurement of the flow rate directly at the mouthpiece of the inhaler
- Keeping the original design and ergonomics of the mouthpiece and the inhaler
- Small measuring probe in order not to interfere with the patient's inhalation manoeuvre
- Sensitive flow measurement technique which is able to identify actuation interferences
- Hygienic design
- Quick connection / ease of use for staff and patient
- Portable system for on-site studies

Material and Methods
In order to comply with our requirements above Inamed developed a custom made system to measure the pressure drop directly at the mouthpiece of the inhalation device.
General Description of the measurement system
A small diameter probe (Adapted cannula, Sterican Ø1.1mmx30mm, Braun, Germany) inserted and fixed safely into the mouthpiece (described in detail below), is connected to a pressure transducer (DSP, FSM Elektronik, Germany) by a flexible tube.

The data acquisition system consists of a notebook with the acquisition software and an analog/digital converter (BNC Box USB 9800, Data Translation, Germany), in order to convert the voltage signal from the pressure transducer. Figure 1 below shows a modified inhaler, and its measuring set up.

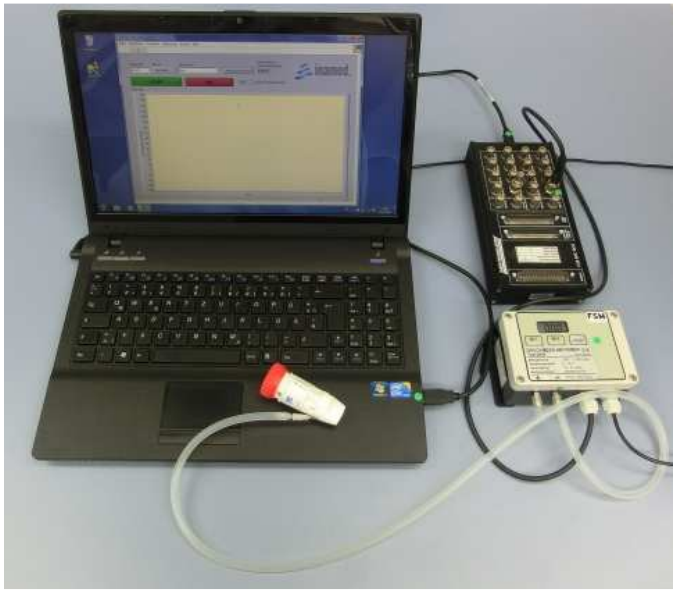

Figure 1: Assembled measurement kit with Turbohaler

The acquisition software records the pressure drop in volts at the mouthpiece over the time and converts the measured voltage into volumetric flow values by using a device type specific calibration curve. Pressure values and converted volumetric flow rate values are saved in a raw data file.

The recorded profiles are characterized by evaluation software, which analyses the flow profiles and generates the study specific parameters of the recorded flow profile (e.g. peak flow rate, inhalation volume, inhalation time, time to reach peak flow rate, etc.).

Preparation of the inhaler:
Devices in the clinical trial should be empty, since drug is not needed for this kind of test and unnecessary drug exposure can be avoided. Therefore, some devices need to be emptied before they can be prepared, which is performed by an external vendor.
At Inamed the devices are physically modified by drilling a channel from the side into the mouthpiece in a way that it will not influence the inhalation process itself or the behavior of the device itself and the subject can use the device in the usual way. To guarantee reproducible drilling a device specific drilling stand was developed. Afterwards this channel was used to guide a thin probe (Adapted cannula, Sterican Ø1.1mmx30mm, Braun, Germany) with rounded edges into the inner part of the mouthpiece where a differential pressure is measured during inhalation [Figure 2]. Then the probe is fixated by using an adhesive, which is biocompatible medical device compliant, to keep it in position. All steps are performed controlled and under clean conditions in order to prevent foreign particles entering the device.

Figure 2: Two examples of modified devices

As quality control measurements following tests were performed:
Each inhaler was tested by measuring the flow rate of the device at 4 kPa differential pressure before and after mounting the probe. Additionally for each device functional capability of the probe was tested as well as verifying the absence of particle residues from the drilling process.

Before preparation an acceptance criterion was defined. All modified devices must be within a flow rate range of +/- two times the standard deviation (SD) of the mean value plus an allowed extra margin of 1%. With this acceptance criterion outliers with respect to flow rate are eliminated for the use in a study.

Results

Quality control of device preparation:

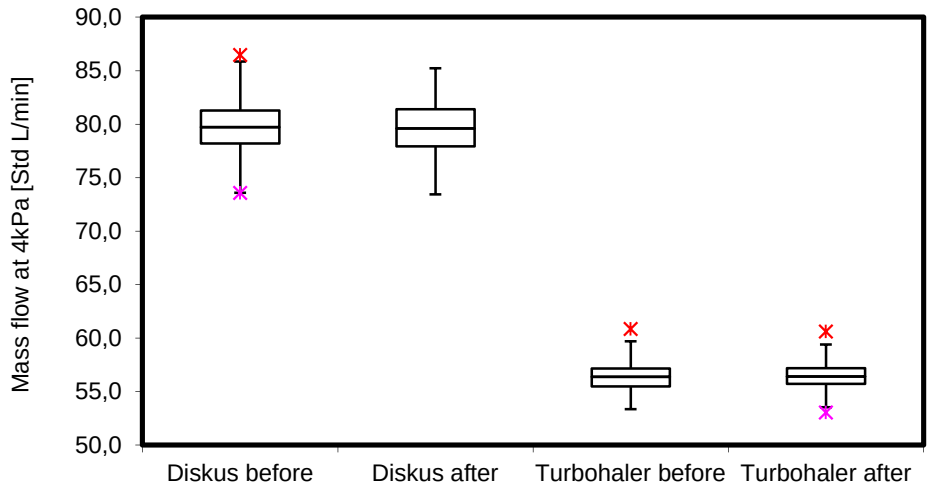

Figure 3: The flow rate at 4 kPa, before and after the modification of the device was Diskus before 79.8 L/min ± 2.6 L/min and after 79.6 L/min ± 2.5 L/min and Turbohaler before 56.3 L/min ± 1.2 L/min and after 56.4 L/min ± 1.2 L/min (mean and SD of 150 devices each).

Calibration curve of the differential pressure versus flow rate

The voltage values of the differential pressure sensor, as mentioned above, are used to calculate the mass flow through the mouth piece. For the calibration curve, the differential pressure in volts and the flow rate are measured simultaneously and drawn in an XY-Graph [Figure 3]. This is performed for five devices of each inhaler type. The mean values of these five measurements are used in the acquisition software as calibration curve for calculating the volumetric flow rate (L/min).

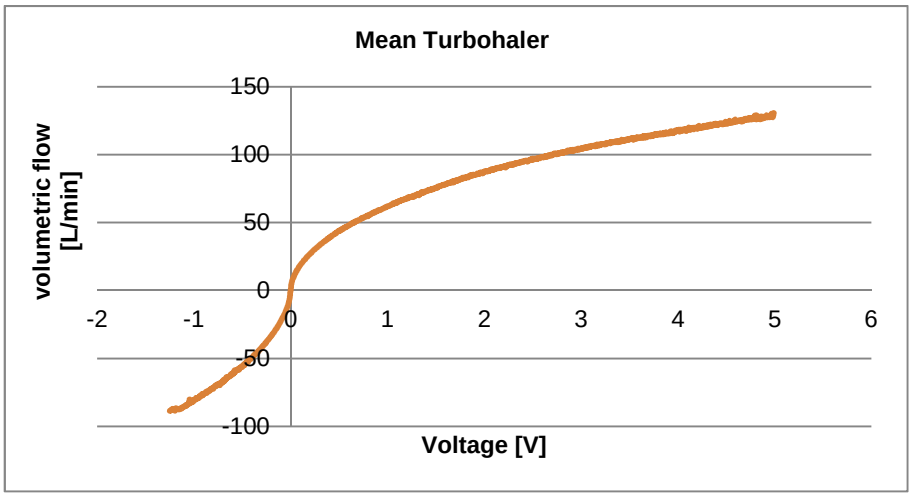

Figure 3: Example calibration curve of the Turbohaler

Evaluation of flow profiles

For the evaluation of the flow profiles a separate program was developed. This software calculates predefined parameters from the measured flow profile like peak inspiratory flow rate, inhalation volume, inhalation time, time to reach peak flow rate, slope of the flow rate increase. Additional parameters can be implemented into the software.

Validation and Qualification

Both the acquisition and the evaluation software were validated and qualified before usage. In general the whole measurement procedure was dismantled into several processing steps (differential pressure sensor – A/D

converter – Laptop – acquisition software – text-file – evaluation software – print out). Then each step was checked separately.

Points for validation
Validated were the differential pressure sensor, the AD converter, the mass flow sensor and the software

Points for qualification
Following steps for qualification were preformed: design qualification of required documents and programs with regard to software and hardware, installation qualification of the measurement system and the software, operational qualification of the measurement system and the evaluation system and qualification of the calibration, maintenance and functional tests.

The acquisition software was tested for the correct calculation of the volumetric flow rate by checking the values at a constant voltage at the A/D converter and comparing with the correlation curve. Another test aimed for the correct creation of the raw data file after inhalation.

For the validation of **the evaluation software** three common representative signals (sinus, triangle and square) have been generated artificially and all predefined parameters like peak inspiratory flow rate etc. were calculated manually. Afterwards these functions were used to check the functionality of the graph and the calculation of the predefined parameters of the software.

After the validation of each software module was completed the functionality of the whole measurement system is proofed by a qualification test which shows the overall suitability of the measurement system (see Figure 4) by comparing a patient flow profile produced by a flow volume simulator measured with our system to flow profile measured by a flow meter (TSI, Germany).

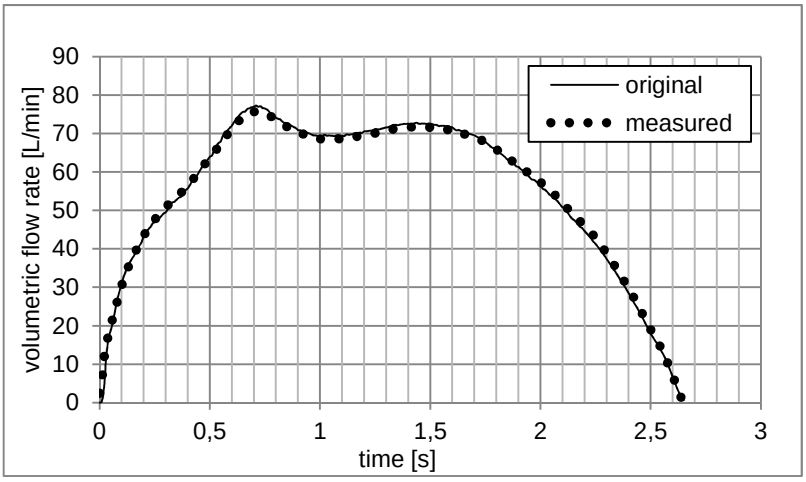

Figure 4: Comparison of measured values by the software to original values

Discussion
Our system was validated and qualified and has proven to be reliable. It is easily to set up and simple to use after minimal training. It has been used so far in 4 studies with 80 to 120 patients/volunteers each. It fulfils the criteria of accurate flow measurement directly at the mouthpiece of the inhaler, without modifying the mouthpiece and only slight modifications on the handling.
The measurement system does not interfere with the patient's inhalation manoeuvre and a breath trigger event of the inhaler can be identified. Measurement systems like Respitrace are not able to detect breath triggering. The hygiene is kept by having one device for each volunteer. Even though, if the volunteer has an over saliva production, the measurement can be hampered since the probe can be blocked but this can be easily detected by the technician. The main advantage of our system is that the subject can inhale through the device with a minimal influence of the measurement system. This is unlike to other systems e.g. to measurement systems using a pneumotachograph were usually a bulky measurement device needs to be attached to the inhaler.

Since we use our system without drug and even without placebo, we do not need to make our device changes according to GMP conditions, but can submit the successive clinical trials under the medical device law. If the device should be used with drug, this system would work too and could be used in combination with pk and scintigraphic deposition studies.

Reference
1. CHMP/EWP/4151/00Rev.1, *Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products Including the Requirements for Demonstration of Therapeutic Equivalence Between two Inhaled Products for use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease.* 2009.