In Vitro Testing of MDI Spacers: A Technique for Measuring Respirable Dose Output with Actuation In-Phase or Out-of-Phase with Inhalation

Scott A Foss and Jean W Keppel PhD

BACKGROUND: Many studies have reported that users of metered dose inhalers (MDIs) have difficulty in coordinating inhalation with actuation of the MDI canister. The purpose of this study was to determine how a lack of coordination affects the respirable dose delivered to the patient’s lungs when an MDI spacer or chamber is used. Measuring respirable dose (the dose in the 1–5 μm particle size range) requires the use of a cascade impactor or other particle sizer. However, a cascade impactor requires a constant flow rate. This would appear to be incompatible with a study of coordination, which requires a variable flow rate to simulate the patient’s breathing through the MDI device. METHODS: We describe herein a new variable flow rate technique for measuring particle sizes and dose output with a cascade impactor (with a constant flow rate), while simultaneously using a breathing machine to regulate the flow of aerosol medication through an MDI device and throat model. Using this technique, we tested 4 hand-held MDI devices: the Airlife Hand-Held MediSpacer, the Aerosol Cloud Enhancer (ACE), the OptiHaler, and the AeroChamber. Each device was tested under two different conditions: (a) in-phase, in which the MDI drug canister (Ventolin) is actuated at the start of inhalation, and (b) out-of-phase, in which the MDI drug canister is actuated at the start of exhalation and some portion of the drug plume may be retained until the following inhalation. RESULTS: For all 4 devices the respirable dose was significantly less in the out-of-phase case than in the in-phase case. At the same time, the devices varied widely in the percentage of the usable aerosol plume that was retained in the out-of-phase case. The percentages retained until the following inhalation (as compared with the amount of drug delivered in the in-phase case) are as follows: MediSpacer 67%, ACE 23%, OptiHaler 9%, and AeroChamber 46%. CONCLUSIONS: Timing greatly affects the amount of drug delivered by an MDI device, even one equipped with a valve. Also, device design has a large influence on the amount of drug delivered and the percentage of the drug plume retained when inhalation is delayed. The variable flow rate technique made this study possible, and this technique may also have applications in studying the effects of unusual breathing patterns. [Respir Care 1999;44(12):1474–1485] Key words: aerosol delivery, metered dose inhaler, spacer device, in vitro testing, dose output, particle size, patient education.

Background

For patient self-medication, metered dose inhalers (MDIs) have been used since 1956 and are convenient and durable devices.1 However, many patients have found it difficult to synchronize inhalation with actuation of the MDI canister, even with some training. A large body of literature addresses this timing difficulty; only a few references are listed here.2–6 Without an auxiliary device, if the MDI canister is actuated after inhalation is completed, the effect of the drug is reduced to almost nil.2

Any spacer or chamber will reduce oropharyngeal deposition of the MDI drug and thus reduce the adverse effects of oral deposition.7 Valved chambers are also designed to reduce the synchronization problem, by retaining a portion of the usable drug plume if the patient’s timing is faulty.8,9

The purposes of the present study were (1) to measure how much of the respirable dose is retained when a valved

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MDI chamber is used with incorrect timing, (2) to compare the usable dose retention among several chamber designs, and (3) to find out whether any portion of the respirable dose is retained by an unvalved spacer when timing is faulty. To achieve these purposes we needed to develop a new laboratory technique. Therefore, it became one of our major purposes also to present this new technique as an alternative to some of the laboratory methods used in the past.

The most relevant dosage measurement is not the total dose contained in all aerosol particle sizes, but rather the dose contained in just the 1–5 μm range, which is more likely to be deposited in the small airways of the lungs. In fact, the dose output in the 1–5 μm range is sometimes referred to as the respirable dose.

To measure the respirable dose, one must measure the amount of active ingredient as a function of particle size. Cascade impaction is not the only method for measuring particle sizes, but it is among the most reliable and most commonly used. One drawback of a cascade impactor has been that the particle size distribution must be measured with a constant airflow, which is not representative of the cycle of a patient’s breathing. Moreover, the effect of varying the timing of actuation relative to inhalation cannot be evaluated if the measurement technique demands a constant flow.

Most cascade impaction studies of respirable dose have been confined to the intake rate required for proper operation of the impactor, such as the 28.3 L/min rate used by Ahrens et al. Some of the drug delivery devices they tested had no holding chamber and had to be attached to the intake port before the drug canister was actuated. For others having a valved chamber to hold the drug plume, the device was attached to the intake port one second after the canister was actuated. This testing method is not ideal, for two reasons: the two styles of delivery device were not tested under comparable conditions, and in neither case could the drug plume develop and be inhaled as it would in actual usage.

To circumvent these problems, we developed a new variable flow rate laboratory technique that measures particle size distribution while mimicking the sinusoidal breathing cycle of a patient, and that can be used reliably for all types of hand-held aerosol drug dispensers.

**Methods**

**Variable Flow Rate Technique**

In the variable flow rate (VFR) technique, a breathing machine regulates the flow of aerosol particles into a throat model, yet at the same time the particle sizes are measured by an 8-stage Andersen cascade impactor at the (constant) standard flow of 28.3 L/min. Figure 1 shows a diagram of the experimental setup. The MDI drug delivery device is attached to the input of an aluminum United States Pharmacopeia throat model. The output of the throat model is attached by a small adapter to a T-piece. One branch of the T-piece feeds into the cascade impactor, whose airflow is kept at a constant 28.3 L/min by means of a flow-regulated vacuum pump. The other branch of the T-piece goes to a Y-piece that has a Harvard breathing machine on one branch and a pressurized air source on the other branch. The pressurized air source is adjusted so that the measured net airflow through the throat model is zero before the breathing machine is turned on.

The traditional constant-flow setup would consist only of the drug delivery device, the throat model, the cascade impactor, and the vacuum pump. In the VFR setup the path of the aerosol is changed only by the addition of the T-piece and a barrel adapter; in Figure 1 the barrel adapter is drawn (only for clarity) as a tube between the T-piece and the throat model. Comparisons between results from the traditional method and the VFR method show that particle size distributions and throat-model depositions are unaffected by the change in method. Dose output to the cascade impactor is affected in some cases, because the introduction of sinusoidal flow through the device changes the dynamics of the aerosol flow. For the purposes of the present study, the VFR method (or one like it) must be used, because there is no way to study timing issues if the flow through the device is constant.

**Method of Operation**

The VFR technique consists of the following steps:

1. The vacuum pump is turned on to produce the constant flow of 28.3 L/min through the cascade impactor.
2. The pressurized air source is turned on and adjusted so that the measured airflow through the throat model and MDI device is zero (with the breathing machine off). This means that the entire airflow in the system is from the air source through the cascade impactor, bypassing the throat model and MDI device, before the breathing machine is turned on. During this setup step, a pair of flow meters is used to measure the net airflow into or out of the throat model, to assure that it is zero, and then the flow meters are removed from the circuit.

3. The breathing machine is turned on, causing a sinusoidal airflow through the throat model and MDI device. In this set of tests the breathing machine was set at 5 breaths per minute, with an inspiratory-time:expiratory-time ratio of 1/1. Tidal volume (VT) was 750 mL and peak inspiratory (and expiratory) flow was approximately 12 L/min.

4. At a known point in the breath cycle, the MDI canister is actuated and the aerosol plume forms in the MDI device.

5. The aerosol plume is drawn through the throat model by the breathing-machine inspiration (which peaks at approximately 12 L/min here); once the aerosol passes the T-piece it is drawn into the cascade impactor by the vacuum pump.

6. The particles in the inhaled aerosol cloud are collected and sorted by aerodynamic size as they pass through the cascade impactor at a flow of 28.3 L/min.

7. During exhalation, the breathing machine causes a flow of air out through the throat model and MDI device, peaking at approximately 12 L/min here.

**Discussion of Operation**

A flow meter inserted temporarily between the T-piece and the throat model showed that the flow was sinusoidal, peaking (in this setup) at 11 ± 1 L/min for both inhalation and exhalation. This verified that the airflow through the throat model and MDI device is regulated entirely by the breathing machine.

At the same time, the breathing machine has no effect on the constant flow through the cascade impactor. If a flow meter is inserted just before the cascade impactor, it shows no cyclic flow variation when the breathing machine is turned on. The vacuum pump, which is flow-regulated, draws a steady 28.3 L/min through the impactor under all conditions. Before the breathing machine is turned on, the entire 28.3 L/min comes from the pressurized air source. When the breathing machine inhales, the 28.3 L/min is a combination of flows from the air source and from the throat model/MDI device. When the breathing machine exhales, the 28.3 L/min is a combination of flows from the air source and the breathing machine, with the excess flowing out through the throat model/MDI device.

Figure 2 illustrates the flow rates in the setup used for this study, at peak of inhalation ("INHALING") and at peak of exhalation ("EXHALING"). The widths of the air pathways have been drawn to be proportional to the flow rates (L/min) through the various sections of the test circuit, at these two points of the breathing cycle. During inhalation, there is a splitting of the airflow at the Y-piece and an addition of two flows at the T-piece. During exhalation, there is an addition of two flows at the Y-piece and a splitting of the airflow at the T-piece (see text). Tee = T-piece. Wye = Y-piece. MDI = metered-dose inhaler.
the 28.3 L/min supplied by the air source, giving a total of 40.3 L/min flowing toward the T-piece. At the T-piece, the vacuum pump takes only 28.3 L/min, leaving the remaining 12 L/min to flow out into ambient air by way of the throat model and MDI device.

With this arrangement the breathing machine sets up a regular and very predictable sinusoidal airflow through the throat model and MDI device: in from the MDI device during inhalation and out through the MDI device during exhalation.

The circuit section between the Y-piece and the T-piece also deserves particular attention. As the breathing machine inhales and exhales, its sinusoidal airflow modulates the base flow of 28.3 L/min from the pressurized air source to the cascade impactor. If the breathing machine were to have a peak inhalation flow of 28.3 L/min, then the flow through this section would be exactly zero at the peak of inspiration. However, if the breathing machine had a peak inhalation flow greater than the impactor flow of 28.3 L/min, it would set up an undesirable net rightward flow from the T-piece toward the Y-piece, robbing the cascade impactor of some of the MDI aerosol particles it should receive.

Thus, for the VFR technique there is one limitation on the breathing machine flow, namely, the inhalation flow must never exceed the impactor flow. This condition was easily satisfied in the current study, given the peak inspiratory flow of approximately 12 L/min. Under proper operation, all of the available drug plume is carried directly into the cascade impactor, because the net flow between the Y-piece and the T-piece is always toward the T-piece. During validation of the technique, a filter placed between the Y-piece and the T-piece collected no drug.

As long as this requirement is satisfied, the setup mimics actual inhalation of an MDI aerosol while the particle size distribution is measured at a standard constant flow. This allows simultaneous measurement of (1) dose output as a function of particle size (via the cascade impactor), (2) throat-model deposition (via rinsings from the throat model), and (3) deposition of drug inside the spacer or chamber (via rinsings from the device) in a realistic “breathing” environment.

Possible Variations of Breathing Pattern

The VFR technique is not restricted to the set of parameters we chose for the breathing pattern ($V_T$ 750 mL, 5 breaths/min, peak inspiratory flow 12 L/min). The setup can be adjusted to mimic various breathing patterns. For example, the $V_T$ could be made smaller to simulate infant or pediatric breathing, or larger to simulate very deep adult breaths. To accommodate larger volumes or faster breathing rates (and therefore higher peak inspiratory flow rates) the single cascade impactor could be replaced by two impactors in parallel. In this case the flow would have to be split into two equal branches below the T-piece, each impactor receiving one branch. Of course, the pressurized air source would then need to be set at 56.6 L/min ($2 \times 28.3$ L/min) to match the flow through the two impactors. In this example, peak inspiratory flow rates up to 56.6 L/min would be allowed.

We chose our particular breathing pattern for three practical reasons. First, it guarantees a peak inspiratory flow below the maximum of 28.3 L/min allowed in the single-impactor setup. Second, the breathing volume of 750 mL is realistic for an adult taking a moderately deep breath (the typical $V_T$ for healthy adults ranges from about 400 mL to about 600 mL). Third, a breathing volume of 750 mL is certain to draw all of the aerosol out of the MDI device and down to the T-piece in a single inhalation. As discussed below, the volumes of the spacer and chambers we tested ranged from about 55 mL to 160 mL. The dead space from the mouthpiece of the MDI device down to the T-piece (that is, the volume of the throat model plus the adapter from the throat model to the T-piece) amounted to an additional 76 mL. Thus the device plus dead space volumes add up to 131–236 mL, or less than a third of each inhaled volume.

A disadvantage of this breathing pattern is the relatively low peak inspiratory flow of 12 L/min. The American Association for Respiratory Care recommends a peak inspiratory flow of $< 30–45$ L/min for a patient using an MDI. A peak flow of 12 L/min would satisfy this recommendation but may be substantially lower than the typical flow seen clinically in adults.

Study Design

We tested 4 brands of MDI device in the VFR circuit: the Airlife Hand-Held MediSpacer, the Aerosol Cloud Enhancer (ACE), the OptiHaler, and the AeroChamber, all of which are illustrated schematically in Figure 3. The MediSpacer, ACE, and AeroChamber are holding chambers with one-way inhalation valves that close upon exhalation. The OptiHaler is a spacer with no valves. The 3 holding chambers are also significantly larger than the OptiHaler, having volumes of approximately 140–160 mL, compared with OptiHaler’s approximately 55 mL. Three of the devices (MediSpacer, ACE, OptiHaler) have an integral nozzle that directs the aerosol plume initially away from the patient’s mouth before inhalation, toward the right in Figure 3. The AeroChamber has an elastomeric adapter to accommodate the drug manufacturer’s nozzle/
mouthpiece, and the aerosol plume is directed initially toward the patient’s mouth.

Devices were tested in a cyclic sequence (A–B–C–D, A–B–C–D, etc), so that no bias was introduced by any minor changes in the drug canister or the test environment. For each trial, the device was placed in the VFR circuit as shown in Figure 1, and Ventolin (albuterol, 90 µg unit dose) was dispensed through the device into the VFR circuit.

We tested each device to simulate two conditions: (a) In-phase: the ideal condition in which the patient actuates the Ventolin canister at the start of inhalation. In this condition the canister was actuated just as the breathing machine started the inspiratory part of its cycle. (b) Out-of-phase: the undesirable condition in which the patient actuates the Ventolin canister at the start of exhalation. In this condition the canister was actuated just as the breathing machine started the expiratory part of its cycle, so the drug plume was not “inhaled” until the breathing machine came around to the next inhalation, 6 seconds later.

Our laboratory setup included a pneumatic actuator, electronically tied to the breathing machine, which automatically depressed the MDI canister at the desired point in the breathing cycle.

For each brand of device and each phase condition (in-phase and out-of-phase), 5 trials were averaged. Each trial was done with a different sample device of the brand being tested, so that 5 samples of each brand were used. Fifty doses were required for each trial, to collect a properly-measurable amount of albuterol on each of the 8 plates of the cascade impactor.

Measurement of Drug

Each plate of the cascade impactor was rinsed with 25 mL of a phosphate buffer (aqueous solution of 0.4M KH₂PO₄ + 0.2M HCl). Ultraviolet spectrophotometric analysis at 275 nm yielded the number of micrograms of albuterol per dose in each of the particle size ranges sorted by the cascade impactor.

A similar procedure was used to measure the amount of each dose trapped in the throat model and in the device, except that the throat model and device were each rinsed with 50 mL of the phosphate buffer.

Data Analysis

From each trial we derived several numbers, normalized to a single-breath cycle through the device:

• Micrograms/dose of albuterol collected on each of the 8 plates of the cascade impactor.
• Respirable dose (the sum of the micrograms/dose of albuterol collected on the 3 cascade impactor plates covering the respirable range of particle sizes [1.1 to 4.7 μm]).
  • The sum of the micrograms/dose of albuterol collected on all 8 plates of the cascade impactor.
  • Micrograms/dose of albuterol trapped inside the spacer or chamber.
  • Total micrograms/dose of albuterol collected throughout the system (all 8 plates of the cascade impactor plus the throat model plus the MDI device).

For each brand of device and each phase condition, we calculated the mean and standard deviation of the latter...
numbers for the 5 trials. These were not paired observations. The in-phase and out-of-phase averages for each individual brand were compared by means of two-tailed t tests with unequal variances; differences were considered statistically significant if p was < 0.05.

Results

Figure 4 shows the in-phase and out-of-phase dose output collected on each of the 8 plates of the cascade impactor, for MediSpacer (Fig. 4a), ACE (Fig. 4b), OptiHaler (Fig. 4c), and AeroChamber (Fig. 4d). The respirable dose was taken to be the sum of the micrograms of albuterol collected, during a single breath cycle, on Plates 3, 4, and 5, covering a particle size range from 1.1 μm to 4.7 μm.

For all 4 brands of device, the respirable dose delivered to the cascade impactor was significantly less in the out-of-phase case than in the in-phase case. These results are shown in Table 1, along with the p values for the t tests comparing the two phase conditions for each device. If the MDI canister is actuated at the start of exhalation, the MediSpacer delivers about two thirds of the dose it would deliver if the MDI canister were actuated properly at the start of inhalation. Similarly, the AeroChamber delivers about half of its best dose, the ACE about one quarter, and the OptiHaler about one tenth, when the actuation is completely mistimed. As shown in the final row of Table 1, the out-of-phase respirable dose is as follows: MediSpacer 67%, ACE 23%, OptiHaler 9%, and AeroChamber 46%.

What happens to the albuterol that does not make it to the cascade impactor in the out-of-phase case? Aside from the cascade impactor, there are two other locations in the VFR circuit where a significant part of the drug plume could accumulate: in the throat model and in the device itself. The drug deposition in these two locations, along with the sum total of albuterol collected (all 8 plates of the cascade impactor plus the throat model plus the MDI device) will tell us where the out-of-phase drug loss occurs.

For each brand of device and each phase condition, Table 2 lists the average amount of albuterol per dose collected in all 8 stages of the cascade impactor, trapped in the throat model, trapped inside the device, and collected throughout the total system, along with the p values for t tests comparing the in-phase dose and out-of-phase dose for each device; differences are considered statistically significant if p < 0.05.

Table 2. Amount of Drug/Dose

<table>
<thead>
<tr>
<th></th>
<th>MediSpacer</th>
<th>ACE</th>
<th>OptiHaler</th>
<th>AeroChamber</th>
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<tr>
<td><strong>Cascade impactor</strong></td>
<td></td>
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</tr>
<tr>
<td>In-phase (μg)</td>
<td>42 ± 4</td>
<td>31 ± 7</td>
<td>18 ± 5</td>
<td>29 ± 3</td>
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<tr>
<td>Out-of-phase (μg)</td>
<td>28 ± 6</td>
<td>8 ± 5</td>
<td>2.6 ± 0.3</td>
<td>14 ± 4</td>
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<tr>
<td>p value</td>
<td>0.003</td>
<td>0.0005</td>
<td>0.002</td>
<td>0.0001</td>
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<td><strong>Throat model</strong></td>
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</tr>
<tr>
<td>In-phase (μg)</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.2</td>
<td>0.8 ± 0.4</td>
<td>1.4 ± 0.6</td>
</tr>
<tr>
<td>Out-of-phase (μg)</td>
<td>1.1 ± 0.4</td>
<td>0.8 ± 0.6</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.2</td>
</tr>
<tr>
<td>p value</td>
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<td>0.8</td>
<td>1.0</td>
<td>0.07</td>
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<td><strong>Inside device</strong></td>
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<td></td>
</tr>
<tr>
<td>In-phase (μg)</td>
<td>51 ± 8</td>
<td>51 ± 2</td>
<td>68 ± 16</td>
<td>51 ± 7</td>
</tr>
<tr>
<td>Out-of-phase (μg)</td>
<td>50 ± 11</td>
<td>47 ± 2</td>
<td>84 ± 8</td>
<td>63 ± 15</td>
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<tr>
<td>p value</td>
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<td>0.02</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Total collected</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-phase (μg)</td>
<td>94 ± 9</td>
<td>83 ± 7</td>
<td>87 ± 19</td>
<td>81 ± 9</td>
</tr>
<tr>
<td>Out-of-phase (μg)</td>
<td>79 ± 15</td>
<td>56 ± 7</td>
<td>87 ± 8</td>
<td>78 ± 16</td>
</tr>
<tr>
<td>p value</td>
<td>0.1</td>
<td>0.0003</td>
<td>1.0</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Collected in all 8 stages of the cascade impactor.
†Trapped in the throat model.
‡Trapped inside the device.
§Total collected (all 8 plates of the cascade impactor plus the throat model plus the metered-dose inhaler device) for each device, expressed in μg of albuterol per dose; mean and standard deviation of 5 trials in each case.

Data from inside device and total collected are graphed in Figure 5. The label claim for Ventolin is 90 μg per unit dose. The p values are from t tests comparing the in-phase dose and out-of-phase dose for each device; differences are considered statistically significant if p < 0.05.

ACE = Aerosol Cloud Enhancer.
Discussion

Accounting for “Lost” Drug

As Table 2 shows, throat-model deposition cannot account for the out-of-phase decrease in respirable dose. The t tests gave p > 0.05 in the comparison of throat-model rinsings for the in-phase and out-of-phase cases for all 4 brands. Throat deposition remains small, independent of the timing of actuation. Therefore the last two categories in Table 2, the amount trapped inside the device and the total collected, are the only possibilities remaining to account for the dose-output differences between the two phase conditions. Figure 5 shows a comparison of the in-phase and out-of-phase amounts of albuterol per dose collected inside the device and in total, for each of the 4 brands.

For MediSpacer and ACE (Figs. 5a and 5b), the amount of albuterol trapped inside the device does not depend strongly on the time of actuation, but the total amount of drug collected decreases in the out-of-phase case. Some drug may have disappeared from the system. This suggests that the decrease in respirable dose could be due to leakage of drug out of the chamber for MediSpacer and ACE.

For OptiHaler and AeroChamber (Figs. 5c and 5d), the situation seems to be reversed. The amount of albuterol trapped inside the device appears to increase somewhat in the out-of-phase case, while the total amount of drug collected stays the same. For OptiHaler and AeroChamber, then, the decrease in respirable dose may be due to increased deposition of drug on the inner walls of the device.

These suggestions about what happens to the “lost” drug require verification, because some of the error bars in Figure 5 are large. For example, the amount trapped inside the OptiHaler is 68 ± 16 μg/dose in-phase and 84 ± 8 μg/dose out-of-phase, and the difference in these values is not statistically significant (p = 0.1). This makes it im-

Fig. 5. In-phase and out-of-phase drug collection, per actuation, trapped inside the device and collected throughout the system. This is a graph of the data from the inside device and total collected sections of Table 2. The amount trapped inside the device would not reach the patient in actual use. Error bars are 1 standard deviation. Note that the total amount of albuterol collected per actuation is within 1 standard deviation of the label claim for Ventolin in all cases except for ACE in the out-of-phase case (see text).
possible to determine unequivocally the fate of the albuterol that does not make it to the cascade impactor.

Assuming that our suggestions can be verified in future testing, we can speculate as to the explanations. Our intention here is to discuss design differences that could lead to different behavior in the 4 devices.

**Devices for which the “lost” drug disappears from the system in the out-of-phase case.** In the MediSpacer the one-way inhalation valve is not located in the mouthpiece. Even so, exhaled breath cannot enter the chamber, because the one-way inhalation valve is closed during exhalation, forming an air pillow inside the chamber. Most of the exhaled air exits through the one-way exhalation valve in the mouthpiece, but as it goes out it may entrain some of the aerosol-laden air from inside the chamber. The ACE does have a one-way inhalation valve in the mouthpiece, but there is nothing to prevent some portion of the aerosol plume from exiting out through the unvalved end. In addition, if the valve leaks, some of the exhaled air may pass through the chamber and carry drug particles out.

**Devices for which the “lost” drug is trapped inside the device in the out-of-phase case.** The OptiHaler has no valves, so the exhaled breath can pass through the spacer and out the small air vents on the other end. When this happens, drug particles can be blown against the spacer walls and be “lost” by impaction. Most particles presumably do not escape from the spacer during this maneuver, because to do so they would have to get through very small holes or around hairpin turns at the end of the spacer. The AeroChamber has a one-way inhalation valve in the mouthpiece that prevents the exhaled air from entering the chamber. In this device the apparent increase in device deposition in the out-of-phase case could be caused by more than one factor. (1) When the MDI canister is actuated with no airflow through the chamber, the aerosol plume does not have the benefit of an inhalation to carry it immediately out through the one-way valve. Instead, some of the drug particles that would have been inhaled will impact directly on the inside of the chamber. (2) Gravitational settling would be insignificant for particles with diameters less than about 5 \( \mu m \), but larger particles could settle out in the time it takes for the exhalation phase (about 6 seconds in these tests). However, if this were an important mechanism for the AeroChamber, we would expect the particle size distribution to shift toward smaller sizes in the out-of-phase case, which is not seen. In Figure 4d, plates 3 through 7 would hardly be affected by gravitational sedimentation over 6 seconds, yet for these plates there is a very clear-cut difference between the two phases. Therefore we conclude that sedimentation is not the primary means by which drug is “lost” in the AeroChamber in the out-of-phase case. (3) During the 6-second delay between actuation and inhalation, the drug plume is not statically suspended inside the chamber. Rather, turbulent motion persists within the aerosol cloud for the few seconds immediately following its ejection from the canister. In the out-of-phase case the several seconds of turbulence could add to the inertial impaction of drug particles onto the chamber walls. Unlike sedimentation, this mechanism would not sort by particle size and therefore is a more plausible explanation of the observations shown in Figure 4d. (4) If electrostatic deposition is occurring inside the chamber, the 6-second delay will increase the amount of drug “lost” by this mechanism.

**Comparison with Other Results**

Although we do not have available any other researchers’ studies that are exactly like this one, Mitchell et al. have recently carried out a study that is closely related to ours, and have observed comparable behavior. Their study compared the total unit dose output of two MDI delivery devices, with actuation at the start of inhalation (our in-phase case) and actuation at the start of exhalation (our out-of-phase case). They found, as we do, that (a) the dose output was highest when actuation was synchronized with inhalation, and (b) a valved holding chamber retains more of the usable aerosol drug plume than does an unvalved spacer, in the event of mistiming.

The Mitchell et al study differed from ours in some respects, yet led to very similar conclusions:

1. They collected what could be called the “patient dose” by means of a filter directly following the mouthpiece of the device, whereas we collected the patient dose by means of the throat model and all 8 plates of the cascade impactor, derived by adding the throat model amount plus the cascade impactor amount from our Table 2. A rough numerical comparison shows the results of the two studies to be similar. Mitchell et al found that the out-of-phase dose is 60% of the in-phase dose for the AeroChamber (a valved holding chamber), whereas we found approximately 50% for the AeroChamber. For an unvalved spacer, they found an out-of-phase to in-phase ratio of 12% (for the MicroChamber) whereas we found approximately 16% (for the OptiHaler). Both studies point to the clear advantage in using a valved chamber if the patient does not synchronize actuation with inhalation.

2. They tested with Flovent (fluticasone propionate, a corticosteroid), whereas we used Ventolin (albuterol, a bronchodilator). Ahrens et al. and Rau et al caution that MDI delivery devices may differ in their relative efficiency depending on the MDI drug being used. Nonetheless, the conclusions of our study are very much in agreement with those of Mitchell et al.
Limitations of VFR Method and Comparison with Other Methods

The main limitation of the VFR technique is the restriction to inhalation flow rates less than the flow required to operate the cascade impactor. As noted above, the maximum allowable flow could be doubled by using two impactors in parallel, but this would make the technique considerably more cumbersome.

Two other groups have recently published particle-size studies with in vitro breathing that is not restricted in this way. Finlay simulated tidal breathing with a piston operated by a computer-controlled stepper motor; an electronic trigger opens a valve to allow ambient air into the system when needed for inhalation, and closes the valve during exhalation. This setup could be used for phase studies like ours, but the work reported so far has not been for this purpose. Instead, the piston was cycled through 5 complete breaths per MDI actuation to simulate infant and pediatric breathing. Presumably, the stepper motor in Finlay’s setup would allow a variety of breathing profiles, but the profile he has used is a square wave, which is less realistic than our sinusoidal profile.

Another electronic inhalation device has been developed by Burnell et al to test particle sizes and doses from dry powder inhalers. The goal here was also to do in vitro testing under realistic breathing conditions. The inhalation can be preprogrammed to follow any desired profile. This device could not be used for an MDI phase study like ours, however, because it cannot exhale through the drug delivery device. It is well suited for dry powder inhaler studies, in which the ideal inhalation rate is higher than for MDIs and breath-hand coordination is not as important an issue as with MDIs.

The simplicity of the VFR technique is both a disadvantage and an advantage. The breathing profile is limited to pediatric flow rates or the lower range of adult rates. However, because the technique requires no specialized or programmable equipment, it has the potential for being used widely and reproducibly.

Particle Size Distributions

The Ventolin particle size distributions peak at Plate 5 (2.1–1.1 μm) for all 4 devices in our study, in both phase conditions. Figure 4 shows that the shape of the overall distribution is similar for all cases tested. The t tests for each of the 8 plates of the cascade impactor show that the MediSpacer and AeroChamber distributions are independent of phase. A meaningful numerical comparison could not be made for the ACE and OptiHaler because the out-of-phase readings were too close to the detection limit.

Ventolin inhalation aerosol is a microcrystalline suspension of albuterol in liquid propellants, with the particle size distribution broadly specified (95% ≤ 10 μm) in the product information insert. Though the particle size distribution may vary from batch to batch of a particular brand of microcrystalline drug, our measurements suggest that it is not affected by time of actuation, size of delivery device, presence or absence of valves in the delivery device, or location of valves in the delivery device.

Future Work with the VFR Method

Many variations and refinements of this work are possible, including:
- Actuating the MDI canister at different phases of the breath cycle, such as one or two seconds before or after the start of inhalation, to map out the drug delivery efficiency as a function of the delay.
- Taking measurements at a different breathing rate, inspiratory-time:expiratory-time ratio, Vᵣ, or peak flow, to simulate a profile corresponding to a different type of patient.
- Checking the hypotheses concerning the leakage (or lack thereof) out of the MDI devices in the out-of-phase case, possibly using low-resistance filters placed at strategic locations.
- Rinsing the T-piece to see if any significant amount of drug is trapped there, but the current results suggest that this could not be a very large factor, because we recovered close to the nominal unit dose of Ventolin in almost all cases; still it should be measured directly.

Conclusions

Patient Education

The main inference to be drawn is that, though device design is important, timing greatly affects the amount of drug delivered to the lung by any spacer or chamber. We found this to be true for all 4 MDI delivery devices we tested. A patient who actuates the MDI canister upon exhalation might receive between two thirds and almost none of the best possible dose, depending on the device.

In our study, the devices that are best at retaining part of the drug plume are true holding chambers; that is, they have a one-way inhalation valve that prevents exhaled air from mixing significantly with the drug plume in the chamber. They also have a chamber volume of ≥ 140 mL. However, even the best devices do not deliver 100% of the drug plume if the patient mistimes actuation and inhalation. Considerations of effectiveness and cost may make a loss of a third or more of the dose unacceptable. If a patient loses half of the expected dose because of mis-
timing, the number of puffs would have to be doubled to get the expected result.

In light of this finding, we conclude that patient training is very important in MDI use, even if a valved chamber is provided. The “Helpful Hints” included in the AeroChamber instruction leaflet state that “The one-way valve allows you to inhale at your own rate so that coordination of inhalation with the actuation of the inhaler is not a problem.” We agree that an MDI chamber helps to retain some of the dose if actuation and inhalation are not coordinated, but a significant portion of the drug may be “lost” if the patient is not trained to actuate the canister at the start of inhalation.

The 1997 “Practical Guide for the Diagnosis and Management of Asthma” instructs the patient, “If you use a holding chamber, first press down on the inhaler. Within 5 seconds, begin to breathe in slowly.” We have shown that, even with a valved holding chamber, a significant portion of the drug will be “lost” if the patient actually waits 4–5 seconds—particularly if the patient is exhaling into the mouthpiece during those few seconds. Ideally there should be no delay between canister actuation and the start of inhalation.

The instructions for use that come with the ACE chamber direct the patient to “Take a second slow, deep breath from the ACE to ensure you’ve received all the drug from the chamber,” after the first inhalation, a 10-second breath-hold, and exhalation. Our study indicates that this second deep breath will not be fruitful.

Although many MDI drugs are not labeled for use by children under 12 years of age, it is possible that some MDIs are used with a reservoir device by children as young as 4 years of age. For such patients, where synchronization of actuation and inhalation may be difficult to control, there will be particular benefit in choosing a valved holding chamber that retains the majority of the drug plume for a few seconds.

In fact, referring back to the sources cited at the beginning of this paper, we suggest that the same statement could be made for many patients of all ages.

**VFR Technique**

This study would not have been possible without the variable flow rate technique, which allowed us to measure particle size distributions (and therefore respirable dose) under realistic conditions simulating the breathing of a patient. Any issues of MDI mistiming obviously cannot be addressed with a purely constant-flow method.

The VFR technique can also be used for special cases in which an unusual breathing pattern may affect respirable dose. Such cases might include pediatrics (small V_T), restrictive pulmonary disease (rapid, shallow breathing), or mechanical ventilation.

Adoption of this technique for bench testing of aerosol drug delivery devices should make it easier to compare properties of various drug/device systems, as studied by different researchers, under laboratory conditions that mimic the conditions of actual use by a patient.

**PRODUCT SOURCES**

**Cascade Impactor**
Andersen 1 ACFM Non-Viable Ambient Particle Sizing Sampler (Mark II), Andersen Instruments, Atlanta GA

**Harvard Breathing Machine**
Harvard Apparatus Dual Phase Control Respirator Pump, Harvard Apparatus, South Natick MA

**MDI Devices**
Airlife Hand-Held MediSpacer, Allegiance Healthcare Corporation, McGaw Park IL
Aerosol Cloud Enhancer (ACE), Diemolding Healthcare Division, Canastota NY
OptiHaler, HealthScan Products, Cedar Grove NJ
AeroChamber, Monaghan Medical Corporation, Plattsburgh NY

**MDI Drug**
Ventolin (albuterol, United States Pharmacopeia), Allen & Hanburys, a Division of Glaxo Wellcome, Research Triangle Park, NC

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**REFERENCES**

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