

Telehealth Ready: Performance of the Amiko Respiro Sense connected technology with Merxin DPIs

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Summary

Data presented in this abstract demonstrate the use of Amiko Respiro Sense technology in the form of an add-on attachment to the blister and capsule based Merxin DPIs, MRX001 and MRX003. The technology can capture clinical and real-world adherence data used to steer treatment regimens and improve patient inhaler technique. Key device usage metrics such as peak inspiratory flow, inhalatory volume, inhalation time and the whole flow profile were collected and assessed using breath simulation apparatus and compared to estimations of these parameters provided by the Respiro Sense technology. Accuracy values were calculated to be around 90% or above for all these respiratory parameters, indicating that the combination of Respiro Sense with the Merxin devices can be used to accurately estimate key measures of inhaler usage and lung health.

Key Message

The Amiko Respiro Sense technology was combined with the Merxin blister and capsule based dry powder inhalers. It can be used to monitor true adherence, helping to improve inhaler technique and provide valuable lung health information to the patient and physician.

Introduction

Asthma and COPD are severe chronic conditions that often require life-long therapies from onset creating huge health and economic burdens.^[1] Many clinical trials have demonstrated that the currently available therapies are effective at reducing exacerbations and improving outcomes in controlled clinical environments, however a disconnect between these studies and real-world results has been observed.^[2] Sub-optimal patient adherence and inhaler technique are thought to be key drivers for this disconnect and can easily be improved with the intervention of a medical professional.^[2,3] Successful interventions start with the physician having detailed, reliable information about the patient's real-world usage of their inhaled therapy and an understanding of the best methods to improve inhaler technique and adherence.^[4] State of the art electronic monitoring devices or "connected devices" have been regarded as one of the most exciting leaps forward for inhaler development in recent years. Their ability to monitor adherence, track patient usage and provide detailed objective information to the physician make them ideal tools for aiding, informing and assessing the success of interventions. Most currently available devices simply track basic usage and adherence metrics, however successful actuation and reliable delivery of the required dose for respiratory medications often requires multiple, non-trivial steps. Many patients make technique errors when using their inhaler, resulting in compromised dose delivery leading to poor overall effectiveness of the treatment. A solution is required that provides a combined measure of correct dosing and accurate inhaler technique and has often been referred to as "true adherence".^[5] A thorough understanding of true adherence in both clinical and real-world settings is crucial for our understanding of effective inhaler usage and will inform personalised interventions promoting adherence and accurate inhaler technique.

Amiko have developed the proprietary Respiro Sense technology that collects advanced data on respiratory medication use and adherence. The Respiro Sense portfolio covers a whole range of integrated smart inhalers and add-ons to marketed and developmental inhalers focussing on the key drivers of functionality, low power consumption and cost-efficiency. Each integrated or add-on sensor uses the same off-the-shelf MEMS sensors and real-time machine learning to monitor digital signals, making the sensor readily transferable to a whole range of respiratory devices from pMDIs and DPIs to nasal devices, soft mist inhalers and nebulisers.

The unique digital fingerprint of each event of the inhalation manoeuvre for each device can be used to monitor when and how accurately a patient follows the user instructions, and the digital signal during each inhalation can be used to determine key measures of device performance and to determine indicators of lung health ^[6,7,8,9]. Critically, the add-on sensors allow the patient to continue using their accustomed therapy and physicians can use the data to optimise the patient's technique. The same handling steps are used to administer each therapeutic dose, the air flow path is not interrupted, and delivery performance is unaffected when using a Respiro sensor.

The Merxin DPI devices are designed to provide 505j substitutable device platforms for the delivery of APIs to the lungs and in particular fluticasone/salmeterol and tiotropium. The devices, MRX001 a blister based dry powder inhaler and MRX003 a capsule based inhaler, have the same user steps, performance characteristics to the respective originator reference devices. MRX001 and MRX003 are currently under clinical evaluation in different settings, from pilot PK to pivotal PD bio-equivalence studies, as well as in vitro setting for new molecules. The purpose of integrating the Merxin devices with the Respiro Sense technology was to test the compatibility of the Respiro Sense technology and its effectiveness in providing the Merxin clients and users with a telehealth option that would increase their chances of success in bio-equivalence studies by spotting outlier performers that could skew the results, and offer new commercial perspectives for new APIs formulated in the Merxin devices, including nicotine and cannabinoid applications.

Experimental methods and materials

Bespoke Respiro Sense attachments were developed for each device, MRX001 and MRX003, as shown in Figure 1. Each attachment contains the same MEMS (micro electro mechanical systems) sensors that provide consistent digital feedback for each critical step in the operation of the device. The requirements of the Respiro Sense attachments were: i) not to interfere with the normal patient handling of the device, ii) not to alter the airflow pathway, and iii) not to affect the effectiveness of dose delivery. For example, with MRX001, the Respiro Sense attachment was engineered not to hinder the operation of the cap and the lever and not to obstruct the air flow pathway. Likewise, use and air flow for the MRX003 device, shown in Figure 1d, should not be hindered by the addition of the Respiro Sense attachment.

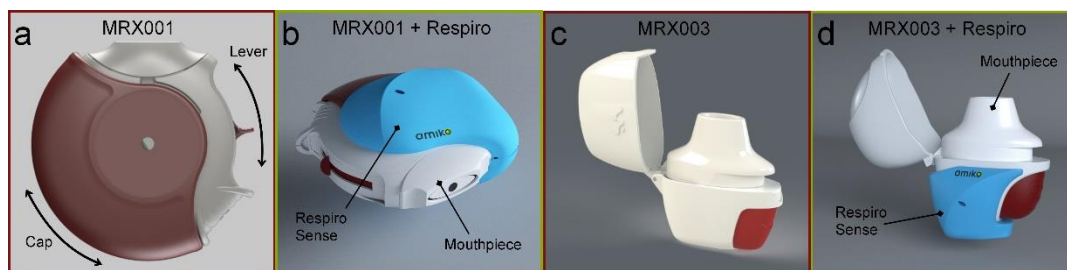


Figure 1 – A graphical representation of the MRX001 device (a) and the MRX003 device (c) with the Respiro Sense device attachments (b & d).

In order to test the sensitivity, compatibility and performance of the Respiro Sense attachments with the Merxin devices, digital fingerprint responses were acquired for each step of the inhalation manoeuvres. The following four key steps were recorded with MRX001 (inclusive of pre and post actuation steps): (i) open the device by rotating the cap to reveal the mouthpiece; (ii) push the lever away from the mouthpiece to move the dose from the blister into the mouthpiece; (iii) performing one inhalation via the mouthpiece; (iv) close the device by sliding the cap back to the original position until you hear a click. For MRX003, the inhalation manoeuvre was defined as the following (i) opening the lid and mouth-piece; (ii) inserting the capsule; (iii) closing the mouth-piece; (iv) piercing the capsule; (v) performing one inhalation; (vi) disposing of the capsule.

An example of the digital signal recorded for the inhalation step of MRX001 is shown in Figure 2 along with the flow rate estimation.

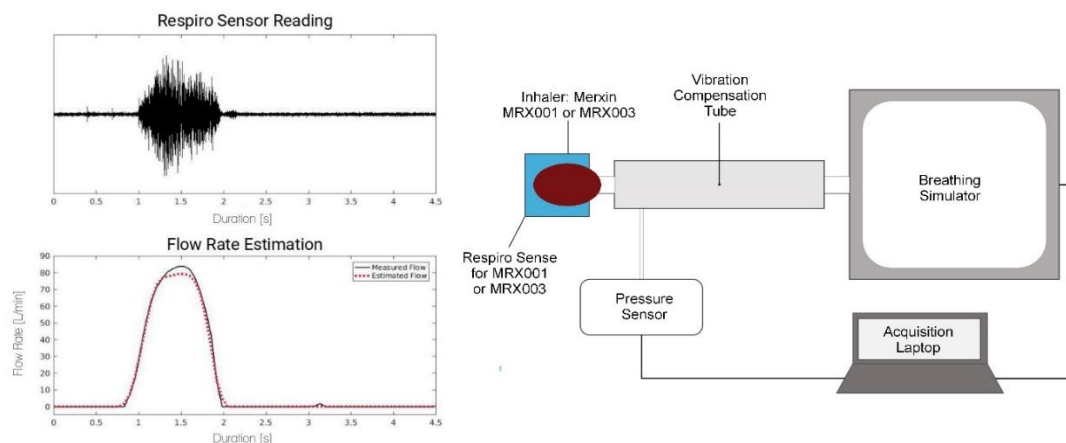


Figure 2 – A digital signal recorded by the Respiro Sense device (top left) translated into a flow rate estimation (bottom left, dotted red line) compared to the flow rate measured by an ASL 5000 instrument. A schematic of the experimental set-up for the Respiro sensor attached to the MRX001 or the MRX003 device connected to a breathing simulator via a vibration compensation tube with a pressure sensor. All data fed data into the acquisition laptop.

In order to assess the performance of the Respiro Sense device a set of test apparatus was designed to simulate human inhalation as depicted in Figure . The Merxin devices with the Respiro Sense attachments were connected to a lung/breath simulator (ASL 5000, Active Servo Lung, IngMar Medical, Pittsburgh, USA) via a vibration compensation tube with a pressure sensor attached. Both the breath simulator and the pressure sensor fed data into the acquisition laptop, which was then compared to data recorded by the Respiro Sense detector attached to the device. Respiro Sense uses real-time machine learning to identify the events in the inhalation manoeuvre and to translate the digital signal into an estimation of flow rate and inhalation volume.

Inhalers such as MRX001 and MRX003 require a forceful deep inhalation to ensure maximum dose delivery.^[10] It has previously been reported that many patients with asthma and COPD cannot produce a sufficiently forceful inhalation for successful dose delivery. We investigated whether the Respiro Sense technology could successfully estimate key parameters that could be indicators of accurate/true delivery of the dose and be indicators of lung health, such as peak inspiratory flow (PIF) and inhalation volume (IV) (depicted in **Error! Reference source not found.**). This was achieved by first creating large datasets of inhalation manoeuvres for each device over a clinically relevant range of peak inspiratory flow rates (28 L/min to 102 L/min for MRX001 and 21 L/min to 61 L/min for MRX003). During these inhalation manoeuvres, peak inspiratory flow and inhalation volume were monitored. The Respiro Sense attachment was then trained by correlating the true values of peak inspiratory flow and inhalation volume to adjust the complex algorithms to accurately estimate the parameters.

Each parameter measured by the Respiro sense technology (P_{est}) was compared to the experimentally determined value (P_{true}) using the following error formula, where N is the total number of inhalation manoeuvres and i is the manoeuvre index. The percentage accuracy of the Respiro Sense measurement over all manoeuvres was then used as an indicator of the performance of the Respiro Sense technology with MRX001 and MRX003.

$$\text{Error}(P_{true}, P_{est}) \text{ in } \% = \frac{1}{N} \sum_{i=1}^N \left| \frac{P_{true}(i) - P_{est}(i)}{P_{true}(i)} \right| \times 100 \%$$

Results and Discussion

Inhalation manoeuvre recognition was tested for both the MRX001 and MRX003 devices. 200 out of 200 manoeuvres were recorded accurately and therefore it was determined that the Respiro Sense technology is capable of identifying 100% of inhalation manoeuvres for the operation of both MRX001 and MRX003. This result shows that the Respiro Sense technology can now be used to monitor basic patient adherence when using the MRX001 and MRX003 devices and the combined connected device monitors inhaler actuations, equally or better than other inhaler electronic monitoring, such as the SmartTurbo^[11] and the SmartInhaler^[12].

The measured and estimated values for peak inspiratory flow (PIF), flow, inspiratory volume (IV) and inhalation time (IT) for the MRX001 device are plotted in **Error! Reference source not found.**. Each graph shows results of the full 200-point dataset except for the flow plot, which shows all flow estimates for each temporally partitioned window of 0.064 s. All graphs show a strong correlation of the measured parameter with the parameter estimated by the Respiro Sense device. The accuracy of flow reconstruction (89.40%), inspiratory volume (91.20%), peak inspiratory flow (88.03%) and inhalation time (94.84%) were all measured to be around 90% or above. This data is comparable to accuracy data acquired for MRX003 device for flow reconstruction (89.41%), inspiratory volume (90.88%), peak inspiratory flow (90.11%) and inhalation time (97.33%). The accuracy of the combined connected device is again better than or equal to other sensors based on auditory response determination of PIF and IC (inspiratory capacity).^[13]

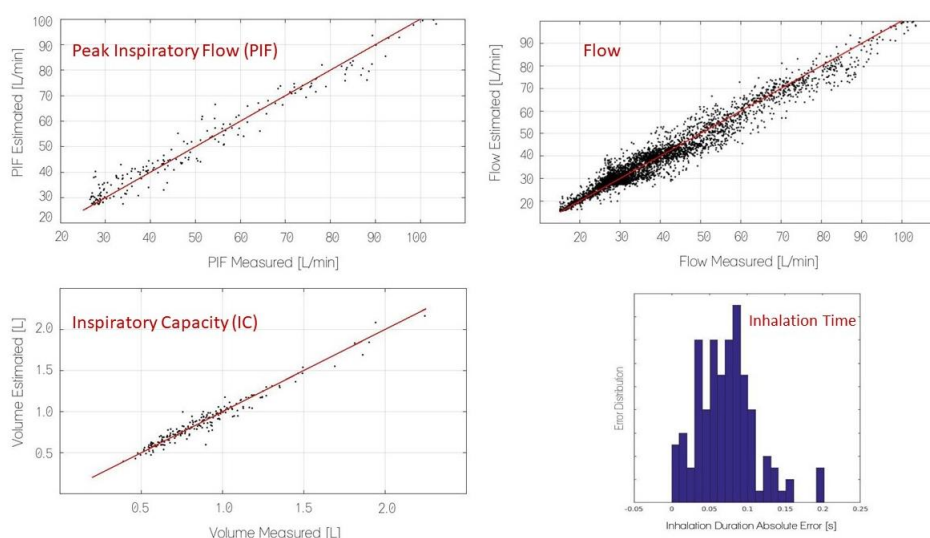


Figure 3 – Values for peak inspiratory flow (PIF), flow, inspiratory capacity (IC) and inhalation time for MRX001 measured using the experimental apparatus and plotted against equivalent values estimated by the MRX001 Respiro Sense detector. Red lines indicate where the measured value is equal to the estimated value.

The accuracy for peak inspiratory flow, inhalation volume and flow reconstruction in both the MRX001 and MRX003 are equal to or better than the of detection for MDIs^[13] or the Ellipta^[6] or Diskus^[14] DPIs when using similar auditory methods.

Conclusion

The Respiro Sense technology has been successfully integrated with the MRX001 and MRX003 devices showing that the devices can be connected with Respiro Sense technology and can provide a range of measures of inhaler usage and true adherence. The Respiro Sense technology and the Merxin blister and capsule devices are fully compatible.

Respiro Sense not only allows basic adherence monitoring but can also provide detailed information about key metrics for inhaler technique and lung health such as peak inspiratory flow and inhalation volume, more accurately than other devices on the market. This detailed information can be used in both clinical research and clinical practice to monitor the effectiveness of a therapy. Clinical researchers can obtain detailed information about the use of the therapy across the whole study facilitating thorough investigation of clinical data sets and monitoring of key indicators of lung health. For physicians, the Respiro Sense device represents a fantastic tool that can monitor ongoing patient use and indicators of lung health that can be used to effectively tailor improved interventions and treatment regimes.

Combined with well-established device platforms like the Merxin DPI devices and the Respiro Sense technology provides product developer and clinician with a ready solution for patient monitoring and adherence improvement.

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