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FLOW MEASUREMENT IN SMART INHALERS FOR CONNECTED DRUG DELIVERY

In this article, Andreas Alt, PhD, Sales Director, Medical, Sensirion, discusses the value of adding sensor technology to inhalers by means of an add-on device, both to help patients track and manage their disease, and to improve compliance by providing feedback on inhalation technique.

Inhalers are the most commonly used devices for treating respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD). With each inhalation the device is designed to deliver a specific dose to the lungs. However, this assumes that the patient is using the inhaler correctly which, more often than not, is not the case.

It is well documented that patients often have problems adopting the correct inhaler technique, which means that they receive insufficient medication. This applies to both metered dose inhalers (MDIs) and dry powder inhalers (DPIs), leading to poor disease control and increased healthcare costs, either as a result of uncontrolled disease, increased drug utilisation for relief medication, preventative therapy or emergency department visits. This remains a serious challenge in the treatment of both asthma and COPD.[1,2]

Global annual costs associated with asthma and COPD management are substantial from both the healthcare payer and societal perspective. Healthcare spending for an uncontrolled patient is more than double that of a controlled patient.[3]

An *in vitro* lung deposition study mimicking real-life patient technique and variable inspiratory flow rates reported that patients make at least one mistake when using an inhaler as often as 70–90% of the time, resulting in only 7–40% of the drug being delivered to the lungs.[4] The two biggest and most serious errors when using an MDI are both related to patient inhalation. The first error is related to the co-ordination between inhalation and triggering the dose release of the inhaler; even a short delay can result in only 20% of the medication being delivered to the lungs.[4] The second most significant error is not breathing deeply enough, which can cause another 10% less medication to reach the lungs.[4]

The opportunity for technological innovation to reduce these common errors, by measuring patient inhalation airflow through the device, is already available. Harnessing such allows for increased drug delivery efficacy, improved medication adherence, reduced healthcare costs and, ultimately, improved patient outcomes.

WHY MEASURE THE INHALATION FLOW PROFILE?

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As discussed prior, the two most frequent and serious errors patients make when using inhalers are related to their inhalation. Measuring the inhaled airflow through the inhaler, and in the case of MDIs also registering the point in time when the drug is dispensed,

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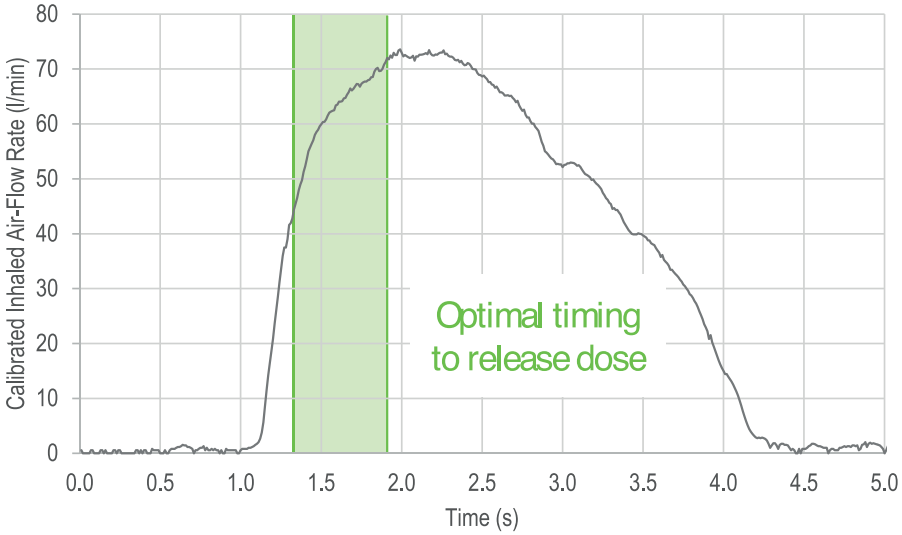

Figure 1: Inhalation flow profile showing the calibrated flow rate in standard litres per minute (l/min) versus the inhalation time in seconds (s).

Figure 2: Figure 2. Schematic illustration of drug deposition when the drug is released in the optimal timing window (left side) and when the drug is released too late (right side).

allows accurate determination of whether the drug was released within the optimal window of the inhalation cycle (Figure 1). This dose-trigger timing versus flow correlation is one critical parameter to understanding if the drug carrying flow reached deep into the bronchi and achieved the desired high lung deposition (Figure 2).

The second critical parameter is the inhaled airflow profile. Borrowing from spirometry, several parameters can be derived from the inhalation airflow profile that provide insights into a patient's inhalation:

- Depth and length of inhalation
- Entire exhalation before inhaling
- Slow inhalation according to instructions
- Lung function and its development over time.

Accurate and calibrated real-time recordings of the inhalation flow profile can provide this information, which can help determine whether or not the patient carried out the inhalation correctly and achieved a high lung deposition of drug product. Other parameters of interest include the inspired vital capacity (IVC) and peak inspired flow rate (PIF), along with the full inhalation airflow characteristics (Figure 3).

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Subsets of parameters, such as forced inspired volume during the first second of inhalation (FIV1) or the airway resistance (RAW), can also be determined from the inhalation airflow profile. The derivation of the latter is shown in Figure 4 (next page).

Some parameters, such as RAW, can be of special interest for patients with COPD, as it may relate directly to the condition of the disease. Adapting an inhaler to additionally serve as a spirometer-like device enables all parameters to be derived upon use without any additional effort or time-related burden to the patient (Figure 5, next page). Besides monitoring every inhalation through the inhaler for its quality and the correct use of the inhaler, monitoring these parameters over time can also be useful for providing feedback on the effectiveness of the medication, course of the disease, alerting a healthcare professional to problems, or be a great motivational tool for the patient to increase their adherence.

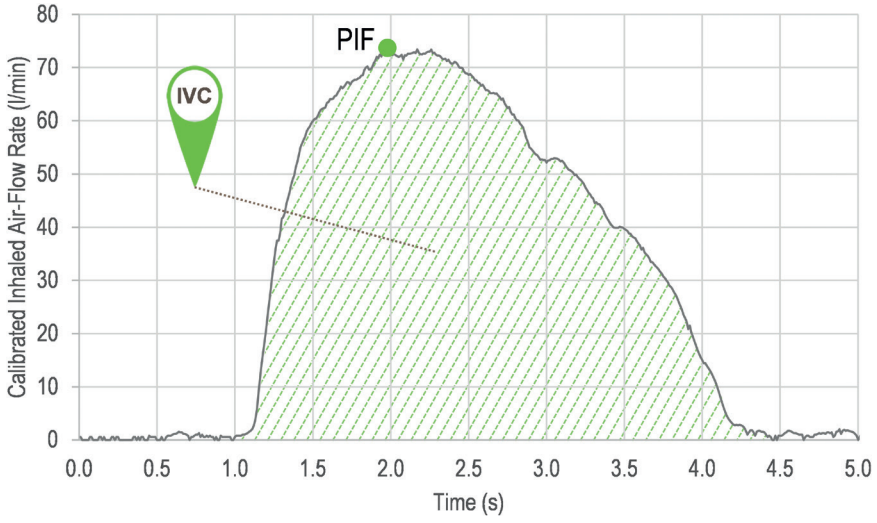

Figure 3. Parameters derived from the inhalation airflow characteristic: inspired vital capacity (IVC) and peak inspired flow rate (PIF).

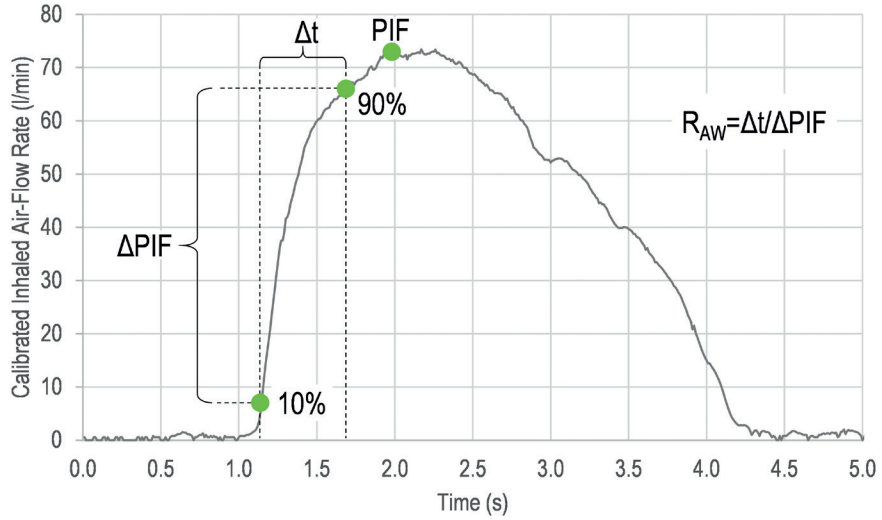

Figure 4. Besides the peak inspired airflow (PIF), the airway resistance (RAW) can be determined from calibrated inhalation airflow characteristics recorded with a sufficient high temporal and flow resolution.

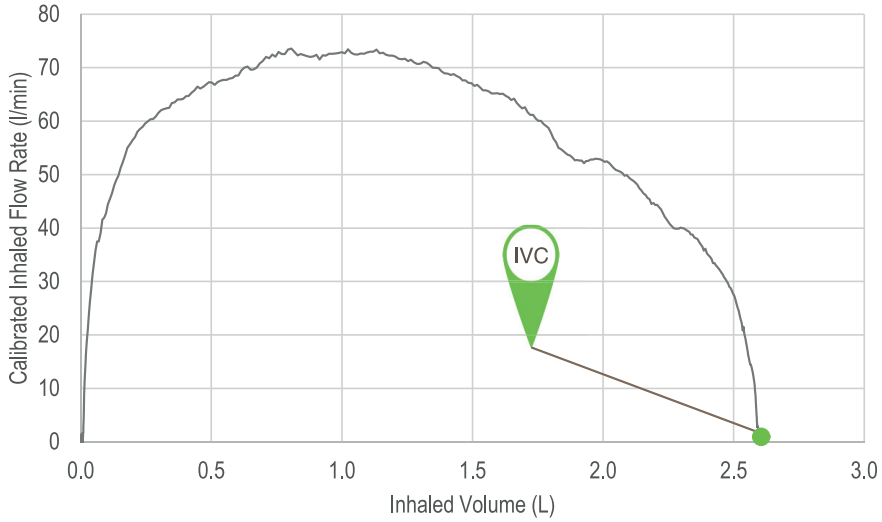

Figure 5. Typical spirometer plot of flow rate versus inhaled volume. The inspired vital capacity (IVC) is the total inhaled volume as the flow rate returns to zero at the end of the inhalation.

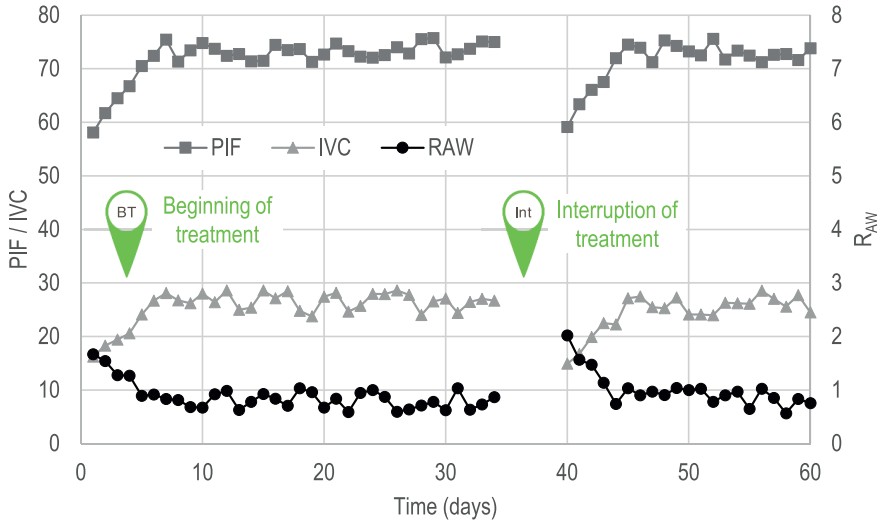

Figure 6. Peak inspired airflow (PIF), inspired vital capacity (IVC) and airway resistance (RAW) monitored over time, providing valuable feedback to the healthcare professional and the patient.

Cohero Health (New York, NY, US) already provides patients with an additional spirometer for exactly this reason, to allow the patients to routinely measure their lung function over the course of the treatment. This assists with direct disease management and sharing the collected data with medical professionals can help patients and clinicians to assess treatment progress. It can also enable a payment-by-results rather than pay-per-dose model. This same development can be observed in the insulin or sleep apnoea industry, where it has led to growing market shares for companies offering connected devices and simultaneously brought down treatment costs and, most importantly, improved patient outcomes.

Figure 6 shows an example of schematic behaviour for PIF, IVC and RAW versus time. It visualises the positive effect of starting the treatment, the stable treatment phase during regular dosage and the negative effect of interrupting the treatment.

Next-generation inhalers – natively incorporating airflow measurements in their design – will facilitate automatic dose release at the optimal point in time, individually tailored to the patient and their specific condition.

HOW TO MEASURE THE INHALATION FLOW PROFILE

Before inhalers natively include electronics and connectivity features by design, existing inhalers and inhaler platforms can be enhanced with the required electronics to achieve connectivity and sensing functionality. This is already being done today by companies such as Propeller Health (Madison, WI, US), Adherium, (San Mateo,

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CA, US) and others that have designed a variety of clip-ons for existing inhalers to add connectivity by monitoring parameters such as date and time of usage, as well as evaluating signals from additional sensors such as accelerometers, GPS and many more. In the past, accurate measurement of the flow through the inhaler was challenging due to the lack of sufficiently robust, yet sensitive devices capable of measuring the smallest flows. To avoid revalidation of the inhaler with the US FDA and maintain approval, the key regulatory requirement for all inhaler clip-ons is that the flow path of the inhaler remains unaltered, in order to ensure that it does not interfere with the inhaler's function.

To demonstrate how accurate flow measurement through an inhaler can be realised without interfering with the flow path, Sensirion has developed a functional inhaler clip-on. Figure 7 shows the 3D-printed inhaler clip-on containing the Sensirion flow sensor SDP3x, as well as a Bluetooth Low-Energy communications chip and a battery power source. It is notable that the inhaler housing has not been altered in any way and the flow measurement principle relies solely on the Venturi/Bernoulli principle at the inhaler inlet. The calibrated inhaler airflow shows excellent agreement to an external flow reference and was used for obtaining the flow profiles depicted in this article.

The unaltered and unobstructed inhaler flow path design is enabled by the extreme sensitivity of the Sensirion micro-electromechanical system-based (MEMS-based) flow-chip solution utilised in the SDP3x flow sensor series. This technology is based on the microthermal flow-through principle, the next-generation hotwire flow sensor technology that has been successfully used in medical ventilators for decades. In clip-ons for existing inhalers as well as newly developed inhalers, the key advantages of Sensirion's CMOSens® flow-chip technology can be summarised as:

Figure 7. 3D-printed inhaler clip-on containing the Sensirion flow sensor SDP3x in the side view (left) and top view (right) showing the unobstructed flow path of the inhaler.

"Robust and accurate flow measurement is an important feature for moving towards better disease management and patient outcomes, and is already realisable today."

- Highest sensitivity down to hundredths of a Pascal
- High temporal and pressure/flow accuracy
- Proven device in the medical and automotive industry
- Robust against being dropped and ultra-sonic welding process steps
- Inherently robust against external disturbances by the two-port design
- Low power consumption for portable and battery operation
- World's smallest commercially available flow sensor.

This makes the Sensirion SDP3x flow sensor series the flow sensor solution of choice for accurately measuring the inhalation flow profile in inhalation devices.

OUTLOOK OF FLOW MEASUREMENT IN SMART INHALERS

Adding a diagnostic unit to the drug delivery device that the patient is already familiar with is a powerful tool in asthma and COPD disease management. Improper inhalation technique leads to decreased efficacy through reduced deposition of drug in the lungs, which in turn leads to increasing disease severity and thus a worse patient outcome and an increase in healthcare costs. The solution of guiding the patient and providing direct feedback as well as supporting the patient in controlling the disease and increasing adherence have already been shown to improve patient outcomes by current connected drug delivery devices.

Thus, robust and accurate flow measurement is an important feature for moving towards better disease management and patient outcomes, and is already realisable today. The high percentage of patients suffering from asthma or COPD and misusing their inhaler, when significantly better outcomes would generally be possible with proper disease management, will continue to drive innovation for connected drug delivery. An increasing number of companies are already implementing digital technologies in their products to provide

an enhanced method of managing asthma and COPD, as well as improving the effectiveness of medication. The industry is advancing towards supporting the patient with the optimal treatment for their disease, not solely as a simple medical tool but as a companion device to remind, coach and provide relevant insight into their treatment and the course of their disease.

ABOUT THE COMPANY

Sensirion AG, headquartered in Staefa, Switzerland, is a leading manufacturer of digital microsensors and systems. The company's product range includes gas and liquid sensors as well as differential pressure and environmental sensors for measuring temperature and humidity, volatile organic compounds, CO_2 and particulate matter ($PM_{2.5}$). An international network, with sales offices in the US, Europe, China, Taiwan, Japan and Korea, supplies international customers with standard and custom-made sensor system solutions for a vast range of applications. Sensirion sensors can commonly be found in the medical, industrial and automotive sectors, analytical instruments, consumer goods and HVAC products.

One of the hallmark features of Sensirion products is the use of its patented CMOSens® technology, which permits intelligent system integration of the sensor element, logic, calibration data and a digital interface on a single chip. Sensirion's credentials as a reliable supplier are underscored by its loyal customers, quality reputation (ISO/TS 16949) and top customer pedigree.

ABOUT THE AUTHOR

Andreas Alt is Sales Director Medical at Sensirion. Dr Alt leads Sensirion's medical business and oversees the worldwide expansion of sensors and sensor solutions for the measurement and control of flow and environmental parameters into medical devices. Furthermore, he is responsible for medical OEM projects. He has a PhD in electrical engineering and experience in strategic market development and international project management.

REFERENCES

1. *Melani AS et al, "Inhaler mishandling remains common in real life and is associated with reduced disease control". Respir Med, 2011, Vol 105(6), pp. 930–938.*
2. *Press VG et al, "Misuse of respiratory inhalers in hospitalized patients with asthma or COPD". J Gen Intern Med, 2011, Vol 26(6), pp 635–642.*
3. *Sullivan SD, "The burden of uncontrolled asthma on the US health care system". Manag Care, 2005, Vol 14(8 Suppl), pp 4–7.*
4. *Biswas R, Hanania NA, Sabharwal A, "Factors Determining In Vitro Lung Deposition of Albuterol Aerosol Delivered by Ventolin Metered-Dose Inhaler". J Aerosol Med Pulm Drug Deliv, 2017, Vol 30(4), pp 256–266.*

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