Inhalation Performance of Dry Powder Inhalers

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The aim of this study was to reveal the relationship between human inspiratory flow patterns and the concomitant drops in pressure in different inhalation devices, and the influence of the devices on inhalation performance. As a model formulation for inhalers, a physically mixed dry powder composed of salbutamol sulfate and coarse lactose monohydrate was selected. The drops in pressure at 28.3 L/min of three inhalation devices, Single-type, Dual-type, and Reverse-type, was 1.0, 5.1, and 8.7 kPa, respectively. Measurements of human inspiratory patterns revealed that although the least resistant device (Single) had large inter- and intra-individual variation of peak flow rate (PFR), the coefficients of variation of PFR of the three devices were almost the same. In tests with a human inspiratory flow simulator in vitro, inhalation performance was higher, but the variation in inhalation performance in the range of human flow patterns was wider, for the more resistant device. To minimize the intra- and inter-individual variation in inhalation performance for the model formulation in this study, a formulation design that allows active pharmaceutical ingredient to detach from the carrier with a lower inhalation flow rate is needed.

Key words dry powder inhaler; inhalation device; inspiratory flow rate; human inspiratory flow simulator; powder formulation

The greatest advantage of inhalation therapy is the direct delivery of a drug to the respiratory system in patients with pulmonary diseases like asthma and chronic obstructive pulmonary disease (COPD).1,2 In recent decades, dry powder inhalers (DPIs) have received much attention because of their portability, low cost and absence of any propellants.3,4 With passive DPIs, because the aerosolization is activated by inhalation, handling is easier than pressurized metered dose inhalers (pMDIs).5 There are many studies on the inhalation performance of dry powders influenced by particle size, morphology, surface roughness, crystallinity, and so on.6–9

In addition, inspiratory flow patterns and inhalation devices have a significant impact on particle dispersion. The clinical performance of inhalable drugs is susceptible to inspiratory patterns.10 de Boer et al. reported that an increase in the peak inspiratory flow rate resulted in greater fine particle output from commercial dry powder inhalers.11 Inspiratory patterns show extensive inter- and intra-individual variation.12 The design of an inhalation device also influences drug dispersion. As a device becomes more complicated, the inspiratory resistance increases, resulting in a lower flow rate.13–15 In addition, turbulent air flow may occur inside the device.16,17 As well as the inspiratory flow rate, the degree of turbulent air flow also determines drug dispersion.

To examine the fundamental relationship between airflow and aerosol performance, standardized entrainment tubes (SETs) were suggested by Louey et al. as simple experimental inhalation devices.18 The objectives of their studies using SETs were to provide a standardized method to examine dry powder dispersion without reliance on a particular inhalation device. Xu et al. established a novel predictive correlation method (PADE; Powder Aerosol Deaggregation Equation) using SETs.19–21 PADE directly correlates the shear stress of SETs with aerosol performance data. It was developed based on the fundamental concept that the forces acting at the particle interface are analogous to those at the molecular level, and that models of molecular surface association described by an adsorption expression can be adapted to fit shear displacement observations.22

As described in our previous study, we constructed a human inspiratory flow simulator, and evaluated the influence of human inspiratory flow patterns on the inhalation performance of inhalation devices, revealing an effect of active pharmaceutical ingredient (API) particle diameter in physically mixed dry powders. The peak flow rate (PFR) was the most influential parameter affecting inhalation performance among three critical parameters selected for the characterization of human inspiratory flow patterns, flow increase rate (FIR), inspiratory flow volume (area under the flow rate-time curve, AUC) and PFR. In the case of the formulation consisting of the micronized API particles and lactose monohydrate carrier, the higher PFR made for better lung deposition.

In the present study, we used a novel inspiratory flow recorder modified with a pressure meter, and examined (1) the relationship between the human inspiratory flow pattern and the concomitant pressure drop in three inhalation devices, and (2) the influence of the resistance of a device on inhalation performance using PADE. A physically mixed dry powder composed of micronized salbutamol sulfate (SS) and coarse lactose monohydrate was used to model DPIs. SS is a selective beta-2 adrenoceptor agonist widely used for the treatment of airway obstruction caused by asthma, chronic bronchitis, and emphysema. The assessment of dry powder inhalation with reproduced human inspiratory patterns in this study was expected to facilitate the development of human inspiratory flow pattern-independent dry powder inhalation.

Experimental

Materials As a model API for DPIs, salbutamol sulfate (SS) (DOLDER Ltd., Switzerland) micronized by Spiral Jet
Mill (100AS, HOSOKAWA MICRON, Japan) (SS-milled, 2.42 μm) was used. As a carrier particle for dry powder inhalation, lactose monohydrate (Pharmatose® 200 M, DMV, The Netherlands) was used. The other reagents and solvents used were of analytical grade and HPLC grade, respectively.

Simultaneous Measurement of Human Inspiratory Flow Patterns and Pressure Drops As shown in Fig. 1A, the inspiratory flow recorder with a pressure meter (Hitachi Automotive Systems, Ltd., Japan), which could visualize human inspiratory flow patterns and pressure drops, consisted of a hot-wire flow meter, a pressure meter, a power-supply box, and a personal computer. The hot-wire flow meter was applied for high time resolution (milli-second order) and low flow resistance. The pressure meter was confirmed not to influence the measurements of inspiratory patterns. In this study, 19 volunteers (21—26 years old; 11 males and 8 females) participated in the measurement of inspiratory flow patterns with three different inhalation devices described below. The pattern for each volunteer and each device was measured in triplicate, and PFR (L/min) was calculated, which was the most critical parameter for the physically mixed dry powder in a previous study.23)

Characterization of Inhalation Devices The three inhalation devices used were as follows: Jethaler® Single-type, Dual-type, and Reverse-type inhalers (Hitachi Automotive Systems, Ltd., Japan). These devices differed in design and resistance, which resulted in various drops in pressure. To ascertain these differences, the pressure drops at the same PFR with a constant flow rate were measured by flow recorder. The devices were connected to an Andersen Cascade Impactor (ACI; European Pharmacopeia Apparatus D, Sibata Scientific Technology Ltd., Japan) and the suction pump was operated at a constant flow rate (28.3 L/min) which was adjusted by a purge meter attached to the ACI.

Reproduction of Inspiratory Flow Patterns Using the Simulator The inspiratory flow simulator was composed of an airtight container evacuated by a vacuum pump, a valve, and a connecting tube (Fig. 1B). The simulator was connected to the outlet port of the twin stage liquid impinger (TSLI; European Pharmacopeia Apparatus A, Copley Scientific Ltd., U.K.), while the inhalation device and the flow recorder were connected to the inlet port in this order. The parameter PFR was regulated by the diameter of the tube. The container was evacuated with a vacuum pump and the valve was closed. After the flow recorder was connected to the inspiratory flow simulator, a customized program was started to collect flow rate data every 10 ms for 30 s. Then the valve was opened rapidly to achieve a high and constant FIR value. Thirty seconds was long enough to monitor a flow pattern which usually took only a few seconds. Simultaneously, the pressure drops were measured at each condition, when the inspiratory patterns were measured.

Preparation of Physically Mixed Dry Powders Physically mixed dry powders were prepared by mixing 0.5 g of SS-milled and 2.5 g of coarse lactose in a glass bottle with a vortex mixer (SCIENTIFIC INDUSTRIES, U.S.A.) for 20 min, as reported.24)

The diameters of particles of the SS and coarse lactose were determined by a laser micron sizer (LMS-30, SEISHIN, Japan) based on laser diffraction. The morphology of these particles was observed with a scanning electron microscope (SEM; JSM-6060, JEOL, Japan). Samples were mounted on carbon sticky tabs and platinum-coated before imaging (Auto Fine Coater, JFC-1600, JEOL, Japan).

In Vitro Testing of Physically Mixed Dry Powders with Different Inhalation Devices Aerodynamic particle deposition was determined using a TSLI equipped with the proposed inspiratory flow simulator. Stages 1 and 2 in the TSLI contained 7 and 30 mL of purified water, respectively. Aliquots (60 mg) of the physically mixed dry powders (10 mg as SS)
were packed in No. 2 hydroxypropyl methylcellulose (HPMC) hard capsules (Shionogi QualiCaps, Japan). After the Jethaler® was connected to the mouthpiece of the TSLI, the capsule containing the physically mixed dry powders was placed in the holder of the Jethaler® with a pin to pierce them. Then, the simulator was operated to disperse the powder in the capsule under several conditions. After dispersion, the dry powders remaining in the capsule and transferred to the device, the throat, and stages 1 and 2 were collected by rinsing with purified water. The concentration of SS in each collected sample was measured by high performance liquid chromatography (HPLC). The tests were performed in triplicate.

PFR was varied from 15 to 80 L/min in the Single-type Jethaler®, FIR and AUC were set at >100 L/min and 2.5 L, respectively.

The inhalation performance of the prepared dry powders was characterized by stage 2 deposition (St2). St2 represents the amount ratio of API particles deposited on stage 2 of the TSLI (Eq. 1).

\[
\text{St2} = \frac{\text{mass recovered from stage 2}}{\text{mass balance}} \times 100
\]

where the mass balance is the mass of SS recovered from all parts of the apparatus (capsule, device, and TSLI).

The cut-off diameter of the TSLI depends on the flow rate being 6.4 μm when operated at a constant flow rate of 60 L/min. This means the cut-off diameter varied when the PFR was changed. Keeping a constant flow rate would be significant for quality control purposes; however, it does not reflect the human inspiration pattern. Even on inhaling particles of the same size, the pulmonary deposition should depend on the inspiration pattern, especially on the PFR. A particle size around 6 μm or less is generally recognized to be suitable for deep lung deposition; however, actual lung deposition in patient usage is influenced by their inspiratory flow patterns. Although the cut-off size for stage 1 varied with the PFR, the St2 determined in the present system may be a better index of the deposition of API in the lungs than that determined at a constant flow rate.

**Analyses Using the PADE** Xu et al. proposed using the PADE to analyze carrier-based dry powder inhalation. They used this method to investigate the relationship between inhalation performance and shear stress. They also used SET to produce various shear stress patterns. On the other hand, we used various inhalation patterns to make various shear stress patterns with each inhalation device. So, we can determine the characteristics specific to each device using the PADE method. The PADE nonlinear (Eq. 2) and PADE linear regression (Eq. 3) are defined as follows:

\[
\frac{\text{St2}}{\text{St2}_{\text{max}}} = \frac{k_d \text{r}_s}{(1 + k_d \text{r}_s)}
\]

(2)

\[
\frac{\text{r}_s}{\text{St2}} = \frac{\text{r}_s}{\text{St2}_{\text{max}} + 1} (k_d \text{St2}_{\text{max}})
\]

(3)

where St2max is defined as the characteristic St2 at shear stress rs which approaches maxima and further increasing St2 would require comminution of the drug/carrier particles; and k_d is defined as the deaggregation constant, analogous to the Langmuir adsorption constant. In our study, we could not calculate rs for each device because these devices differ in the ability to generate turbulence. Instead of shear stress, power was used as an indicator of comminution intensity for each inspiratory pattern in this study. Power is the rate of work done by airflow through the inhalation devices, described as follows:

\[
\text{power} = \Delta P \cdot \text{PFR}
\]

(4)

where ΔP is the pressure drop and PFR is the peak volumetric flow rate. Power is equivalent to the rate of inspiratory effort during inhalation. Because Louey et al. indicated that power, in addition to shear stress, correlated with fine particle mass values, power was applied to the PADE analysis in our study.

The reason for our application of the PADE linear regression is to calculate the St2 value by plugging the power value of the human inspiratory pattern into the PADE linear regression of each device. The values of St2 at minimum and maximum power were used to compare the variation among the inspiratory patterns.

**Measuring Salbutamol Sulfate Concentrations by HPLC**

The HPLC system (Agilent Technologies, Inc., U.S.A.) consisted of a quaternary pump (G1311A), a degasser (G1322A), a UV-vis detector (G1314B), a column oven (G1316A), and an auto sampler (G1329A). The mobile phase was composed of 0.025 m phosphate buffer (pH 2.8), acetonitrile, and methanol (90:9:1, volume ratio). The flow rate was set at 1.0 mL/min. The column (ZORBAX Eclipse XDB-C18, 5 micron, 4.6×150 mm; Agilent Technologies, Inc., U.S.A.) was heated at 35°C. The injection volume was 100 μL. The UV (UV) absorbance of each sample was measured at 224 nm. It was confirmed that the UV absorbance correlated linearly with the concentration of SS between 1.0 and 150 μg/mL.

Fig. 2. Scanning Electron Micrographs of Physically Mixed Dry Powder; (A) Low Magnification, (B) High Magnification
Results and Discussion

Preparation of Physically Mixed Dry Powers: The morphology of physically mixed dry powders composed of SS-milled and coarse lactose monohydrate is shown in Fig. 2. As expected, micronized SS powders uniformly attached to the coarse lactose particles, as reported elsewhere. The volume median diameter of SS-milled and coarse lactose monohydrate was approximately 2.4 μm and 17 μm, respectively.

Properties of Inhalation Devices: Three inhalation devices were used in this study, Jethaler® Single-type, Dual-type and Reverse-type. The resistance of inhalation differed with their design, and the strength of the resistance was substituted for pressure drops. The pressure drops at a constant inspiratory flow rate (28.3 L/min) of the Single, Dual and Reverse devices were 1.0 kPa, 5.1 kPa and 8.7 kPa, respectively. Inspiratory flow is the trigger of detachment of the micronized SS from the carrier lactose monohydrate, and the inspiratory flow rate is one influential factor. Along with the inspiratory flow rate, the resistance of the device has an impact on inhalation performance. The three devices used in this study differed in resistance, as represented by pressure drops at the same flow rate. A device with higher pressure drops is more complicated, resulting in stronger turbulence with higher shear stress.

Analysis of Human Inspiratory Patterns Using Different Devices: Representative human inspiratory flow patterns of different inhalation devices are shown in Figs. 3A—C. PFRs changed dramatically between devices, and the lower the resistance of the device, the higher the PFR and the change of PFR. The highest and lowest PFR in Single were 115 L/min and 34 L/min, respectively. On the other hand, those in Reverse were 40 L/min and 12 L/min, respectively. The averages (±S.D.) of the PFR of the Single, Dual, and Reverse devices were 83.5±21.5, 36.0±8.4, and 28.2±6.7 L/min, respectively. In addition, the averages (±S.D.) of the 19 standard deviations of the PFR determined for the triplicated determinations were 3.8±1.7, 1.7±0.8, and 1.3±0.5, respectively. Although the least resistant device (Single) had large inter- and intra-individual variation of PFR, the coefficients of variation of PFR of the three devices were almost the same.

The relationship of PFR in each device is shown in Fig. 3D. There are correlations between the PFR of Single and that of the other two devices. These results suggest that measurement of the PFR of one device accomplished by patients can help to calculate the approximate PFR values of the other devices by the same patient. Using these methods, we can easily determine the optimized device for each patient.

Simultaneous Measurement of Human Inspiratory Flow Patterns and Pressure Drops: In this study, pressure drops were measured simultaneously with inspiratory flow patterns by a pressure meter connected to the inhalation device. The relationship between PFR and the pressure drop of human inspiratory patterns is shown in Fig. 4. As the PFR increased, the peak pressure drop increased in an exponential manner, and the rate of increase differed with the devices. These results can be explained by the following equation:

\[ Q \times R_0 = \Delta P^{0.5} \]

where \( Q \) is the inspiratory flow rate and \( \Delta P \) is the pressure drop across devices. The \( R_0 \) is the devices specific resistance depended on the internal dimensions and geometry of the airflow path of the inhalation device. The \( R_0 \) values of the three devices; Single, Dual, and Reverse, were 0.031, 0.075, and 0.098 kPa·L·min⁻¹, respectively. These relationships were also confirmed in the reproduced patterns using the inspiratory flow simulator. Power also had an exponential relationship with the PFR. From the simultaneous measurement of PFR and pressure drop, we can confirm the relationship between the PFR and the pressure drop not only of the human inspiratory pattern, but also of the reproduction patterns using the inspiratory flow simulator. That result means the inspiratory flow simulator can closely reproduce the human inspiratory flow pattern. Therefore, the inspiratory flow simulator was ap-

![Fig. 3. Typical Inspiratory Flow Patterns of Three Healthy Volunteers with Three Different Inhalation Devices, a Single-Type (A), Dual-Type (B) and Reverse-Type (C) and the Relationship of the Averaged PFR between the Single-Type and Other Two Devices (D)](image)

The equations for the Single-Dual and Single-Reverse devices were \( y = 0.3672x + 5.339 \), and \( y = 0.2734x + 5.3801 \), respectively.
Influence of Peak Flow Rate on Inhalation Performance of Dry Powders in Different Devices

Inhalation performances of dry powder and PFR in different devices are shown in Fig. 5. In this study, the range of PFR was set from 15 to 80 L/min in the Single-type Jethaler®. But in more resistant devices, the range of PFR became narrower. The range of actual measured PFR values in the three inhalation devices; Single, Dual, and Reverse, was 14—73 L/min, 13—53 L/min, and 13—50 L/min, respectively. In each device, the higher PFR made higher stage 2 deposition. The Single device showed higher device and stage 1 deposition than the other two devices. Among the three devices, stage 2 deposition increased as the inhalation resistance increased. In all three devices, the lowest PFR (15 L/min) was not enough to emit the powder from the capsule. For a physically mixed dry powder as DPI, a higher PFR and inspiratory resistance were needed to achieve greater inhalation performance. For all three devices, as the PFR increased, stage 2 deposition also increased. These results were reported for the Single-type device previously, and means that the bottleneck for increasing stage 2 deposition is the detachment of the micronized SS particles from the lactose monohydrate carrier particle. Stage 2 deposition was also increased by increasing the inspiratory resistance of the inhalation device at the same flow rate. It was generally observed that a higher resistance, that is to say, pressure drop, caused higher shear stress, and a complicated device produced strong turbulence, resulting in greater shear stress and stage 2 deposition.

Relationship between Power and Inhalation Performance of Dry Powders

As a parameter of inhalation performance, St2 was compared with inspiratory parameters: that is, PFR, pressure drop, and power. In the case of PFR, as described in the previous section, a higher PFR resulted in greater stage 2 deposition. The highest PFR was achieved by the Single-type device, but stage 2 deposition was greatest for the Reverse-type device, which had a lower PFR. The pressure drop of the Single device was the lowest among the three devices, and stage 2 deposition was also lowest. Then, we used the value of power instead of PFR. Power is the product of PFR and pressure drop, and is equivalent to the rate of inspiratory effort during inhalation. The correlation of stage 2 deposition with power calculated from PFR and pressure drop with each device is shown in Fig. 6A. As power increased, the parameters of inhalation performance also increased, and as power increased more, these parameters did not change (plateau). These results were obtained in other studies, but in this study, we found that the plateau values of the inhalation parameters depended on the device. The result means the device as well as the formulation of the dry powder determines the inhalation performance of the dry powder. In all inhalation devices,
a greater initial increase in stage 2 deposition at lower power was followed by a smaller increase at higher power until stage 2 deposition approached a plateau, as reported elsewhere. These plateau values represent maximum stage 2 deposition, and the detachment of micronized API particles was saturated in this state and didn’t increase in the presence of excess power. The difference in the plateau value of stage 2 deposition in the three inhalation devices depended on the specific turbulence of the device. Specific turbulence depended on the pressure drop in the device and the complexity of the device. As the device becomes more complicated, the pressure drops become larger and the turbulence becomes stronger.

**PADE Analysis of Dry Powders** The correlation of stage 2 deposition with the power value of each device by PADE nonlinear regression and PADE linear regression analysis is shown in Fig. 6. In the PADE linear regression analysis (Fig. 6B), the coefficient of correlation values ($R^2$) of all devices were over 0.99. The $St_{2\text{max}}$ value calculated from the slope of the PADE linear regression of each device increased as the resistance of the inhalation device increased. In the range of power values calculated from human inspiratory patterns, the $St_2$ of Single, Dual and Reverse inhalers was 4.88—12.42%, 8.59—17.63% and 9.60—34.65%, respectively (Table 1). Within the power range of human inspiratory patterns, the $St_2$ varied widely. For minimum intra- and inter-individual variation and maximum inhalation performance, it is necessary to design dry powder formulations to allow API to detach from the carrier with a lower inhalation flow rate attainable by a high resistance inhalation device.

**Conclusions**

In this study, we used three different inhalation devices to disperse the physically mixed dry powder. The analysis of human inspiratory flow patterns revealed that although the least resistant device (Single) had large inter- and intra-individual variation of PFR, the coefficients of variation of PFR of the three devices were almost the same. The inspiratory flow simulator could reproduce not only the PFR but also pressure drops with accuracy. So the simulator is suitable for the assessment of various inhalation systems.

From the results of TSLI testing with the inspiratory flow simulator, the device with the highest resistance, the Reverse inhaler, had the highest value for stage 2 deposition. On the other hand, in the range of the PFR of human inspiratory patterns, the variation in stage 2 deposition was greatest for the highest resistance device than lowest resistance device. With the highest resistance device, while the PFR variation was narrowest, the variation in power was the widest. The physically mixed dry powder used in this study resulted in wide variation. The physically mixed powder used in this study was a model formulation and required relatively high power to reach $St_{2\text{max}}$. Within the power range of human inspiratory patterns, the $St_2$ varied widely. For minimum intra- and inter-individual variation and maximum inhalation performance, it is necessary to design dry powder formulations to allow API to detach from the carrier with a lower inhalation flow rate attainable by a high resistance inhalation device.
of the inhalation device.

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