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RESEARCH PAPER

Investigation of Some Commercially Available Spacer Devices for the Delivery of Glucocorticoid Steroids from a pMDI

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ABSTRACT

Five commercially available spacers were investigated to determine their influence on the percentage of drug retained in the spacer device, percentage fine particle fraction (FPF), percentage deposited in the induction port, mass median aerodynamic diameter (MMAD), and geometric standard deviation (GSD). Betamethasone valerate (BMV) and triamcinolone acetonide (TAA) were used as model drugs in the pressurized metered dose inhaler (pMDI) formulations containing the propellant HFA 134a. The BMV was dissolved in an ethanol/HFA 134a system, and the TAA was suspended in HFA 134a using ethanol as a dispersing agent. The metering chamber volume of the valve was either 50 μl or 150 μl. The spacer devices investigated included the ACE®, Aerochamber®, Azmacort®, Easivent®, and Ellipse® spacers. Each spacer device was attached to an Andersen Cascade Impactor powered by a vacuum pump. Cascade impaction data were used to derive the percentage drug deposited in the induction port, MMAD, GSD, and FPF. The BMV particles emitted from the spacers were finer than the TAA particles because the dissolved drug precipitated as the cosolvent evaporated. The TAA particles had significantly larger MMADs because many undissolved drug particles were contained within each droplet following actuation. After evaporation of the liquid continuous phase, the suspended drug aggregated to form larger agglomerates than those particles precipitated from the BMV pMDI solution droplets. The addition of a spacer device

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lowered the MMAD to less than 4.7 μm for particles from both the BMV pMDI solution and the TAA pMDI suspension. The addition of a spacer device also lowered the percentage drug deposited in the induction port. The FPF was significantly increased when a spacer device was used. The MMAD significantly decreased when a spacer device was added for the two model drugs when using the 150-μl metering valves, but the difference was not statistically significant when the 50-μl valves were used ($P < .05$*). The GSD was not influenced by the use of a spacer device. The use of a spacer device will enhance pMDI therapy by reducing the amount of drug deposited in the oropharyngeal region, which will lead to fewer instances of local and systemic side effects. In addition, the spacer devices investigated will allow a higher dose of drug to reach the deep lung, which may permit the use of lower dosage regimens with increased therapeutic efficacy.*

Key Words: *Betamethasone valerate; HFA 134a; pMDI; Spacer devices; Triamcinolone acetonide.*

INTRODUCTION

In the United States, 1 of every 10 people suffers from asthma (1–3). Asthma is an allergic response that is brought on by triggers, which are allergens specific to a particular patient. When a susceptible person is subjected to an allergenic substance, an inflammatory process is triggered within the muscular bronchiolar region of the lung. This inflammatory reaction, led by the release of histamine, causes the bronchioles to constrict, thus cutting off the air supply. Therefore, environmental air is not able to reach the alveoli, in which the exchange of oxygen (O_2) for carbon dioxide (CO_2) occurs.

Treatment of asthma consists of both environmental and pharmacological management of the underlying epidemiology of the asthmatic process. The avoidance of triggers is one way to prevent asthma attacks from occurring. Environmental management is not completely successful in controlling asthma since it is not always possible to avoid triggers. Pharmacological management is key for complete suppression of asthmatic attacks. Pharmacological treatment utilizes medications that manage asthma systemically by oral ingestion or injection and/or locally via administration directly to the bronchiolar region. Systemic administration, either oral or parenteral, is advantageous for rapid control of acute asthmatic attacks when bronchiolar constriction prevents administration of drugs directly to the lungs. Drugs that are administered systemically in the hospital setting to sequester an acute asthmatic attack include β_2 agonists (albuterol), xanthines (theophylline, aminophylline), and corticosteroids (methylprednisolone, prednisone). In addition to rapid relief of acute symptoms, systemic administration also leads to significant adverse effects by the medications. Side effects experienced include tachycardia (β_2 agonists); hypothalamic-pituitary-adrenal axis suppression, which results in diminished corticosteroid secretion from the adrenal gland (corticosteroids); and cardiac arrhythmia and epilepticlike seizure abnormalities (xanthines) (4). Therefore, it is important to switch from systemic to pulmonary administration of medications as soon as possible after therapy is initiated.

Pressurized-metered dose inhalers (pMDIs) are scientifically proven to be as effective as nebulizers in delivering drug to the lungs when used with a spacer device (9–12). The pMDIs are significantly less expensive than the nebulizers, and the pMDIs require only 1/5 to 1/50 of the dose given via nebulizer to achieve the same therapeutic effect in patients (4,13). Despite the advantages, pMDIs have many inherent disadvantages. When actuated, the active ingredient–propellant plume is emitted from the mouthpiece at such a rapid velocity (approximately 100 km/h) that at least 80% of the dose collides with the back of the throat and deposits on the larynx and pharynx regions. There is 10% deposited in the actuator, leaving only approximately 10% to reach the lung for desired therapeutic action (4,5–7,14). This phenomenon can lead to several undesirable outcomes. Coughing and hoarseness result from particle deposition in the throat region and from the cold propellant effect produced as the propellant evaporates from the back of the throat (15). For steroid maintenance therapy, deposition of the anti-inflammatory agent in the oropharyngeal region leads to an overgrowth of *Candida albicans*, which ultimately causes thrush. Thrush is the major cause of therapeutic failure of the orally inhaled corticosteroids. Many of these problems occur because the patient is not able to coordinate inhalation of drug particles with the emission of drug following actuation (9).

In the last several years, studies have been reported that assessed the augmentation of spacer devices for the delivery of drugs to the respiratory tract using pMDIs (8–12,15–17). However, comparative in vitro investigations of commercially available spacer devices are lacking. Therefore, this study focused on comparing the dosing efficiency of five commercially available spacer devices. In general, a spacer functions to slow or decelerate the plume emitted from the aerosol canister (16,17). This allows the dose of drug to be delivered to the patient using the patient's own breathing rate as the velocity of administration instead of the unnatural velocity produced from the force of the propellant. Therefore, any voluntarily breathing patient, whether ambulatory or nonambulatory, can benefit from the use of pMDIs when spacer devices are attached (15). Many authors have shown that these spacer devices actually increase the fraction of an actuation delivered to the lungs up to 60%, while reducing the amount of active compound deposited in the oropharyngeal region to almost zero (9–12,15–17). Thus, the therapeutic response is better, and the incidence of side effects, both systemic and local, is significantly reduced.

The objective of this study was to investigate the influence of five commercially available spacers in combination with model pMDI drug products on the emitted dose. Two steroids, betamethasone valerate (BMV) and triamcinolone acetonide (TAA), were chosen as the model drugs to investigate differences in drug delivery characteristics with respect to whether the drug was in solution (BMV) or suspension (TAA) in the propellant. Last, the influence of the size of the metering chamber on dose delivery was investigated.

MATERIALS AND METHODS

Betamethasone valerate USP was purchased from Spectrum Quality Products (Gardena, CA), and micronized triamcinolone acetonide (Upjohn Fine Chemicals, Kalamazoo, MI) was used as received. Aluminum cans were kindly supplied by Cebal S. A. (Bellegarde, France). Valves with metering chamber sizes of 50 µl (DF10-50RC) and 150 µl (DF10-150RC) were purchased from Valois of America, Incorporated (Greenwich, CT). Dymel Ultrapure HFA 134a (1,1,1,2-tetrafluoroethane) was purchased from DuPont Chemicals (Wilmington, DE). Ethanol was purchased from AAPER Alcohol and Chemical Company (Shelbyville, KY), and methanol was acquired from EM Science (Gibbstown, NJ). The spacers investigated in this study included the ACE® (DHD Healthcare, Canastota, NY), Aerochamber® (Forest Pharmaceuticals, St. Louis, MO), Easivent® (Dey Laboratories, Napa, CA), Ellipse® (Glaxo Wellcome, Research Triangle Park, NC), and Azmacort® spacer, available with the product from Rhone-Poulenc Rorer (Collegeville, PA). The control pMDIs employed an oral actuator (type KN-1, Valois of America, Inc.).

The TAA suspension was prepared by sonicating the drug into anhydrous ethanol for 4 min to make a 23.1% w/w dispersion (18). The compounding procedure was carried out at 0°C to minimize ethanol evaporation and crystal growth (19). An aliquot of approximately 130 mg of the drug/ethanol slurry was metered into each aluminum can and immediately crimped with either a 50- or a 150-µl metering chamber valve using a Pamasol P2005/P2008 (Pamasol Willi Mader AG, Pfaffikon, Switzerland) (18). For each spacer device tested, three samples with 50-µl valves and three samples with 150-µl valves were prepared. Each canister was filled with 10 g of HFA 134a (20). The TAA pMDI samples were then equilibrated in the inverted position (valve tip down) at 25°C for 3 days.

The pMDIs containing BMV were prepared by weighing approximately 20 mg of BMV directly into each aluminum can and then adding 1 ml of anhydrous ethanol into the can. The 50- and 150-µl valves were immediately crimped onto each of three cans for each valve size as was done with the TAA suspension. Then, 10 g of HFA 134a propellant was pressure filled through the valve into each canister. The BMV pMDI canisters were equilibrated in the inverted position at 25°C for 3 days.

An eight-stage cascade impactor (Andersen I ACFM nonviable eight-stage cascade impactor with a USP induction port, Mark II, Andersen Instruments, Smyrna, GA) was used to determine mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), percentage fine particle fraction (FPF), percentage deposited in the induction port (%IP), and percentage retained in the spacer device. Cascade impaction measurements were conducted in triplicate for each spacer investigated. The vacuum flow rate was controlled at 28.3 L/min to the impactor using a General Electric motor (model 1531-107B-G557X, GAST Manufacturing Corp., Benton Harbor, MI).

The mass of BMV and TAA deposited in the spacer devices and cascade impactor was recovered using methanol. The spacer device, mouthpiece, and induction port were each separately rinsed with about 45 ml of methanol. The final volume of each sample was brought to 50 ml with methanol. Samples were collected from each of the eight stages of the Andersen cascade impactor using glass fiber filters (Andersen Instruments). After each test, the filters were carefully removed and placed into 25-ml scintillation vials containing glass fiber filters. Into each

vial, 5 ml of methanol was metered. The filter was completely submerged into the methanol. These samples were then capped and sonicated for 5 min. Each aliquot was filtered through a 0.45-μm polypropylene membrane filter (Acrodisc, Pall Gelman Laboratory, Ann Arbor, MI), and the drug content was quantitated by ultraviolet (UV) spectroscopy using a Hewlett-Packard 8452A diode array spectrophotometer (Palo Alto, CA).

Dose delivery through the valve (DDV) was determined using a USP sampling apparatus equipped with a firing adapter (Jade Corp., Huntington Valley, PA). Testing was conducted using a five-shot DDV measurement. DDV measurements were performed in triplicate. The firing adapter was carefully removed and thoroughly rinsed with methanol into a collection vessel. The sampling apparatus was then rinsed with methanol. The rinse was added to the collection vessel containing the firing adapter aliquot. This volume was then brought to 50 ml with methanol. The aliquot was then used to determine the mass of BMV and TAA deposited in the sampling tube by UV spectroscopy. The amount of drug delivered through the valve for each actuation was measured by dividing the amount of drug recovered from the USP sampling apparatus by the number of actuations. The DDV was then used to determine the mass balance for the recovery of drug after actuation during the investigation.

Results were analyzed using Kaleidagraph 3.0 (Synergy Software, Reading, PA). One-way analysis of variance (ANOVA) was used to determine statistical significance. For the 95% confidence interval, $P < .05$ was considered statistically significant.

RESULTS AND DISCUSSION

Spacers approved by the FDA are indicated to enhance positive outcomes for patients being treated with orally inhaled asthma medications because the spacer devices reduce side effects and increase the amount of drug delivered to the lungs compared to using an actuator only. However, different spacers can produce significantly different deposition patterns and aerodynamic particle size distributions. Studies comparing the influence of the design of a spacer device on aerodynamic particle size distribution are lacking. An investigation of the shape and volume of each of the spacers may help to explain why some spacers are more efficacious than others at emitting particles that are more likely to be respirable.

The ACE spacer (Fig. 1a) is a conically shaped device that is narrow at the end at which the pMDI is mated and

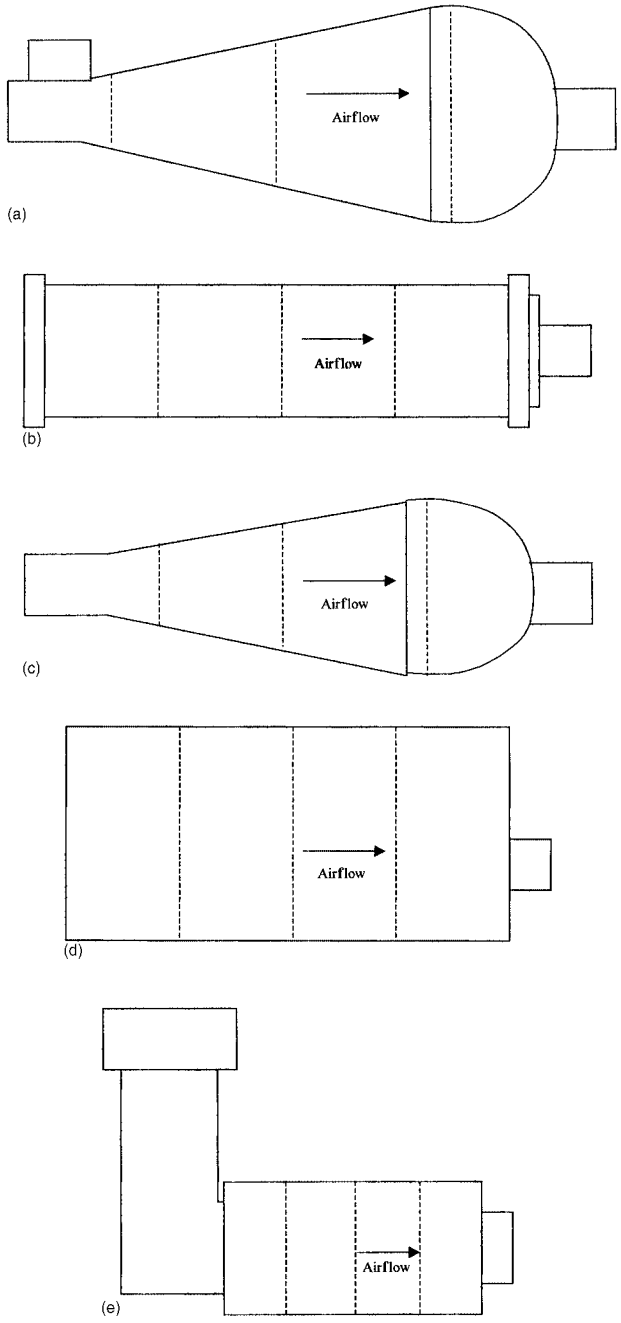

Figure 1. Schematic representations of the (a) ACE, (b) Aerochamber, (c) Easivent, (d) Ellipse, and (e) RPR spacer devices. The dashed lines represent the cross-sectional diameters of the spacer devices moving from left to right at 25%, 50%, and 75% the length of the spacers.

actuated, and it broadens in diameter toward the orifice for delivery of drug to the patient. A separate actuator is not required for this spacer because there is a built-in actuator located on top of the spacer; the canister is placed here in the inverted position for actuation. The ACE spacer has an expansion volume capacity of 160 ml and a length of 20 cm. The cross-sectional diameters of the spacer at 25%, 50%, and 75% points along the spacer length are 2.8, 4.9, and 4.0 cm, respectively.

The Aerochamber spacer (Fig. 1b) is a cylindrical device that is 14.5 cm long. The orifice for a pMDI and actuator is at the opposite end of the spacer from the mouthpiece for drug delivery. This spacer device has an expansion volume capacity of 125 ml available for the aerosol cloud to expand and disintegrate into finite individual droplets as the HFA 134a evaporates. The cross-sectional diameter of the Aerochamber is 4.5 cm throughout the entire length of the spacer.

The Easivent spacer (Fig. 1c) is an elliptically shaped spacer with a cross-sectional area that increases in the direction of the airflow from the introduction of the aerosol plume to the delivery of the aerosol cloud from the spacer to the patient. The spacer has an orifice at the narrow end; a canister mated to an actuator can be placed here to deliver drug from a pMDI into the spacer. From the actuator orifice to the mouthpiece, the spacer broadens to form an increasingly elliptical shape. This spacer device has an expansion volume capacity of 145 ml and is 15 cm long. The cross-sectional width increases from 4.5 to 5.5 to 6.0 cm in the direction of the airflow at points 25%, 50%, and 75%, respectively, along the length of the spacer, while the cross-sectional height increases from 3.8 to 4.8 cm, then decreases to 4.7 cm.

The Ellipse spacer (Fig. 1d) has the largest volume of the spacer devices investigated. Its expansion volume capacity is 200 ml. The Ellipse spacer has the shape of an elliptical cylinder. The spacer is 13 cm long and 4.2 cm wide, and it is 6.4 cm high for the entire length of the spacer device. The actuator orifice and mouthpiece for delivery of drug out of the spacer are at opposing ends of the device.

Last, the Azmacort RPR spacer (Fig. 1e) is supplied with the commercial pMDI drug product. It consists of an actuator and spacer combination, which is mechanically operated to fold into an all-in-one container to enhance portability. When dosing is desired, the container can be pulled apart to reveal the pMDI and actuator. Once the actuator is snapped into place, the device is ready to deliver drug from the pMDI. This spacer is the smallest of the spacers investigated, having an expansion volume capacity of 75 ml. The RPR spacer is 7.5 cm long and is cylindrically shaped with a 4.2-cm diameter throughout its entire length.

Each of these spacers requires a cleaning-and-drying procedure before use. The spacers have residual static electricity, which has the capability to capture drug and prevent delivery out of the spacer device. A soak in warm soapy water, followed by a thorough rinse with warm tap water eliminates the residual static electricity from the spacer devices. Care must be taken, however, to allow the spacers to dry thoroughly in air after washing and rinsing. Wiping with a cloth has been shown to reintroduce the static electricity to the spacers (15).

The data in Tables 1 and 2 show the aerodynamic particle deposition characteristics for the BMV pMDI solution and the TAA pMDI suspension based on metering chamber volume and type of spacer used. The data obtained from Tables 1 and 2 were further analyzed to determine MMAD and GSD. The MMAD is defined as the aerodynamic particle size in micrometers at 50% of the particle size distribution as determined from cascade impaction. The GSD is defined as the square root of the ratio of the particle size at 84.13% to the particle size at 15.87% of the particle size distribution (21). The Kaleidagraph 3.0 software allowed the results obtained from the cascade impaction data in Tables 1 and 2 to be transformed to a log particle size versus percentage cumulative less than stated probability graph (Fig. 2). This type of graph was generated for each of the experiments. Data obtained from this graph allowed the calculation of MMAD and GSD.

Mass balances were greater than 90%, which was an indicator of good recovery of drug following actuation. Mass balances ranged from 91% with the RPR spacer to 99% recovery with the Aerochamber spacer using the BMV pMDI solution with the 150-μl metering chamber valve. For the TAA pMDI suspension using the 50-μl metering chamber valve, mass balances ranged from 92% recovery with the Easivent spacer to 106% recovery using the ACE spacer. Mass balances for the BMV pMDI solution with the 50-μl metering chamber valve and the TAA pMDI suspension with the 150-μl metering chamber valve were of similar magnitudes.

The results shown in Fig. 3 indicate that the spacers generally captured between 50% and 90% of each emitted dose, with the exception of the Ellipse spacer. Using a 150-μl valve for the BMV solution, the Ellipse spacer retained 65.7% of the emitted dose. In all other trials, the Ellipse spacer retained less than 50% of the dose delivered following actuation. The lower deposition in the Ellipse spacer may be due to the large expansion volume

Table 1

Particle Deposition Characteristics of the Betamethasone Valerate (BMV) Pressurized Metered Dose Inhaler (pMDI) Solution Based on Metering Chamber Volume and Type of Spacer Used

Sample Description		No Spacer (Actuator Only), Cumulative Mass %		ACE, Cumulative Mass %		Aerochamber, Cumulative Mass %	
Stage	Cutoff	50 µl	150 µl	50 µl	150 µl	50 µl	150 µl
Stage 0	9	100	100	100	100	100	100
Stage 1	5.8	95.54	88.73	98.3	97.59	99.57	99.31
Stage 2	4.7	92.53	83.57	96.68	95.28	98.75	98.47
Stage 3	3.3	89	81.53	94.45	93.2	97.17	96.09
Stage 4	2.1	84.08	72.43	91.63	90.54	93.26	91.11
Stage 5	1.1	71.75	42.47	83.81	85.03	76.66	72.94
Stage 6	0.7	42.58	21.74	49.75	62.81	45.55	38.62
Stage 7	0.4	22.56	8.67	23.18	36.44	21.62	20.68
After filter (AF)	0	9.61	4.33	8.15	16.51	6.24	8.91
Sample Description		Easivent, Cumulative Mass %		Ellipse, Cumulative Mass %		RPR, Cumulative Mass %	
Stage	Cutoff	50 µl	150 µl	50 µl	150 µl	50 µl	150 µl
Stage 0	9	100	100	100	100	100	100
Stage 1	5.8	97.5	97.92	98.75	98.47	96.39	96.36
Stage 2	4.7	94.64	92.87	97.03	96.66	94.58	93.24
Stage 3	3.3	90.98	90.26	94.41	92.74	91.95	90.25
Stage 4	2.1	83.83	85.89	89.87	84.17	87.7	86.16
Stage 5	1.1	72.85	75.34	77.87	57.31	77.2	73.82
Stage 6	0.7	41.49	47.95	45.6	25.76	38.36	51.37
Stage 7	0.4	20.26	25.16	21.7	12.17	20.56	32.83
After filter (AF)	0	9.62	11.12	8.72	4.98	7.81	10.92

of the spacer. Having the highest volumetric capacity of all the spacers investigated, the aerosol plume emitted into the Ellipse spacer had more volume to decelerate before colliding with the spacer wall. In addition, the width and height dimensions of the Ellipse spacer were large enough to give the spacer a shape in which there were no narrow areas to capture drug within the device. This design minimized the amount of drug deposited onto the walls of the spacer because the spacer walls were far enough from the initial aerosol plume following actuation to avoid impact by the high-velocity particles.

In contrast, the RPR spacer, which was the smallest of the spacers tested, captured between 75% of the dose using the BMV solution with a 50-µl metering chamber to 89% of the dose using the BMV solution with a 150-µl chamber. Besides the ACE spacer, the RPR spacer retained the highest amount of drug per actuation.

The ACE spacer has the second-largest volume of the spacers investigated, but it is a narrow, cone-shaped device. In contrast to the Ellipse spacer, drug impacted and deposited onto the narrowing walls of the ACE spacer following actuation. Because of its design, the ACE spacer captured more drug following actuation than any of the other spacers investigated.

Even though the Aerochamber and the Easivent spacers have smaller volumes than the ACE spacer, the width and height dimensions are larger for the Aerochamber and the Easivent. Therefore, there are no narrow areas within these two spacers to serve as surfaces for impaction and deposition of drug for the initial high-velocity aerosol plume immediately following actuation. Besides the Ellipse spacer, the Aerochamber and Easivent spacers captured the least amount of drug per actuation of all the spacer devices investigated. Therefore, both

Table 2

Particle Deposition Characteristics of the TAA pMDI Suspension Based on Metering Chamber Volume and Type of Spacer Used

Sample Description		No Spacer (Actuator Only), Cumulative Mass %		ACE, Cumulative Mass %		Aerochamber, Cumulative Mass %	
Stage	Cutoff	50 µl	150 µl	50 µl	150 µl	50 µl	150 µl
Stage 0	9	100	100	100	100	100	100
Stage 1	5.8	91.31	62.44	94.14	94.36	92.23	91.86
Stage 2	4.7	76.66	38.35	85.83	86.79	74.98	75.39
Stage 3	3.3	62.82	26.98	76.76	78.01	57.73	58.55
Stage 4	2.1	40.26	12.86	57.69	62.2	31.89	35.26
Stage 5	1.1	22.5	4.77	40.13	40.34	14.92	15.93
Stage 6	0.7	13.59	2.5	26.16	24.93	9.25	11.17
Stage 7	0.4	8.8	1.69	16.63	16.75	4.94	7.31
After filter (AF)	0	4.82	0.9	7.99	8.42	2.73	3.98
Sample Description		Easivent, Cumulative Mass %		Ellipse, Cumulative Mass %		RPR, Cumulative Mass %	
Stage	Cutoff	50 µl	150 µl	50 µl	150 µl	50 µl	150 µl
Stage 0	9	100	100	100	100	100	100
Stage 1	5.8	92.48	95.02	91.31	90.99	89.48	84.43
Stage 2	4.7	78.52	87.81	74.62	71.39	70.8	65.67
Stage 3	3.3	62.98	77.11	59.72	55.61	53.21	47.9
Stage 4	2.1	40.68	56.21	30.81	24.65	29.15	23.25
Stage 5	1.1	22.05	33.46	11.5	7.52	13.57	6.6
Stage 6	0.7	14.26	17.38	5.26	2.81	8.2	2.51
Stage 7	0.4	10.89	9.38	3.65	1.8	4.69	1.68
After filter (AF)	0	6.34	4.56	2.13	0.72	3.94	1.39

expansion volume and dimension design were important factors of spacer devices, and their influence on drug deposition must be investigated to optimize drug delivery following actuation from a pMDI.

The results shown in Fig. 3 also indicate that the smaller metering chamber volume caused less BMV and TAA to be retained in the spacer. This was statistically significant ($P < .05$) when using the ACE and Ellipse spacers for both the BMV and TAA pMDIs and the RPR spacer for the BMV pMDI only. This phenomenon occurred because, with the smaller metering chamber volume, less formulation was emitted per actuation. This lower dose, in turn, would allow secondary disintegration (further droplet division into smaller droplets) to occur more easily because there were fewer particles to occupy the same volume. Consequently, smaller particle sizes with lower densities would be formed. These lighter particles would collide and adhere to the walls of the spacer less often, correlating with less of the actuated dose being captured in the spacer device.

In general, this high percentage of deposition of large particles retained within the spacer device led to a subsequent increase in the FPF (Fig. 4). The FPF is defined as the amount of drug captured on the stages of the cascade impactor divided by the total amount of drug delivered per actuation from the aerosol canister into the induction port and subsequent stages of the cascade impactor (21). All of the spacer devices investigated significantly increased the FPF for both drugs compared to that delivered using the actuator only with no spacer ($P < .05$). When spacers were used, the FPF increased to as high as 96.5% for the BMV pMDI using the Ellipse spacer in conjunction with the 150-µl valve. When an actuator was used without a spacer, the maximum FPF was 41.4%, obtained

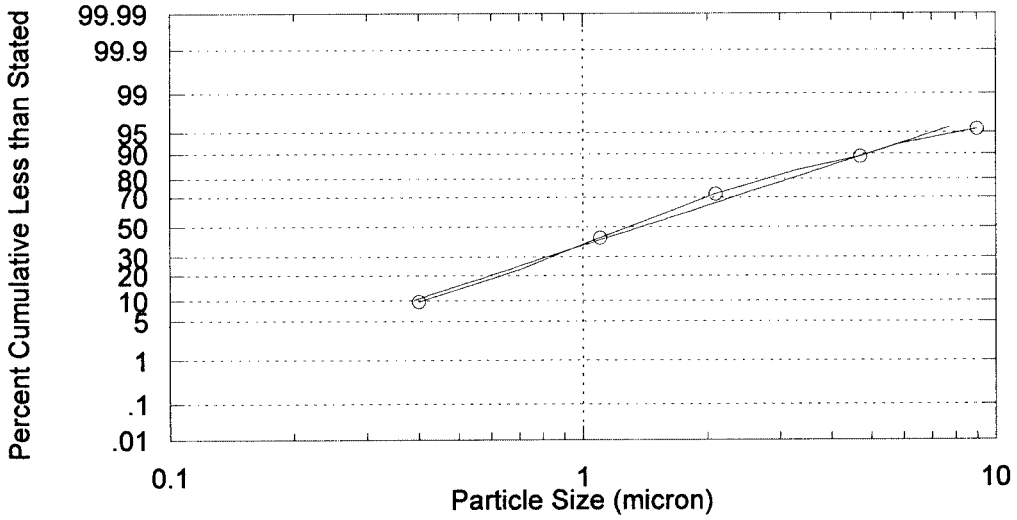

Figure 2. Log particle size versus cumulative percentage less than stated plot for the BMV pMDI solution with a 50-µl metering valve using an actuator only (no spacer device).

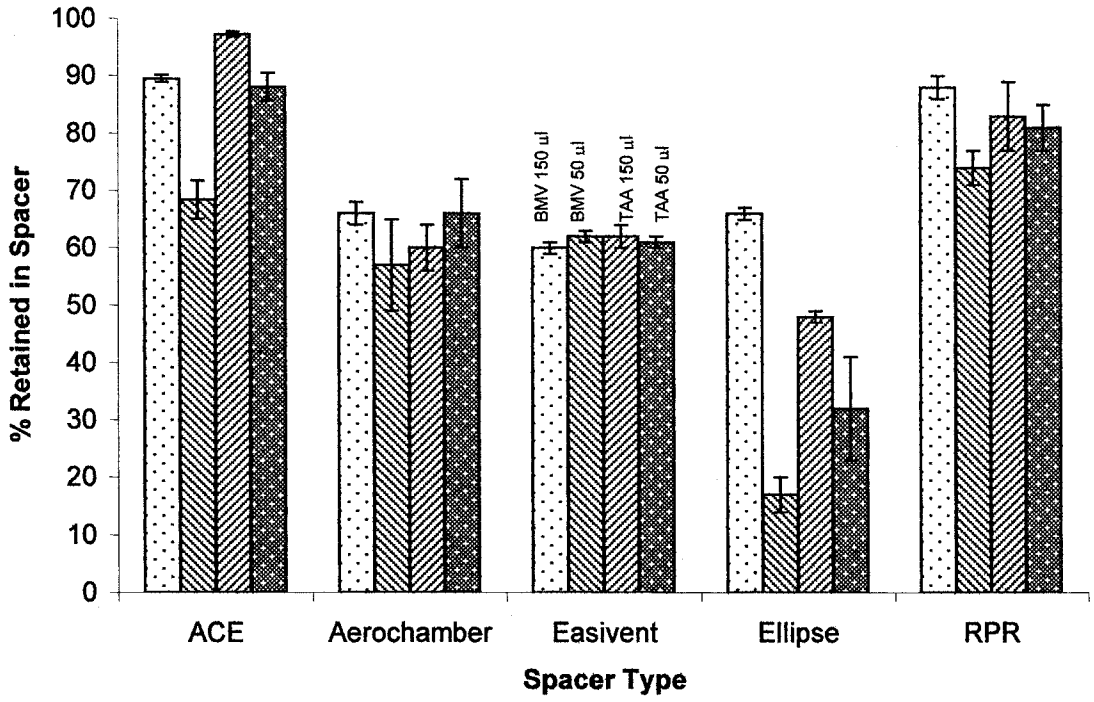

Figure 3. Percentage of the dose retained in the spacer per actuation as a function of the type of spacer device used.

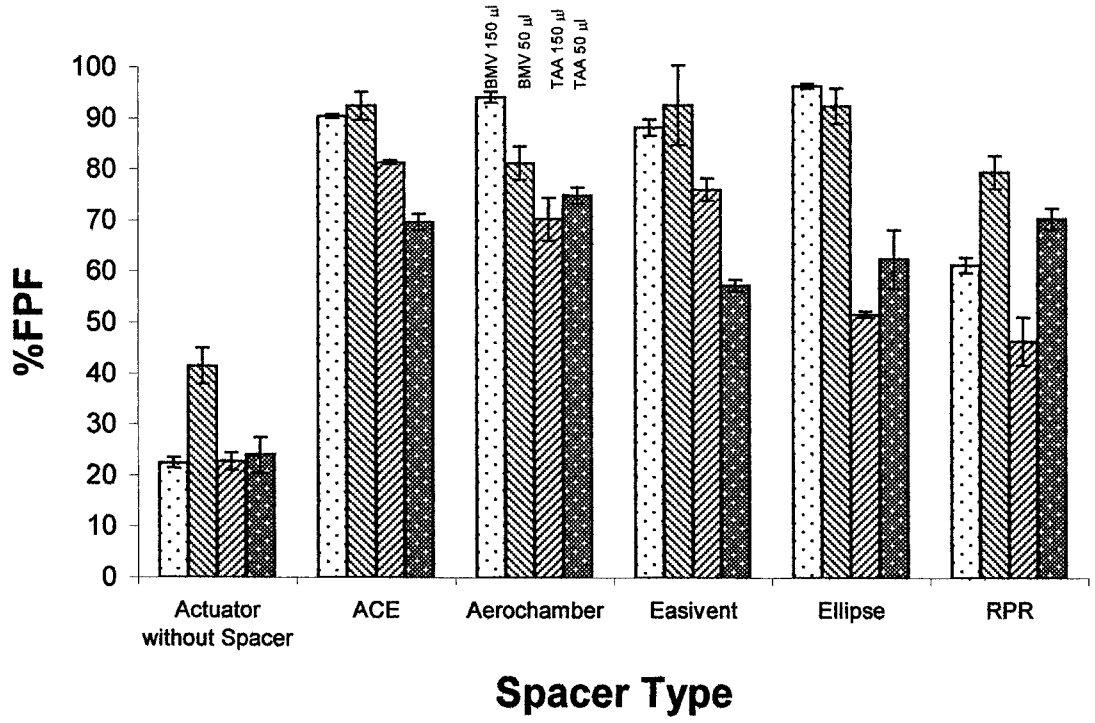

Figure 4. Influence of spacer type on fine particle fraction (FPF) versus FPF resulting from actuation without a spacer device.

using the BMV pMDI solution with a 50-µl metering chamber valve.

The results presented in Fig. 4 indicate that, when an actuator was used without a spacer device, higher FPFs resulted from use of the BMV solution atomized from the 50-µl metering chamber valve as compared to the 150-µl valve. This result occurs because of the fact that, in the induction port, the aerosol plume emitted from a 50-µl metering chamber valve has more volume capacity to undergo secondary disintegration into smaller droplets than the aerosol plume emitted from the 150-µl valve. Only the RPR spacer produced a significantly higher FPF when actuating from the 50-µl metering chamber valve as compared to actuating from the 150-µl valve for both the BMV pMDI solution and TAA pMDI suspension. The Aerochamber and the Ellipse, the other two cylindrical spacers, have greater volumetric capacities than the RPR spacer and do not have narrow areas to serve as surfaces for impaction following actuation. These two spacers allowed secondary disintegration of the large BMV solution aerosol plume emitted from the 150-µl metering chamber valve to occur, subsequently resulting in a significantly higher FPF compared to the BMV solution aerosol plume actuated from the 50-µl valve.

The TAA pMDI suspension produced a significantly lower FPF when using the Aerochamber and Ellipse spacers with the 150-µl metering chamber valves compared to the 50-µl metering chamber valves. The high-density TAA particles suspended within the aerosol droplets impacted onto the walls of the Aerochamber and Ellipse spacers before secondary disintegration could occur. When the 50-µl metering chamber valves were used with the TAA pMDI suspension, secondary disintegration occurred because fewer particles were present in the aerosol plume to occupy the same volume. Thus, the FPF would increase, and impaction onto spacer walls would decrease.

The ACE and Easivent spacers, the two cone-shaped spacers, produced different deposition patterns than the cylindrically shaped spacers. With these two cone-shaped spacers, BMV droplets emitted from the BMV pMDI solution produced a slightly lower FPF when emitted from the 150-µl metering chamber valve. This result was not statistically significant. TAA droplets emitted from the TAA pMDI suspension produced a significantly higher FPF when emitted from the 150-µl metering chamber valve than droplets emitted from the 50-µl metering chamber valve ($P < .05$). These spacers are longer than the cylindrical spacers and also increase in diameter as the aerosol plume travels away from the metering valve

following actuation. Due to the length of the conical spacers, the aerosol plume was allowed to decelerate and expand. This design minimized impaction of TAA particles onto the walls of the ACE and Easivent spacers. Secondary disintegration of large, dense droplets of TAA suspension into smaller, lighter droplets produced a higher FPF from the TAA pMDI suspension actuated using the 150-μl metering chamber valves.

The TAA pMDI suspension showed a significantly lower FPF compared to the BMV solution ($P < .05$) for all spacers investigated. When drug was emitted through the actuator from the pMDI, agglomerates were formed as the propellant and cosolvent evaporated. These agglomerates were smaller when formed from the BMV pMDI solution since BMV was dissolved in the formulation. As the propellant and ethanol evaporated from the droplets following actuation, the BMV would precipitate into a fine powder composed of agglomerated precipitates (22). In contrast to the BMV solution, the TAA existed as suspended drug particles dispersed in the ethanol/HFA 134a system. Following actuation, the atomized droplets containing solid TAA crystals formed agglomerates as the ethanol and HFA 134a evaporated. The result was solid TAA agglomerates with larger diameters than those agglomerates produced from the BMV pMDI solution (see discussion below regarding MMAD). These TAA agglomerates were too large and could not enter the lower stages of the cascade impactor.

The results shown in Fig. 5 indicate that as much as 60% of a dose emitted from a pMDI was deposited into the induction port. When a spacer device was added, deposition in the induction port was significantly reduced to less than 6% regardless of the type of spacer used ($P < .05$). Therefore, the devices could actually minimize side effects, thus increasing patient compliance and consequently decreasing frequency of asthma attacks. Accordingly, instances of thrush and hoarseness due to deposition of corticosteroid in the oropharyngeal region should be dramatically reduced after the addition of a spacer device to inhalation therapy in in vivo studies (15).

For drug to reach deep in the lungs to exert its effect, the particles must be small enough to avoid deposition in the oropharyngeal region. As mentioned, BMV was dissolved in the ethanol–HFA 134a propellant system, while TAA was suspended in the same liquid carrier system. Particles that are considered to be respirable must be less than 4.8 μm (23). Achieving this size was possible with the BMV pMDI solution because the drug formed precipitates of very fine particle size as the propellant system was evaporated. On the other hand, the TAA pMDI suspension produced aggregates of TAA with much larger diameters because of the fact that the droplets contained suspended drug rather than dissolved drug. As the cosolvent system evaporated from the droplets containing suspended TAA, the suspended particles formed relatively larger aggregates of particles than those

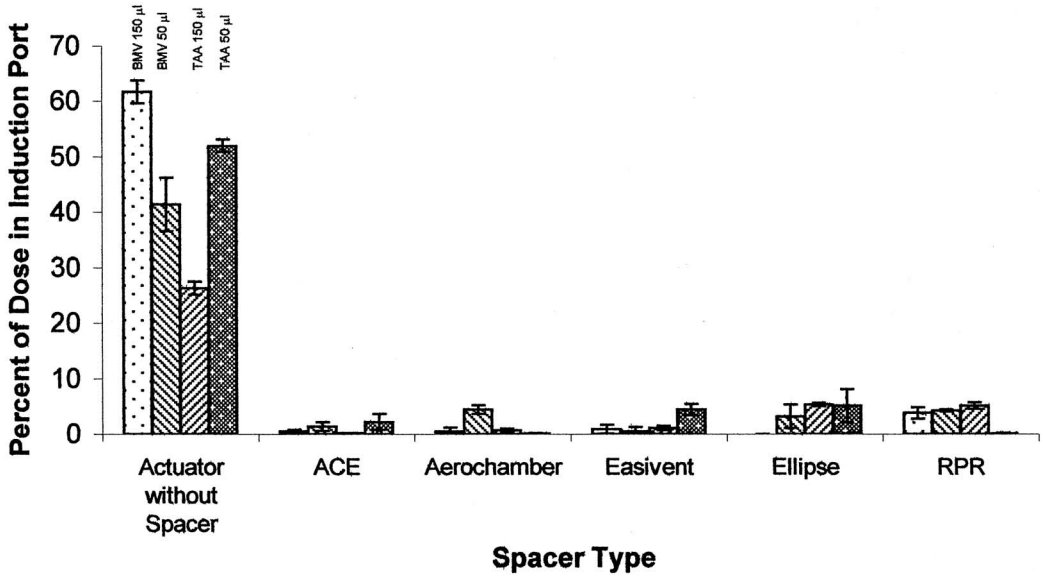

Figure 5. Influence of the spacer type on percentage of the dose deposited in the induction port (%IP) per actuation versus %IP resulting from actuation without a spacer device.

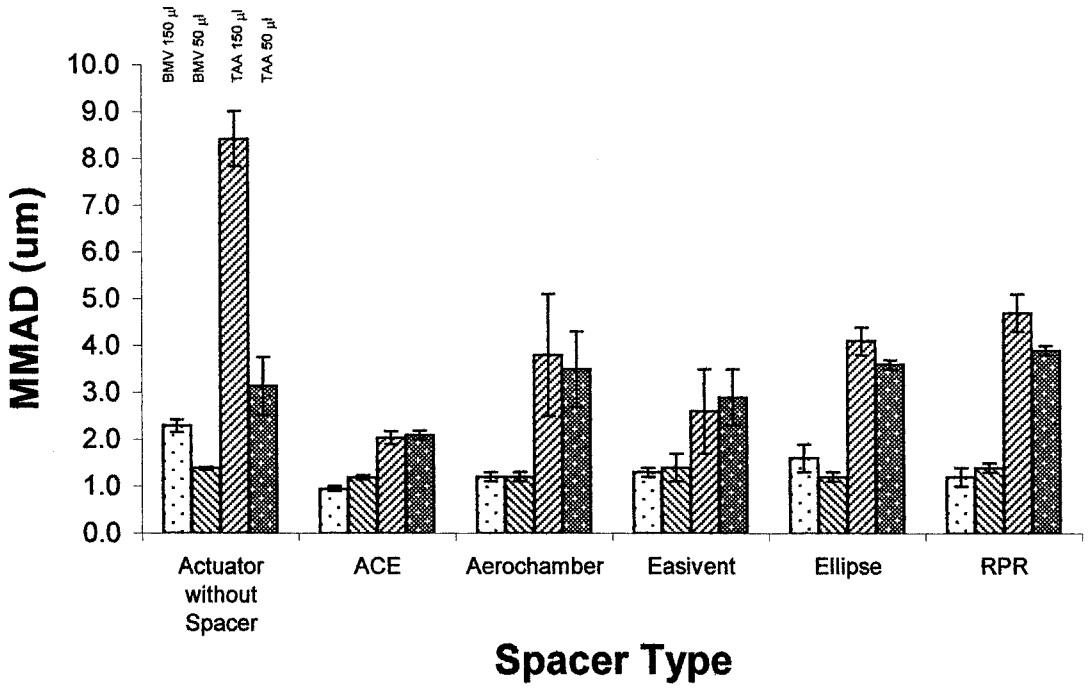

Figure 6. Influence of spacer type on mass median aerodynamic diameter (MMAD) versus MMAD resulting from actuation without a spacer device.

particles from the BMV solution. The results presented in Figs. 6 and 7 show the MMAD and GSD of the aerosol systems investigated. The magnitude of the GSD ranged from 2 to 2.5 regardless of the formulation or type of spacer used. From these data, the pMDI systems investigated in this study are polydisperse with broad aerodynamic particle size distributions (24).

The results from Fig. 6 indicate that, with the exception of the TAA 150-µl metering chamber valve/no spacer combination, the MMAD was less than 4.8 µm regardless of the spacer type, formulation, or metering chamber volume used. The TAA 150-µl metering chamber valve/no spacer combination produced a MMAD of 8.4 µm. For the BMV solution with a 150-µl metering

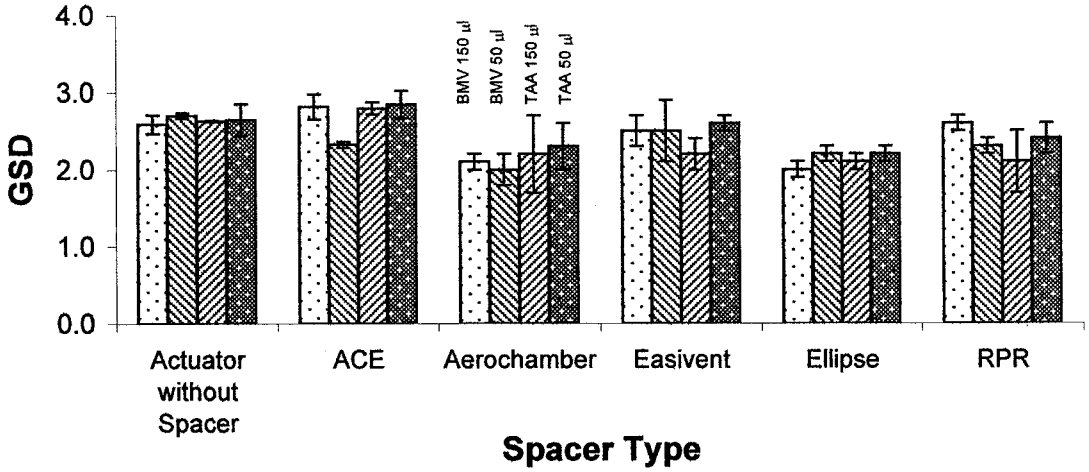

Figure 7. Comparison of geometric standard deviation (GSD) as a function of spacer type.

chamber, the spacer devices significantly reduced the MMAD from 2.3 μm using no spacer to 0.9 μm using the ACE spacer ($P < .05$). MMADs ranged from 1.6 μm using the Ellipse spacer to as low as 0.9 μm using the ACE spacer for the BMV pMDI solution with a 150-μl metering chamber valve. For the TAA pMDI suspension with a 150-μl metering chamber valve, addition of a spacer significantly reduced the MMAD from 8.4 μm with no spacer to less than 4.8 μm regardless of the type of spacer used ($P < .05$). Hence, for both BMV and TAA pMDIs, the addition of a spacer device allowed for evaporation of propellant and solvent, leaving fine particles, which were smaller in diameter than those emitted from the actuator alone. This result was statistically significant only when 150-μl valves were used for either formulation.

Metering chamber volume was a significant factor that influenced the magnitude of the MMAD for the TAA suspension, but not for the BMV solution. The results shown in Fig. 6 indicate that the 150-μl valve tended to produce a slightly higher MMAD when using no spacer, the Ellipse spacer, and the RPR spacer ($P < .05$) for the TAA pMDIs. This trend was not apparent when investigating the ACE, Aerochamber, or Easivent spacers. This could occur because more drug product is emitted per unit of air volume with the 150-μl valve than with the 50-μl valve. Since the same amount of air capacity is available for expansion and secondary disintegration of the aerosolized droplets regardless of which metering chamber was used, more secondary disintegration occurred when a 50-μl valve was used, producing particles with a lower MMAD. Droplets emitted from a 150-μl metering chamber valve would be more concentrated in the same air space volume compared to those droplets emitted from a 50-μl valve, thus increasing the likelihood of aerosol droplet coalescence and decreasing the likelihood of secondary disintegration into smaller droplets. Regarding the BMV pMDI solution, metering chamber volume was not a factor due to the complete dissolution of BMV within the cosolvent system. Regardless of the degree of secondary disintegration following actuation, particles having a very small MMAD resulted when the HFA 134a and ethanol cosolvent mixture evaporated from the droplets containing BMV, leaving a very fine drug precipitate.

CONCLUSION

Spacer volume capacity, shape, and dimensions played a significant role in aerosol drug delivery using a pMDI. Spacers with a large volume capacity, such as the Ellipse, provided more space for the aerosol plume to decelerate and undergo secondary disintegration of drops into smaller droplets. Spacers with wide cross-sectional diameters improved deposition characteristics of the drug particles as well. Regardless, the addition to a pMDI of any of the spacer devices investigated significantly enhanced the delivery of drug from an inhalation aerosol irrespective of the metering chamber volume or type of drug used. This investigation confirmed that the influence of a spacer device on pMDI therapy must be considered during development of the drug product.

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