**RESEARCH ARTICLE**

# Real-Time Particle Emission Monitoring for the Non-Invasive Prediction of Lung Deposition via a Dry Powder Inhaler

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**Abstract**

Although inhalation therapy represents a promising drug delivery route for the treatment of respiratory diseases, the real-time evaluation of lung drug deposition remains an area yet to be fully explored. To evaluate the utility of the photo reflection method (PRM) as a real-time non-invasive monitoring of pulmonary drug delivery, the relationship between particle emission signals measured by the PRM and *in vitro* inhalation performance was evaluated in this study. Symbicort® Turbuhaler® was used as a model dry powder inhaler. *In vitro* aerodynamic particle deposition was evaluated using a twin-stage liquid impinger (TSLI). Four different inhalation patterns were defined based on the slope of increased flow rate (4.9–9.8 $L/s^2$) and peak flow rate (30 L/min and 60 L/min). The inhalation flow rate and particle emission profile were measured using an inhalation flow meter and a PRM drug release detector, respectively. The inhalation performance was characterized by output efficiency (OE, %) and stage 2 deposition of TSLI (an index of the deagglomerating efficiency, St2, %). The OE × St2 is defined as the amount delivered to the lungs. The particle emissions generated by four different inhalation patterns were completed within 0.4 s after the start of inhalation, and were observed as a sharper and larger peak under conditions of a higher flow increase rate. These were significantly correlated between the OE or OE × St2 and the photo reflection signal ($p < 0.001$). The particle emission signal by PRM could be a useful non-invasive real-time monitoring tool for dry powder inhalers.

**Keywords** dry powder inhaler · lung deposition · non-invasive · photo reflection method · real-time monitoring

## Introduction

Inhalation therapy has been widely used for the treatment of respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD) [1, 2]. On the treatment of these respiratory diseases, inhalation therapy plays an important role because of its promising efficacy at low drug doses and few systemic adverse events due to direct delivery of the drug to the target sites [3, 4]. The efficacy of pulmonary drug delivery depends on several factors, such as the respiratory function and the inhalation flow profiles of patients, device design and formulation, and operational errors [5–8]. Particularly, the inhalation flow profile is composed of intricate parameters; instances reported peak flow rate (PFR), flow increase rate (FIR), and inspiratory volume [9–11]. Drug particles with an aerodynamic particle diameter around 1-5um are required for delivery to treatment sites such as bronchi and lungs [12, 13]. However, micronized drug particles tend to be highly cohesive and less flowable, resulting in lower inhalation

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**Fig. 1** Schematic diagrams of the *in vitro* evaluation system with Symbicort® Turbuhaler® using the particle emission monitoring system. **a** The particle emission signal monitoring system was composed of a particle emission signal detector with PRM **A**, a hot-wire flow meter **B**, and a personal computer **C**. **b** The twin stage liquid impinger (TSLI, **D**) was connected to the human inhalation flow simulator consisting of a vacuum pump and flow-control valve. **c** Typical outputs from the particle emission signal monitoring system
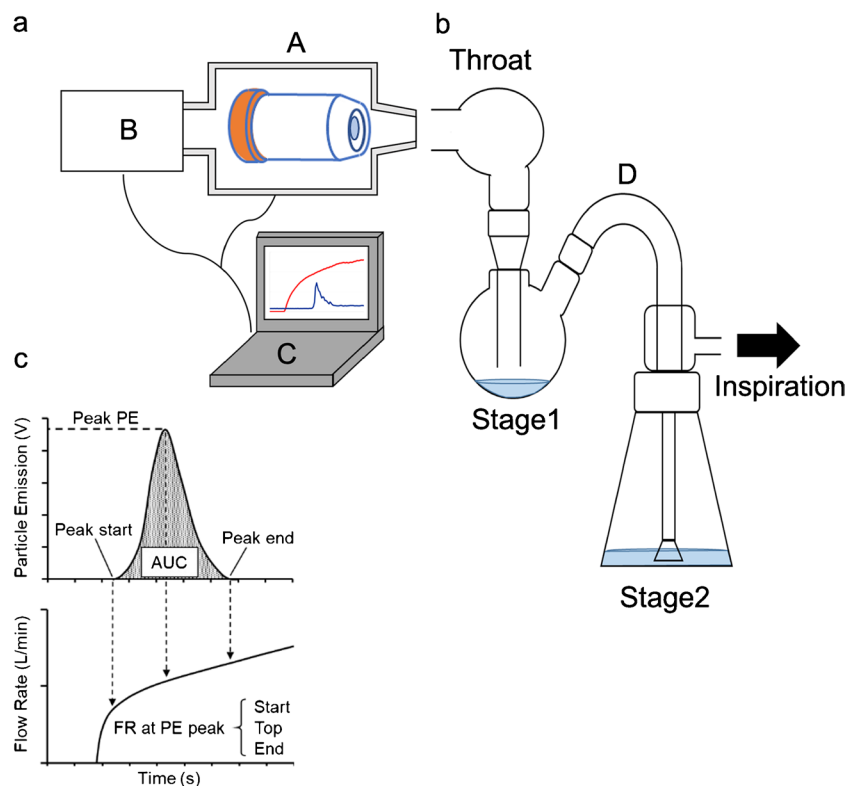


performance [14, 15]. Coarse lactose carriers have long been studied for attaching micronized drug particles to prevent adhesion and aggregation to the inhaler [16]. Other methods to reduce adhesion to inhalers, such as using large porous particles and agglomerates, have been reported and are being applied clinically [17–21]. With the proper utilization of the device, these factors are attained, leading to an enhancement in drug delivery [6, 22, 23]. Therefore, the education and assessment of inhalation maneuver is conducted in clinical practice using training tools, such as whistle trainer and flow meter (In-Check-DIAL® [24–26]. However, the real-time evaluation methods of inhalation flow profiles and lung drug deposition during actual inhalation remain an area yet to be fully explored. Although scintigraphy with radioisotope is available for quantifying pulmonary drug delivery [4], its complicated procedure and invasiveness limit its routine application. Thus, the development of a non-invasive method for predicting drug delivery into the lungs is urgently needed. Kondo *et al.* created the photo reflection method (PRM) as a non-invasive, real-time monitoring system for drug release during inhalation [27]. However, the relationship between the parameters for PRM and the amount of drug delivered into the lungs has yet to be characterized.

In this study, the correlation between particle emission signals measured by PRM and *in vitro* inhalation performance was evaluated to develop a technique for the real-time non-invasive monitoring of pulmonary drug delivery.

## Materials and Methods

### Materials

Symbicort® Turbuhaler® 60 doses (AstraZeneca K.K., Osaka, Japan) containing 160 µg of budesonide (BUD) and 4.5 µg of formoterol fumarate dihydrate (FOR) was used as a model inhaler. 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.

### *In Vitro* Testing with Various Inhalation Patterns Through PRM

Schematic diagrams of the *in vitro* evaluation system of Symbicort® Turbuhaler® using PRM are provided in Fig. 1. The particle emission signal monitoring system (Fig. 1a) was composed of an airtight box with PRM, a hot-wire flow meter (Tokico System Solutions Ltd., Japan), and a personal computer. The Symbicort® Turbuhaler® was loaded according to the instructions in the patient leaflet, and set in the airtight box. The intensity of the reflected light generated by drug particles during inhalation was measured as the particle emission signal [27]. The time-course graphs of inhalation flow rates and particle emission signals were simultaneously output into the personal

**Table I** Profiles of Flow Pattern and Particle Emission Signal

| Inhalation pattern | Quick60 | Mild60 | Slow60 | Quick30 |
|---|---|---|---|---|
| Actual PFR (L/min) | $51.3 \pm 2.1$ | $51.8 \pm 1.5$ | $56.0 \pm 1.0$ | $28.8 \pm 0.2$ |
| Defined PFR (L/min) | 60 | 60 | 60 | 30 |
| FIR (L/s$^2$) | $9.8 \pm 0.6$ | $5.6 \pm 1.2$ | $6.0 \pm 0.3$ | $4.9 \pm 0.3$ |
| AUC$_{PE}$ (V·s) | $0.20 \pm 0.02$ | $0.16 \pm 0.03$ | $0.12 \pm 0.03$ | $0.10 \pm 0.03$ |
| AUC$_{FR \times PE}$ (V·s·L/min) | $7.5 \pm 0.8$ | $4.31 \pm 1.0$ | $4.67 \pm 1.2$ | $1.94 \pm 0.5$ |
| Peak PE (V) | $3.4 \pm 0.2$ | $1.5 \pm 0.2$ | $1.2 \pm 0.1$ | $0.82 \pm 0.1$ |
| FR at PE peak start (L/min) | $4.3 \pm 2.4$ | $9.4 \pm 3.3$ | $17.8 \pm 2.2$ | $3.1 \pm 4.1$ |
| FR at PE peak top (L/min) | $38.9 \pm 2.1$ | $26.7 \pm 2.7$ | $38.5 \pm 2.2$ | $19.9 \pm 0.2$ |
| FR at PE peak end (L/min) | $45.1 \pm 2.5$ | $36.8 \pm 4.7$ | $46.6 \pm 1.1$ | $21.5 \pm 0.4$ |

Data are presented as the mean $\pm$ standard deviation (n = 3). AUC: area under the curve; PFR: peak flow rate; FR: flow rate; PE: particle emission

computer. As indices for particle emission, the following parameters were calculated (Fig. 1c): peak value of particle emission (Peak PE, V), area under the time-particle emission curve (AUC$_{PE}$, V·s), area under the time-product of particle emission and flow rate curve (AUC$_{FR \times PE}$, V·s·L/min), and inhalation flow rates at the start (FR at PE peak start, L/min), top (FR at PE peak top, L/min), and end (FR at PE peak end, L/min) of the particle emission signal. AUC$_{FR \times PE}$ is the time integrated value of the multiplication of the inhalation flow rate and particle emission signal intensity. Based on the hypothesis that the particle emission signal represents particle concentration in the detection area of the PRM system, AUC$_{FR \times PE}$ was used in this study to correct for the effect of inhalation flow rate.

The aerodynamic particle deposition of BUD was determined using a twin-stage liquid impinger (TSLI) (European Pharmacopoeia Apparatus A; Copley Scientific Ltd., U.K.) with an human inhalation flow simulator (Fig. 1b) [28]. The drug-loaded particle emission signal monitoring system was connected to the TSLI. Then, four different flow profiles of inhalation were generated by a human inhalation flow simulator to inhale the drug particle into the TSLI. Considering the flow patterns of the COPD patients [10], the inhalation profiles were characterized by PFR (30–60 L/min) and FIR (4.9–9.8 L/s$^2$). Here, the FIR was regulated by a valve connected with a vacuum pump, and calculated as the slope of increased flow rate during the early inhalation phase. The profiles of the inhalation flow pattern are summarized in Table I. Quick60 and Quick30 were generated by quickly opening the valve. Conversely, Slow60 was generated by gently opening the valve. Mild60 was generated by increasing the flow rate following the startup of the vacuum pump without the use of valves.

After a 5-s inhalation, the deposited BUD on each stage of TSLI was collected using 50 mL of 20% ethanol. The concentration of BUD in each sample was determined by the HPLC–UV method [29]. TSLI consists of throat (oral cavity and throat area), stage 1 (trachea area), and stage 2 (bronchus and lung area). The aerodynamic particle diameter of drug delivered into stage 2 was indicated 6.4 μm or less at a flow rate of 60 L/min. The inhalation performance was characterized by the output efficiency (OE, %) and the stage 2 deposition (St2, %). OE stands for the amount ratio of the total emitted drug from the inhaler to the theoretical released dose (Eq. 1). St2 represents the amount ratio of BUD particle deposited on stage 2 of the TSLI to the mass recovered from TSLI (Eq. 2), an index of the deagglomerating efficiency. OE × St2 (Eq. 3) is defined as the amount ratio delivered in stage 2 to the theoretical released dose, an index of therapeutic efficiency. The theoretical released dose was indicated as the nominal dose of BUD (160 μg). Three independent analyses were conducted for each inhalation pattern:

$$OE(\%) = \frac{Mass\ recoverd\ from\ TSLI}{Theoretical\ released\ dose} \times 100 \qquad (1)$$

$$St2(\%) = \frac{Mass\ recoverd\ from\ stage\ 2}{Mass\ recovered\ from\ TSLI} \times 100 \qquad (2)$$

$$OE \times St2(\%) = \frac{Mass\ recoverd\ from\ stage\ 2}{Theoretical\ released\ dose} \times 100 \qquad (3)$$

## Statistical Analysis

Statistical analysis of the data was performed using EZR (Easy R version 1.40, Saitama, Japan) [30]. The analysis of the inhalation performance of each inhalation pattern was conducted using a one-way ANOVA followed by the Tukey's multiple comparison test. The correlation between the monitoring parameters and the inhalation performance was assessed using Pearson's correlation coefficient. The level of significance was set at $p < 0.05$.
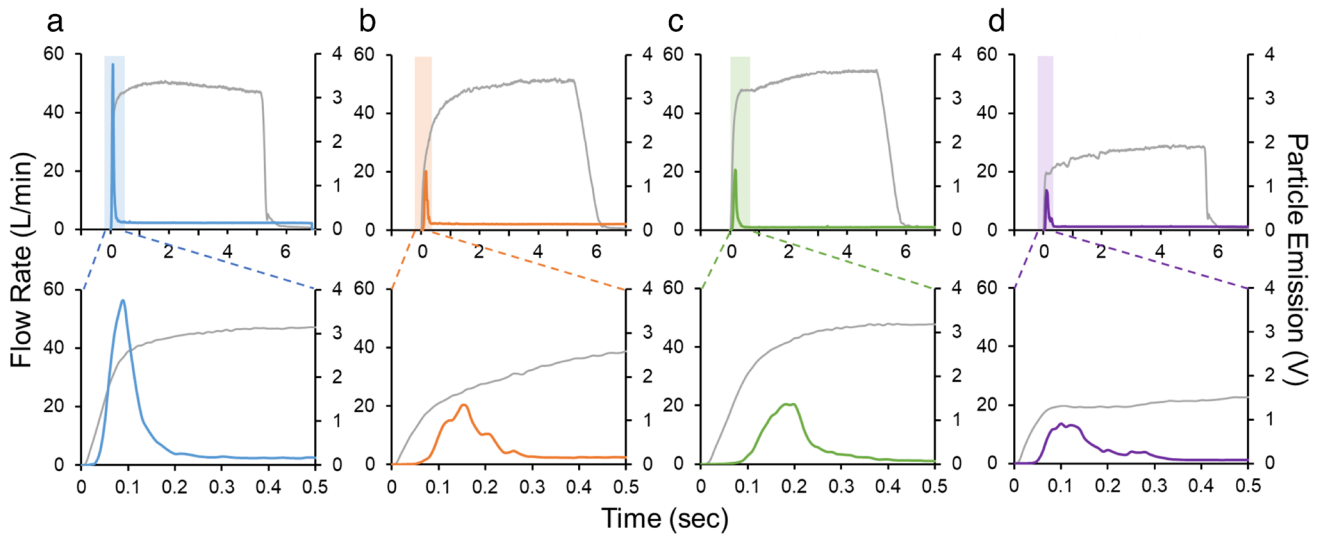
**Fig. 2** Typical profiles of flow rate and particle emission signal of the four inhalation patterns. **a** Quick60: inhalation method defined in the European Pharmacopoeia (60 L/min, 5 s) showed a steep rise in inhalation flow rate. **b** Mild60: the FIR was lower than that of Quick60, and the acceleration gradually decreased after the onset of inhala-

tion, showing a diphasic increase. **c** Slow60: the FIR was lower than Quick60 and inhalation flow rate linearly increased. **d** Quick30: the PFR was set to 30 L/min. The gray and colored lines show typical profiles of flow rate and particle emission signal, respectively
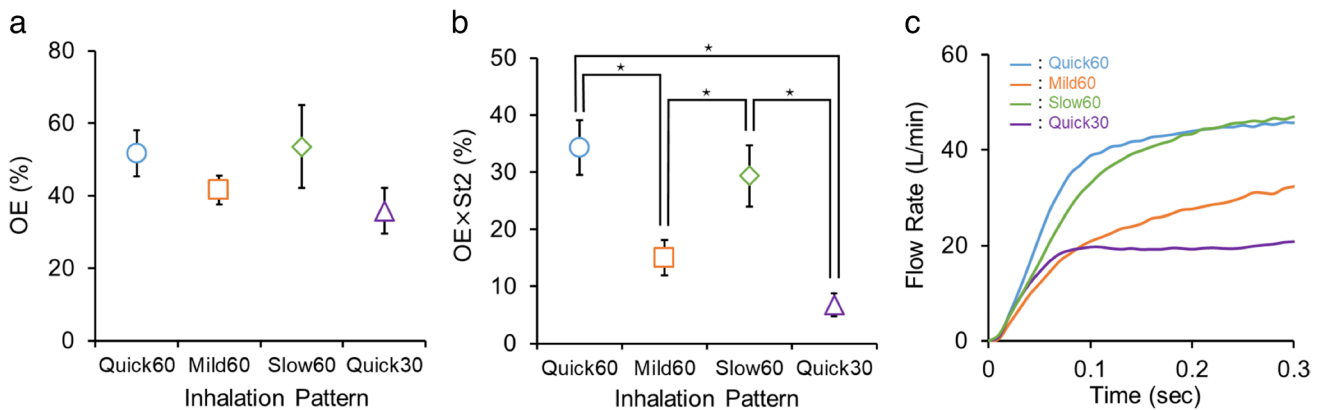


**Fig. 3** Influence of the inhalation patterns on inhalation performance. **a** The amount of drug released from the device, **b** the amount of drug delivered into the lung, and **c** the flow increase profiles of the differ-

ent inhalation patterns (n = 3, mean ± S.D., *p < 0.05, Tukey's multiple comparison test)

## Results

The typical inhalation profiles of flow rate and particle emission signal measured under different inhalation patterns are shown in Fig. 2. Table I summarizes the profiles of the inhalation flow pattern and particle emission signal based on the four different inhalation patterns. Under all conditions, particle emission completed within 0.4 s after the onset of inhalation before reaching PFR (Fig. 2). The particle emission signals in higher FIR resulted in sharper and larger peaks. The particle emission finished at lower

inhalation flow rate than the defined PFR under lower PFR and FIR conditions.

The influence of the inhalation patterns on the inhalation performance of Symbicort® Turbuhaler® is depicted in Fig. 3. The OE × St2 ranged from 4.9% to 39.7%, depending on the variations in PFR and FIR. Both OE and OE × St2 increased with higher PFR and FIR. In particular, not only Quick60, but also Slow60 with a constant and slow increased FIR (Fig. 3c), achieved significantly higher OE × St2 compared with Mild60 and Quick30.

The relationships of the inhalation flow rate or particle emission signal and the inhalation performance are shown in
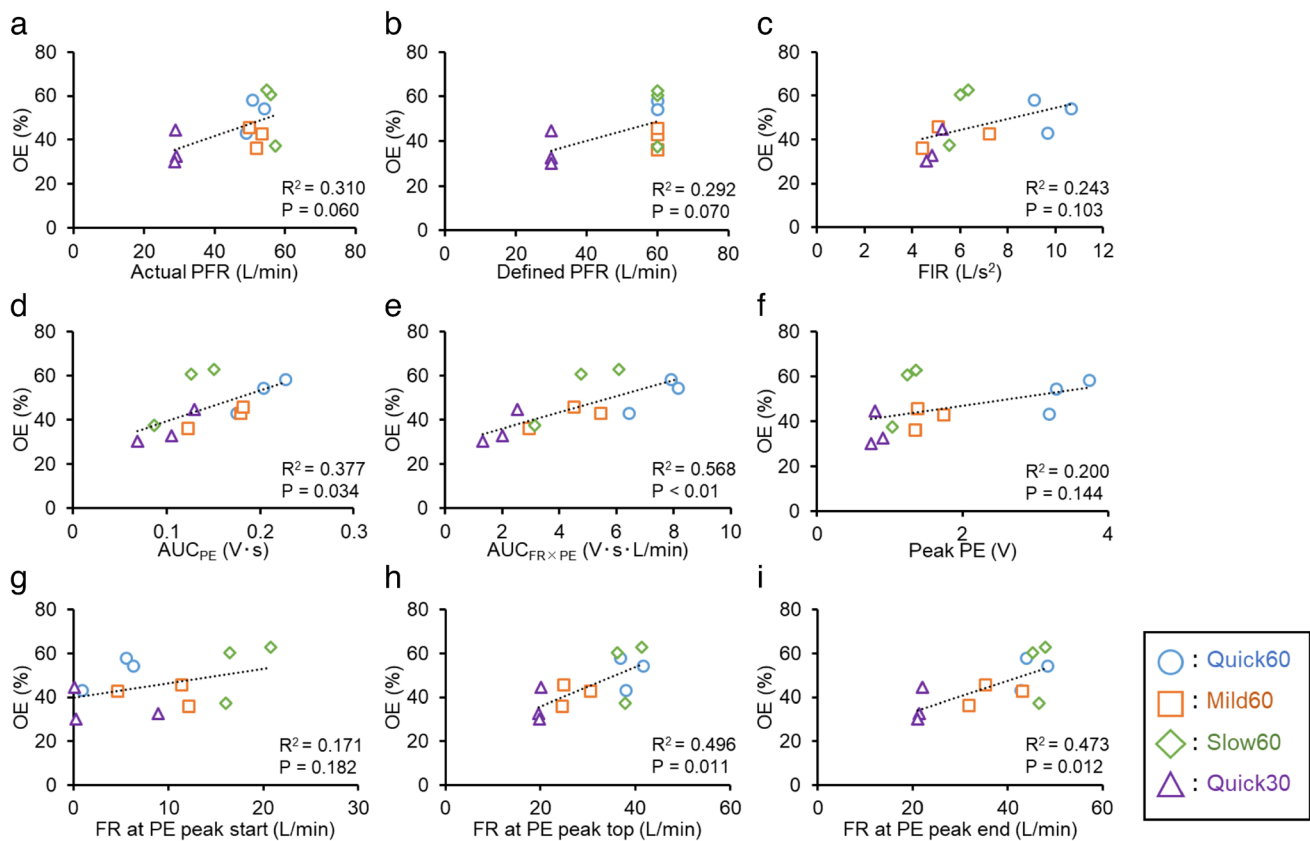
**Fig. 4** Relationships of inhalation flow rate or particle emission signal and output efficiency. Each dotted line represents a regression line

Fig. 4 and 5. The $AUC_{FR \times PE}$ (Fig. 4e and 5e), FR at PE peak top (Fig. 4h and 5h), and FR at PE peak end (Fig. 4i and 5i) showed stronger and more significant correlations with OE and OE × St2 compared to the inhalation flow rate evaluation parameters, such as PFR and FIR (Fig. 4a-c and 5a-c).

## Discussion

In this study, the correlation between particle emission signals and *in vitro* inhalation performance were analyzed using the real-time non-invasive monitoring system based on PRM and flow meter. As results, we clearly demonstrated that significant and strong correlations were observed between the particle emission signals and *in vitro* lung deposition.

Previous studies have reported that drug release and particle size distribution in the Turbuhaler® strongly depends on the peak inhalation flow rate [31–33]. Therefore, the assessment of PFR is typically conducted using a whistle trainer or an In-check dial® in clinical practice [24]. These tools are designed to assess successful inhalation based on patients' ability to achieve an optimal flow rate. Although the optimal PFR of Turbuhaler® was reported as 30–60 L/min [6], lung deposition in this study was significantly decreased by the decreased FIR even under the optimal PFR condition. This result is consistent with those of previous studies using Turbuhaler® [34, 35]. Other DPIs, such as Rotahaler®, Spinhaler®, and Breezhaler®, have also demonstrated a correlation between FIR and lung deposition [5, 36]. In contrast, some reports have found that FIR does not affect inhalation performance using capsule DPIs [9, 36]. Therefore, the impact of FIR on the inhalation performance of DPIs is controversial. This conflict is attributed to differences in the structure of the devices or drug amounts. In general, dose emission occurs earlier from the reservoir and blister type DPI than the capsule DPI [37]. In particular, because the internal volume of the Turbuhaler® is small, most of the drug particles are released before reaching the PFR [34]. For this reason, Turbuhaler® is hypothesized to be sensitive to PFR and FIR during initial inhalation. The present study revealed that particle emission via Turbuhaler® completed within 0.4 s after the start of inhalation, and the flow rate at the particle emission was lower than the defined PFR, especially under the lower FIR conditions (Fig. 2 and Table I). These results provide a reasonable mechanism for the hypothesis of FIR sensitivity of the Turbuhaler®.

The flow rate modified particle emission signal ($AUC_{FR \times PE}$) or the particle emission signal modified flow rate (FR
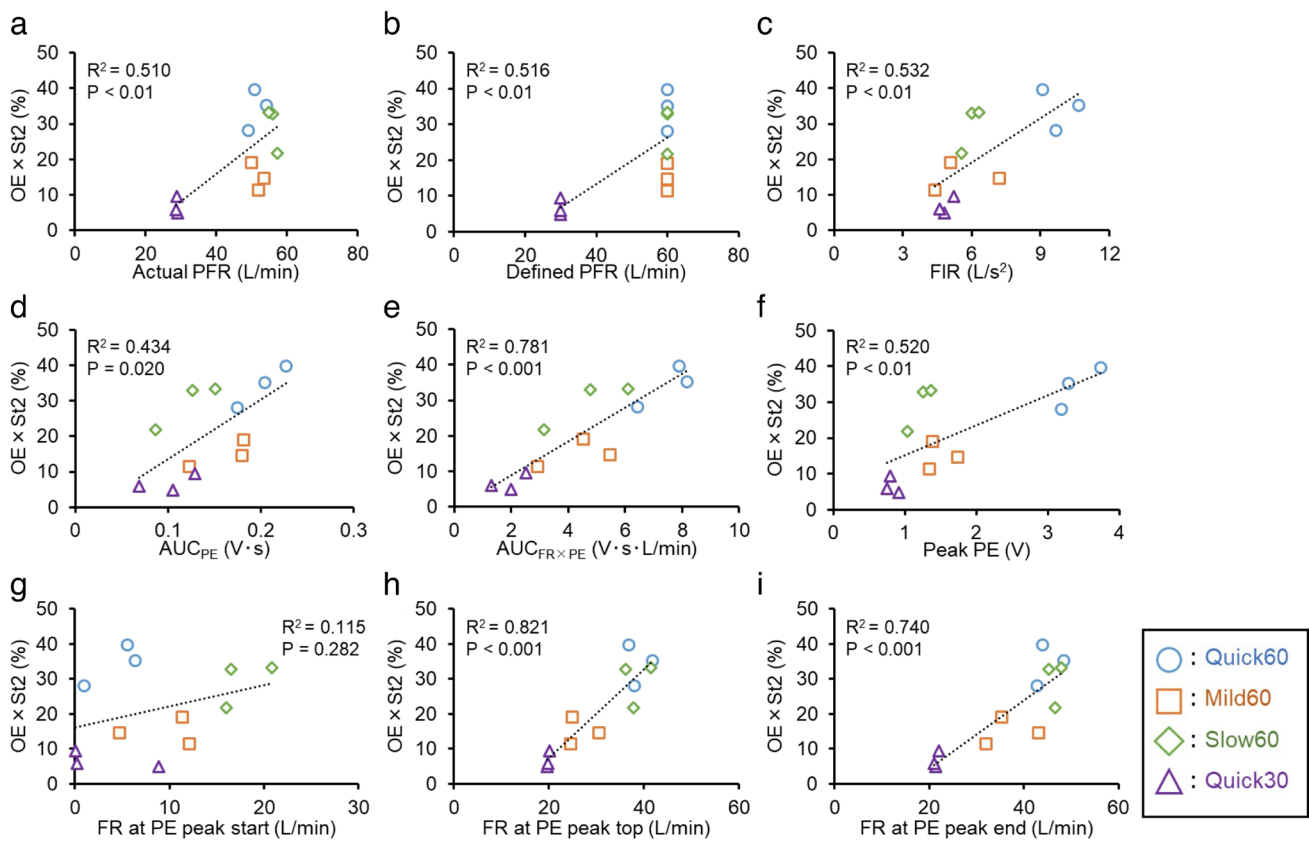
**Fig. 5** Relationships of inhalation flow rate or particle emission signal and lung deposition. Each dotted line represents a regression line

at PE peak top and FR at PE peak end) were more accurate prediction factors for lung deposition than the flow rate or particle emission signal alone ($AUC_{PE}$ and peak PE). Assuming that the particle emission signal reflects the concentration of released drug, the particle emission signal should be affected by the duration of particle retention on the detection area of the PRM system. Under the low flow rate condition, the duration of particle retention will be prolonged, and the particle emission signal will be increased. To adjust the overestimation, we calculated $AUC_{FR \times PE}$, which is the time integrated value of the multiplication of the inhalation flow rate and particle emission signal intensity. Kondo *et al.* also demonstrated that the particle mass released from pressurized metered dose inhaler could be calculated by multiplication of particle emission signal and instantaneous flow [38]. Therefore, parameters that consider both the flow rate and particle emission signal could improve the prediction of pulmonary delivery.

The mean lung deposition for all inhalation patterns in this study was 21.4%, which is comparable to previous research on BUD deposition from the Turbuhaler®. In *in vitro* experiments using an inhalation simulator produced with a vacuum pump, the average lung deposition ranged from 23.1% to 29.1% [10, 31, 39]. Several studies have reported a mean deposition of BUD into the lung ranging from 21.8% to 29.1% in asthmatic patients [40–42]. However, it is essential to note that the results of these studies remain independent from the patient's inhalation technique. Numerous reports have highlighted that an inadequate inhalation technique by patients leads to suboptimal symptom control [43]. In some studies, improper usage rates of Turbuhaler® among patients have been found to range from 32 to 69% [44–46], with frequent errors observed during steps, such as breathing out completely before inhalation, holding the inhaler upright, and breath-holding after inhalation [46, 47]. The impact of these errors on lung drug deposition has been reported in many previous studies [48–51]. Moreover, in asthma or COPD patients, disease exacerbations and advanced age often impede the attainment of an optimal inhalation flow rate, leading to suboptimal delivery [52, 53]. The monitoring system presented in this study can be directly connected to the patient's inhaler and detecting the particle emission signal and inhalation flow pattern. Real-time measurement of the flow rate modified particle emission signal, such as $AUC_{FR \times PE}$, can predict the pulmonary delivered dose in real-time in a non-invasive manner. By using the monitoring system, dose adjustment could be realized according to the patient's daily respiratory function.

There are some possible limitations in this study. Firstly, the particle emission signals were influenced by both carrier lactose particles and drug particles. Although a clear relationship between the particle emission signal and the inhalation performance was observed in Symbicort® Turbuhaler®, further evaluation should be conducted for the application of the PRM to other inhalers. Secondly, administering corticosteroids to asthma patients aims to suppress inflammation in the peripheral airways, with an expectation of favorable drug distribution to deep lung regions, leading to improved disease treatment [54]. Therefore, prediction of the drug distribution within the lungs is desired in clinical practice. Further detailed analysis should be conducted to reveal the correlation between particle distribution within the lungs and PRM parameters. Lastly, we were unable to assess the relationship between the monitoring parameters of particle emission signals and the clinical outcomes. Consequently, future clinical research is imperative to demonstrate the predictability of clinical effects through particle emission signal monitoring.

## Conclusion

Non-invasive and real-time monitoring using flow rate and particle emission signal by PRM could be a useful tool for the prediction of pulmonary drug delivery. In addition, this study provides useful information for the development of personalized inhalation therapy to prevent the practice of an inadequate inhalation technique.

## Declarations

**Conflict of Interest** Dr. Susumu Sato reports grants from Philips Japan, ResMed, Fukuda Denshi, Fukuda Lifetec Keiji, Fuji Film corporation and Nippon Boehringer Ingelheim, outside the submitted work. Dr. Satoshi Hamada reports grants from Teijin Pharma, outside the submitted work. All the other authors have no conflict of interest to declare.

## References

1. Global initiative for asthma. 2022 GINA Report, Global strategy for asthma management and prevention. https://ginasthma.org/gina-reports/. Accessed 7 Feb 2024.

2. Global initiative for chronic obstructive lung disease. 2023 GOLD Report, Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. https://goldcopd.org/2023-gold-report-2/. Accessed 7 Feb 2024.

3. Chandel A, Goyal AK, Ghosh G, Rath G. Recent advances in aerosolised drug delivery. Biomed Pharmacother. 2019;112:108601.

4. Pleasants RA, Hess DR. Aerosol delivery devices for obstructive lung diseases. Respir Care. 2018;63:708–33.

5. Abadelah M, Chrystyn H, Larhrib H. Use of inspiratory profiles from patients with chronic obstructive pulmonary disease (COPD) to investigate drug delivery uniformity and aerodynamic dose emission of indacaterol from a capsule based dry powder inhaler. Eur J Pharm Sci. 2019;134:138–44.

6. Haidl P, Heindl S, Siemon K, Bernacka M, Cloes RM. Inhalation device requirements for patients' inhalation maneuvers. Respir Med. 2016;118:65–75.

7. Price DB, Román-Rodríguez M, McQueen RB, Bosnic-Anticevich S, Carter V, Gruffydd-Jones K, et al. Inhaler Errors in the CRITIKAL Study: Type, frequency, and association with asthma outcomes. J Allergy Clin Immunol: Pract. 2017;5:1071-1081.e9.

8. Al-Awaisheh RI, Alsayed AR, Basheti IA. Assessing the pharmacist's role in counseling asthmatic adults using the correct inhaler technique and its effect on asthma control, adherence, and quality of life. Patient Prefer Adherence. 2023;17:961–72.

9. Hira D, Okuda T, Kito D, Ishizeki K, Okada T, Okamoto H. Inhalation performance of physically mixed dry powders evaluated with a simple simulator for human inspiratory flow patterns. Pharm Res. 2010;27:2131–40.

10. Bagherisadeghi G, Larhrib EH, Chrystyn H. Real life dose emission characterization using COPD patient inhalation profiles when they inhaled using a fixed dose combination (FDC) of the medium strength Symbicort® Turbuhaler®. Int J Pharm. 2017;522:137–46.

11. Hamilton M, Leggett R, Pang C, Charles S, Gillett B, Prime D. In vitro dosing performance of the ELLIPTA a dry powder inhaler using asthma and COPD patient inhalation profiles replicated with the electronic lung (eLung). J Aerosol Med Pulm Drug Deliv. 2015;28:498–506.

12. Taki M, Marriott C, Zeng X-M, Martin GP. Aerodynamic deposition of combination dry powder inhaler formulations in vitro: A comparison of three impactors. Int J Pharm. 2010;388:40–51.

13. Labiris NR, Dolovich MB. Pulmonary drug delivery. Part I: physiological factors affecting therapeutic effectiveness of aerosolized medications. Br J Clin Pharmacol. 2003;56:588–99.

14. Karner S, Anne UN. The impact of electrostatic charge in pharmaceutical powders with specific focus on inhalation-powders. J Aerosol Sci. 2011;42:428–45.

15. Telko MJ, Hickey AJ. Dry powder inhaler formulation. Respir Care. 2005;50:1209–27.

16. Young PM, Kwok P, Adi H, Chan HK, Traini D. Lactose composite carriers for respiratory delivery. Pharm Res. 2009;26:802–10.

17. Edwards DA, Hanes J, Caponetti G, Hrkach J, Ben-Jebria A, Lou Eskew M, et al. Large porous particles for pulmonary drug delivery. Sci. 1997;276:1868–71.

18. Ferguson GT, Hickey AJ, Dwivedi S. Co-suspension delivery technology in pressurized metered-dose inhalers for multi-drug dosing in the treatment of respiratory diseases. Respir Med. 2018;134:16–23.

19. Tamura G, Choi JW, Takeda S, Nishina N, Hayashi A. Aerosol velocity of two pressurized metered-dose inhalers using AEROSPHERE® delivery technology. Respir Investig. 2021;59:153–4.

20. Otake H, Okuda T, Hira D, Kojima H, Shimada Y, Okamoto H. Inhalable spray-freeze-dried powder with L-leucine that delivers particles independent of inspiratory flow pattern and inhalation device. Pharm Res. 2016;33:922–31.

21. Farinha S, Sá JV, Lino PR, Galésio M, Pires J, Rodrigues MÂ, et al. Spray freeze drying of biologics: A review and applications for inhalation delivery. Pharm Res. 2023;40:1115–40.

22. Bryant L, Mclinpharm LB, Bpharm CB, Chew C, Hee S, Bpharm B, et al. Adequacy of inhaler technique used by people with asthma or chronic obstructive pulmonary disease. J Prim Health Care. 2013;5:191–8.

23. Chorão P, Pereira AM, Fonseca JA. Inhaler devices in asthma and COPD – An assessment of inhaler technique and patient preferences. Respir Med. 2014;108:968–75.

24 Lavorini F, Levy ML, Corrigan C, Crompton G. The ADMIT series-issues in inhalation therapy. 6) training tools for inhalation devices. Prim Care Respi J. 2010;19:335–41.

25. Sanders MJ. Guiding inspiratory flow: Development of the In-Check DIAL G16, a tool for improving inhaler technique. Pulm Med. 2017;2017:1495867.

26. Hira D, Koide H, Nakamura S, Okada T, Ishizeki K, Yamaguchi M, et al. Assessment of inhalation flow patterns of soft mist inhaler co-prescribed with dry powder inhaler using inspiratory flow meter for multi inhalation devices. PLoS ONE. 2018;13: e0193082.

27. Kondo T, Tanigaki T, Yokoyama H, Hibino M, Tajiri S, Akazawa K, et al. Impact of holding position during inhalation on drug release from a reservoir-, blister- and capsule-type dry powder inhaler. J Asthma. 2017;54:792–7.

28. Hira D, Okuda T, Mizutani A, Tomida N, Okamoto H. In vitro evaluation of optimal inhalation flow patterns for commercial dry powder inhalers and pressurized metered dose inhalers with human inhalation flow pattern simulator. J Pharm Sci. 2018;107:1731–5.

29. Suenaga K, Hira D, Ishido E, Koide H, Ueshima S, Okuda T, et al. Incorrect holding angle of dry powder inhaler during the drug-loading step significantly decreases output efficiency. Biol Pharm Bull. 2021;44:822–9.

30. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. Bone Marrow Transplant. 2013;48:452–8.

31. Tarsin WY, Pearson SB, Assi KH, Chrystyn H. Emitted dose estimates from Seretide Diskus and Symbicort Turbuhaler following inhalation by severe asthmatics. Int J Pharm. 2006;316:131–7.

32. Abdelrahim ME. Emitted dose and lung deposition of inhaled terbutaline from Turbuhaler at different conditions. Respir Med. 2010;104:682–9.

33. Buttini F, Brambilla G, Copelli D, Sisti V, Balducci AG, Bettini R, et al. Effect of flow rate on in vitro aerodynamic performance of NEXThaler in comparison with Diskus and Turbuhaler dry powder inhalers. J Aerosol Med Pulm Drug Deliv. 2016;29:167–78.

34. Everard ML, Devadason SG, Le Souëf PN. Flow early in the inspiratory manoeuvre affects the aerosol particle size distribution from a Turbuhaler. Respir Med. 1997;91:624–8.

35. De Boer AH, Bolhuis GK, Gjaltema D, Hagedoorn P. Inhalation characteristics and their effects on in vitro drug delivery from dry powder inhalers Part 3: the effect of flow increase rate (FIR) on the in vitro drug release from the Pulmicort 200 Turbuhaler. Int J Pharm. 1997;153:67–77.

36. Chavan V, Dalby R. Effect of rise in simulated inspiratory flow rate and carrier particle size on powder emptying from dry powder inhalers. AAPS PharmSci. 2000;2:1–7.

37. Chrystyn H, Price D. What you need to know about inhalers and how to use them. Prescriber. 2009;20:47–52.

38. Kondo T, Tanigaki T, Hibino M, Tajiri S, Horiuchi S, Maeda K, et al. Dynamic analysis of aerosol release from a pressurized metered dose inhaler combined with a valved holding chamber using simplified laser photometry. J Aerosol Med Pulm Drug Deliv. 2023;36:181–8.

39. Horváth A, Farkas Á, Szipőcs A, Tomisa G, Szalai Z, Gálffy G. Numerical simulation of the effect of inhalation parameters, gender, age and disease severity on the lung deposition of dry powder aerosol drugs emitted by Turbuhaler, Breezhaler and Genuair in COPD patients. Eur J Pharm Sci. 2020;154: 105508.

40. Thorsson L, Kenyon C, Newman SP, Borgström L. Lung deposition of budesonide in asthmatics: a comparison of different formulations. Int J Pharm. 1998;168:119–27.

41. Wildhaber JH, Devadason SG, Wilson JM, Roller C, Lagana T, Borgström L, et al. Lung deposition of budesonide from turbuhaler in asthmatic children. Eur J Pediatr. 1998;157:1017–22.

42. Hirst PH, Bacon RE, Pitcairn GR, Silvasti M, Newman SP. A comparison of the lung deposition of budesonide from Easyhaler, Turbuhaler and pMDI plus spacer in asthmatic patients. Respir Med. 2001;95:720–7.

43. Usmani OS, Lavorini F, Marshall J, Dunlop WCN, Heron L, Farrington E, et al. Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. Respir Res. 2018;19:10.

44. Molimard M. How to achieve good compliance and adherence with inhalation therapy. Curr Med Res Opin. 2005;21(Suppl):4.

45. Pothirat C, Chaiwong W, Limsukon A, Phetsuk N, Chetsadaphan N, Choomuang W, et al. Real-world observational study of the evaluation of inhaler techniques in asthma patients. Asian Pac J Allergy Immunol. 2021;39:96–102.

46. Ding N, Zhang W, Wang Z, Bai C, He Q, Dong Y, et al. Prevalence and associated factors of suboptimal daily peak inspiratory flow and technique misuse of dry powder inhalers in outpatients with stable chronic airway diseases. Int J Chron Obstruct Pulmon Dis. 2021;16:1913–24.

47. Tajiri S, Kondo T, Tanigaki T, Hibino M, Asano K. Daily inhaled flow profiles and drug release from dry powder inhalers in patients with bronchial asthma. Respir Med. 2022;201:106950.

48. Farkas Á, Tomisa G, Kugler S, Nagy A, Vaskó A, Kis E, et al. The effect of exhalation before the inhalation of dry powder aerosol drugs on the breathing parameters, emitted doses and aerosol size distributions. Int J Pharm X. 2023;5: 100167.

49. Farkas Á, Tomisa G, Szénási G, Füri P, Kugler S, Nagy A, et al. The effect of lung emptying before the inhalation of aerosol drugs on drug deposition in the respiratory system. Int J Pharm X. 2023;6: 100192.

50. Horváth A, Balásházy I, Tomisa G, Farkas Á. Significance of breath-hold time in dry powder aerosol drug therapy of COPD patients. Eur J Pharm Sci. 2017;104:145–9.

51. Kadota K, Inoue N, Matsunaga Y, Takemiya T, Kubo K, Imano H, et al. Numerical simulations of particle behaviour in a realistic human airway model with varying inhalation patterns. J Pharm Pharmacol. 2020;72:17–28.

52. Broeders MEAC, Molema J, Hop WCJ, Vermue NA, Folgering HTM. The course of inhalation profiles during an exacerbation of obstructive lung disease. Respir Med. 2004;98:1173–9.

53. Janssens W, VandenBrande P, Hardeman E, De Langhe E, Philps T, Troosters T, et al. Inspiratory flow rates at different levels of resistance in elderly COPD patients. Eur Respir J. 2008;31:78–83.

54. Mastalerz L, Kasperkiewicz H. Effect of inhaled corticosteroids on small airway inflammation in patients with bronchial asthma. Pol Arch Med Wewn. 2011;121:264–9.