Regular Article

Incorrect Holding Angle of Dry Powder Inhaler during the Drug-Loading Step Significantly Decreases Output Efficiency

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It is well known that correct use of inhalers plays a critical role in optimal inhalation therapy, but the impact of incorrect inhaler use on pulmonary drug delivery has not been quantitatively evaluated. The aim of this study was to investigate the frequency of holding inhalers at incorrect angles during the drug-loading step while using Turbuhaler® and to quantify the influence of the inhaler angle on *in vitro* pulmonary delivery. Thirty patients prescribed Turbuhaler® at Shiga University of Medical Science Hospital were enrolled. During inhalation, the participants' inhalation techniques were assessed by clinical pharmacists. Additionally, the influence of the inhaler angle on pulmonary delivery of budesonide *via* Symbicort® Turbuhaler® was investigated using a Twin-Stage Liquid Impinger. Output efficiency (OE), stage 2 deposition (St2), and OE × St2 were calculated. An incorrect angle during the drug-loading step was observed in 33.3% of the participants. *In vitro* testing demonstrated that OE, an index of the loaded dose, significantly decreased by 73.3% at an incorrect angle, while St2, an index of the deagglomerating efficiency, was stable independent of the holding angle. OE × St2, indicating the bronchial and pulmonary drug delivery amount, decreased by 76.9%. An incorrect holding angle reduced the loaded dose, resulting in decreased pulmonary delivery. Error in the inhaler angle occurs frequently and demonstrates a considerable impact on pulmonary drug delivery. Hence, it is necessary to assess the Turbuhaler® angle during inhalation.

Key words inhalation instruction; pulmonary drug delivery; inhaled corticosteroid; anti-asthmatic drug; inhalation therapy

INTRODUCTION

Inhalation therapy plays an important role in the treatment of respiratory diseases such as bronchial asthma and chronic obstructive pulmonary disease (COPD).[1,2] In the treatment of these local respiratory diseases, inhalation therapy has several advantages, including extremely low therapeutic doses and a low incidence of systemic adverse events, owing to direct drug delivery to the target treatment site.[3,4] Conversely, inhalation therapy also presents difficulties in inhaler use because of their complex drug-loading procedures, with widely different inhalation flow patterns required for each inhaler.[4–6] Previous studies have demonstrated the clinical impacts of incorrect inhaler use.[7–10] AL-Jahdali *et al.* have reported that incorrect inhaler usage increases the frequency of visits to the emergency department owing to subsequent poor asthma control.[5] Molimard *et al.* have reported that in the patients demonstrating a critical error in inhaler use, the incidence of COPD exacerbations increased by two-fold higher when compared with patients with no-error.[7] Therefore, in clinical practice, appropriate instructions for inhalation techniques should be provided to ensure optimal therapeutic efficacy.

Although dry powder inhalers (DPIs) are widely used in clinical practice, it has been noted that many patients fail to accurately use inhalers. Additionally, the error frequency was significantly dependent on the type of inhalers.[11,12] Particularly, the patients using Rotahaler®, Spinhaler®, Turbuhaler®, and the pressurized metered dose inhalers (pMDIs) present a higher risk for critical errors during inhaler use.[12] Currently, more than 20 different DPI devices are available in clinical practice, with several more under development or in clinical trials.[13] However, the accurate procedure for inhaler use widely differs among inhalers. Therefore, at the time of dispensing instructions regarding appropriate inhaler usage, medical professionals should monitor various checkpoints, such as the drug-loading procedure, inhalation flow rate, and breath-holding.[4,6,14]

Globally, Turbuhaler® is one of the most frequently prescribed DPI devices, with a distinctive structure in the drug-loading step as follows: a single dose of the drug is loaded by turning the grip anticlockwise and back until a "click" with the inhaler held upright.[15] Hence, the Turbuhaler® should be held "upright" during the drug-loading step. However, quantitative information regarding the acceptable range of the device angle is scarce. These limited information about incorrect usage of inhaler is a barrier to proper inhalation therapy in clinical practice. The purpose of the present study is to investigate the frequency of incorrect Turbuhaler® usage in clinical practice and to quantitatively evaluate the influence of the inhaler angle during the drug-loading step on pulmonary

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drug delivery.

MATERIALS AND METHODS

Materials Symbicort® Turbuhaler®, containing 160 μg of budesonide (BUD) and 4.5 μg of formoterol fumarate hydrate (FM), was purchased from AstraZeneca K.K. (Osaka, Japan). Analytical grade BUD was purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). The other reagents and solvents used were of analytical grade and HPLC grade, respectively.

Inhalation Errors in Clinical Practice In total, 30 patients prescribed Turbuhaler® (Symbicort®, Pulmicort®, or Oxis®) at the Shiga University of Medical Science Hospital between Feb. 2016 and Mar. 2017 participated in this study. Following the inhalation instructions dispensed by clinical pharmacists, the participants' inhalation techniques, including the angle at which the inhaler was held (hereinafter referred to as the inhaler holding angle), grip rotation, exhalation before inhalation, inhalation flow rate, breath-holding after inhalation, and gargle after inhalation, were assessed based on a predefined checklist for Turbuhaler® as shown in Table 1. The inspiratory flow rate *via* Turbuhaler® was measured using the inspiratory flow meter provided by Tokico System Solutions, Ltd. (Kanagawa, Japan).[16] Briefly, the inspiratory flow meter consisted of a hot-wire flow meter, a power-supply box, and a personal computer. An orifice, 4.03 mm in diameter, was utilized to imitate the inhalation resistance of the Turbuhaler®. This clinical study was performed in line with the principles of the Declaration of Helsinki, and approved by the Ethics Board of the Shiga University of Medical Science (Approval No. R2015-014). All participants provided written informed consent for study participation.

***In Vitro* Inhalation Performance *via* Various Holding Angles** Aerodynamic particle deposition of BUD *via* Symbicort® Turbuhaler® was determined using the Twin-Stage Liquid Impinger (TSLI, Fig. 1, European Pharmacopeia Apparatus A, Copley Scientific Ltd., U.K.). After drug loading by grip rotation of Turbuhaler® at the correct holding angle (upright with the mouthpiece facing upward, 0°) or incorrect holding angles (45, 90, 135, 180° tilt from the correct angle), the drugs were inhaled at a fixed-angle of 90°, which imitates a holding angle during inhalation by patients. The inhalation was conducted under the designated condition (60 L/min, 5 s), and monitored using the inspiratory flow meter.[16] After a single inspiration, the amount of BUD that transferred to the throat, stage 1, or stage 2 of TSLI was collected using 50 mL of 20% ethanol, and the BUD amount was determined by the HPLC-UV method, in accordance with our previous study.[17] Briefly, the mobile phase was composed of 20 mM phosphate buffer (pH 2.8) and acetonitrile at a flow rate of 0.5 mL/min using the following gradient conditions: 40% acetonitrile for 3 min; 40–70% acetonitrile for 2 min; holding 70% acetonitrile for 4 min; holding 40% acetonitrile until 20 min. The column (Shim-pack XR-ODS 3.0 × 75 mm, Shimadzu GLC,

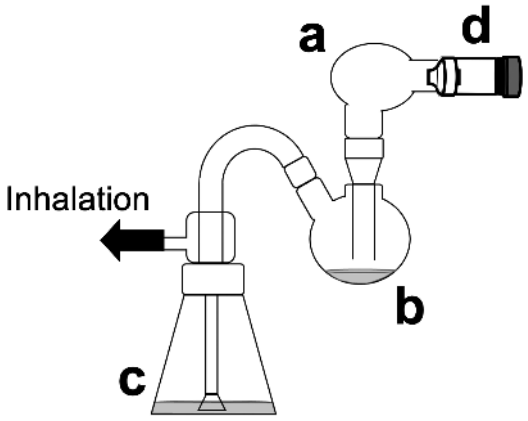

Fig. 1. Schematic Diagram of Twin-Stage Liquid Impinger (TSLI)

TSLI consists of throat (a, oral cavity and throat area), stage 1 (b, trachea area), and stage 2 (c, bronchus and lungs area). An inhalation device (d) is connected to throat part, and inhaled under the designed condition (60 L/min, 5 s).

Table 1. Error Frequencies of Turbuhaler® in Clinical Practice

Checkpoints		Number of patients with errors (error frequency, %)[a]
Patients with errors in one or more checkpoints		21 (70.0)
Set operation	Turn the cap off and remove the inlet properly	0 (0)
	Hold the inhaler at an upright angle	10 (33.3)
	Turn the rotating grip center or right	2 (6.7)
Inhalation	Exhale to the extent that it does not become painful before inhalation (do not breathe into the inlet)	10 (33.3)
	Inhale deeply and quickly	4 (13.3)
	Inhalation flow rate (L/min), median (min-max)	46.7 (16.7–89.3)
	Hold the breath for about 5 s	11 (36.7)
	Exhale slowly	0 (0)
Set operation	Close the cap after using	0 (0)
Notes	Gargle after inhalation	3 (10.0)
	Check the amount of remaining drug before inhalation	0 (0)
	Understand the importance and method of gargle	0 (0)
	Understand how to dispose of devices	0 (0)
	Understand how to care and store your device	0 (0)
	Set one dose medicine	2 (6.7)

a) The error frequency is the percentage of the patients with errors out of 30 participants. Some patients make multiple errors.

Kyoto, Japan) was heated to 40 °C, and the injection volume was 50 μL. BUD was spectrometrically determined at a wavelength of 248 nm. The calibration curve of BUD was linear from 0.039 to 20 μg/mL ($R^2 > 0.995$). Owing to a lower dose of FM (4.5 μg) when compared with BUD (160 μg), it would be difficult to detect FM after a single inspiration. Hence, in the present study, only BUD was evaluated as an active pharmaceutical ingredient of Symbicort® Turbuhaler®.

The inhalation performance evaluated by TSLI was characterized by output efficiency (OE) and stage 2 deposition (St2). OE represents the amount ratio of drug particles emitted from an inhalation device to the theoretical released dose (Eq. 1). In the present study, the theoretical amount of BUD particles released, as indicated by the drug labeling (160 μg), was defined as the theoretical released dose. St2 represents the amount ratio of BUD particles deposited on stage 2 of the TSLI to BUD particles emitted from the inhalation device, which indicates the amount ratio of particles with an aerodynamic particle size of 6.4 μm or less to the emitted dose (Eq. 2). Thus, St2 is defined as an index of the deagglomerating efficiency. Here, OE × St2 (Eq. 3) is defined as the bronchial and pulmonary drug delivery amount ratio to the theoretical released dose, an index of therapeutic efficiency.[18]

$$\mathrm{OE}\,(\%) = \frac{\text{Mass recovered from TSLI}}{\text{Theoretical released dose}} \times 100 \quad (1)$$

$$\mathrm{St2}\,(\%) = \frac{\text{Mass recovered from stage 2}}{\text{Mass recovered from TSLI}} \times 100 \quad (2)$$

$$\mathrm{OE} \times \mathrm{St2}\,(\%) = \frac{\text{Mass recovered from stage 2}}{\text{Theoretical released dose}} \times 100 \quad (3)$$

The experimental design to analyze the influence of the inhaler holding angle on inhalation performance was as follows; three times for correct holding angle (control phase), six times for incorrect holding angles (45, 90, 135, or 180°, testing phase), followed by three times for a correctly held angle again (recovery phase). For the testing and recovery phases, changes in OE, St2, and OE × St2 were compared with the control phase. A previous clinical study has reported large between-batch variances in clinically available inhalers.[19] Therefore, to determine the impact of the incorrect holding angle on inhalation performance, it is necessary to continuously compare correct and incorrect holding angles with the same inhaler. The above-mentioned twelve subsequent inspirations were conducted by the same researcher using the same Symbicort® Turbuhaler® lot.

Observation of the Dispensing Unit of Turbuhaler® with Various Holding Angles In order to visually assess the impact of the inhaler holding angle on the drug-loading profile, the dispensing unit of Turbuhaler® was observed by a digital video camera (HC-VX985M, Panasonic, Osaka, Japan). The mouthpiece of Turbuhaler® was removed to observe the dispensing unit. The experimental design was as follows; three times for correct holding angle (control phase), six times for incorrect holding angles (45, 90, 135, or 180°, testing phase). After each observation, the loaded drugs were removed by 60 L/min inspiration before the next drug-loading step. Drug-loading profiles in the dispensing unit were analyzed by Image J (NIH Image, Bethesda, MD, U.S.A.). The dark color area was defined as drug-unloading area. The drug-unloading area ratio was calculated with 0% for completely loaded by correct holding angle (control phase) and 100% for completely unloaded after inspiration. The drug-loading efficiency was calculated as 100%-drug-unloading area ratio. All analyses were conducted in triplicate.

Statistical Analysis The differences in inhalation performances from "*In Vitro* Inhalation Performance *via* Various Holding Angles" and loaded volume from "Observation of the Dispensing Unit of Turbuhaler® with Various Holding Angles" at each holding angle (45, 90, 135, or 180°) were compared with the control phase using one-way ANOVA, followed by Dunnett's multiple comparison test. All p-values were two-sided and a p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS statistics for Macintosh, (Version 25.0, IBM Corp, Armonk, NY, U.S.A.) and EZR (Easy R, version 1.40).[20]

RESULTS

Inhalation Errors in Clinical Practice The frequencies of each error using Turbuhaler® are shown in Table 1. Overall, 21 patients (70.0% of 30 patients) prescribed Turbuhaler® failed to effectively use their inhaler. The most frequent errors included breath-holding after inhalation (36.7%), inhaler holding angle at the drug-loading step (33.3%), and exhalation before inhalation (33.3%). Although most of patients achieved the recommended inhalation flow rate (30 L/min or more[16]), only 4 patients failed to achieve the recommended value. The median of inhalation flow rate was 46.7 L/min (16.7 to 89.3 L/min).

***In Vitro* Inhalation Performance *via* Various Holding Angles** Figure 2 demonstrates the influence of the inhaler holding angles on inhalation performance under the following conditions; three times for a correct inhaler holding angle (control phase), six times for incorrect inhaler holding angles (testing phase), followed by three times for a correct inhaler holding angle again (recovery phase). During the control phase, OE and OE × St2 were constantly maintained at approximately 90 and 40%, respectively. In the testing phase using incorrect angles, the inhalation performances gradually decreased depending on the number of inspirations, reaching a plateau after the 7th inspiration (4th inspiration in the testing phase). In the subsequent recovery phase, the inhalation performances recovered gradually, comprehensively improved at the 12th inspiration (3rd inspiration in the recovery phase). These qualitative trends regarding inhalation performance were independent of the inhaler holding angles. However, quantitative influences of inhaler holding angles were observed on inhalation performance. Although no significant difference was observed in OE and OE × St2 at an angle of 45°, a significant decrease was recorded at an angle of 90° and higher. The largest decrease in OE and OE × St2 was observed at a holding angle of 180°, and the rate of decline in OE and OE × St2 was 73.3 and 76.9% in the control phase, respectively. Conversely, St2 was constant around 40–50% and independent of the inhaler holding angle.

Observation of the Dispensing Unit of Turbuhaler® with Various Holding Angles As shown in Figs. 3 and 4, the drug dispensing unit of Turbuhaler® consists of five small holes. After drug-loading procedure with upright holding

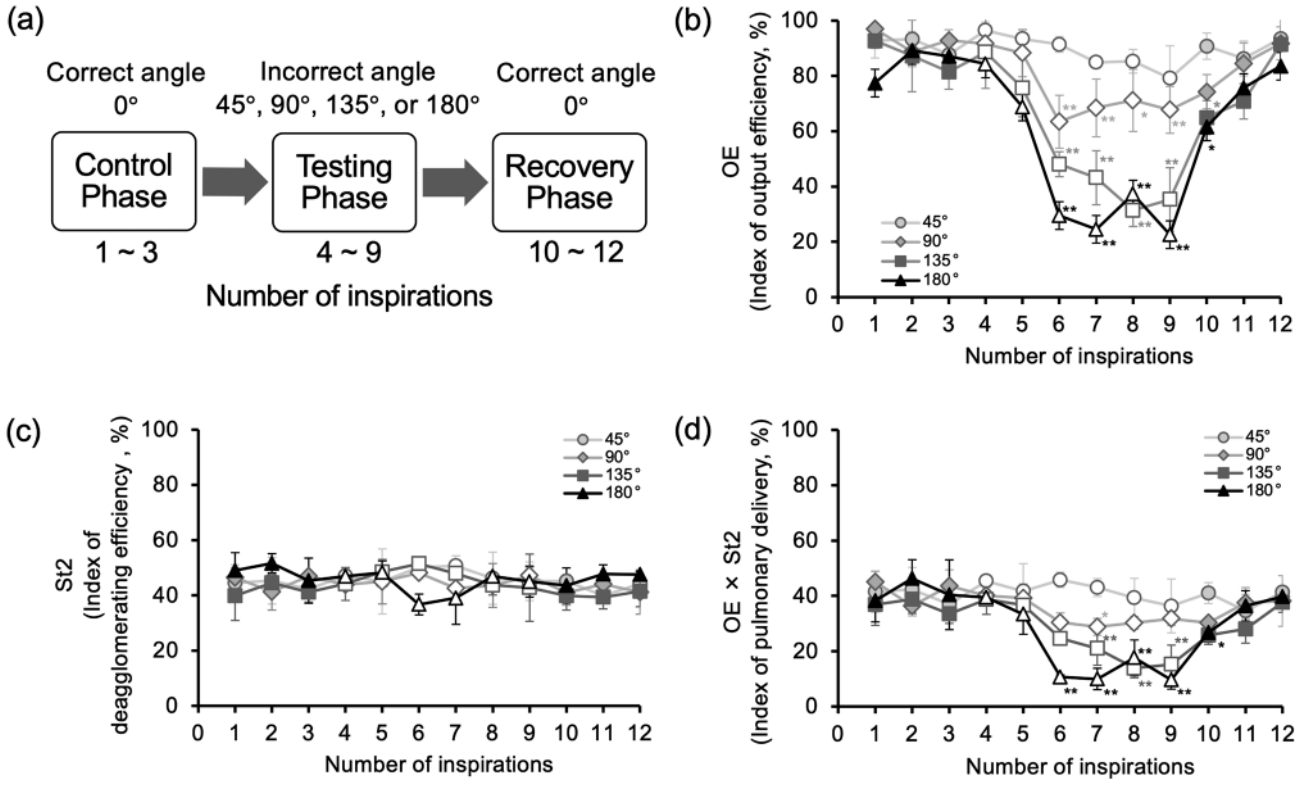

Fig. 2. Influence of Inhaler Holding Angles on *in Vitro* Inhalation Performances

(a) The experimental design to analyze the influence of the inhaler holding angle on inhalation performance. (b) Influence of inhaler holding angle on OE: emission amount from inhaler, an index of output efficiency. (c) Influence of inhaler holding angle on St2: Stage 2 deposition based on emission amount, an index of deagglomerating efficiency. (d) Influence of inhaler holding angle on OE × St2: Stage 2 deposition based on theoretical released dose (160 μg), an index of pulmonary delivery. Three times for correct holding angle (control phase), six times for incorrect holding angles (45, 90, 135, or 180°, testing phase), followed by three times for a correctly held angle again (recovery phase). Circles, rhomboids, squares, and triangles represent the inhaler holding angle of 45, 90, 135, and 180°, respectively. Closed and open plots present the data *via* the correct and the incorrect holding angles, respectively. $N = 3$, mean ± standard deviation (S.D.), $*p < 0.05$, $**p < 0.01$, Dunnett's multiple comparison test *vs.* the prior correct holding angle (control phase, 1st–3rd inspirations).

angle (control, 0°), the drug dispensing unit was fully loaded by drug powder. The loaded amounts decreased as the holding angle became larger. In the holding angles over 90°, the loaded amounts were obviously decreased after Nos. 5–7 of inspirations. Additionally, there is no drug loaded at the holding angle of 135 and 180° in Nos. 8 and 9 of inspirations. It is also demonstrated by image analysis that the drug-loading efficiency significantly decreased in the holding angles over 90° (Fig. 3c).

DISCUSSION

In this study, 70.0% of patients in clinical practice were unable to use the Turbuhaler® correctly. Among the various checkpoints for Turbuhaler®, the inhaler holding angle was detected as a highly frequent error, as well as exhaling before inhalation and breath-holding. Additionally, *in vitro* evaluation indicated significantly lower inhalation performance under incorrect inhaler holding angle conditions. The impact of inhaler holding angle on inhalation performance was quantitatively demonstrated for first time. Several studies have shown that the frequency of misuse for the Turbuhaler® is between 26 and 94%.[11,12,21–24] Furthermore, it has been demonstrated that common errors with Turbuhaler® usage include failure to exhale before inhalation (13–77%) and failure to maintain the device in an upright position until loaded (10–44%).[11] These findings observed in the present clinical study were comparable with previous reports.

Among the three frequently observed errors: exhaling before inhalation, inhaler holding angle, and breath-holding after inhalation, quantitative assessments regarding the influence of exhaling before inhalation, as well as breath-holding after inhalation, on the pulmonary drug delivery rate have been previously reported. Reportedly, breath-holding is an important factor for enhancing the therapeutic efficacy of formulations. However, longer breath-holding times marginally increase the drug delivery rate.[14,25,26] Horváth *et al.* have reported that lung deposition is enhanced by 24.8% following 5 s breath-holding and by 49% with 25 s of breath-holding when compared to no breath-holding using Symbicort® Turbuhaler®. Using computational fluid dynamics simulation, Kadota *et al.* have demonstrated that breath-holding improved the particle deposition of DPI formulations in the bronchi by approximately 3%, while breath-holding had a greater impact on the throat.[25] Furthermore, bronchial simulation has indicated that the breath-holding increases the air turbulence in the airways, prompting particle deposition.

Exhaling before inhalation is also considered an important factor for enhancing the therapeutic efficacy of formulations. Kondo *et al.* have reported that exhaling before inhalation increased the peak inhalation flow rate (PIFR) from 48.0 to 51.0 L/min and the inhaled volume from 1.28 to 1.86 L with Turbuhaler® usage.[27] Our previous reports have demonstrated that the drug delivery rate significantly increases following an increase in PIFR, but not with an increase in the inhaled volume.[6] Therefore, exhaling before inhalation could enhance

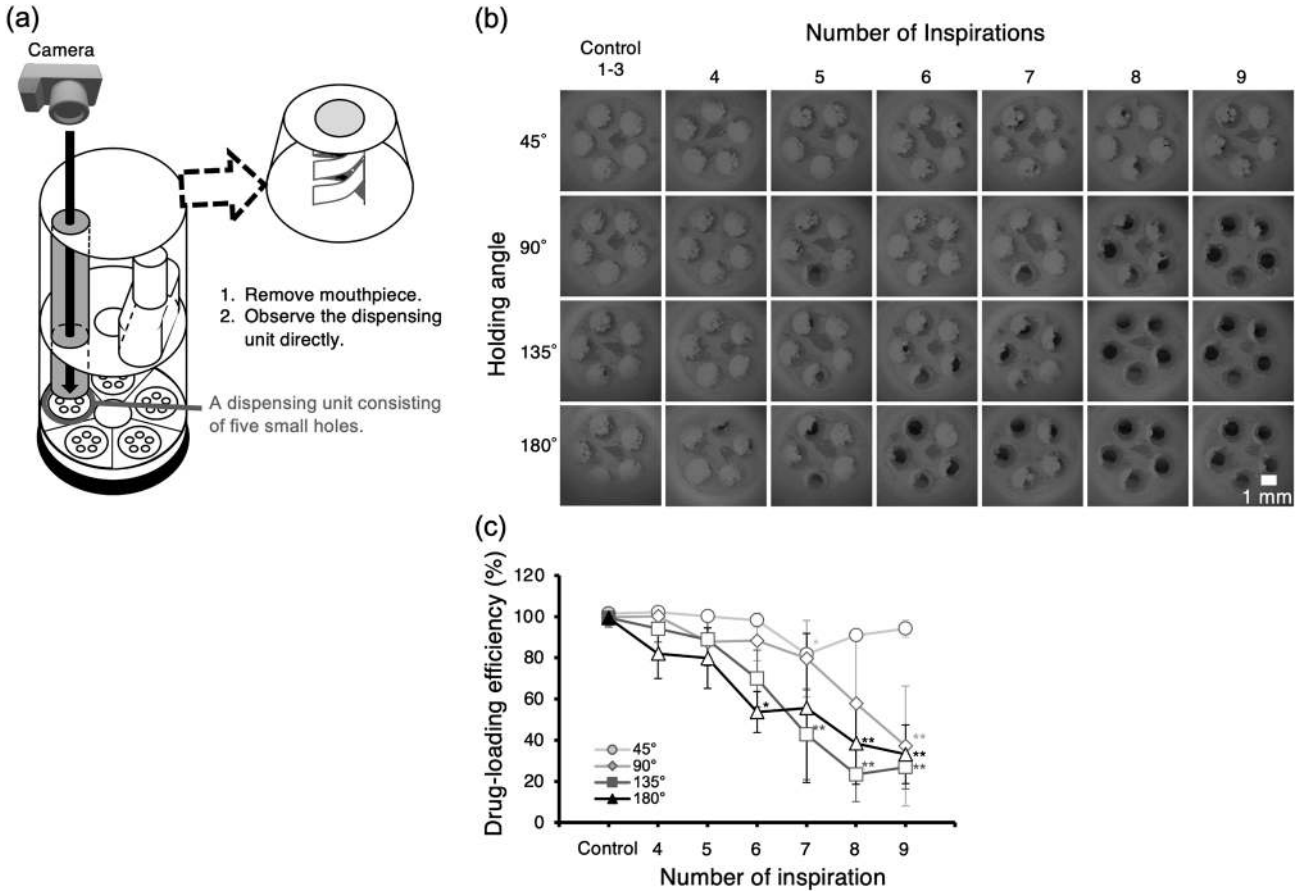

Fig. 3. Method (a) and Results of the Assessment of Drug-Loading Profiles (b) and Drug-Loading Efficiency (c) at Various Holding Angles in the Dispensing Unit of Turbuhaler®

To assess the drug-loading profile in the dispensing unit of Turbuhaler®, the mouthpiece was removed and the dispensing unit was directly observed. After the drug-loading in correct holding angle (control phase), six times for incorrect holding angles (45, 90, 135, or 180°, testing phase) were performed. The scale bar is 1 mm. Circles, rhomboids, squares, and triangles represent the inhaler holding angle of 45, 90, 135, and 180°, respectively. Closed and open plots present the data *via* the correct and the incorrect holding angles, respectively. $N = 3$, mean ± S.D., $^{*}p < 0.05$, $^{**}p < 0.01$, Dunnett's multiple comparison test *vs.* the prior correct holding angle (control phase, 1st–3rd inspirations).

inhalation performance by increasing the PIFR. However, the impact of PIFR on pulmonary delivery has been reported as 5.5%, following an increase in PIFR from 40 to 60 L/min.[6] Thus, it may fail to demonstrate a considerable impact on pulmonary delivery if exhaling before inhalation enhances PIFR *via* Turbuhaler® from 48.0 to 51.0 L/min.

In the present study, we demonstrated, for the first time, that the pulmonary drug deposition rate (OE × St2) drastically decreased due to incorrect Turbuhaler® holding angles during the drug-loading step. Therefore, extensive inhalation instructions regarding the inhaler holding angle are required as the impact of holding angle is larger than that of breath-holding and exhaling before inhalation as reported previously.[6,14,25,27] The present study established the novel quantitative definition of a critical error, in which the correct holding angle of the Turbuhaler® is in the range of a ±45° tilt from the upright position.

Figure 4 presents the hypothetical mechanism of the gradual decrease in the inhalation performance after using incorrect holding angles. The Symbicort® Turbuhaler® has a rotating dosing disk to measure a defined dose as specially designed plastic scrapers placed just over the rotating dosing disk will actively load the holes with the drug compound in a reproducible way.[28] The rotating dosing disk has five sets of dispensing units, consisting of a set of five small holes. On turning the grip counterclockwise until stop and clockwise until "click," a single drug powder dose is gravitationally loaded from the drug powder storage into a dispensing unit.[28,29] Here, under the condition of the incorrect holding angle during the drug-loading step, the amount of the loaded drug powder is reduced, as the dispensing unit cannot face the direction of gravitational force. This phenomenon is visually confirmed in Fig. 3. Therefore, the decreased pulmonary delivery in the incorrect holding angles is mainly due to the decreased amount of the loaded drug in the dispensing unit. Here, at an incorrect holding angle, it is possible that a part of the drug loaded in the dispensing unit may fall into the inhalation channel (the checked part in Fig. 4). Although the drug-loading efficiency by image analysis decreases due to the fall of the drug into the inhalation channel, it is considered that the OE does not decrease as much as the drug-loading efficiency because the fallen drug in the inhalation channel is released into the inhalation. Therefore, the calculated drug-loading efficiency at a holding angle of 90° (Fig. 3c) was lower than the OE value at the same holding angle (Fig. 2b).

Additionally, the drug-loaded dispensing unit is transported from the bottom of the drug powder storage to the bottom of the inhalation channel after 2–3 times loading procedures. Therefore, the influence of a reduced loaded dose owing to incorrect holding angles should be gradually apparent after

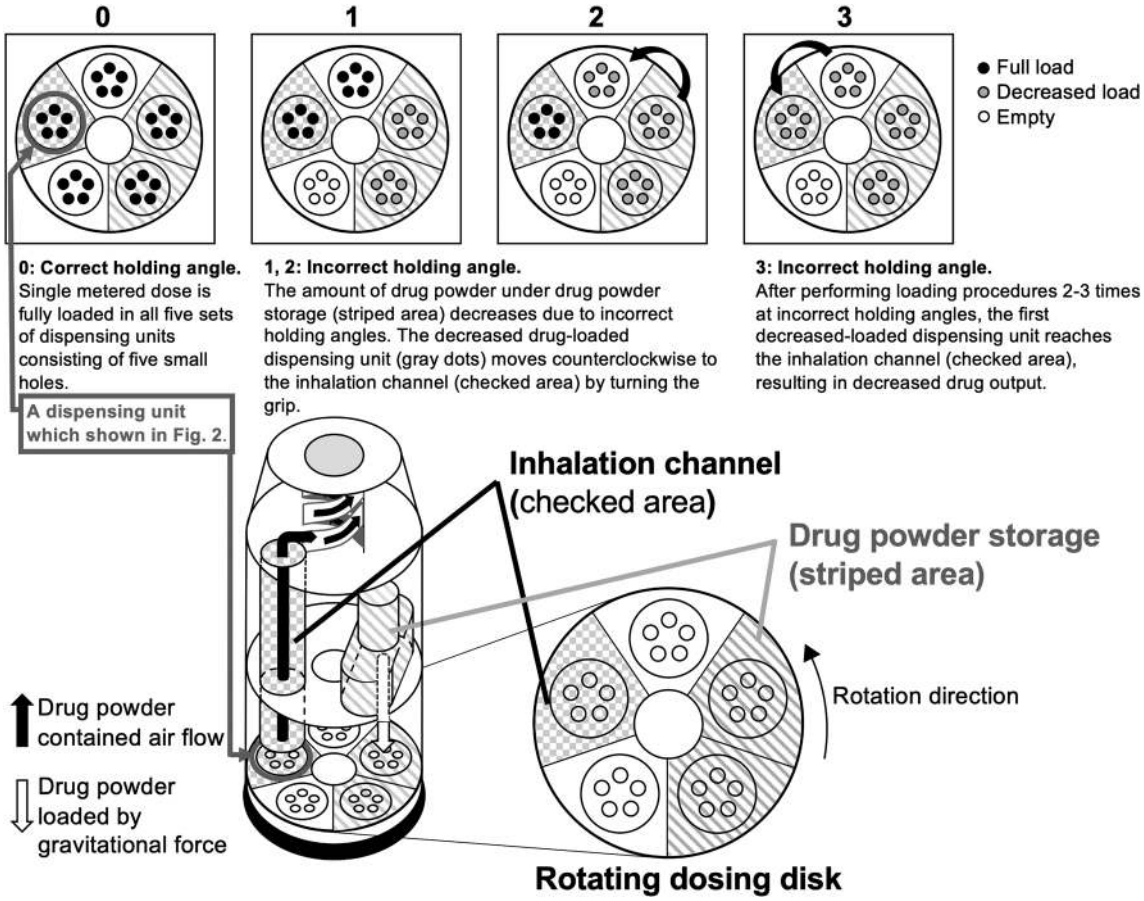

Fig. 4. The Hypothetical Mechanism of a Gradual Decrease in the Inhalation Performance under Incorrect Holding Angles in Turbuhaler®

2–3 inhalations. This is consistent with the instructions for the Turbuhaler® indicated by the pharmaceutical company, necessitating the loading step to be performed thrice before initial use. As shown in Fig. 2, the inhalation performance during the recovery phase improved from the testing phase and returned to the same level as the control phase, suggesting that an incorrect holding angle has no influence on drug powder properties, but influences the drug-loading amount. However, during the recovery phase, the inhalation performance improved in gradual manner as observed in the testing phase. In clinical practice, a medical professional should instruct patients regarding the three times priming necessary before initial use, particularly on encountering patients demonstrating incorrect holding angles.

To define the inhalation performance of dry powder *via* the Turbuhaler®, two processes exist, the drug-loading process and powder deagglomerating process. Under conditions of incorrect inhaler holding angles, as the drug-loading process was critically damaged as described above (Fig. 3), the particle deagglomerating process could also be damaged. The loaded powder in the Turbuhaler® is deagglomerated following collisions between particles and the inner walls of the inhaler during inhalation, as a result of the turbulence created by the inhalation airflow.[30] Here, under the condition of an incorrect inhaler holding angle, the loaded powder may gravitationally fall into the inhalation channel before inhalation, which may result in a reduced collision distance to the inner wall of the inhaler, and insufficient deagglomeration. In this *in vitro* study, while a decrease in the drug-loading process was reflected in OE and OE × St2, a decrease in the powder deagglomerating process would be reflected by St2. However, St2 remained constant and independent from the inhaler holding angles, while OE and OE × St2 decreased under incorrect holding angles. The inhalation channel of Turbuhaler® consists of two parts, a linear part and a subsequent spiral part. We speculate that the gravitational fall of the loaded powder under the incorrect holding angle may have an unfavourable influence on the linear part to reduce collision distance of inhalation channel, but less influence on the spiral part of inhalation channel. However, because the turbulent air flow inside the Turbuhaler® occurs in the spiral part of inhalation channel, the deagglomerating process may not be affected by incorrect holding angle. Notably, the impact of decreased drug loading on the inhalation performance of dry powder *via* the Turbuhaler® was greater than that observed in the powder deagglomerating process.

As shown above, the Turbuhaler® has a mechanism in which the drug powder is loaded by the gravitational force, hence the inhaler holding angle during the drug-loading step significantly influences the drug-loading amount. A possible solution to this problem is to replace the gravity-dependent loading process in the dispensing units with the gravity-independent loading process such as spring pressing the drug powder to the dispensing units. However, in the current clinical practice, since Turbuhaler® with gravitationally loading system is one of the most frequently prescribed DPI devices, it is necessary to assess the inhaler angle during inhalation instructions provided by medical professionals.

As a limitation of the present study, we could not assess the relationship between the holding angle error and clinical efficiency. Further clinical studies should be conducted to demonstrate the clinical impact of the holding angle of Turbuhaler®.

CONCLUSION

In clinical practice, errors are frequently associated with the angle at which the Turbuhaler® is held during loading. Moreover, the holding angle error demonstrates a major impact on the pulmonary drug delivery rate *via* Turbuhaler®. The pulmonary drug delivery rate significantly decreases at an angle exceeding 45°. Therefore, it is necessary to assess the inhaler angle during inhalation instructions provided by medical professionals.

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Conflict of Interest The authors declare no conflict of interest.

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