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A narrative review on the Synchrobreathe™: A novel breath-actuated pressurised metered-dose inhaler for the treatment of obstructive airway diseases

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ABSTRACT

Pressurised metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs), are widely used to deliver drugs for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Incorrect use of inhalers is one of the main obstacles to achieving better clinical control. Indeed, with pMDIs, patients fail to synchronise actuation with inhalation due to a lack of coordination and with DPIs insufficient inspiratory effort compromises drug deposition in lungs. More than 50% of patients desire to switch their pMDIs and DPIs for a better device. This led to the development of pressurised breath-actuated inhalers (BAIs) with the aim of combining the beneficial features of pMDIs and DPIs and mitigating their problems. BAIs, e.g., Synchrobreathe™, are designed such that they are activated by a low inhalation effort and mechanically actuate the dose in synchrony to inspiration, thereby resolving the need to coordinate actuation with inspiration. BAIs have advantages, including ease of use, high lung deposition of medication, and greater patient preference. We discussed the design features, operating procedure, and clinical evidence of the Synchrobreathe™ device (Cipla Ltd, India), a BAI available with a wide range of drug combinations. Studies have shown that a higher number of patients (68.19%) used the Synchrobreathe™ without any error than the pMDI (56.21%), and that the vast majority of them (92%) found it easy to understand and use.

The Synchrobreathe™ is an innovative, easy-to-use inhaler that may overcome many limitations associated with pMDIs and DPIs, thus potentially improving management of obstructive airway diseases and patients' quality of life.

1. Introduction

There are an estimated 339 million patients with asthma [1] and 391.9 million patients with chronic obstructive pulmonary disease (COPD) in the world [2], and these numbers are likely to increase in the future. Most of the suffering and deaths associated with asthma and COPD occur in low- and middle-income countries [3,4], where inhalation therapy remains a challenge, not only for the limited availability, accessibility, and affordability but also for the frequent incorrect use of these devices by patients [3,5].

Inhalation therapy, including bronchodilators and corticosteroids, have improved asthma and COPD management because of increased efficacy along with an acceptable safety profile, leading to better quality of life [6–9]. Pressurised metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs) are widely used to treat asthma and COPD [10].

The key factors influencing the selection of an inhaler include its characteristics, such as efficacy (i.e., high lung deposition) and, ease of use, as well as patient's characteristics, such as severity of the disease, age, preference and economic condition [11]. The choice of a device should be tailored considering patient's features such as the degree of

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airway obstruction, presence of comorbidities, ability to correctly use the inhaler, particularly to produce enough inspiratory flow [12]. pMDIs provide the advantages of low cost, portability and reproducible dosing, but the drawback is difficulty in using them correctly. Many patients do not coordinate their breathing with pMDI actuation and often breathe in either too early or too late, resulting in suboptimal drug deposition to the lung and consequently poor disease outcomes [13–18]. Although DPIs do not need coordination like pMDIs, drug deposition depends entirely on the patient's own inspiratory flow rate. Some studies indicate that in elderly or patients with severe disease, drug delivery can be compromised when using DPIs with an insufficient inspiratory effort [19]. Moreover, DPIs differ in drug loading technique prior to inhalation and are affected by moisture and humidity that may compromise substantially drug delivery and efficacy [20,21].

It is well known that incorrect inhaler use is associated not only to poor outcomes but also to high degree of non-adherence to prescribed medicines. Further, many reason(s) may account for this finding, including poor knowledge by Healthcare Professionals (HCPs), and consequently lack of correct patients' education as well as the difficulty to combine in a single inhaler, ease of use and satisfaction for patients [22–24]. Notably, despite a continuous improvement in inhaler technology, the percentage of patients using inhalers incorrectly has remained unchanged over the past four decades [25]. An ideal inhaler should be easy to use, offer consistent dose delivery to the exact location in the respiratory tract, and be capable of delivering multiple drugs and should be patient centric [26,27]. Even though various types of inhaler devices are being used by patients, no single device has been recognised as the ideal inhaler. But even as research continues in the field of inhaler devices, BAIs show promising evidence of being a step in the direction of an ideal inhaler for patients. Pressurised metered-dose breath-actuated inhalers (BAIs) combine the two beneficial features of both pMDIs and DPIs: they do not need an) inspiratory flow >30 L/min, and do not need to coordinate inhaler activation with inhalation. In this article, we review the technical characteristics, the operating procedures and clinical evidence regarding the real-life effectiveness of the Synchrobreathe™ inhaler, a BAI that is available for delivering a wide range of drugs and drug combinations, including inhaled corticosteroids/long-acting beta$_2$-agonists (ICS/LABAs), long-acting muscarinic antagonists (LAMAs), and short-acting beta$_2$-agonists (SABAs) in India, and salmeterol/fluticasone in other countries [Table 2].

2. BAIs: bridging the design gaps in the current inhaler devices

Inability to coordinate pMDI actuation with inhalation is one of the most frequent errors that may reduce drug deposition in the airways and consequently their clinical efficacy [11,28]. Patients who are aware of the correct use of their device or their therapy would alleviate their respiratory symptoms are more likely to be adherent to prescribed treatments. Santus et al., showed that one of the major key factors for successful therapy of patients with chronic respiratory disorders is patients' engagement with the physician having the role to instruct patients about the importance of the correct inhaler usage [29]. Over time, DPIs gained attention as an alternative option due to their associated benefits in terms of portability, compactness, being easy to teach and use, and the absence of need for a spacer [30]. However, factors such as poor dose reproducibility, detrimental effects of moisture and humidity on the device's performance, and the need for a good inspiratory flow rate, i.e., the *correct* flow, differs substantially for each DPI and are the key limitations associated with them [31].

Therefore, BAIs were designed in a way that these devices will detect the patient's inhalation flow through a sensor and mechanically actuate the dose in synchrony, thus resolving the need to coordinate actuation with inhalation [32]. To the best of our knowledge, only few BAIs have been developed so far – these include the Autohaler® (3 M Healthcare Ltd, United States of America), the K-haler® (Mundipharma International Ltd, Cambridge, United Kingdom), the Easi-Breathe® (Teva Pharmaceutical Industries Ltd, Petach Tikva, Israel), and the Synchrobreathe™ (Cipla Ltd, India) [33]. A BAI automatically gets ready for usage when the patient opens the mouthpiece cover. The mechanism is activated, and a dosage is automatically delivered into the airstream when the patient inhales [34]. The detection mechanism of inspiratory flow differs among different BAIs. However, while most BAIs are available only with one drug or combination, the Synchrobreathe™ enables the use of various drug classes, viz. SABAs, ICS/LABAs, and LAMAs. Several studies have provided evidence that BAIs fulfil most of the criteria with regard to the desirable features of an ideal inhalation device [35]. These include patient preference, ease of use, better drug deposition, and improved efficacy. Furthermore, studies with these inhalers have corroborated evidence regarding the benefits of using BAIs over pMDIs and DPIs, particularly in elderly patients [36–49].

2.1. Understanding physician and patient perceptions of available inhalation devices in India: the INSPECT survey

A cross-sectional questionnaire-based survey named 'The INhalation deviceS: Physicians' PErCepTions (INSPECT) was conducted across different parts of the country to understand physician (n = 83) and patient (n = 1486) perceptions regarding the currently available inhalation devices, viz. pMDIs, pMDI with spacer, DPIs, and BAIs [46]. The survey was not limited to one disease condition and included patients with Asthma, COPD, ACO and rhinitis. The mean age of the patients in the study was 44.16 ± 10.95 years. The main findings were the following: a) *Fewer steps of use* and *simple and easy instructions to follow* were the top two attributes in which the patients desired a change over their current device; b) Inability to use the inhaler device was the most common reason cited by doctors for poor control. Hence, more than 50% of patients using pMDIs, pMDI + spacer, and DPIs, desired a change in their current devices. The complexity of the device and the difficulty in using it were the factors responsible for reduced adherence and satisfaction with treatment; and c) According to physicians' scores, *simple to understand and easy to follow* was the most important desirable attribute of an inhaler device for their patients, followed by *breath-actuated*, *integrated dose counter*, *compactness and portability*, and *minimal steps to use* (Fig. 1). Therefore, findings of the INSPECT survey suggest the need to have devices easier to understand and use, requiring few operative steps, breath-actuated, and cost-effective [50,51].

2.2. Overview of the Synchrobreathe™

The Synchrobreathe™ inhaler is a pressurised BAI that incorporates the compactness, portability and ease of use of a pMDI with the actuation on inspiration feature of a DPI. A characteristic feature of the Synchrobreathe™ is a built-in dose counter that advances when a dose is inhaled but not by opening or closing the dust cap [52]. Synchrobreathe™ has been evaluated in Asthma as well as COPD patients [Supplementary Table-1].

2.3. Design features and mechanism of operation

The Synchrobreathe™ inhaler is engineered to deliver a standard, uniform dose with just the simple trigger of inhalation by the patient (Fig. 2). It has a dome-shaped design to ensure that patients store the device in the upright position for optimal drug delivery. The integrated dust cap primes the device by preparing the inhaler for the next dose when it is closed. This also ensures that the dust cap cannot get lost and prevents potential foreign bodies from entering the inhaler. The internal design ensures that the biasing spring inside the device is kept compressed until the dust cap has been opened (Fig. 2) and the patient inhales at a flow rate that triggers the movement of the flap. With the help of a compressed spring, the collapsing of the engine mechanism causes the spring to force the canister downward to fire a dose. The inhaler's engine mechanism works in a reproducible and reliable manner to

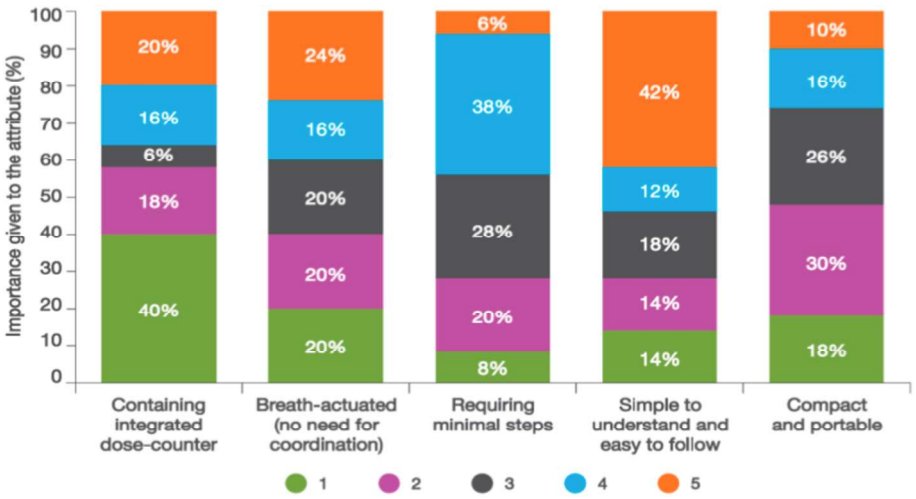

Fig. 1. Physicians' perceptions regarding attributes of inhalation devices [1 to 5 represent the scale for each of the attributes of inhalation devices (1 being least important and 5 being most important)].

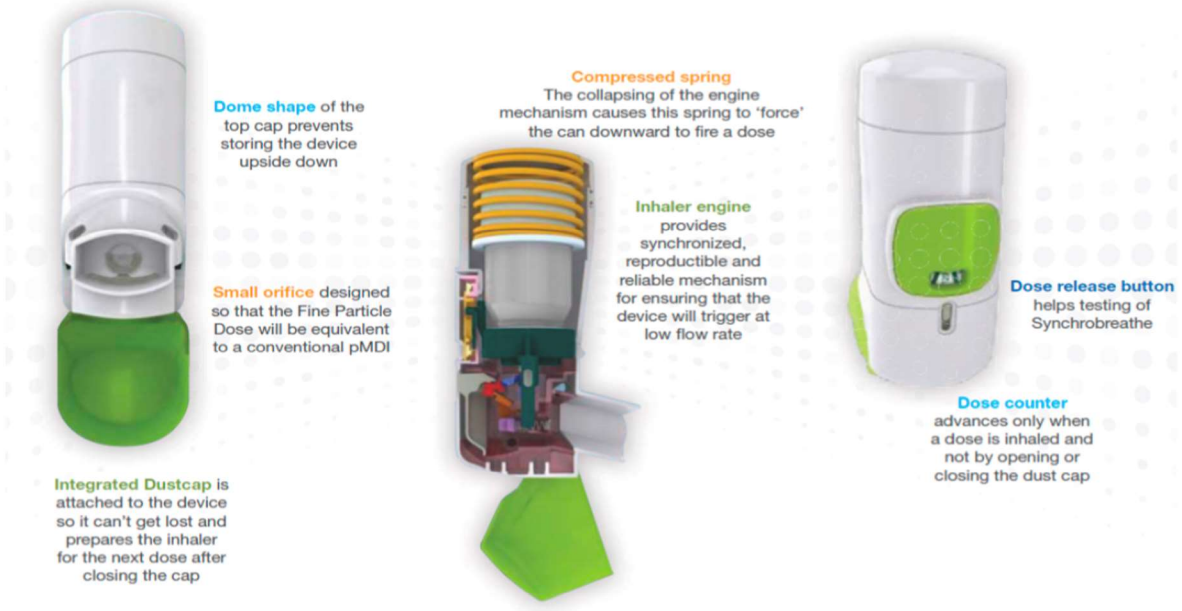

Fig. 2. External and internal components of the Synchrobreathe™.

ensure that the device will trigger at an inhalation flow rate ranging from 25 to 35 L/min, a flow level attainable by the vast majority of asthma and COPD patients even during an exacerbation [53]. The simple steps for using the Synchrobreathe™ are reported in Table 1 along with errors and their potential resulting consequences.

The dose counter counts each dose and moves every 20 puffs. When 40 doses remain, the colour on the dose counter changes from green to red, indicating that it's time for the patient to plan on getting a new device. The dose counter does not lock out at 0, but the device should no longer be used when the counter reaches 0. The dose counter has been designed keeping in mind the needs of patients and physicians and following the US FDA's guidance on 'integrated dose counters [54]. These dose counters undergo 100% in-process testing and process analytical technologies. The dose counter forms an integral part of the Synchrobreathe™ actuator and includes both numeric-counting mechanism to indicate doses remaining in the inhaler, as well as dose-indicating mechanisms via colour coding and numbering. It's a downward counting dose counter and starts slightly above the doses claimed on the label in order to take care of doses lost for priming. The last 40 doses are shown in red colour, which gives warning about few drug doses remain in the inhaler and '0' reading on the counter indicates to the user that the inhaler should not be used any further. However, the Synchrobreathe™ still works even if the counter shows '0.' This is in line with FDA's guidance that even partially therapeutic dose could be lifesaving.

2.4. Maintenance of the device

The Synchrobreathe™ inhaler should be cleaned periodically, ideally once a week. The mouthpiece should be cleaned by wiping it with a clean, dry cloth or tissue. Patients should not push a cloth or anything else into any part of the device as this may damage its operating parts. It is important to note that the Synchrobreathe™ should never be washed. It should always be kept dry.

Table 1
Correct operation procedures and errors with related consequences when using the Synchrobreathe™ inhaler.

Step Number	Procedure	Errors and resulting consequences
Step 1	**Shake and open.**	Not shaking the inhaler before use could cause insufficient drug delivery since shaking is required to make a homogeneous suspension when drug is suspended in the propellant. Not opening the device is an error as patient will not be getting any medication.
Step 2	**Inhale** **A:** Hold the device in an upright position. **B:** Breathe out normally as far as is comfortable (to empty the lungs). **C:** Place the mouthpiece of the device in your mouth and close your lips firmly around it. Start breathing slowly and deeply through the mouthpiece. It is important to keep breathing in after the puff is released. Maintain a slow and deep inhalation, through the mouth until your lungs are full of air. **D:** At the end of the inhalation, take the mouthpiece out of your mouth and close your lips. Continue to hold the breath for 10 s, or for as long as it is comfortable.	Not tightening the lips around the mouthpiece may reduce the negative pressure and hence Synchrobreathe™ device triggering. It also leads to the loss of actuated drug. Not holding the breath does not give sufficient time for the drug to deposit in the lungs and hence there is a loss of drug during exhalation.
Step 3	**Close** Close the mouthpiece cover immediately after every puff.	Not closing the mouthpiece cover after every puff, the device would not be prepared for the next dose. If the device mouthpiece cover is not closed between two acuations, and patient try to take the next dose, he/she would not get anything at all.

2.5. Composition, dosage, and administration

Currently, the Synchrobreathe™ inhaler model that is available in several countries (Table 2) delivers a suspension containing salmeterol 25 μg and fluticasone propionate 125/250 μg per actuation. In India, the Synchrobreathe™ is also available with single (levosalbutamol or tiotropium) as well as combination (salmeterol/fluticasone propionate, formoterol/budesonide; formoterol/fluticasone propionate) formulations (Table 2).

2.6. Studies on the Synchrobreathe™ device

2.6.1. In vitro lung deposition study

In an *in vitro* study, the measurement of the amount of drug delivered by the Synchrobreathe™ to the lungs was assessed in the form of fine-particle mass (FPM) using a cascade impactor. Salmeterol/fluticasone propionate (25/250 μg) doses for the Synchrobreathe™ and a pMDI were aerosolised into the cascade impactor. The results showed that the FPM measured with the Synchrobreathe™ was similar to that with pMDI for both salmeterol (Synchrobreathe™: 9.72 μg; pMDI: 9.24 μg) and fluticasone propionate (Synchrobreathe™: 95 μg; pMDI: 91.79 μg) [52]. A similar study was conducted with the Synchrobreathe™ formoterol/budesonide (6/200 μg) and pMDI formoterol/budesonide (6/200 μg) using the Next Generation Impactor. As for salmeterol/-fluticasone propionate, the FPM for both formoterol and budesonide were similar (2.29 μg with pMDI versus 2.43 μg with the Synchrobreathe™: for budesonide, 80.04 μg with pMDI versus 79.66 μg with the Synchrobreathe™) [55].

2.6.2. Consistency of dosing

The *in vitro* delivered dose uniformity analysis measures the uniformity of the delivered dose of drug over any inhalation device's initial, middle and end doses [56]. This test was also performed with the Synchrobreathe™ inhaler for the salmeterol and fluticasone propionate combination. Observations showed a steady dose delivery throughout the 120 doses of the test samples, thereby supporting the ability of the Synchrobreathe™ to maintain consistency of dosing from the very first dose to the last delivered actuation [52].

2.6.3. Spray pattern and plume geometry

A study was conducted using an aerosol drug spray analyser to identify the spray pattern and particle size to characterise the plume geometry for the Synchrobreathe™ and a conventional pMDI. Spray pattern and plume geometry was evaluated by using an aerosol drug spray analyzer (ADSA) instrument (Innovasystems Inc. USA). The laser supplied with the ADSA emits a continuous beam of light at a nominal wavelength that is cut and lighted horizontally while recording using a high-speed imaging. The device was placed in the ADSA actuation station, and the inhaler canister primed. The laser light sheet and actuator position were adjusted. Further a point marker was made to track the position where the light sheet intersects the orifice of the actuator. In the ADSA software, frame rate was adjusted at 30 frames per second and the exposure at 100%. As soon as the process spray/plume was clicked, spray got actuated, and plume was recorded automatically. The findings demonstrated a similar spray pattern (Ovality Ratio (Dmax/Dmin) of 1.2; Spray Area Ratio of 0.98, Plume Width Ratio of 0.97 and Plume Angle Ratio of 0.99), suggesting a comparable drug delivery with both inhaler types [57]. The experiment for the evaluation of spray angle, plume width and spray pattern for Synchrobreathe™ has been

Table 2
Drugs available with the Synchrobreathe™.

Drugs	Available strength	Frequency recommendations	Number of actuations available	Year of launch	Propellant/other ingredients	Countries Marketed
Salmeterol/Fluticasone Propionate	25/50 μg 25/125 μg 25/250 μg	2 actuations twice daily	120	2017[a]	HFA134a/Absolute alcohol Lecithin	India, Nepal, Iran, South Africa, UAE, Oman
Levosalbutamol	50 μg	PRN	120	2018	HFA134a/Absolute alcohol Lecithin	India
Formoterol/Budesonide	6/200 μg 6/400 μg	1–2 actuations twice daily	120	2020	HFA227/PEG1000 PVP K 25	India
Tiotropium	9 μg	2 actuations once daily	120	2021	HFA227/PEG1000 PVP K 25	India
Formoterol/Fluticasone Propionate	6/125 μg 6/250 μg	1–2 actuations twice daily	120	2021	HFA134a	India

Abbreviations: PRN: *pro re nata;* HFA: *Hydrofluoroalkane;* PEG: *Polyethylene glycol;* PVP: Polyvinyl pyrrolidone.
[a] Launch year in South Africa.

performed in triplicates. The mean spray angle was found to be 23.67 ± 1.27 (Mean ± SD) whereas the mean plume width was reported to be 3.48 ± 0.22 (Mean ± SD).

2.6.4. *In vivo gamma scintigraphy study*

In ten adult (age ranging from 18 to 70 years) asthma patients of both genders in stable condition, lung deposition of salmeterol and fluticasone propionate (25/125 μg) delivered by the Synchrobreathe™ was compared to that obtained using a conventional pMDI. According to a prospective, randomised, open-label, crossover, two-period, single-dose study, patients correctly inhaled one puff of Technetium-99 m radiolabelled salmeterol and fluticasone propionate combination (25/125 μg) via either the Synchrobreathe™ or a conventional pMDI (both from Cipla Ltd, India). The study results demonstrated (Fig. 3) a significantly greater lung deposition of the drug formulation with the Synchrobreathe™ (mean ± SD: 22.33 ± 3.1%) compared with the pMDI (mean ± SD: 17.32 ± 2.4%; $p < 0.05$) [52].

2.6.5. *Robustness studies*

The Synchrobreathe™ inhaler was tested extensively for its robustness in various conditions. In the drop test, robustness was tested by dropping the device from a height of 5 feet at various orientations – inverted, supine, and upright. Then the trigger flow rate (the flow rate at which the inhaler triggers the release of the drug formulation) and shot weight (the average weight of formulation per metered dose) were measured. The test results showed that there was no change in the trigger flow rate and the shot weight of the medication puff released. Similarly, it was further tested for robustness by storing it at 50 °C along with room humidity of 75% and then measuring the trigger flow rate and shot weight. Again, there was no change in the trigger flow rate and the shot weight of the medication puff released. The device was also tested for other robustness studies such as Vibration Test, Low & High Temperature Exposure and Dose counter Accuracy as per ISO 20072 [58]. All the robustness studies of Synchrobreathe™ have been reported in Table 3. These observations support and indicate the robustness of the Synchrobreathe™ [59].

2.6.6. *Device-handling study*

In an open-label, prospective, 2-week, multicentre study, we assessed the device usage, human factors, ease of use, errors, and perceptions regarding the Synchrobreathe™ inhaler compared with a pMDI in patients with asthma (n = 239), COPD (n = 162), and inhaler-naïve healthy volunteers (n = 59) [60]. On day 1, the number of participants using the Synchrobreathe™ without any error after reading the instructions in the patient information leaflet (PIL) was significantly lower than those using the pMDI (23.09% versus 29.41%; $p < 0.05$). It should be noted that, most of patients were already using a pMDI before enrolment into this study and, therefore, it was likely that they had received prior training in pMDI usage from health care professionals. However, healthy participants who used the Synchrobreathe™ without errors after reading only the PIL were more in number compared with those using a pMDI (25.42% versus 10.17%; $p < 0.01$). This shows that in case of the participants who were naïve to both the devices, the results favoured the Synchrobreathe™ in the beginning of the study. The participants were then trained and asked to use both the devices at home regularly for 14 days. On day 14, a significantly higher number of participants (68.19%) used the Synchrobreathe™ without any error compared with the pMDI (56.21%; $p < 0.001$). This suggests that the Synchrobreathe™ is an easier-to-learn device than a pMDI device [60] (Fig. 4).

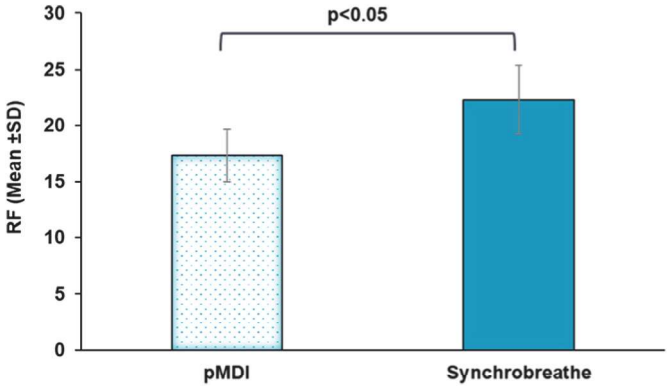

Fig. 3. Mean (SD) respirable fraction (RF) of salmeterol and fluticasone propionate fixed-dose combination (25/125 μg) delivered with the Synchrobreathe™ versus the conventional pMDI in patients with stable persistent asthma *$p < 0.05$.

The total number of inhaler errors before and after training were significantly lower in patients using the Synchrobreathe™ than those using the pMDI (2.83 versus 3.46; $p < 0.001$) on Day1. Other endpoints, including the average time required to perform the inhalation technique correctly (65.84 s versus 67.70 s; $p < 0.01$) and average number of attempts to inhale correctly (1.26 versus 1.69; $p < 0.001$) were significantly lower with Synchrobreathe™ than the pMDI on Day 1. Overall, 88.5% of participants preferred Synchrobreathe over the pMDI (6.1%). Similarly overall satisfaction was also very high with Synchrobreathe (89.4% participants) compared with the pMDI (5.23% participants). Synchrobreathe was the preferred choice of device over the pMDI in about 90.5% of participants. Synchrobreathe was also the preferred choice of inhaler along with higher overall device preference, satisfaction and choice of inhaler over the pMDI (in 90.5% of participants) in the subgroups of asthma, COPD and healthy participants. Further, 92% of patients stated that *Synchrobreathe™ is an easy-to-use device*, 88.5% of patients said that *steps of Synchrobreathe™ were easy to understand*, and 88% of patients opined that *Synchrobreathe™ was easy to learn*. Overall, the patient feedback showed that more patients preferred the Synchrobreathe™ over a pMDI [60].

2.6.7. *Real-world studies*

A real-world, multicentre study in India assessed asthma control and device usability with respect to the salmeterol/fluticasone propionate combination administered through the Synchrobreathe™ in 490 patients with persistent asthma (CTRI/2018/12/016629) [60]. The study demonstrated a significant reduction in the mean Asthma Control Questionnaire-6 (ACQ-6) score (−1.2 versus −1.9) and significant improvement in the peak expiratory flow rate at the end of week 12 from baseline with significant changes from week 4 (35.1 L/min versus 56.72 L/min; $p < 0.0001$ and $p < 0.005$, respectively). Up to 77.10% of patients achieved well-controlled asthma at the end of week 12, and over 90% of the patients gave a high rating for the device on the basis of ease of use, confidence when using, satisfaction, and device preference. The safety assessment reported 13 adverse events and two deaths, which were not related to the study drug. Therefore, the results overall indicated that the salmeterol/fluticasone combination administered through the Synchrobreathe™ was effective for asthma control and well tolerated in patients, and device usability also received high ratings [61]. In the recently concluded ERS a study of ICS/LABA delivered through Synchrobreathe™ in COPD patients was presented. The study subjects showed a significant reduction in the CAT score and 97.58% patients preferred Synchrobreathe™ over their previous inhalers [62].

We also performed a cross-sectional, questionnaire-based survey to evaluate the perceptions and experiences of 141 doctors (mostly [~90%] chest physicians and internal medicine practitioners) from Nepal regarding BAIs. This survey was conducted after almost 1 year of the Synchrobreathe™ inhaler being available in Nepal. Up to 95% of the physicians preferred to prescribe a BAI to their newly diagnosed patients. If their current patients were shifted to a BAI, 88% of physicians believed that it could improve their patients' inhalation technique and 80% said it would increase patient compliance/adherence. More than

Table 3
Robustness studies of Synchrobreathe™[5,4].

	Study Design	Parameters Recorded	Observation and Conclusion
Triggering flow rate through container life	The study was conducted on 10 sprays each at initial, middle and end stage of the container. The study was conducted using a Dosage Unit Sampling Apparatus (DUSA, Copley Scientific, UK).	Visual check, triggering flow rate and Counting accuracy.	No visual defects were observed for the Synchrobreathe™ device. The counting accuracy of Synchrobreathe™ was found to be satisfactory. The triggering flow ranged from 28.10 to 30.4 lpm through container life.
Shot weight through container life	The study was conducted on 10 sprays each at initial, middle and end stage of the container. The shot weight was determined by calculating the difference between before and after weight of Synchrobreathe™.	Shot weight	The individual shot weight ranged from 73.2 to 78.6 mg which was within the pre-established acceptance criteria. It can be concluded that the spray actuated through Synchrobreathe™ is well within the specifications, throughout the container life.
Influence of different temperature conditions	The study includes subjecting samples at, a. −20 °C±5 °C in deep-freezer for 96 h, b. 50 °C±2 °C in oven for 96 h, The samples from the deep freezer/oven were then removed and subjected at room temperature for minimum 5 h before testing. Visual check, shot weight and counting accuracy was evaluated pre and post exposure.	Visual check, shot weight and Counting accuracy of Synchrobreathe™.	The individual shot weight ranged from 72.2 to 78.2 mg for −20 °C±5 °C condition and 73.7–75.2 mg for 50 °C±2 °C condition, which are well within the acceptance criteria. The counting accuracy of Synchrobreathe™ was found to be satisfactory. Also, no visual defects were observed after subjecting the samples to the said temperature conditions. The study concludes that Synchrobreathe™ can withstand varying environmental conditions.
Drop test	It was evaluated by dropping the Synchrobreathe™ with cap closed and cap open. To study the impact resistance, each Synchrobreathe™ was subjected to different falling conditions and in Valve down, Valve up and Valve horizontal orientations.	Visual check, Shot weight and Counting accuracy of Synchrobreathe™.	After every fall, Synchrobreathe™ was visually evaluated for the damage, no such observation was reported for the three falls conducted as per the study design. The Synchrobreathe™ could register the count after each fall. The individual shot weight was found in the range of 73.5–78.5 mg with cap closed and 73.5–78.9 mg for cap open. The counting accuracy of Synchrobreathe™ was found to be satisfactory.

Abbreviations: DUSA: Dosage Unit Sampling Apparatus.

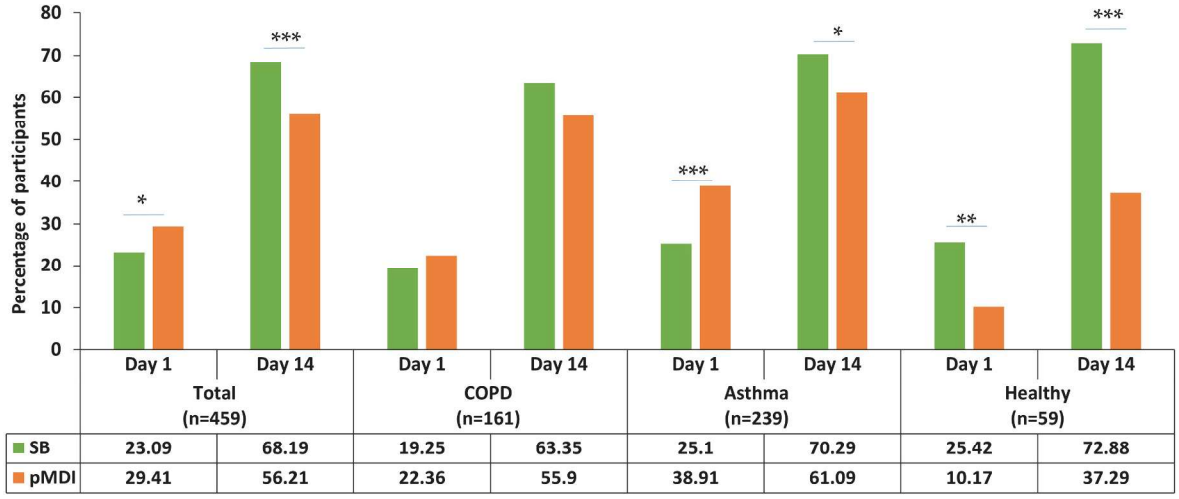

Fig. 4. Percentage of participants who used the Synchrobreathe™ (SB) and the pMDI without errors after reading the patient instruction leaflet. *p < 0.05; **p < 0.01; ***p < 0.001 versus pMDI. Reprinted from Respiratory Medicine, VOLUME 161, 105707, Santhalingam Balamurugan, Komalkirti Apte, Bhanu Pratap Singh, Ashish Kumar Deb, Chandrahas Deshmukh, Kinjal Modi, Ajay Godse, Raja Dhar, Keya Rani Lahiri, Virendra Singh, Hiren Pandya, Sujeet Rajan, Abhijit Vaidya, Vaibhav Gaur, Jaideep Gogtay, "Device-handling study of a novel breath-actuated inhaler, Synchrobreathe®,versus a pMDI", Pages No. 1-9, Copyright (2020), with permission from Elsevier.

90% of physicians agreed that BAIs were the easiest and least time-consuming to teach with regard to the inhalation technique and the cleaning process. BAIs were considered easy to use, with a technique that was easy to teach, learn and remember, by almost all interviewed physicians (~99%) in the survey [63].

Usability and efficacy of Synchrobreathe ™ in children with special needs was communicated in a clinical correspondence letter by a clinician. He found in the study that major benefit of BAI is that it solves the issue of children having to breathe through a spacer for at least 6 to 10 breaths after the device is actuated. In addition, BAI makes it simpler for kids to operate by requiring a low inspiratory flow rate. As the medication is delivered more slowly with BAIs, decreased oropharyngeal deposition and increased lung deposition have also been observed [64]. Overall, Synchrobreathe ™ can be considered as beneficial in pediatric population too as compared to pMDIs.

3. Summary and conclusion

Currently, pMDIs and DPIs are still the most widely used inhaler devices despite their well-known limitations in usability that negatively affect disease outcomes. The Synchrobreathe BAI is a simple-to-use, convenient, cost-effective, and patient-friendly inhaler that can overcome many limitations associated with pMDIs and DPIs. It integrates the *compactness, portability, and ease of use* of pMDIs with the '*actuation on inspiration*' feature of DPIs. There are only a few companies that manufacture BAIs in various parts of the world and Synchrobreathe™ is a state-of-the-art BAI researched, developed in-house, and patented by Cipla Ltd (India) to help patients in using inhalers correctly every day.

For healthcare providers, the Synchrobreathe™ inhaler is easy to demonstrate and teach; for the patients, it is easy to learn, remember, and use correctly.

Overall, real word evidence establishes the superiority of the Synchrobreathe™ over pMDIs, mainly overcoming the widely acknowledged problem of coordination between actuation and inhalation in pMDIs and resulting in greater lung deposition of the medication compared with a pMDI. Therefore, the Synchrobreathe™ truly represents a real innovation in inhaler devices that can aid in better management of airway diseases and in improving the quality of life of patients. Further, as the Synchrobreathe™ BAI is available with multiple drug formulations (individual and combination), we believe that this type of inhaler device will also realise its true potential in the near future. Further, we can also expect data on device usage among various groups of patients, such as the elderly and children with severe asthma and severe COPD, with the diverse drug formulations available with the Synchrobreathe™.

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Declaration of competing interest

There is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2023.107435.

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