Factors Determining *In Vitro* Lung Deposition of Albuterol Aerosol Delivered by Ventolin Metered Dose Inhaler

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Abstract

**Background:** The effectiveness of metered dose inhalers (MDIs) in delivering medication to the lungs highly depends on its correct usage technique. Current guidelines state optimal technique for high lung deposition should include a slow inhalation (>5 seconds) at an inspiratory flow rate of 30L/min and inhaler actuation at the start of inhalation. However, these recommendations were based on clinical studies using CFC (chlorofluorocarbon)-MDIs and on in vitro studies of HFA (hydrofluoroalkane)-MDIs using idealized MDI techniques of uniform inhalation and actuation, disregarding the non-uniform techniques of actual patients.

**Methods:** To better understand the effects of time-varying MDI usage parameters on lung deposition of aerosol delivered by an HFA-MDI, we conducted an in vitro study modeled on real-life variable inspiratory flow and actuation techniques recorded from 15 subjects with asthma/COPD. We developed a model representing the time-varying inspiratory flow waveforms and actuation timings based on 43 MDI techniques recorded from patients. Further, we constructed an in vitro experimental setup using a mouth-throat cast, programmable MDI actuator, and breath simulator to evaluate lung deposition for the MDI techniques derived from our model.

**Results:** High inspiratory flow rates, 60-90L/min, consistently resulted in high in vitro lung deposition (>40%) of aerosol (albuterol delivered from Ventolin HFA-MDI) compared to 30L/min when MDI actuation occurred in the first half of inhalation. Further, positive coordination resulted in higher in vitro lung deposition compared with negative or zero coordination (actuating before or at the start of inspiration). Furthermore, variation in coordination affected lung deposition more significantly (23%) than flow rate or duration of inspiration (≤5%).

**Conclusions:** In an in vitro experimental model based on inhalation data from patients with asthma and COPD, we demonstrated that aerosol lung deposition emitted from Ventolin HFA-MDI is most optimal for MDI actuation in the first half of inspiration at high flow rates (60-90L/min).

**Keywords:** Aerosol, lung deposition, metered dose inhaler, inhaler technique, asthma, COPD

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Introduction

Optimal delivery of inhaled medications to the lung is highly dependent on the accuracy of the technique using the inhaler device. The metered dose inhaler (MDI) is the most commonly used device that delivers a variety of rescue and maintenance medications for asthma and COPD. However, several studies have demonstrated that patients often commit various errors using such devices leading to wasted medication and thus, suboptimal control of their disease.

Lung deposition of an aerosol delivered by an MDI may be dependent on all or a combination of the following five factors: (i) inspiratory flow rate, (ii) duration of inhalation, (iii) time of MDI actuation (time of actuating the MDI relative to the start of inspiration), (iv) duration of breath-hold after inhalation and (v) fine fraction (the fraction of aerosol particles smaller than 5µm in diameter). The first four factors depend solely on the patient’s technique of using MDIs, while the fifth factor, amount of fine fraction released from the MDI, depends on the design of the formulation and construction of the components of the MDI delivery device involved with the aerosol formation process, and not on the patient’s MDI technique. A high fine fraction results in higher deposition of medication in the lungs. Thus, optimum lung deposition is achieved when the patient uses an MDI that releases a large fine fraction with the correct technique.

The proper technique of using an MDI is based on the first four factors, inspiratory flow rate, duration of inhalation, time of MDI actuation and duration of breath-hold after inhalation, and is outlined by published GINA guidelines. These guidelines are based on the results of numerous in vivo and in vitro studies previously conducted to quantify lung deposition of aerosol delivered by an MDI. For instance, in vivo studies by Newman et al. and Lawford et al. during the 1980s using CFC (chlorofluorocarbon)-MDIs demonstrated that slow inspiration of duration greater than 4s, and MDI actuation at the start of inhalation resulted in the most optimal lung deposition. Furthermore, the effect of inspiratory flow rate was studied extensively for these CFC inhalers by Newman et al. in the 1990s, who demonstrated that higher lung deposition was achieved at low flow rates (~28L/min). Based on those results, published guidelines for correct use of MDIs currently recommend a low inspiratory flow rate of 30L/min, long duration of inhalation of at least 5 seconds and MDI actuation at the start of inhalation, for optimal lung deposition.

However, since the early 2000s, the CFC MDIs have been discontinued due to their potential environmental hazards and were replaced with HFA (hydrofluoroalkane)-MDIs. The aerosol deposition characteristics for medication particles emitted from CFC MDIs are very different from that of HFA-MDI due to the difference in fine fraction content of the two inhalers. HFA-MDIs have a much higher fine fraction content than the CFC counterparts.

The disparity in lung deposition is demonstrated in more recent in vivo studies by Usmani et al., Leach et al. and in vitro studies by Cheng et al. and Rahmatalia et al. using HFA-MDIs, which indicate that lung deposition increased with higher inspiratory flow rates, contrary to the lung deposition characteristics of CFC-MDIs. In particular, Usmani et al. showed that for particles of diameter 1.5µm, the lung deposition for fast inhalation was higher than that for slow inhalation. However, as the particle size was increased from 1.5 - 6µm, the lung deposition gradually decreased with increase in inspiratory flow rate.

Recent literature investigating the effects of duration of inhalation and MDI actuation timing for HFA-MDIs has been limited to in vitro studies using idealized techniques, having either constant inspiratory flow rates, fixed duration of inhalation and fixed actuation time; the idealized techniques do not represent actual patient’s time-varying inhalation airflow profile and variable MDI actuation timings observed in a real-world setting. The correct HFA-MDI use technique in a real world setting for both maximizing lung deposition and minimizing oropharyngeal deposition of medication is, therefore, unknown. The effect of the fourth factor, breath hold after inhalation, has been well documented through the abovementioned in vivo studies. Holding the breath for up to 10 seconds after inhalation minimizes any portion of the medication to be exhaled out of the lungs and is the recommended current guideline for MDI use.

In this study, we developed a novel in vitro experimental setup to evaluate the lung deposition for time-varying realistic HFA-MDI techniques derived from techniques recorded from subjects with airway disease (asthma or COPD) using a Placebo HFA-MDI in a clinic setting. We conducted the in vitro experiments to assess the effects of variation in the steps using the MDI (i)-(iii) listed in the beginning of this section: inspiratory flow rate, duration of inhalation and time of MDI actuation on lung deposition of aerosol emitted from a albuterol HFA-MDI, Ventolin (GlaxoSmithKline, North Carolina, USA).

Materials and Methods

This was a two-phase study. We first recorded the MDI technique of 15 subjects, 18-80 old, with physician-diagnosed asthma or COPD using Placebo HFA-MDI. The patients were seen in the Pulmonary Function Testing Laboratory at Ben Taub Hospital, Houston, Texas. We then conducted an in vitro lung deposition study, modeled on the recorded real-world HFA-MDI techniques. Both Baylor College of Medicine and Rice University institutional review boards approved the
study and all subjects signed an informed consent form. The clinical study was registered at clinicaltrials.gov, with the registration number is NCT02447575.

We used a calibrated turbine flow meter attached to a plastic cap with a force sensor, fitted tightly to a Placebo HFA-MDI to measure the three factors; inspiratory flow rate as a function of time, duration of inhalation and time of MDI actuation (see Figure 1). Out of the 15 subjects, 7 took more than one MDI puff with the attached cap, bringing the total number of techniques recorded to 43. The system added an average resistance of 30 Pa/L/s, which did not interfere with inspiration through the MDI. However, the addition of the flow meter to the MDI may have added unfamiliarity to the subjects. Thus, before recording data, the subjects were instructed to actuate the MDI attached with the flow meter setup into the air (away from their mouth) to familiarize them with the system.

![MDI Technique Schematic](image)

**FIG. 1.** Schematic illustrates the MDI technique recording setup utilized in recording MDI techniques. The MDI is fitted with a plastic cap that connects to a calibrated flow meter. During inhalation through the MDI, the air flows in from the vent at the top of the flow meter and passes through the MDI as shown. The flow meter is also attached to a force sensor that synchronously detects and records the time of MDI actuation. The inhalation and actuation data are stored on the flow meter and are retrieved later on a PC. MDI, metered-dose inhaler; PC, Personal Computer.

Figure 2 illustrates histograms of peak inspiratory flow rates (PIFR), duration of inspiration and time of actuation with respect to the start of inhalation, and Table 1 contains the summary statistics for recorded data. Data recorded illustrate significant variability in MDI use techniques among the test subjects and deviations from the current recommendations. Figure 3a represents a subset of the recorded inhalation waveforms demonstrating variable peak inspiratory flow rates (PIFR) and durations of inhalation, thereby, confirming that actual MDI use is time-varying and not adequately approximated using idealized MDI techniques of constant inspiratory flow rates, duration, and MDI actuation. Figures 3b-d show the MDI technique model derived from the subject data.

**Data-driven MDI Use Technique Model**

We developed a data-driven model for MDI technique based on the usage data recorded from subjects with asthma and COPD. The model assumes a fixed inspiratory capacity (IC), i.e. the maximum volume of air that can be inspired from a resting respiratory level, of 3L (IC ranges 2.5-3.5L in adults). The main variables of MDI use examined in our model were 1) PIFR, 2) duration of inhalation and 3) time of actuation, corresponding to the three out of five factors, (i)-(iii), governing lung deposition. We defined a trapezoidal approximation to the patient inspiratory flow waveforms (Figure 3a), accounting for the range of inhalation duration and PIFRs observed from our recorded waveforms shown in Figure 3b. The area under the flow-time curve represents the fixed volume (IC of 3L); we derived the following model for inhalation during MDI use:

\[
\text{Area of trapezoid} = IC = \frac{1}{2} f_p (t_d + t_h) = 3L \quad (1)
\]

where,

\[f_p = \text{peak inspiratory flow rate or PIFR}\]
\[t_d = \text{duration of inhalation} = \text{base 1 of trapezoid}\]
\[t_h = \text{hold time} = \text{duration that flow rate is held at } f_p = \text{base 2 of trapezoid}\]

We also defined a third parameter, \(t_r = \text{rise-time, used in the later sections to define the time of MDI actuation. \(t_r\) refers to the duration of time it takes for the flow rate to reach } f_p \text{ from 0 and vice versa (symmetrical waveform). Thus,}\]

\[t_d = 2 * t_r + t_h \quad (2)\]

The volume constraint equation (1) is predicated on the assumption that the relationships between \(f_p, t_d\) and \(t_h\) are linearly dependent. We can further rewrite the equation as follows:

\[IC = \frac{1}{2} f_p t_h \left(1 + \frac{t_d}{t_h}\right) = \frac{1}{2} f_p t_h (1 + \tau) \quad (3)\]

where \(\tau\) is the ratio of the two durations corresponding to the bases of the trapezoid, \(\frac{t_d}{t_h}\).

We considered \(f_p\) and \(\tau\) as two independent factors of MDI technique from our model; \(t_h\) is the dependent parameter. The ratio \(\tau\) is a shape parameter, as it governs the profile of the trapezoid, ranging from 1 to \(\infty\), from square \((t_h = t_d)\) to triangular \((t_h = 0)\). Figure 3c
FIG 2. Histogram of 43 MDI techniques collected from 15 subjects with asthma and COPD. Data collected consist of the inspiratory flow waveform and the time of MDI actuation. The distribution of three MDI technique steps of interest, (a) peak inspiratory flow rate, (b) duration of inhalation and (c) time of actuation, are shown in figures (a), (b) and (c) respectively. The black bars correspond to the correct technique as recommended by GINA guidelines, (a) peak flow rate between 30 and 60L/min, (b) minimum inhalation of at least 5 seconds and (c) time of actuation immediately after the start of inhalation (a positive value, 0-0.5s). The grey bars correspond to the errors in MDI use, (a) peak inspiratory flow rate less than 30L/min or greater than 60L/min, (b) inhalation of less than 5 seconds and (c) MDI actuation before the start of inhalation (a negative value) or late in the inhalation (a large positive value, greater than 0.5s).

Table 1. MDI technique data recorded from 15 subjects with asthma and COPD.

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<thead>
<tr>
<th></th>
<th>Peak Inspiratory Flow (L/min)</th>
<th>Duration of inhalation (sec)</th>
<th>Time of actuation (sec)</th>
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<tr>
<td></td>
<td>$f_p$</td>
<td>$t_d$</td>
<td>$t_a$</td>
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<tr>
<td>Mean (SD)</td>
<td>57 (32)</td>
<td>1.85 (0.93)</td>
<td>-0.05 (0.48)</td>
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<td>Recommended Guidelines</td>
<td>30-60</td>
<td>&gt;5</td>
<td>0-0.5</td>
</tr>
<tr>
<td>Percentage with Incorrect MDI uses</td>
<td>60%</td>
<td>100%</td>
<td>79%</td>
</tr>
</tbody>
</table>
FIG. 3. The inspiratory flow waveforms recorded during MDI use by subjects with asthma and COPD, and the trapezoidal approximation to the waveforms are presented. (a) Shows a subset of the 43 waveforms collected from 15 subjects, representing the different inspiratory flow rates, duration of inhalation and waveform shapes. (b) Shows the trapezoidal model for a particular 3L flow waveform. Here, \( f_p = 60\text{L/min (or 1L/s)} \), \( t_d = 4.5\text{s} \) and \( t_h = 1.5\text{s} \). Thus the total inhalation volume is Area of trapezoid = \((1/2) f_p (t_d + t_h) = 1/2 * 1 * (4.5 + 1.5) = 3\text{L} \). (c) Shows the different combinations of 3L waveforms generated for \( f_p = 30, 60 \) and 90 L/min and the ratio \( \tau = 1.33, 3, 8 \), corresponding to long, medium and short duration of inhalation respectively. As an example, a 90L/min medium duration (\( \tau = 3 \)) and a 60 L/min short duration (\( \tau = 1.33 \)) are highlighted in bold. (d) Shows the trapezoidal approximation (dashed lines) for two of the waveforms recorded.

Demonstrates the range of flow waveforms generated based on the constraint equation (3) by varying \( f_p \) and \( \tau \). A higher value of \( \tau \) for a particular \( f_p \) denoted longer inhalation duration (large \( t_d \)) with a small \( t_h \), i.e. a triangular trapezoid and vice versa.

For example, a 3L waveform associated with a given \( f_p \) with high \( \tau \) required a long time to attain the peak flow, i.e. a high rise-time, and resulted in a smaller average flow rate; vice versa. Thus, the flow waveforms with a particular \( f_p \) generated from the trapezoidal model had varying shapes (ranging from square to triangular) and varying average flow rates (ranging from low to high), due to the different \( t_r \) and \( t_h \) governed by the value of \( \tau \). In our study, we varied the flow waveforms by choosing the factors \( f_p \) in the range from 0 to 90L/min, and the ratio \( \tau = 1.33, 3, 8 \), corresponding to a short, medium and long duration of inhalation respectively. Figure 3d illustrates how the flow waveforms generated from the trapezoidal waveforms fit inspiratory flow waveforms from actual patients.

The third independent parameter of MDI technique investigated was the time of MDI actuation, \( t_a \), which was the time of firing the MDI relative to the start of inhalation, also known as coordination. Here, \( t_a = 0 \) conveyed that the inhaler was actuated at exactly the time instant when the patient started to inhale through
the MDI; a negative $t_a$ conveyed that the inhaler was actuated before the start of inhalation and a positive $t_a$ denoted that the inhaler was actuated after the start of inhalation. In this study, we investigated the effects of coordination on in-vitro lung deposition by varying $t_a$ for $-0.5s$, $0s$, $+0.6^*t_r$, $0.5t_h = 0.5t_d$, and $(t_d - 0.6^* t_r)$. The three positive $t_a$ values are derived such that the MDI is actuated during the rising $(+0.6^*t_r)$, constant $(0.5t_d)$ and falling edges $(t_d - 0.6^*t_r)$ of the trapzoidal inspiratory waveform. Note that the choice of values for $f_p$, $\tau$ and $t_a$ were based on the data reported in previous literature on the range of PIFRs, duration of inhalation and MDI actuation time$^{24}$ and also on the 43 MDI usage techniques recorded from the 15 patients in our study as shown in Table 1.

**In vitro experimental setup**

We constructed an in vitro lung deposition experimental setup to generate the time-varying MDI techniques based on $f_p$, $\tau$, and $t_a$ and analyzed corresponding lung deposition (see Figure 4a for a schematic diagram, Figure 4b for photograph of the setup). A programmable robotic arm was built using Robotis’ Dynamixel RX-64 servomotor (Trossen Robotics, Illinois, USA) to actuate the MDI at the predefined values of $t_a$. We used Albuterol Sulphate Ventolin HFA-MDIs (GlaxoSmithKline, NC) in our experiments, labeled to dispense 108 mcg of Albuterol sulfate at every actuation. The inhaler was fitted to the same turbine flow meter used to record the maneuvers by the study subjects (Figure 1), and connected with the anatomically correct mouth-throat cast. The mouth-throat cast used was an adult Alberta Idealized Throat or AIT (manufactured by Copley Scientific Ltd., UK), the accuracy of which had been validated by previous studies$^{15,21,22,24,29}$. The AIT was connected to the collection filter, Respirgard 303 (manufactured by Vital Signs, USA), representing in vitro lungs. The filter was connected through another flow meter, Thor SpiroTube (manufactured by THOR Research and Development, Hungary), to the ATS and ISO certified Pulmonary Waveform Generator or PWG (manufactured by Piston Ltd., Hungary). The setup was sealed using silicone connectors to ensure the maximum leakage was below 0.15L (5%). A PC controlled the robotic arm, the two flow meters, and the PWG to generate MDI use-cases, monitor the procedure and record observations. We performed MDI techniques based on $f_p$, $\tau$, and $t_a$, derived from our model (equation 3), using the combination of PWG and a robotic arm in the experimental setup.

Lung deposition testing was performed using AIT according to the guidelines provided by previous in vitro studies$^{15,21,22,29}$. At the beginning of each experiment, we cleaned, dried and coated the inner surfaces of the AIT with silicone release spray, Molykote 316 (manufactured by Dow Corning, Michigan, USA), to reduce aerosol particle bounce. For each MDI use-case, we repeated the experiment 3 times ($n$=3), including multiple MDI actuations and rinsing of each component to recover the deposited drug. The first two repetitions were conducted with 10 MDI actuations and the third with 15 actuations to reduce the dose-to-dose variability, as previous studies have shown that the amount of medication delivered by MDIs for each actuation is imprecise$^9$. Furthermore, we employed a waiting period of 1 minute between actuations and vigorously shook the MDI 20 times before each actuation, as guided in previous studies$^{31}$.

The total drug dispensed by the MDI comprises of the amount of drug deposited in the MDI actuator mouthpiece, AIT and collection filter. Thus the mass of the total drug delivered can be represented as:

$$m_t = m_{MP} + m_{AIT} + m_{Filter} \quad (4)$$

where,

- $m_t$ is the mass of total delivered drug
- $m_{MP}$ is the mass of drug deposited in the MDI actuator mouthpiece
- $m_{AIT}$ is the mass of drug deposited in the AIT or the mouth-throat deposition
- $m_{Filter}$ is the mass of the drug deposited in the filter or in-vitro lung deposition.

In this study, the mass of the drug deposited in the filter, $m_{Filter}$, is an approximation of the total lung deposition and fraction of medication exhaled into the air.

The percentage in-vitro lung deposition is computed as following:

$$p_{ivl} = \frac{m_{Filter}}{m_t} * 100\%$$

$$= \frac{m_{Filter}}{m_{MP} + m_{AIT} + m_{Filter}} * 100\% \quad (5)$$

$$= 100 - p_{MP} - p_{AIT} \quad (6)$$

where,

- $p_{MP} = \frac{m_{MP}}{m_t} * 100\%$,
- $p_{AIT} = \frac{m_{AIT}}{m_t} * 100\%$ \quad (7)

$p_{ivl}$ is the percentage in-vitro lung deposition of Albuterol

$p_{MP}$ is the percentage drug deposition in the MDI actuator mouthpiece

$p_{AIT}$ is the percentage drug deposition in the AIT.
The mouthpiece, AIT and filter were repeatedly rinsed with de-ionized water as outlined in previous studies and the recovered solutions were analyzed using a UV spectrophotometer, Thermo Scientific™ GENESYS™ 10S UV-Vis Spectrophotometer, at 224 nm.

**FIG. 4.** (a) Schematic to illustrate the in vitro experimental setup used in our work. A PC controls the motorized robotic MDI actuator, two flow meters, and the PWG. All the parts of the system are sealed using silicone connectors to minimize air leaks. The MDI is connected to the AIT, which represents the mouth–throat part of the body. The AIT is then connected to the collection filter, which acts as the lungs of the body. The different combinations of MDI techniques, inspiratory flow rates, duration of inhalations, and time of actuation are produced using the combination of the programmable PWG and motorized actuator. (b) Is a photograph of the actual setup used in the in vitro lung deposition experiments. AIT, Alberta Idealized Throat; PWG, pulmonary waveform generator.
For our experiments, first $f_p$ was varied from 0 to 90L/min in steps of 30, and $t_d$ was varied as a short, medium and long inhalation for the ratio $\tau$ of 1.33, 3, 8, respectively. $t_d$ was kept constant at 0.6$t_r$ for all values of $f_p$ and $\tau$, that is, actuation in the rising edge of the waveform or the first half of the inspiration. Next, the 60L/min long inhalation waveform ($\tau = 8$) was selected and $t_d$ was varied for small intervals from 0.5 seconds before the start of inspiration (-0.5$s$) to $(t_d - 0.6$t_r$) (falling edge of the waveform at the end of inspiration) to study the effect of coordination on the in-vitro lung deposition. The in vitro lung deposition data obtained was analyzed using one-way ANOVA and Tukey HSD for multiple comparisons at different $f_p$, $\tau$ and $t_d$ values, where a p value <0.05 was considered to be statistically significant.

Results

The results are divided into two categories based on the inhalation variables $f_p$, $\tau$, and coordination variable $t_d$. The mean $p_{wL}$ for $f_p = 0$L/min was found to be 5.7% and considered the baseline condition, and was, as expected, associated with the lowest drug deposition. The baseline is of similar magnitude to previously reported results, e.g. 7% deposition using CFC inhalers.

The first category demonstrates the effect of inhalation waveform parameters, $f_p$, $\tau$, on lung deposition. Table 2a lists the $p_{wL}$, $P_{MF}$ and $p_{AIR}$ for the MDI use-cases with different values of $f_p$ and $\tau$ (and corresponding $t_d$), at $t_a = 0.6$t_r$. There were three repetitions (n=3) of all MDI use-cases except for $f_p = 90$L/min, $\tau = 8$ (n=4). The results are further visualized graphically in Figures 5a-c, corresponding to the inspiratory flow rates 30, 60 and 90L/min respectively.

The results show that mean $p_{wL}$ was lowest for $f_p = 30$L/min, always below 40% for all values of $\tau$. Further, the mean $p_{wL}$ for both $f_p = 60$L/min and $90$L/min was higher than 40% for all values of $\tau$ (correspondingly, all values of $t_d$) and therefore, significantly higher than the mean $p_{wL}$ for $f_p = 30$L/min (p<0.001). The increase in mean $p_{wL}$ for $f_p = 30$L/min to corresponding waveforms of $f_p = 60$-90L/min was found to be 5% (p<0.001). There was no significant difference in $p_{wL}$ for $f_p = 60$ and 90L/min (p>0.05). Further, the graph 5a shows a steady increase in $p_{wL}$ for $f_p = 30$L/min with increasing $\tau$ (increase in the duration of inhalation). There was an increase of 3% in mean $p_{wL}$ for all flow rates due to an increase in $\tau$ from 1.33 to 3 and 8 (p<0.05, n=3). There was no significant effect on $p_{wL}$ for a change in $\tau$ from 3 to 8 (p>0.05).

The next category of results demonstrates the effect of coordination, i.e. $t_d$, on lung deposition. As we obtained higher $p_{wL}$ for $f_p = 60$L/min and 90L/min, and for $\tau = 3$ and 8, we selected the inspiration waveform of $f_p = 60$L/min and $\tau = 8$ (long duration of 5.33$s$) to determine $p_{wL}$ for different values of $t_d$. Table 2b illustrates the $p_{wL}$, $P_{MF}$ and $p_{AIR}$ data collected for $t_d = -0.5$s$, 0$s$, 0.6$t_r$, 0.5$t_d$ and $(t_d - 0.6$t_r$), and the results are graphically shown in Figure 5c. There were three repetitions (n=3) of all MDI use-cases. We found that the $p_{wL}$ steadily increased with an increase in $t_d$ for $t_d \leq 0.5$t_d$.

Furthermore, the lung deposition value reached a plateau at the highest point in inspiratory flow rate, at $t_a = 0.5$t_d$; the increase in $p_{wL}$ from $t_a = -0.5$s to $t_a = 0.5$t_d$ was of 23% (p<0.001). The $p_{wL}$ for $t_a = -0.5$s was significantly less than $p_{wL}$ for all other $t_a$ (p<0.001); similarly, the $p_{wL}$ for $t_a = 0$s was significantly less than $p_{wL}$ for all positive $t_a$ (p<0.001). There was no significant difference in $p_{wL}$ for $t_a = 0.6$t_r$ and 0.5$t_d$. Further, $p_{wL}$ for $t_a = (t_d - 0.6$t_r$)$ was significantly smaller than $p_{wL}$ for $t_a = 0.6$t_r$ and 0.5$t_d$ (p<0.01).

Discussion

Our study results demonstrate that for a positive coordination in the first half of inspiration, a higher $f_p$ (=60-90L/min) yielded better lung deposition compared to lower $f_p$ (=30L/min), independent of the duration of inspiration; the increase in mean $p_{wL}$ was found to be 5%. Thus, the positive effect of high PIFR on lung deposition of Albuterol from Ventolin HFA MDI observed in our in vitro experimentation is not only of opposite trend but also less critical (an increase of 5% only) from what has been reported in the past literature.

As mentioned earlier, a number of recent publications, particularly the work of Usmani et al. have suggested that the particle of smaller sizes (1.5μm) delivered from various HFA inhalers have better lung deposition (4.6% increase) at high mean flow rates (67.1 ± 16.7L/min) compared to low mean flow rates (30.8 ± 4.7L/min). However, for particles of 3μm, the lung deposition at high mean flow rates decreased slightly (1.4% decrease) compared to low flow rates; decreasing more dramatically for larger particles of size 6μm (24.7% decrease).

Further, Cheng et al. had demonstrated for the in vitro study using Albuterol Sulphate HFA MDI (Proventil) with MMAD of 2.21μm that the mouth-throat deposition decreased significantly on increasing flow rate from 30 to 90L/min, consequently increasing the in vitro lung deposition. A high oropharyngeal deposition at low flow rates was attributed to the higher speed of aerosol droplets as compared to the inspiratory flow rate. Therefore, at higher inspiratory flow rates, a possibly more efficient momentum transfer occurred between the
Table 2a. Percentage lung deposition for \textit{in vitro} experiments for variation in inspiratory parameters, PIFR ($f_p$) and shape ($\tau$), where the time of actuation is in the first half of inspiration, set at $t_a = 0.6t_r$. The trial numbers 1-2 correspond to experiments conducted with 10 doses and the number 3 corresponds to experiments repeated with 15 doses. The first row corresponds to baseline case of no flow rate.

<table>
<thead>
<tr>
<th>No</th>
<th>Trial No</th>
<th>PIFR (L/min) $f_p$</th>
<th>Shape Parameter $\tau$</th>
<th>Time duration $t_d$ (s)</th>
<th>Time of actuation $t_a$ (s)</th>
<th>Percent MP deposition $p_{MP}$ (%)</th>
<th>Percent AIT deposition $p_{AIT}$ (%)</th>
<th>Percent \textit{in-vitro} lung deposition $p_{\text{int}}$ (%)</th>
<th>Mean Percent \textit{in-vitro} lung deposition (%)</th>
<th>Mean $p_{\text{int}}$</th>
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<tr>
<td>1</td>
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*Note that the 4th repetition for some of the experiments (with 10 doses) was carried out as we noticed a larger variation for that data point.

Aerosol droplets and airflow, such that a larger fraction of aerosol droplets followed the air stream into the lungs, resulting in a lower mouth-throat deposition.

Furthermore, the authors also suggested that at higher flow rates, the evaporation of aerosol emitted from the MDI is more efficient in generating smaller droplets resulting in lower oropharyngeal deposition. In addition, the authors also stated that the impact force of the aerosol sprays from HFA MDIs are much smaller than CFC MDIs due to the smaller orifice diameters of HFA MDIs, which changes the plume characteristics (softer due to smaller aerosol velocities) and reduces oropharyngeal deposition.
FIG. 5. The percentage deposition in the in vitro lung (black bar), AIT (gray bar), and MDI mouthpiece (white bar) for the in vitro experiments are presented. The graph shows the results from experiments performed for inhalation (flow, duration)- dependent MDI techniques with MDI actuation fixed at the first half of inspiration. Each group of bars represents one MDI technique; the error bars show the range due to three repetitions of each experiment. The baseline result is shown in the beginning marked 0 L/min. The error margins for in vitro lung deposition ranged from –0.2% to –2.3%, average –1.3%. Three flow rates, 30, 60, and 90 L/min, were used for each of the experiments. 

(a–c) Show the variation in lung deposition with shape ratio, s (corresponding to the duration of inhalation), for the three different flow rates 30, 60, and 90 L/min, respectively. The short, medium, and long labels on the x-axis refer to s equal to 1.33, 3, and 8, respectively. The inhalers were actuated at the beginning of the inhalation, ta = 0.6tr. We found that the mean in vitro lung deposition (black bar) is higher for 60–90 L/min than 30 L/min ( p < 0.001), always greater than 40%. The maximum mean in vitro lung deposition was found to be 44.2% for the case of inspiration with PIFR 60 L/min and duration of 4.5 seconds. PIFR, peak inspiratory flow rate.

Furthermore, Rahmatalla et al. also demonstrated that with Beclomethasone HFA MDI (QVAR), which has a high fine fraction close to 1μm, the increased in vitro lung deposition at high flow rates was due to alternate mechanisms of aerosol deposition in addition to impaction; such as sedimentation and diffusion. Hoye et al. also demonstrated that the MMAD (Mass Median Aerodynamic Diameter) of Ventolin Albuterol HFA MDIs was 2.07μm. Therefore, we conclude from our observed experimental results and past literature that due to a combination of mechanisms governing the deposition of albuterol aerosol delivered by Ventolin HFA MDIs, having small particle size (MMAD 2.07μm) as compared to CFC counterparts, the in vitro lung
deposition is slightly higher for PIFRs in the range 60-90L/min than low PIFRs. A further extension of our work would be to measure particle size distribution using a cascade impactor for our dynamic trapezoidal inspiration waveforms to confirm higher fine fraction of aerosol delivered by HFA Albuterol MDI (Ventolin) and the corresponding dependency of PIFR on lung deposition obtained in our experiments.

Table 2b. Percentage lung deposition for in vitro experiments with actuation time $t_a$, ranging from 0.5 second before start of inhalation (-0.5s) to falling edge of the waveform at the end of inspiration ($t_d - 0.6t_r$), for the inspiratory waveform with $f_p = 60$L/min and $\tau = 8$ (or $t_d = 5.33$). The trial numbers 1-2 correspond to experiments conducted with 10 doses and the number 3 corresponds to experiments repeated with 15 doses.

<table>
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<th>No</th>
<th>Trial No</th>
<th>Time of actuation(s)</th>
<th>Percent MP deposition (%)</th>
<th>Percent AIT deposition (%)</th>
<th>Percent lung deposition (%)</th>
<th>Mean Percent lung deposition(%)</th>
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Our results on the study of the effects of coordination on in vitro lung deposition demonstrated that the highest lung deposition occurred with positive coordination, especially actuation in the first half of the inspiratory waveform. The increase in $p_{\text{IOL}}$ from $t_a = -0.5s$ to $t_a = 0.6t_r$ was of 23% suggesting that coordination was the most critical parameter in determining $p_{\text{IOL}}$. Further, compared to flow and duration parameters, a negative coordination caused the maximum loss in $p_{\text{IOL}}$. As seen from the Figure 6, at negative and zero coordination, the mean $p_{\text{MP}}$ is much higher (almost double) than for positive coordination. Thus, when the MDI is actuated without any inspiratory flow rate, about 20–32% of the medication is deposited in the plastic mouthpiece of the inhaler (as compared to 12% for positive coordination), thereby reducing the amount of respirable aerosol medication. The baseline case of $f_p = 0$L/min, therefore, has the highest amount of $p_{\text{MP}}$ (32%) and $p_{\text{AIT}}$ (62.5%) of all cases as there is no inspiratory flow rate even after MDI actuation. Note that for very late actuation, that is actuation in the second half of the inspiration with $t_a = (t_d - 0.6t_r)$, the presence of inspiration at the time of actuation ensured that the $p_{\text{MP}}$ is low (13%). However, due to the small volume of air inhaled coupled with a decreasing flow rate post actuation, the $p_{\text{AIT}}$ (48%) increased and the $p_{\text{IOL}}$ (39%) decreased as compared with actuation in the first half of inspiration ($t_a = 0.6t_r + 0.5t_d$).

The two categories of results investigating the effect of PIFR ($f_p$), duration of inspiration ($t_d$), defined here by the shape of inspiration waveform $\tau$, and coordination ($t_a$) suggest that the optimal technique for maximizing
the lung deposition of aerosol emitted from an HFA Ventolin MDI for 3L IC is an inspiration with PIFR of 60-90L/min of any duration in the range 2.28-5.33s with a positive coordination in the first half of inspiration.

In summary, in our in vitro experiment modeling of MDI technique based on the maneuvers recorded from subjects with asthma and COPD, we demonstrated that coordination of MDI actuation is the most important factor governing lung deposition of aerosol emitted by an Albuterol HFA-MDI (Ventolin). While higher inspiratory flow rates and increased duration of inspiration also yielded higher lung deposition, the increase was lower than the effect of coordination. Based on our results, the recommendation for optimal lung deposition for patients using an HFA containing MDI would be to inhale at high inspiratory flow rates, in the range from 60 to 90L/min, and actuate the MDI in the first half of inspiration.

FIG. 6. The percentage deposition in the in vitro lung (black bar), AIT (gray bar), and MDI mouthpiece (white bar) as a function of coordination or time of MDI actuation relative to the start of inspiration are presented. Each group of bars represents one MDI technique, the error bars show the range due to three repetitions of each experiment. The baseline result is shown in the beginning marked 0 L/min. The other bars correspond to the MDI technique of PIFR 60L/min and duration 5.33 seconds, actuated at -0.5, 0 seconds, 0.6t_r, 0.5t_d, and (t_d - 0.6t_r). The error margins for in vitro lung deposition ranged from -0.2% to -2.3%, average -1.3%. We found that the mean in vitro lung deposition is highest for actuation in the first half of inspiration, 43.8%, and lowest for negative coordination.

Our study also has some limitations. As is the case with using simplified models to represent complex human maneuvers, our trapezoidal breathing model suffers from some disadvantages. The trapezoid model we developed has a symmetrical form, which is not the case for most inhalation curves recorded; see Figure 3a. The human inhalation waveforms have previously been approximated by asymmetric sinusoidal curves. The asymmetric sinusoidal approximations yield waveforms much closer to actual breathing curves and hence may be a better choice for in vitro experimental procedures. However, because MDI actuation in the first half of the inhalation has the highest impact on lung deposition, we believe that the asymmetric trapezoidal waveforms may have similar lung deposition characteristics as that of symmetric trapezoidal waveforms, and thus, is a valid first order approximation. Finally, the results obtained in our in-vitro experimentation are an approximation to the actual in-vivo lung deposition. Further investigation into this work would be to explore in vitro lung deposition using a more realistic lung model with lung airways of different sizes and in vivo lung deposition on human subjects, to explore the distribution of aerosol in different parts of the lung due to the variation in MDI technique.

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Author Disclosure Statement
Dr. Ashutosh Sabharwal is a Professor, Department of Electrical and Computer Engineering at Rice University, Houston, Texas. He is also a co-founder of Cognita Labs LLC. Ms. Rajoshi Biswas is a PhD candidate in the Department of Electrical and Computer Engineering at Rice University. She is an also employee of Cognita Labs LLC. Dr. Nicola Hanania is an Associate Professor, Baylor College of Medicine; Director, Airways Clinical Research Center, Houston, Texas. No conflicts of interest exist.

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