Analysis of Drug Release Dynamics of the Reservoir-type Dry Powder Inhalers

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Objective: Dry powder inhalers (DPIs) are classified as capsule, blister, and reservoir types. Currently, two reservoir-type DPIs, i.e., Turbuhaler™ (TBH) and Genuair™ (GNA), are available, but their physical characteristics differ. Therefore, we compared their drug release patterns.
Methods: An inhalation flow simulator was set to reach peak inhalation flow (PIF) at two time points, 0.4 s (rapid) or 1.5 s (moderate), and then the drug release from both the DPIs were compared.
Results: The amount of drug release from the TBH increased linearly with increase in PIF, and the amounts were higher during rapid inhalation than during moderate inhalation. The GNA had a threshold flow for drug release, above which the flow was PIF-dependent (rapid) or independent (moderate). With rapid inhalation, drug release was dependent on the peak value and releasing time in both the DPIs. With moderate inhalation, the peak flow dependency of the TBH was attenuated, whereas that of the GNA remained time-dependent.
Conclusion: Rapid and strong inhalation are best for drug release in both the DPIs, but a longer inhalation was required for the GNA. Therefore, if a patient cannot inhale rapidly, then a moderately rapid and long inhalation could be considered, but strong inhalation is still mandatory for TBH.

Key words: Turbuhaler™, Genuair™, peak inhalation flow, drug release

INTRODUCION

Inhalation therapy is the cardinal strategy for the treatment of airway diseases such as bronchial asthma and chronic obstructive pulmonary disease (COPD) [1]. Dry powder inhalers (DPIs), in which fine particle drugs require inhalation by the patient, are most frequently used for this purpose [1]. They are classified as capsule, blister, and reservoir types according to their drug release mechanisms [2]. Therefore, the drug release patterns for each type of DPI differ [2]. Genuair™ (GNA) is a relatively new DPI and has a reservoir-based mechanism. It has been described as an easy-to-handle, high-performing device in a review by Chrystyn and Niederlander [3]. On the other hand, Turbhaler™ (TBH), which was designed approximately 30 years ago [4], is a representative reservoir-type DPI that is still widely distributed [1]. Although both inhalers have reservoirs, their intrinsic resistances and drug deagglomeration mechanisms are quite different [3, 4]. Therefore, whether the inhalation pattern for different DPIs with same release mechanism should be the same or not is an important issue in inhalation therapy. In the present study, we compared the drug release patterns from both the DPIs with the aim of clarifying the best inhalation flow pattern for these DPIs.

METHODS

In this study, we used an inhalation simulator, and the drug release pattern was estimated using a photo-reflection method. The system is described in detail elsewhere [5, 6]. In brief, the simulator was composed of six sequentially arranged parts: a vacuum pump, flow regulator, drug measuring unit constructed from a copper tube and photo unit, an air-tight box that housed the DPI, and a pneumotachometer (Fig. 1). In the unit measuring drug powder release, particles that passed through the tube were irradiated by a laser light, and the intensity of the reflected light was measured using IC-photo diodes. All the inhalation flows showed a triangular pattern with a gradual increase followed by gradual decrease. The time taken to reach the peak inhalation flow (PIF) was either 0.42 or 1.4 s for rapid or moderate inhalation, respectively, whereas the descending time was maintained at 1.4 s. Study materials included were five TBHs for Symbicort™ and six GNAs for inhalation training. Each DPI was selected from a different lot. Signals of inhaled flow and drug release were stored in a data analyzing system (PowerLab, ADInstruments, New South Wales, Australia) with a sampling rate of 1.0 kHz. Statistical analyses were conducted using an unpaired *t*-test,

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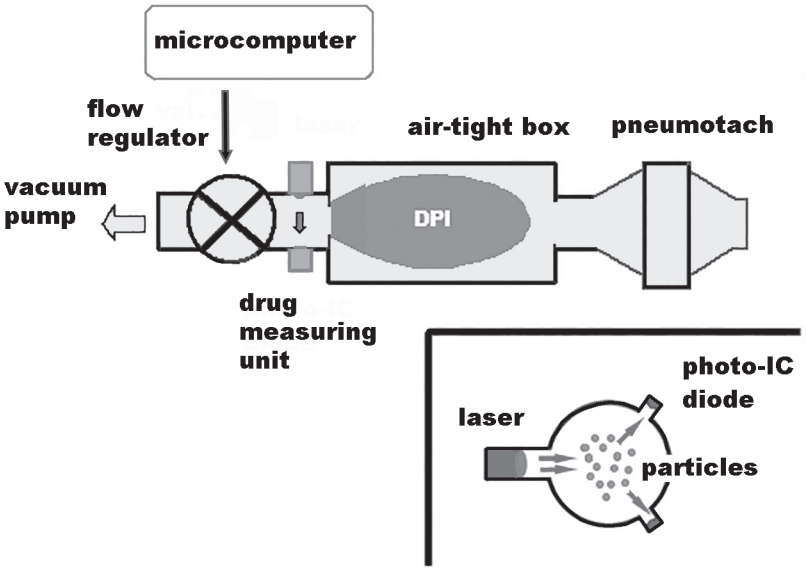

Fig. 1 The inhalation simulator is composed of a vacuum pump, flow regulator, drug measuring unit, an air-tight box, and a pneumotachometer. *Inset;* A transverse view of the measuring unit. A laser irradiates the drug particles passing through the tube, and the intensity of the reflected light is measured with IC-photo diodes.

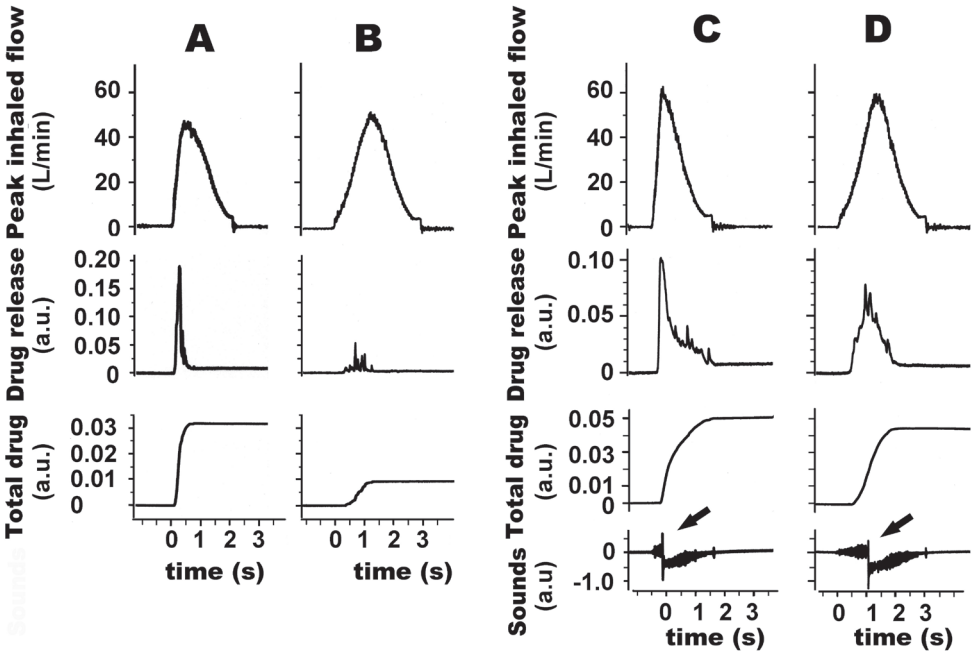

Fig. 2 Representative records from (A and B) Turbuhaler (TBH) and (C and D) Genuair (GNA). (A) Rapid inhalation from the TBH (time to reach the peak inhalation flow (T_{PIF} = 0.42 s)), (B) moderate inhalation from the TBH (T_{PIF} = 1.4 s), (C) rapid inhalation from the GNA (T_{PIF} = 0.42 s), and (D) moderate inhalation from the GNA (T_{PIF} = 1.4 s). Total drug: amount of powder released from DPI. Sounds: sounds representing motion of appropriate-flow indicator. When inhalation was initiated, airstream sounds appeared. A click sound, indicated by an arrow, shows motion of the flow indicator.

ANCOVA and Mann–Whitney's *U* test. The difference was considered significant if $p < 0.05$.

In the GNA, an audible click and changes of the control window from green to red indicate correct inhalation [3]. Consequently, in the GNA experiment, such clicks were detected using a small microphone attached to the DPI.

RESULTS

Representative drug release pattern from the two DPIs, which exhibit two different inhalation patterns, are shown in Fig. 2. An apparently longer drug release time (T_{drg}) and smaller drug release were observed with moderate inhalation (Fig. 2B and D) than with rapid (Fig. 2A and C) inhalation for both the DPIs. In contrast, changes in these values for each DPI were more prominent in the TBH (Fig. 2A, B) than in the GNA (Fig. 2C and D). The bottom traces in Fig. 2C and D depict sounds collected from the GNA. The motion of the flow indicator, designated as clicking sounds (arrows), appeared later during moderate inhalation than that during rapid inhalation. The results showed that the directed appropriate flow rates during rapid and moderate inhalations were almost the same

Table Drug release parameters at rapid and moderate inhalations (mean ± SD).

	Rapid	Moderate	Rapid	Moderate
	TBH (PIF > 15 L/min)		**GNA (PIF > 25 L/min)**	
Peak/tot	9.56 ± 4.38	8.95 ± 12.23*	2.24 ± 0.80#	1.23 ± 0.34*, #
T_{drg} (s)	0.39 ± 0.11	1.18 ± 0.32*	1.76 ± 0.40#	2.08 ± 0.44*, #
	TBH (PIF > 50 L/min)		**GNA (PIF > 45 L/min)**	
Peak/tot	8.47 ± 2.44	4.55 ± 1.56*	2.42 ± 0.91#	1.28 ± 0.36*, #
T_{drg} (s)	0.40 ± 0.11	1.30 ± 0.20*	1.71 ± 0.38#	1.82 ± 0.27#
Flow at click sound development (L/min)			51.38 ± 3.90	49.33 ± 2.47

*$p < 0.05$ between rapid and moderate inhalations (unpaired *t*-test). #$p < 0.001$ between Turbuhaler (TBH) and Genuair (GNA) (unpaired *t*-test). Statistical analyses of peak/tot with PIF were performed using Mann–Whitney's *U* test.

(see Table).

Fig. 3 shows the relationship between PIF and the amount of drug released by both the DPIs. For the TBH, the drug release started at approximately 10 L/min and then linearly increased with rising PIF during both rapid (Fig. 3A) or moderate inhalation rates (Fig. 3C). The linear regression lines at PIF > 15 L/min were:

$Y = 0.0008X - 0.009$, $R^2 = 0.575$, $p < 0.001$ (rapid inhalation, Fig. 3A),

and

$Y = 0.00048X - 0.005$, $R^2 = 0.469$, $p < 0.001$ (moderate inhalation, Fig. 3C).

The slope and intercept of the regression lines were significantly different (ANCOVA, $p = 0.028$ and 0.0013, respectively). Drug release from the GNA started abruptly when the inhaled flow exceeded approximately 20 L/min (Fig. 3B and D) suggesting a drug release threshold followed by increase in drug release in a linear fashion with increasing PIF.

The linear regression lines at PIF > 25 L/min were:

$Y = 0.0013X + 0.029$, $R^2 = 0.221$, $p = 0.001$ (rapid inhalation, Fig. 3B),

and

$Y = 0.0006X + 0.096$, $R^2 = 0.007$, $p < 0.001$ (moderate inhalation, Fig. 3D).

The slope of regression lines for rapid inhalation was significantly greater (ANCOVA, $p = 0.025$) than that for moderate inhalation; however, the difference found in the intercept was not significant (ANCOVA, $p = 0.653$). Therefore, above the threshold PIF ranges, drug release from the GNA was almost flow-dependent.

Fig. 4 also shows the drug release parameters of both DPIs above threshold flow rates for both rapid and moderate inhalations. The peak values of the drug release were PIF-dependent in the TBH (Fig. 4A) and the GNA (Fig. 4B). The linear regression lines for the TBH were:

$Y = 0.006X - 0.058$, $R^2 = 0.514$, $p < 0.001$ (rapid inhalation)

and

$Y = 0.002X - 0.01$, $R^2 = 0.95$, $p = 0.02$ (moderate inhalation).

The slope and intercept of the regression lines were significantly different for rapid and moderate inhalation (ANCOVA, $p < 0.0011$ and < 0.0001, respectively).

Those for the GNA were:

$Y = 0.006X - 0.078$, $R^2 = 0.45$, $p = 0.08$ (rapid inhalation)

and

$Y = 0.002X - 0.03$, $R^2 = 0.312$, $p = 0.18$ (moderate inhalation).

The slope and intercept of the regression lines were significantly different for rapid and moderate inhalations (ANCOVA, $p < 0.0001$ and < 0.0001, respectively). Therefore, higher drug peaks appear with rapid inhalation than with moderate inhalation for both the DPIs. For further analysis, we created a parameter by dividing the peak value by the total amount of drug released (peak/tot) (Fig. 4C and D). The high peak/tot values suggested that most of the drug was released in a short burst. Peak/tot values with moderate inhalation were smaller than those with rapid inhalation, especially at higher PIFs. For both rapid and moderate inhalation, peak/tot values for the TBH (Fig. 4C) were a few folds higher than those for the GNA (Fig. 4D). The bottom panels show the T_{drg} at different PIFs. T_{drg} during moderate inhalation were longer than those during rapid inhalation in the TBH, but the difference in the GNA was minimal.

The quantitative data of peak/tot values and T_{drg} are listed in Table. Based on previous studies, we considered that the flow required for fine particle dispersions would be higher [3, 4]; therefore, we assessed the peak/tot values and T_{drg} at higher PIF range as well. We found that peak/tot value decreased significantly and T_{drg} prolonged significantly with moderate inhalation in the TBH, whereas peak/tot values in the GNA decreased significantly decreased, but T_{drg} remained unchanged.

The function of the suitable flow indicator in the GNA is also shown in Table. The color of the indicating window changed from red to green at approximately 50 L/min, and no significant difference were observed (unpaired *t*-test) in the flow rates during rapid and moderate inhalation.

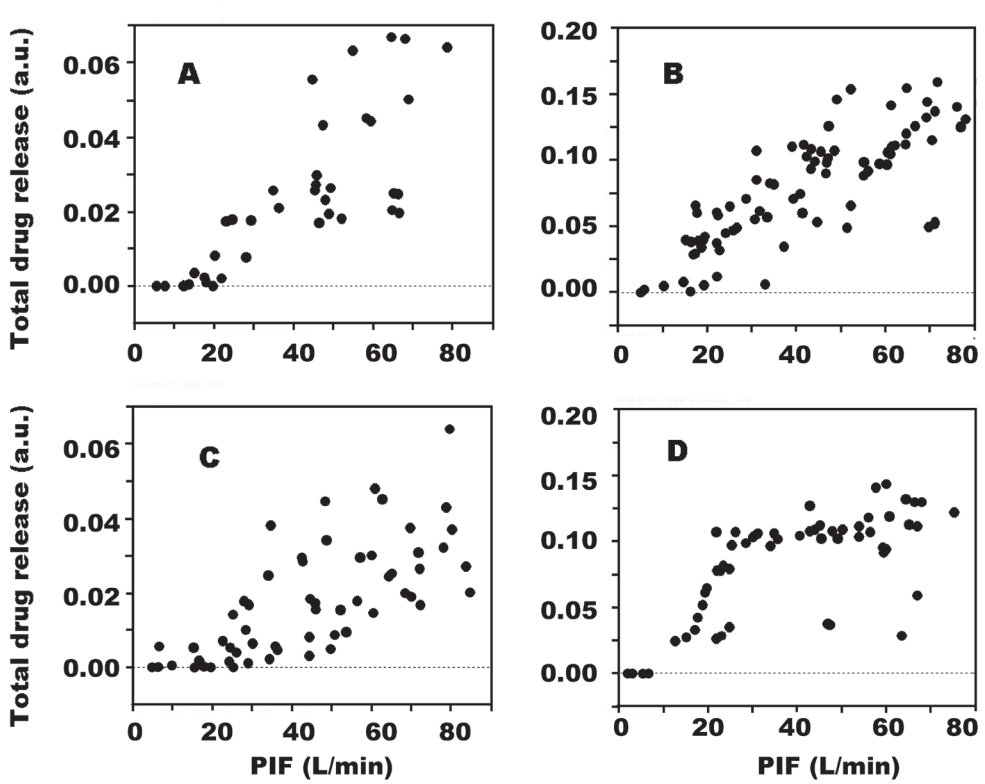

Fig. 3 Peak inhalation flow (PIF) vs. drug release relationships in TBH (A and C) and GNA (B and D) with rapid (upper panels) and moderate (lower panels) inhalations. For the TBH, the drug release was flow-dependent, and drug release with rapid inhalation was significantly larger than that with moderate inhalation (A and C). The GNA had a threshold flow in drug release, and thus, was not flow-dependent.

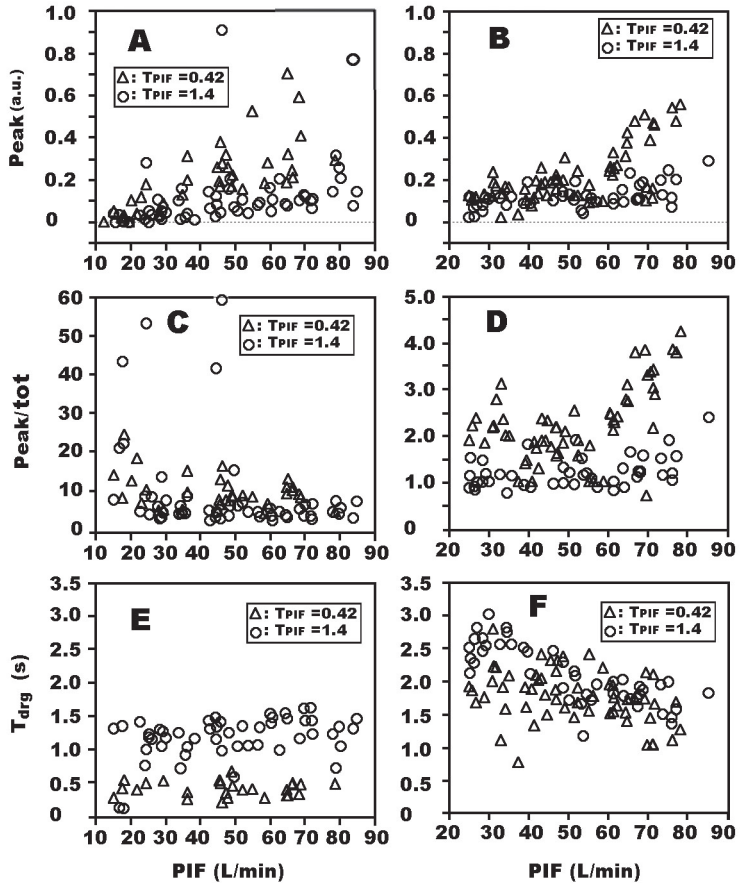

Fig. 4 Drug release parameters at different PIF and T_{PIF} in TBH (A, C, and E) and GNA (B, D, and F). Top panels: peak drug release; middle panels: peak value divided by total amount of drug release. This parameter indicates contribution of burst component to total drug dispersion. Bottom panels: drug releasing time (T_{drg}) at different PIFs. Note that scale of panel C is 10 times than that of D.

DISCUSSION

Several studies have shown an importance of inhalation strength in drug release from the DPI [7, 8]. For example, Farkas *et al.* reported that 48 of 49 patients achieved sufficient peak inhalation flow through the Breezhaler while only 27 patients exceeded the threshold PIF through TBH [7]. Although most of the previous studies concerned with inhalation strength (i.e., PIF) the present investigation highlighted importance of inhalation flow patterns.

Our data indicates that drug release from the TBH is PIF-dependent, whereas that from the GNA had a threshold, thus, it was not PIF-dependent, especially during moderate inhalation. These different characteristics are consistent with findings reported in previous studies [3, 9]; however, in those studies, the inhaled flow rates were increased in a gradual manner. The present study provides novel information showing that the DPI-specific drug release patterns were still observed with a flow pattern resembling human inhalation. Rapid inhalation was also shown to induce higher drug release than moderate inhalation from both the DPIs investigated here. Therefore, a rapid (short T_{PIF}) and strong (large PIF) inhalation was crucial for achieving an appropriate inhalation pattern for the TBH. The GNA also achieved the highest drug release with rapid and strong inhalation. However, because the GNA is not flow-dependent during moderate inhalation, weaker and moderate inhalation may be acceptable.

Although the importance of the inhalation flow pattern is apparent in DPI use [2], dynamic analyses of drug release related to inhalation pattern are scarce [10–12]. Our investigation, using two drug-emission parameters, highlighted the effects of the inhalation pattern on drug release. During rapid inhalation, the contribution of drug bursting, as represented by the peak/tot value, in the TBH was four times larger than that in the GNA. On the other hand, the contribution of T_{drg} in the TBH was almost a quarter of that in the GNA. Therefore, the TBH was peak-dependent and the GNA was time-dependent. With moderate inhalations, the TBH exhibited a larger peak/tot value than the GNA, but peak dependency was considerably attenuated. Conversely, T_{drg} in the TBH was elongated with moderate inhalation and the difference between T_{drg} in the TBH and the GNA was not notable. Hence, the peak dependency of the TBH was attenuated during moderate inhalation, whereas time dependency of the GNA was maintained.

The changes in the drug release pattern and parameter indicated that strong inhalation was mandatory for TBH use. However, for some patients who cannot inhale rapidly, moderately rapid inhalation, during which the peak dependency of the TBH was attenuated, and longer inhalation could be considered. Although strong and rapid inhalation is preferred for the GNA, this DPI was found to be a time-dependent device, therefore it requires an inhalation time of at least 2 s (time to start drug release plus T_{drg}) for effective drug release. However, strong, rapid, and long inhalation might be difficult for some patients. In such cases, moderate (PIF > 45 L/min), moderately rapid ($T_{PIF} < 1.4$ s), and slightly long inhalation ($T_{drg} > 2$ s) may be performed.

The suitable flow indicator built into GNA indicated 50 L/min as the appropriate inhalation rate, which was close to what we proposed as a moderately strong rate (> 45 L/min). Therefore, any instruction for adopting this indicator should recommend longer inhalation. As discussed above, the inhalation flow pattern and PIF are important for providing instructions for DPI use. Although a flow pattern trainer is currently unavailable, visualization of the inhaled flow trajectory in a graphic display is not difficult [6, 10] and if necessary, the drug trajectory could be included on the display [5, 6].

In our study the inhalation simulator provided lots of merits comparing with a human inhalation study. For example, the simulator generated numerus number of inhalations with different rapidity and strength. Almost free running cost was also beneficial. On the other hand, although this study depicted drug releases from the DPI, drug delivery of the released drug to the lower airways was unknown. Furthermore, simulation study does not guarantee the results to clinical application. Clinical investigation based on present knowledge should be prosecuted in future.

In conclusion, this study revealed differences in the drug release pattern of the TBH and GNA. Drug release from the TBH was primarily peak value-dependent, whereas that from the GNA was T_{drg}-dependent. Although simplified flow patterns highlighted the DPI's drug release characteristics, patients' inhalation patterns are more complex [11]. Therefore, a further study that simulating these inhalation patterns may provide more practical information.

DISCLOSURE OF COI.

The authors have disclosed no conflicts of interest.
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