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Device-handling study of a novel breath-actuated inhaler, Synchrobreathe®, versus a pMDI

Santhalingam Balamurugan[a], Komalkirti Apte[b,*], Bhanu Pratap Singh[c], Ashish Kumar Deb[d], Chandrahas Deshmukh[e], Kinjal Modi[f], Ajay Godse[g], Raja Dhar[h], Keya Rani Lahiri[i], Virendra Singh[j], Hiren Pandya[k], Sujeet Rajan[l], Abhijit Vaidya[m], Vaibhav Gaur[m], Jaideep Gogtay[m]

[a] Sri Muthukumaran Medical College Hospital and Research Institute, Chennai, India
[b] Chest Research Foundation, Pune, India
[c] Midland Hospital, Lucknow, India
[d] Sudbhawana Hospital, Varanasi, India
[e] KEM Hospital and SGS Medical College, Mumbai, India
[f] Meeti Lifeline Hospital, Mumbai, India
[g] Bhaktivedanta Hospital, Mumbai, India
[h] Fortis Hospital, Kolkata, India
[i] Padmashree Dr. D. Y. Patil Medical College, Hospital & Research Centre, Navi Mumbai, India
[j] Asthma Bhawan, Jaipur, India
[k] Ratandeep Multispecialty Hospital, Ahmedabad, India
[l] Bhatia General Hospital, Mumbai, India
[m] Medical Affairs Department, Cipla Ltd, Mumbai, India

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ABSTRACT

Introduction: Synchrobreathe®, a new-generation, novel breath-actuated inhaler (BAI) can address the key issues arising during the use of both pressurised metered dose inhalers ([pMDIs]; hand-breath coordination) and dry powder inhalers ([DPIs]; high inspiratory flow required) with respect to optimal drug deposition.

Materials and methods: This was an open-label, prospective, 2-week, multicentre study that assessed device handling, ease of use, errors and participant perception regarding the use of Synchrobreathe® versus a pMDI in patients with chronic obstructive pulmonary disease (COPD) (n = 162) or asthma (n = 239) and inhaler-naïve healthy volunteers (n = 59). Ability to use the device without errors at the first attempt, total number of errors before and after training, time taken to use the device correctly and total number of training sessions, and number of attempts to perform the correct technique on Day 1 and Day 14 were evaluated. Device handling and preference questionnaires were also administered on Day 14.

Results: Of 460 participants, 421 completed the study. The number of participants using Synchrobreathe without any error after reading the patient information leaflet (PIL) was significantly low ($p < 0.05$) on Day 1. On Day 14, significantly more number of participants used Synchrobreathe without any error ($p < 0.001$). The total number of errors before and after training with Synchrobreathe was significantly less ($p < 0.001$). The average time required to perform the inhalation technique correctly ($p < 0.01$) and the total number of attempts ($P < 0.001$) with Synchrobreathe were significantly lower. The average number of attempts to inhale correctly was significantly ($p < 0.001$) less with Synchrobreathe on Day1 and Day 14. Most participants rated Synchrobreathe as their choice of inhaler.

Conclusion: Synchrobreathe is an easy-to-use and easy-to-handle device with significantly less number of errors, which may have positive implications for disease control in asthma and COPD.

1. Introduction

Inhalation therapy is the cornerstone of successful management of obstructive airway diseases (OADs) such as asthma and chronic obstructive pulmonary disease (COPD) due to its two-fold benefits – drug delivery to the target organ, and less systemic exposure with minimal

* Corresponding author.
E-mail address: drkomalapte@crfindia.com (K. Apte).

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adverse effects on other organs [1–3]. Different types of inhaler devices such as pressurised metered-dose inhalers (pMDIs) with or without spacers, dry powder inhalers (DPIs), breath-actuated inhalers (BAIs) and nebulisers are available, which provide the physician and the patient the opportunity to select/use a device based on the ability of patients and preference of patient and physicians.

Despite this, a majority of physicians report poor inhaler technique and non-adherence to inhaler devices among their patients, which can result in a high economic burden on healthcare cost and utilisation, both directly and indirectly, involving exacerbations, increased hospitalisations/hospital visits, poor quality of life and increased morbidity and mortality [4]. Although the pMDIs are convenient and relatively inexpensive, the coordination between actuation and inhalation through a pMDI remains a key challenge. The DPIs require a high inspiratory flow rate for optimum drug delivery to the lungs. The lung deposition can be reduced if the inhalation is too slow or if the time to peak inspiratory flow is too long [5]. While selecting an inhaler for a patient, parameters such as the patient's ability to inhale through the device (inspiratory flow rate), intrinsic property of the device to resist the airflow and the degree of release of drug on inspiration must be considered and then a conscious choice can be made [6].

A breath-actuated inhaler (BAI) contains a conventional pressurised canister, which releases the dose during inhalation due to negative pressure within the device and overcomes the need to facilitate coordination of the actuation and inhalation [5,7,8]. As such, BAIs could further improve treatment adherence and outcomes in patients with OADs [9]. In comparison with a pMDI, BAIs have demonstrated consistent lung deposition not only in patients with good hand-mouth coordination but also in patients with poor hand-mouth coordination while using a pMDI [10,11]. In a study with 100 patients and seven different devices, 91% of patients demonstrated good technique with BAIs [12]. In one of our previous studies, it was found that patients also preferred a BAI over the conventional pMDI [13].

Synchrobreathe is a new-generation, novel BAI with an integrated dose counter, which combines the salient features of both pMDIs and DPIs. It has a soft-triggering mechanism and gets actuated at lower inspiratory flow rates of approximately 27–30 L/min, which can be generated by almost all patients with OADs [14–16]. This helps Synchrobreathe overcome the key issues of both pMDIs (hand-breath coordination) and DPIs (high inspiratory flow required) with respect to optimal drug deposition [17].

The present study was conducted to evaluate device handling, human factors, ease of use, errors, and participant perception regarding Synchrobreathe inhaler (BAI) versus a pMDI in patients with COPD or asthma and inhaler-naïve healthy volunteers. However, any comparison between the inhalation drugs used either in combination or alone was beyond the scope of this study.

2. Materials and Methods

2.1. Study design and methods

This was an open-label, prospective, comparative, 2-week, multicentre (11 centres in India) study assessing the device handling, human factors, ease of use, errors and participants' perception regarding the use of Synchrobreathe versus a pMDI in patients with COPD or asthma and inhaler-naïve healthy volunteers. The first patient's first visit was on 26/06/2016, and the last patient's last visit was on 06/03/2017.

This study was performed in compliance with the Declaration of Helsinki and Indian Good Clinical Practices (GCP). Approval from the Institutional Ethics Committee was obtained before commencing the study. The study was registered under the Clinical Trials Registry of India (CTRI) number: CTRI/2015/08/006092. Written and signed informed consent was obtained from all participants before commencement of the study. Sponsorship of the study and devices was provided by Cipla Ltd, India. Data management and statistical analysis were performed by an external agency.

2.2. Participants

The study included healthy volunteers, patients with a confirmed diagnosis of asthma [18] aged between 5 and 80 years and patients with a confirmed diagnosis of COPD [19] aged between 40 and 80 years, without gender bias/preference. On Day 1, spirometry procedure was performed on the patients to confirm the diagnosis and assess disease severity. In children who were unable to perform spirometry, an alternate procedure was done using a peak flow meter. It was mandatory for the participant to have been using a pMDI for a minimum of 3 months. Participants were required to be able to read, write and understand the English language to provide responses to the questionnaire. Participants who were current or past users of any BAIs were excluded.

On Day 1, the patients with asthma and COPD already using a pMDI were asked to perform the inhalation technique with a pMDI with placebo and patients using a pMDI + spacer were asked to read a device-handling leaflet for pMDI and, later, asked to demonstrate the pMDI usage once. All the errors performed by the patients were recorded. Patients were provided training on using the pMDI and the time and number of training sessions required to perform the inhalation technique correctly were recorded. Healthy volunteers were provided a pMDI device-handling leaflet to read and then asked to perform it once and all the errors made were recorded. Healthy volunteers were trained on using a placebo pMDI and the time and number of training sessions required to perform the inhalation technique correctly were recorded.

Later, all the participants were provided with the patient information leaflet (PIL) for Synchrobreathe inhaler and were asked to demonstrate the device usage. All the errors were recorded and all the participants were provided training once on the use of the device.

Patients with COPD and asthma were to continue taking their regular medication as prescribed for their therapy from a pMDI and along with that, one puff twice daily through placebo-based Synchrobreathe inhaler. For the study period of 2 weeks, healthy volunteers and participants/caregivers using pMDI + spacer for their regular medication therapy were to take one puff twice daily from both placebo Synchrobreathe inhaler and a placebo pMDI. A telephonic contact was made to the participants after one week to ensure compliance of study device at home.

On Day 14, all the participants/patients demonstrated the inhalation technique only once, without training, with both the devices and number of errors were recorded. If the first attempt had errors, participants were provided training again on both inhaler techniques until accuracy was achieved. The time and number of training sessions required to perform the technique correctly with each device were recorded. Participants were given a device-handling and ease-of-use questionnaire for Synchrobreathe at the end of 14 days of use. This was a non-validated questionnaire developed internally considering the different steps that are involved in using Synchrobreathe. The questionnaire was self-administered with 19 questions divided into seven sections (Table 5).

All participants were asked to record their responses about ease of use, device handling, portability, dose-counter efficiency, usage confidence and satisfaction, and Synchrobreathe device preference through this questionnaire. The percentage of participants who preferred using Synchrobreathe inhaler over a pMDI was recorded. The study design is depicted in Fig. 1.

The safety endpoints were incidence and nature of adverse events (AEs). Every AE was recorded from the time of administration of study drug to the end of the study. AEs were coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA 17.1) terminology, coded to the corresponding System Organ Class (SOC) and Preferred Team (PT). The number of deaths was summarised; the number of patients who had at least one serious AE (SAE) and which

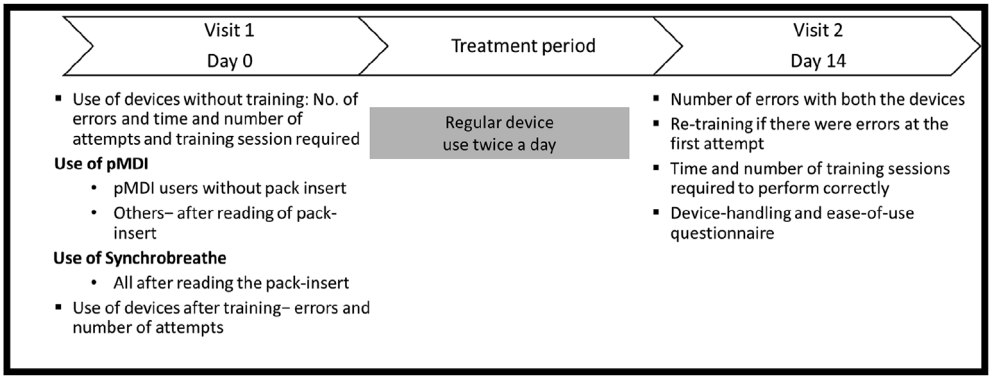


Fig. 1. Study design: Open-label, prospective, comparative, multicentre (11 centres) study; 460 subjects (59 healthy, 239 asthma, and 162 COPD patients).

was judged by the investigator to be causally related by SOC and PT to the treatment group were also summarised. The World Health Organization Drug Dictionary (WHODD; June 02, 2014 or later) was used for coding medication.

Study Device and Treatment – Synchrobreathe (Placebo images)

2.3. Statistical analysis

2.3.1. Efficacy analysis

The demographic and baseline characteristics such as age, gender and body mass index were analysed and summarised using descriptive statistics. Personal, medical and surgical history was recorded at the screening visit.

Percentage of participants who used the Synchrobreathe inhaler without any errors after reading the PIL and thus meeting the primary endpoint were summarised descriptively. The mean change from Visit 1 to Visit 2 for healthy volunteers, asthma patients and COPD patients was calculated using paired two-tailed *t*-test at 95% confidence interval (CI), and the p-value was provided. The number of errors without training at Visit 1, for both devices, was recorded using numbers, standard deviation (SD), standard error (SE), median and range. The statistically significant differences between both visits were calculated using paired two-tailed *t*-test at 95% CI. The statistically significant differences between healthy and asthmatic participants, healthy and COPD participants, and between Synchrobreathe and the pMDI were calculated using independent two-tailed *t*-test at 95% CI of significance. Device-handling and ease-of-use questionnaire responses and participants having overall preference for Synchrobreathe over the pMDI were analysed using numbers and percentages.

2.3.2. Safety analysis

Descriptive statistics of incidence rates were used to evaluate AEs, including SAEs, AEs leading to withdrawal and deaths (if any), and reasons for early withdrawal from the study. All SAEs were summarised using number and percentage.

3. Results

3.1. Baseline and demographic characteristics

In this study, 460 participants (235 males and 225 females), consisting of 59 healthy volunteers, 239 patients with asthma and 162 patients with COPD, were enrolled [Table 1 and Fig. 2]. Out of the 460 participants, 421 participants (52 healthy, 219 patients with asthma and 150 patients with COPD) completed the study. Altogether, 39 participants discontinued from the study and reasons for withdrawal included patients lost during follow-up (10), protocol violation (19), inability to use the study device (1) and protocol deviation (3). Data of 1 patient categorised as COPD was not considered for analysis as patient was not diagnosed as per recommendation in guidelines and age defined in the protocol. There was only one withdrawal due to inability to use the Synchrobreathe device.

Table 1
Demographic characteristics at baseline (Safety Population).

Parameters	Total (N = 460)	COPD (n = 162)	Asthma (n = 239)	Healthy (n = 59)
Age (mean ± SD) (years)	47.69 ± 24.03	62.25 ± 9.28	41.07 ± 26.04	34.58 ± 24.50
Male n (%)	235 (51.09)	83 (51.23)	120 (50.21)	32 (54.24)
Duration of disease, n (years), (mean ± SE)	7.90 ± 0.38	7.13 ± 0.40	8.43 ± 0.57	NA
Severity of disease				
Mild	76 (16.52)	7 (4.32)	69 (28.87)	-
Moderate	171 (37.17)	71 (43.83)	100 (41.84)	-
Severe	154 (33.48)	84 (51.85)	70 (29.29)	-

NA = not applicable.

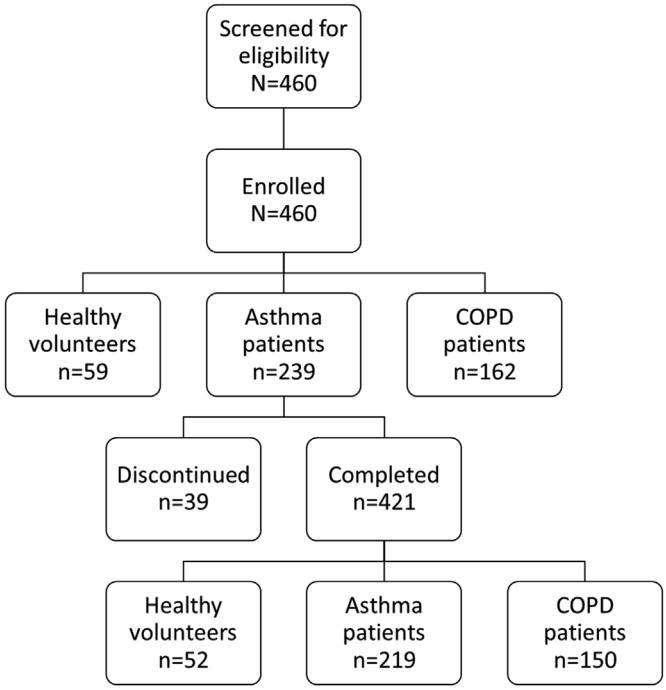


Fig. 2. Patient flowchart for patient enrolment and follow-up diagram.

3.2. Efficacy results

3.2.1. Device use and errors after reading PIL only

Overall, the number of participants using the Synchrobreathe inhaler without any error after reading the PIL was significantly low (23.09%; $p < 0.05$) compared with pMDI (29.41%) on Day 1. Similarly, significantly less number of patients with asthma performed correctly with Synchrobreathe compared with the pMDI. However, no difference was observed between the Synchrobreathe and pMDI devices in the patients with COPD. Significantly more number of healthy participants used Synchrobreathe without error compared with the pMDI.

On Day 14, significantly ($p < 0.001$) more number of participants (68.19%) used Synchrobreathe without any error compared with the pMDI (56.21%). Similar results were observed with Synchrobreathe in the asthma population ($p < 0.05$) and in healthy volunteers ($p < 0.001$) compared with the pMDI. No statistically significant difference was observed in the COPD subgroup between Synchrobreathe and the pMDI. Additionally, on Day 14, the percentage of participants using both Synchrobreathe and the pMDI without errors after reading the PIL only showed significant increase ($p < 0.001$) compared with Day 1 usage results with both the devices. Similarly, a significant ($p < 0.001$) increase in the number of participants demonstrating correct usage was observed in all the subgroups of COPD, asthma and healthy volunteers compared with Day 1 [Fig. 3].

3.2.2. Number of errors without training on day 1

Overall, on Day 1, the total number of errors when using Synchrobreathe (mean ± SD, 2.12 ± 1.29) without training was significantly lower ($p < 0.001$) compared with pMDI (2.56 ± 1.50). Similarly, on Day 1, the total number of errors was significantly lower when using Synchrobreathe, compared with pMDI, in asthmatic patients ($p < 0.05$) and in healthy volunteers ($p < 0.05$). No significant differences between Synchrobreathe and pMDI usage were found in patients with COPD.

3.2.3. Number of errors after training on days 1 and 14

On Day 1, the total number of errors after training was significantly lower with Synchrobreathe (2.83 ± 0.17) compared with pMDI (3.46 ± 0.18) in the overall population. Similarly, the number of errors with Synchrobreathe was lower than with pMDI in both the COPD ($p < 0.05$) and healthy volunteers ($p < 0.05$) groups. Synchrobreathe usage showed numerically lower number of errors compared with pMDI; however, statistical significance was not achieved. The total number of errors was significantly ($p < 0.0001$) reduced from Day 1 to Day 14 in the overall population as well as in all the subgroups. On Day 14, there was no difference in total number of errors between Synchrobreathe and pMDI in the overall population and in all the subgroups [Fig. 4].

3.2.4. Time and number of training sessions

On Day 1, the average time required to perform the inhalation technique correctly with Synchrobreathe (65.84 ± 3.69 s) was significantly ($p < 0.01$) lower compared with pMDI (67.70 ± 2.71 s) in the overall population. Similarly, the average time was significantly ($p < 0.01$) low with Synchrobreathe compared with pMDI in healthy volunteers. On Day 14, the average time required to perform the inhalation technique correctly with Synchrobreathe (37.08 ± 1.63 s) was significantly ($p < 0.05$) lower compared with pMDI (41.33 ± 1.38 s) in the overall population. A significant ($p < 0.0001$) reduction in the training time was observed on Day 14, compared with Day 1, in the overall population as well as in all subgroups [Table 2].

3.2.5. Number of attempts for correct technique

On Day 1, it took, statistically, significantly fewer attempts to inhale correctly with Synchrobreathe (1.26 ± 0.06) compared with the pMDI (1.69 ± 0.08, $p < 0.001$). The results were also statistically significant for all three subgroups (all $p < 0.05$). On Day 14 also, the average number of attempts to inhale correctly were significantly less with Synchrobreathe (0.54 ± 0.05) compared with the pMDI (0.72 ± 0.05). Significant decreases ($p < 0.0001$) in the average number of attempts were noticed on Day 14, compared with Day 1, in the overall population and in all the subgroups for both the devices [Table 3].

3.2.6. Device-handling and ease-of-use questionnaire

Table 4 shows the responses to the device-handling and ease-of-use questionnaire for Synchrobreathe. Overall, most participants found that the Synchrobreathe device was easy to use and handle. Most of the participants were confident and satisfied with the Synchrobreathe device. Similarly, participants found the dose counter easy to read and to determine how many doses were left in the inhaler. It was also easy for most of the participants to interpret the colour change in the Synchrobreathe dose counter.

3.2.7. Device preference

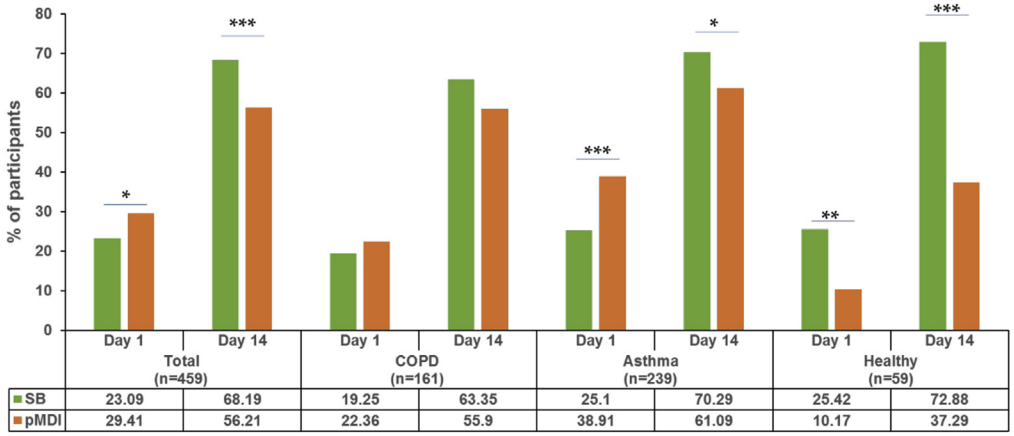
Overall, 88.5% of participants preferred Synchrobreathe over the pMDI (6.1%). Similarly, overall satisfaction was also very high with Synchrobreathe (89.4% participants) compared with the pMDI (5.23% participants). Synchrobreathe was the preferred choice of device over the pMDI in about 90.5% of participants. Synchrobreathe was also the preferred choice of inhaler along with higher overall device preference, satisfaction and choice of inhaler over the pMDI in the subgroups of asthma, COPD and healthy participants [Table 5].

3.2.8. Steps with maximum errors

The steps that showed maximum errors were evaluated for Synchrobreathe as well as the pMDI [Table 6]. The detailed information about the pre-specified steps for both the devices is given in the online Appendix 1b. For both Synchrobreathe and the pMDI, frequent usage errors were observed in their respective steps 4, 7 and 8.

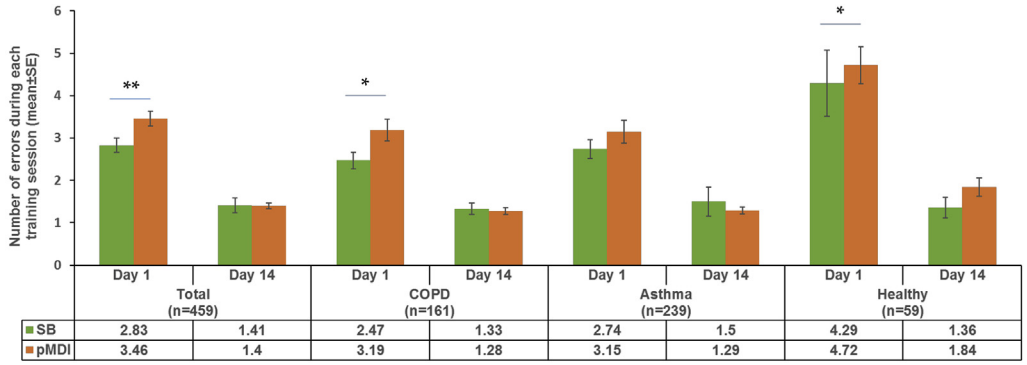
3.3. Safety results

A total of 13 AEs were reported during the study. Mild AEs, which



*p<0.05; **p<0.01; ***p<0.001; SB (Synchrobreathe) versus pMDI (pressurised metered dose inhaler)

Fig. 3. Percentage of participants who used both inhaler devices without errors after reading the PIL only.



Differences between Day 1 and Day 14 are all significant <0.0001; *p<0.05; **p<0.01; SB (Synchrobreathe) versus pMDI (pressurised metered dose inhaler); SE-standard error

Fig. 4. Number of errors during each training session until the participants were able to perform the inhalation technique correctly for both the devices.

were unlikely to be associated with placebo, were seen in 6 out of 239 (2.51%) patients with asthma and 7 out of 162 (4.32%) patients with COPD. No AEs were reported in the healthy participants. No SAEs were reported during the study.

4. Discussion

Synchrobreathe is a novel BAI with a built-in dose counter. The design of the Synchrobreathe device incorporates the compactness, portability and ease of use of pMDIs with the 'actuation on inspiration' feature of DPIs. Synchrobreathe gets actuated at a low inspiratory flow rate (~28 L/min) that can be generated by almost all the patients with OAD, including young patients, elderly patients and patients with severe airflow obstruction. In this study, overall, Synchrobreathe was found to be easy to use, easy to handle and had an inhalation technique that was easy to learn and remember, thereby making it an easy-to-teach device. Similar results were also observed in all three subgroups of participants, i.e. healthy volunteers, patients with asthma, and patients with COPD. More participants preferred Synchrobreathe and were satisfied with it compared with a pMDI. Given a choice, most participants (> 95%) chose Synchrobreathe over a pMDI. Training on the correct use of the device, however, is crucial to achieve the optimal effect of the medication.

Both GINA and GOLD recommend that a new inhaler device should

Table 2
Average time required to perform inhalation technique correctly during first and second visit for both the devices.

Visit	Total % (N = 459)		COPD % (n = 161)		Asthma % (n = 239)		Healthy % (n = 59)	
Device	SB	pMDI	SB	pMDI	SB	pMDI	SB	pMDI
Day 1 (n)	355	323	131	125	179	145	45	53
Time in sec (mean ± SE)	65.84 ± 3.69**	67.70 ± 2.71	59.47 ± 3.73	62.32 ± 3.03	66.08 ± 5.10	63.34 ± 3.31	83.46 ± 17.83**	92.33 ± 11.33
Day 14 (n)	136	192	56	69	64	87	16	36
Time in sec (mean ± SE)	37.08 ± 1.63*	41.33 ± 1.38	37.48 ± 2.45	40.51 ± 2.00	36.09 ± 2.33	40.89 ± 1.83	39.63 ± 5.78	44 ± 4.50

Differences between Day 1 and 14 are all significant < 0.0001; *p < 0.05; **p < 0.01; SB (Synchrobreathe) versus pMDI (pressurised metered dose inhaler); SE – standard error.

Table 3
Average number of attempts required to perform the inhalation technique correctly during the first and second visit for both devices.

Visit	Total (N = 459)		COPD (n = 161)		Asthma (n = 239)		Healthy (n = 59)	
Device	SB	pMDI	SB	pMDI	SB	pMDI	SB	pMDI
Day 1 (n)	365	341	138	132	181	156	46	53
Average number of attempts (mean ± SE)	1.26 ± 0.06***	1.69 ± 0.08	1.30 ± 0.09*	1.67 ± 0.11	1.13 ± 0.08*	1.47 ± 0.11	1.65 ± 0.25*	2.42 ± 0.22
Day 14 (n)	168	223	67	82	79	102	22	39
Average number of attempts (mean ± SE)	0.54 ± 0.05**	0.72 ± 0.05	0.55 ± 0.08	0.70 ± 0.07	0.49 ± 0.07	0.64 ± 0.06	0.64 ± 0.15	0.97 ± 0.14

Differences between Day 1 and 14 are all significant < 0.0001; *p < 0.05; **p < 0.01; ***p < 0.001; SB (Synchrobreathe) versus pMDI (pressurised metered dose inhaler).

only be prescribed when the correct inhalation technique is demonstrated and full instructions are provided by a healthcare professional (HCP) [2,3,5,20]. Errors made while using the inhalation devices can significantly reduce or completely inhibit the delivery of the medication into the lungs. The literature suggests that critical errors are being committed by both patients with COPD (36–49%) and asthma [21–23]. The development of an easy-to-use and easy-to-learn inhaler is important to achieve better management of the OADs [24].

In this study, we recorded errors with both Synchrobreathe and the pMDI, without and with training. On the first visit, when participants were given the devices and asked to use the devices only after reading the PILs, a significantly lower number of participants used the Synchrobreathe without errors compared with the pMDI. Given this, it looks like the pMDI was comparatively easier to use only after reading the PIL; however, it is important to mention that the patients (both asthma and COPD subgroups) were already using a pMDI before enrolment into this study and, therefore, it was likely that they already had been trained in pMDI usage by their HCPs. To check this assumption/hypothesis, we did a sub-group analysis of the participants and found that it was indeed the case. More number of patients with asthma used the pMDI correctly compared with Synchrobreathe, and no difference was observed in patients with COPD. Very interestingly, the number of healthy participants who used Synchrobreathe without errors was more compared with a pMDI. This shows that in the patients who were naïve to both the devices, the results were in favour of Synchrobreathe. The participants then were trained on Day 1 and asked to use the device at home regularly for 14 days. On Day 14, the number of participants who used the Synchrobreathe correctly was higher compared with the pMDI and similar trend of results was seen even in the subgroup analyses. Similarly, overall, the mean number of errors without training on Day1 with Synchrobreathe was less than with the pMDI.

It is evident from multiple studies that training has a positive impact on the correct use of inhalation device [25,26]. In the current study too, we observed a positive effect of training on the device usage. There was a significant decrease in the number of errors after training versus before training both on Day 1 and Day 14. These findings are in line with the literature wherein the effect of training with different devices has been demonstrated [14,26,27]. Moreover, the average number of errors was less with Synchrobreathe compared with the pMDI, which reflects better learning with Synchrobreathe compared with the pMDI. A study by Yusuf et al. also demonstrated that, with a pMDI, the effect of training did not seem to last and patients kept on making mistakes even after training [28].

The literature suggests that patients learning the inhalation technique from the PIL or reading material had been found to have a very low rate of success [29–32]. In the actual clinical practice, a low proportion of patients receive adequate training for proper inhaler technique use. Moreover, an even lesser number of such patients get their technique reviewed later [31]. In the present study, on Day 14, there were significantly more participants in the Synchrobreathe group who used the device correctly without training versus the pMDI. This suggests that the participants had sustained the learning for a longer time with Synchrobreathe versus the pMDI. Further, the percentage of participants using the Synchrobreathe inhaler without errors after reading the PIL only was statistically increased on Day 14 as compared with Day 1 ($p < 0.001$). This suggests that learning the inhalation technique with the Synchrobreathe device was comparatively easier for patients as well as inhaler-naïve healthy volunteers.

4.1. Patient preference and satisfaction

Patient preference and satisfaction regarding an inhaler device may contribute to improved adherence with therapeutic regimens [33]. The literature suggests that the ease of use and preference is associated with improved adherence to treatment [34–36], which is further associated with improved clinical outcomes [22,37–39]. In a real-world study of physician-observed compliance and clinical/patient-reported outcomes, an improved health status and fewer exacerbations were reported with improved device satisfaction in the majority of patients [36]. In this study too, after the completion of the 2-week study period, most of the participants preferred the Synchrobreathe device over the pMDI. Also, the number of participants (92%) satisfied with the Synchrobreathe device was greater compared with the pMDI device.

4.2. Strengths and limitations of the study

The large sample size was one of the strengths of the study. It also demonstrated the results as per the subgroups of the participants (asthma, COPD and healthy volunteers). Additionally, patients were allowed to continue their regular therapy with their regular devices, which could also be considered as another strength of the study. However, the relationship between the ability to use the inhaler devices with the disease severities was not assessed, which can be attributed as one of the limitations. Further, the study duration of 2 weeks could also be counted as a limitation. However, as participants were to use the device two times daily and only the placebo devices were used in the study, it could have brought more challenges in terms of compliance with the protocol had we done a longer study in the current setting. Moreover, in this study, we could see appreciable differences between the devices both on Day 1 and on Day 14. One limitation can be attributed to unavoidable sequence bias in the study, where all the participants were given the pMDI first for measuring all the parameters and the Synchrobreathe was given later. All the patients (asthma and COPD) were already using a pMDI and, hence, there was a high probability that they had received training in device usage from a doctor or healthcare practitioner. As they were familiar with the pMDI device and could have learnt it comparatively faster than Synchrobreathe which intern could have influenced the results of the study. In the process of avoiding this possible bias, we unintentionally introduced a sequence bias into the study. However, we have also measured several parameters post-training, which could potentially reduce the impact of this bias on the overall inferences of the study.

Ease of use and handling of the inhaler are important factors in determining patient satisfaction, which, in turn, can affect adherence to the treatment [24,40]. Furthermore, the easier an inhaler is to use and

Table 4
Responses to the device-handling and ease-of-use questionnaire.

EASE OF USE	VERY EASY % (n)	SOMEWHAT EASY % (n)	NEITHER EASY NOR UNEASY % (n)	NOT VERY EASY % (n)	NOT EASY AT ALL % (n)
How easy was it to understand how to prime the Synchrobreathe inhaler using the override button?	65.65 (302)	21.96 (101)	4.13 (19)	5.00 (23)	0.22 (1)
How easy was it to learn how to prime the Synchrobreathe inhaler after reading the device-handling leaflet?	63.48 (292)	24.57 (113)	3.91 (18)	5.00 (23)	0.00 (0)
How easy was it to understand how to use the Synchrobreathe inhaler?	70.43 (324)	21.74 (100)	3.70 (17)	0.87 (4)	0.22 (1)
How easy was it to learn how to use the Synchrobreathe inhaler after reading the device-handling leaflet?	65.43 (301)	23.04 (106)	5.00 (23)	3.04 (14)	0.43 (2)
DEVICE HANDLING					
How easy was it to open the dust cap of the Synchrobreathe inhaler?	89.13 (410)	6.30 (29)	1.09 (5)	0.22 (1)	0.22 (1)
How easy was it to hold the mouthpiece of the Synchrobreathe inhaler between your teeth and lips?	68.91 (317)	23.04 (106)	2.39 (11)	2.39 (11)	0.22 (1)
How easy was it to inhale through the mouthpiece of the Synchrobreathe inhaler?	67.39 (310)	22.39 (103)	4.57 (21)	2.61 (12)	0
How easy was it to hold the Synchrobreathe inhaler while using it?	72.17 (332)	18.48 (85)	4.35 (20)	1.96 (9)	0
How easy was it to close the dust cap of the Synchrobreathe inhaler after you finished using it?	87.39 (402)	7.17 (33)	1.09 (5)	1.09 (5)	0.22 (1)
How easy was it to carry the Synchrobreathe inhaler in your pocket/bag?	76.96 (354)	11.96 (55)	3.26 (15)	4.57 (21)	0
DOSE COUNTER					
How easy was it to read the number appearing in the dose counter window?	62.83 (289)	25.87 (119)	4.35 (20)	3.70 (17)	0.22 (1)
How easy was it for you to tell that the number appearing in the dose counter window had decreased after using the Synchrobreathe inhaler?	55.65 (256)	20.87 (96)	8.04 (37)	7.39 (34)	4.78 (22)
How easy was it for you to determine the number of doses left?	49.57 (228)	23.70 (109)	9.35 (43)	9.78 (45)	4.57 (21)
How easy was it for you to interpret change in the colour coding on the dose counter?	50.22 (231)	24.57 (113)	9.57 (44)	7.39 (34)	4.78 (22)
CONFIDENCE OF USE	**VERY CONFIDENT % (n)**	**SOMEWHAT CONFIDENT % (n)**	**NEITHER CONFIDENT NOR UNSURE % (n)**	**SOMEWHAT UNSURE % (n)**	**NOT CONFIDENT AT ALL % (n)**
How confident are you about using the Synchrobreathe inhaler correctly?	75.87 (349)	19.78 (91)	0.87 (4)	0.43 (2)	0
Overall, how confident are you about using the Synchrobreathe inhaler?	75.43 (347)	19.13 (88)	1.30 (6)	0.65 (3)	0.43 (2)
SATISFACTION ON USE	**VERY SATISFIED/ LIKELY % (n)**	**VERY SATISFIED/ LIKELY % (n)**	**NEITHER SATISFIED/LIKELY NOR UNSATISFIED/UNLIKELY % (n)**	**SOMEWHAT UNSATISFIED/ UNLIKELY % (n)**	**NOT SATISFIED AT ALL/ UNLIKELY % (n)**
How satisfied are you with the appearance of the Synchrobreathe inhaler (colour, shape, size)?	78.48 (361)	16.52 (76)	1.30 (6)	0.43 (2)	0.22 (1)
How likely is it that you will recommend the Synchrobreathe inhaler to other people you know who use inhalers?	77.17 (355)	16.74 (77)	1.96 (9)	0.43 (2)	0

Table 5
Device preference in all subjects.

	Total, N = 459 N (%)			Asthma, n = 239 n (%)			COPD, n = 161 n (%)			Healthy, n = 59; n (%)		
	SB	pMDI	Both	SB	pMDI	Both	SB	pMDI	Both	SB	pMDI	Both
Overall preference	406 (88.5)	28 (6.10)	11 (2.40)	216 (90.38)	10 (4.18)	6 (2.51)	135 (83.85)	17 (10.56)	4 (2.48)	55 (93.22)	1 (1.69)	1 (1.69)
Overall satisfaction	411 (89.4)	24 (5.23)	10 (2.18)	215 (89.96)	11 (4.60)	6 (2.51)	142 (88.20)	11 (6.83)	3 (1.86)	54 (91.53)	2 (3.39)	1 (1.69)
Choice of inhaler	417 (90.5)	28 (6.10)	0 (0.00)	220 (92.05)	12 (5.02)	0 (0.00)	142 (88.20)	14 (8.70)	0 (0.00)	55 (93.22)	2 (3.39)	0 (0.00)

SB, Synchrobreathe; pMDI, pressurised metered dose inhaler.

learn, the lower the likelihood of errors when using it. In this study, Synchrobreathe was found to be easy to open, hold, inhale and carry by most of the participants. Participants also found it easy to understand how to prime and use the device after reading the device-handling leaflet. Most of the patients responded that it was easy to read the Synchrobreathe dose counter and also interpret the change in colour coding. At the end of the study, patients were also very confident about using the Synchrobreathe device and very satisfied with it. These parameters were assessed in a large and heterogeneous patient population, which can be considered as one of the strengths of the study. However, the absence of a comparator arm for these assessments brings in a limitation to the study.

Efficient dose delivery by the Synchrobreathe can be achieved by proper priming of the device, correct positioning of the device and normal inhalation through the device. Holding the breath after complete inhalation is equally critical when using Synchrobreathe. Monitoring the inhalation technique and re-training is important during follow-up visits as it is important for determining the therapeutic outcomes of the treatment, which differ as per the choice of device.

5. Conclusion

From this device-handling study in healthy volunteers and patients with COPD or asthma, we can conclude that Synchrobreathe was an easy-to-use and easy-to-handle device. Overall, the participants made significantly less number of errors with the use of the Synchrobreathe device as compared with the pMDI, which could potentially lead to optimum drug deposition in the lungs. Most of the participants preferred and rated Synchrobreathe as their choice of inhaler over a pMDI. Overall, participants expressed satisfaction with the use of the Synchrobreathe device. Further, ongoing clinical studies with the drug device combination will complement the overall benefits of Synchrobreathe in clinical practice. This study also highlights the need for appropriate training and periodic assessment followed by reinforcement of training.

6. Declaration of interest

The study was funded by Cipla Ltd. Dr Balamurugan has contributed as an Advisory Board member of Cipla and has received honoraria for delivering guest lectures. Dr Raja Dhar, Dr Virendra Singh and Dr Bhanu Pratap Singh have been part of Advisory Board meetings, lectures and various symposia conducted or supported by Cipla. They have received honoraria and participated in the research projects funded by Cipla. Dr Sujeet Rajan has been part of Advisory Board meetings, lectures and various symposia conducted or supported by Cipla. He has received honoraria and participated in the research projects funded by Cipla. He has also served as a speaker and received grants from Boehringer Ingelheim. Dr C T Deshmukh, Dr Keya Rani Lahiri, Dr Komal Kirti, Dr Kinjal Modi, Dr Ajay Godse, and Dr Ashish Kumar Deb have no conflict of interest. Abhijit Vaidya, Vaibhav Gaur and Jaideep Gogtay are the permanent employees of Cipla Ltd. Jaideep Gogtay and Abhijit Vaidya al hold stock options in Cipla Ltd. The other authors have no conflict of interest.

Conflict of interest

The study was funded by Cipla Ltd. Dr Balamurugan has contributed as an Advisory Board member of Cipla and has received honoraria for delivering guest lectures. Dr Raja Dhar, Dr Virendra Singh and Dr Bhanu Pratap Singh have been part of Advisory Board meetings, lectures and various symposia conducted or supported by Cipla. They have received honoraria and participated in the research projects funded by Cipla. Dr Sujeet Rajan has been part of Advisory Board meetings, lectures and various symposia conducted or supported by Cipla. He has received honoraria and participated in the research projects funded by Cipla. He has also served as a speaker and received grants from Boehringer Ingelheim. Dr C T Deshmukh, Dr Keya Rani Lahiri, Dr Komal Kirti, Dr Kinjal Modi, Dr Ajay Godse, and Dr Ashish Kumar Deb have no conflict of interest. Abhijit Vaidya, Vaibhav Gaur and Jaideep Gogtay are the permanent employees of Cipla Ltd. Jaideep Gogtay and Abhijit Vaidya hold stock options in Cipla Ltd. The other authors have

Table 6
Step-wise common usage errors without and with training on Day 1 and Day 14.

Steps	Day 1				Day 14			
	Without training		After training		Without training		After training	
	SB	pMDI	SB	pMDI	SB	pMDI	SB	pMDI
Step 1	93 (20.26)	131 (28.54)	65 (14.16)	82 (17.86)	21 (4.58)	32 (6.97)	8 (1.74)	12 (2.61)
Step 2	73 (15.90)	57 (12.42)	43 (9.37)	39 (8.50)	6 (1.31)	11 (2.40)	6 (1.31)	7 (1.53)
Step 3	38 (8.28)	53 (11.55)	24 (5.23)	35 (7.63)	8 (1.74)	10 (2.18)	1 (0.22)	3 (0.65)
Step 4	112 (24.40)	151 (32.90)	106 (23.09)	142 (30.94)	26 (5.66)	73 (15.90)	8 (1.74)	40 (8.71)
Step 5	45 (9.80)	50 (10.89)	65 (14.16)	47 (10.24)	5 (1.09)	17 (3.70)	9 (1.96)	11 (2.40)
Step 6	96 (20.92)	103 (22.44)	108 (23.53)	140 (30.50)	21 (4.58)	33 (7.19)	14 (3.05)	25 (5.45)
Step 7	159 (34.64)	146 (31.81)	156 (33.99)	272 (59.26)	35 (7.63)	61 (13.29)	23 (5.01)	49 (10.68)
Step 8	103 (22.44)	111 (24.18)	132 (28.76)	143 (31.15)	41 (8.93)	34 (7.41)	27 (5.88)	25 (5.45)
Step 9	30 (6.54)	26 (5.66)	29 (6.32)	31 (6.75)	7 (1.53)	10 (2.18)	3 (0.65)	1 (0.22)

Each value represents the number of errors and the number in the round brackets represents the % of the population who made errors. SB, Synchrobreathe; pMDI, pressurised metered dose inhaler.

no conflict of interest.

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Appendix A. Supplementary data

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