Influence of Metering Chamber Volume and Water Level on the Emitted Dose of a Suspension-Based pMDI Containing Propellant 134a

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Purpose. To determine the influence of metering chamber volume of a valve and water content of an aerosol formulation containing propellant 134a on dose delivery through the valve (DDV) and aerodynamic particle size distribution of the emitted dose.

Methods. The drug was admixed with ethanol, sonicated, and metered into cans. Valois DF10 RC valves were crimped onto the cans and propellant 134a was gassed through the valve. The DDV was determined using a dosage sampling tube. Aerodynamic particle size distributions were determined by cascade impaction. The water content was determined by Karl Fisher titration.

Results. The DDV increased linearly and the aerodynamic particle size distribution was not influenced as the metering chamber volume of the valve was increased. More drug was emitted from the valve from the initial actuations of the can than from the end. Valves with larger metering chamber volumes demonstrated less variability in DDV than those with smaller metering chamber volumes for the initial actuations. The DDV determined for actuations at the end of the can decreased as water was added extemporaneously. The mass median aerodynamic diameter (MMAD) increased as the water level was increased in the formulation. The geometric standard deviation (GSD) and percent respirable fraction (RF) were not influenced by metering chamber volume or water content.

Conclusions. The valve chosen for the development of pressurized metered dose inhaler (pMDI) formulations with propellant HFA 134a must be investigated to determine the uniformity of drug delivery. The presence of water influences the characteristics of the emitted dose.

KEY WORDS: pMDI; propellant 134a; metering chamber; water content; suspension formulation.

INTRODUCTION

Pressurized metered-dose inhalers provide a convenient delivery system for drugs intended for pulmonary and nasal delivery. They have the benefits of low cost, reliability, and patient acceptability over other inhalation modes of delivery such as nebulizers, pump sprays, and dry powder inhalers (1,2). However, Farr *et al.* (3) points out that drug delivery by pMDIs is not efficient and provides only a small fraction of the emitted dose traveling beyond the oropharynx. *In vitro* optimization of the pMDI device and formulation are critical aspects during product development in order to reduce the variability of the delivered dose (4). The coefficient of variation or relative standard deviation is the established criterion to judge variability during product development, and is targeted to be $\leq$ 15% (4,5). Reproducible drug delivery *in vivo,* which depends upon complex interactions between device, formulation, and patient, will be improved by minimizing the variability arising from the device and formulation (4).

The majority of the currently marketed pMDI products contain one or more types of chlorofluorocarbons (CFC) propellants, primarily CFC 12, that have been reported to damage the ozone layer (6). Therefore, the products containing CFCs must be reformulated with nonozone depleting hydrofluorocarbon (HFA) propellants (7). HFA 134a (1,1,1,2-tetrafluoroethane) has recently become available as a suitable replacement for CFC 12. Although HFA 134a and CFC 12 have similar vapor pressures and boiling points, the density of HFA 134a is less than the density of CFC 12, and its solubilizing capability was found to be different from that of CFC 12 (8). Therefore, direct substitution of HFA 134a for CFC based propellants (e.g. CFC 12) may result in products that are unacceptable. The components that are currently used with CFC based pMDI products, including the valve and actuator, may give different results with HFA 134a. Compatibility between the formulation and the pMDI components, such as adherence of the drug to the valve components or canister lining and swelling of the elastomeric gaskets, has been shown to influence the characteristics of the emitted dose (1,9). Water uptake during storage at elevated humidity conditions is a significant factor in the performance of pMDIs. The presence of moisture enhances hydrolysis of susceptible drugs or may cause aggregation of drug particles suspended in the propellant, and this may be enhanced because HFA 134a is more polar than CFC 12 (10). Aggregation of the suspended particles will cause an increase in the aerodynamic particle size of the emitted dose resulting in a decrease in the amount of drug that will be available for pulmonary deposition. Other factors reported to influence pMDI formulations include valve equilibration time and initial water content of the raw materials (11–13).

Valve performance and the influence of water on product performance are critical parameters to investigate during the development of pMDI formulations. The objective of this study was to investigate the influence of the metering chamber volume of the valve on the dose delivery through the valve (DDV) and aerodynamic particle size distribution for a pMDI formulation containing a model drug suspended in HFA 134a. In addition, the influence of increasing levels of water spiked into the same pMDI formulation on the DDV and aerodynamic particle size distribution was investigated.

MATERIALS AND METHODS

Materials

HFA 134a (Dymel® 134a) was obtained from DuPont Chemicals (Wilmington, DE). Anhydrous ethanol (McCormick Distilling Co., Inc., Weston, MO) and methanol (EM Science, Gibbstown, NJ) were used as received. The model drug was micronized and used as received.

Type DF10 RC metered valves were obtained from Valois of America, Inc. (Greenwich, CT). A schematic diagram of the valve is shown in Figure 1. The volume of the metering chamber of the valves was 50, 75, or 100 μl. The actuators (Type KN1;

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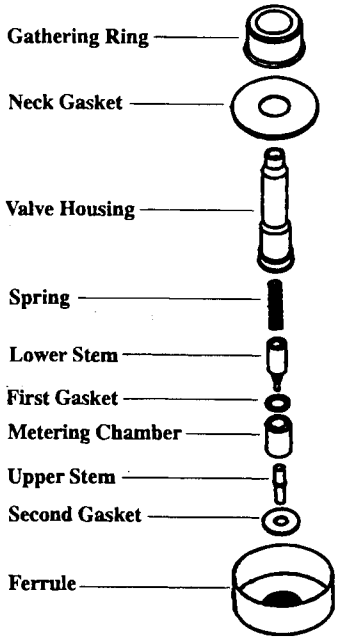

Fig. 1. Schematic representation of the Type DF10 RC Valois valve used in this investigation.

0.3 mm spray orifice) also were obtained from Valois of America, Inc., and did not have a spacer. The aerosol cans (donated by Cebal S.A., Bellegarde, France) measured 20 × 21 × 57 mm, and the interior surface was epoxy coated.

Formulation of Suspension pMDI

The model drug was admixed with anhydrous ethanol to prepare the drug slurry. The drug slurry was kept at about 0°C throughout the entire manufacturing process. The drug slurry was sonicated (Sonicator Cell Disrupter, Model W-220F, Heatsystems Ultrasonics, Inc., Farmingdale, NY) prior to filling into the cans in order to deaggregate the drug particles. The concentration of drug in the slurry was 23.1% w/w. An aliquot of 130 mg of drug slurry was transferred into each can. A valve was crimped onto each can and the unit was filled with the desired weight of HFA 134a through the valve using a propellant compressor pump (Pamasol Model P2005, Pamasol Willi Mader AG, Pfaffikon, Switzerland) and a small scale crimping and pressure filling machine (Pamasol Model P2008, Pamasol Willi Mader AG, Pfaffikon, Switzerland). The crimp height was maintained at 5.33 mm (Socoge Gauge, Socoge Int., Rueil-Malmaison, France). The final formulation was composed of 0.30% w/w model drug, 0.99% w/w anhydrous ethanol, and 98.72% w/w HFA 134a. The filled pMDI units were stored inverted for a minimum of three days to allow for valve equilibration prior to testing. For the spiked water experiments, purified water was added extemporaneously (6, 9, and 12 μl) to the cans containing the drug slurry using a 10 or 50 μl syringe (Hamilton Co., Reno, NV) prior to crimping and gassing. The spiked water experiments were conducted with the valve having the 75 μl metering chamber volume. The control samples had no water added extemporaneously.

Particle Size Distribution of Model Drug

The particle size distribution of the model drug was obtained by laser light diffraction (Shimadzu SALD 1100, Columbia, MD) and reported as a number distribution. An aliquot of the drug substance was dispersed in an aqueous solution containing 0.05% w/v Tween 80 in purified water, sonicated for 10 seconds, and stirred continuously during the measurement.

Dose Delivery Through the Valve Measurement

A dosage unit sampling tube (26.6 × 37.7 × 103.2 mm; 50 ml volume) was obtained from Jade Corporation (Huntingdon Valley, PA), and was similar in design to the collection tube designed by 3M Pharmaceuticals (St. Paul, MN). The collection tube consisted of an outer end cap, a firing adapter for valve actuation, a sampling tube for sample collection, and an inner end cap. The pMDI can was shaken prior to actuation. Two puffs were actuated through the firing adapter into the sampling tube. The firing adapter was removed and an aliquot of methanol was added to dissolve the drug. The sampling tube was sonicated for 20 minutes for complete solubilization of the drug. The drug was assayed by UV spectroscopy (Hewlett Packard Diode Array 8425A Spectrophotometer, Hewlett Packard, Germany) at 240 nm. The DDV was determined at the beginning and end of each pMDI can for the valve experiments, and at the beginning, middle, and end for the water experiments. The beginning, middle, and end of the can were defined by the volume of the metering chamber as follows: beginning and end actuations for the 50 μl metering chamber volume were shots 1 to 35 and 115 to 160, respectively; beginning, middle and end actuations for the 75 μl metering chamber volume were shots 1 to 35, 36 to 64, and 65 to 100, respectively; and beginning and end actuations for the 100 μl metering chamber volume were shots 1 to 35 and 40 to 80, respectively.

Aerodynamic Particle Size Distribution

The aerodynamic particle size distribution was obtained by cascade impaction (Andersen 1 ACFM Non-Viable 8-Stage Cascade Impactor (Mark II) with a USP Induction Port, Graseby-Andersen, Smyrna, GA). The airflow was maintained at 28.3 L/min during the sampling process. Glass fiber filter paper (Graseby-Andersen, Smyrna, GA) was used as the collection substrate. For each determination, the pMDI can was shaken, actuated three times to waste, and actuated 20 times into the cascade impactor using a mouthpiece adapter (Jade Corporation, Huntingdon Valley, PA) to join together the actuator and the USP induction port (14). The USP induction port was made of aluminum, and the flow path consisted of 1.9 cm cylinders intersecting at a 90 degree angle. The total flow path was approximately 20 cm. The can was shaken after each five actuations. Methanol was used to solubilize the drug from the glass filter substrate. Analysis of drug content was performed as described for the DDV measurement. Each measurement was conducted in triplicate. The MMAD, GSD, and percent RF were calculated according to the United States Pharmacopeia (14).

Water Content Determination

The amount of water contained in the dose emitted from the pMDI can was determined by Karl Fisher titration (Aquatest 8, Photovolt, Indianapolis, IN) as previously described (11). The titrator was blank titrated to less than 10 μg of water. Each

pMDI can was shaken for 20 seconds followed immediately by actuating three shots to waste. Then the unit was shaken for 10 seconds and actuated five times into the titrator. The unit was removed, shaken for five seconds, and actuated an additional five times into the titrator. Ten actuations were used for each water determination. The water content in the emitted dose was determined for the beginning of the can (actuations 9 to 18), middle of the can (actuations 55 to 64), and end of the can (actuations 86 to 95). Also, the water content of the model drug, anhydrous ethanol, and HFA 134a were determined separately.

Statistical Analysis

The data were compared using one-way ANOVA to evaluate each treatment effect. Results were judged to be significant based upon the 95% probability values ($p < 0.05$).

RESULTS AND DISCUSSION

Model Drug

The particle size distribution of the model drug was described by the cumulative percent undersize at 10% (M_{10}), 50% (M_{50}) and 90% (M_{90}) and was 0.75, 3.2, and 10 μm, respectively. The distribution was observed to be non log-normal when the frequency was plotted on a linear scale against the log of the particle size. The aerodynamic particle size distribution of the emitted dose may be similar to the particle size distribution of the bulk drug before addition to the formulation (15). Rees *et al.* (16) reported that drug particles should be 3 to 5 μm in diameter in order to be deposited in the smaller airways of the lung periphery as opposed to the large bronchi, and that particles with a diameter less than 2 μm may be pneumatically conveyed from the respiratory tract during the expiration following inhalation of the dose from a pMDI. The percent of particles in the 3 to 5 μm range for the model drug was about 12%. A review article by Stahlhofen *et al.* (17) discussed regional deposition data and concluded that for particle aerodynamic diameters ranging from 0.1 to 15 μm and different breathing patterns, tracheobronchial deposition increases with particle aerodynamic diameter while alveolar deposition approaches a maximum value near 3.5 μm. The particle size distribution of the model drug contained respirable particles that can penetrate the tracheobronchial tree and enter the pulmonary-alveolar region (18). Swift (18) stated that the particle size distribution of the drug being delivered from a pMDI must be defined and controlled. He explained that the generation of the aerosolized particles occurs explosively as the propellant containing the drug forms liquid droplets 50 to 75 μm in diameter which undergo a very rapid decrease in diameter with propellant evaporation to the final size of the suspended particle. The initial size distribution of the aerosolized droplets of propellant containing formulation is influenced by the components of the formulation, and the aerodynamic size distribution of the particles after evaporation of the propellant is influenced by the particle size distribution of the drug, concentration of drug in propellant, and the initial droplet size distribution (19).

Influence of Valve Metering Chamber Volume

The results of the DDV measurements obtained for the three metering chamber volumes investigated are shown in Table 1. The results indicated that the DDV was slightly higher for doses taken from the initial actuations (actuations 0 to 35) of the can than those from the end (actuations 65 to 100) of the can. The differences between the initial and end DDVs were not significant ($p > 0.05$). The variability of the DDV measurement determined for the initial actuations of the can was greater for the smallest (50 μl) metering chamber volume investigated and least for the largest (100 μl) metering chamber volume studied as indicated by the percent RSD of 5.34% and 0.37%, respectively. Similar results were found for the DDV measured at the end of the can. The primary function of a metering valve is to reproducibly deliver an accurate portion of the liquid phase of the can in which the drug is dispersed (10). The dose delivered through the valve should correspond to the metering chamber volume. The accuracy of the dosing is dependent on the selection of a suitable valve. Variable dose delivery may indicate nonuniformity of the formulation or incompatibilities of the valve components with the components of the formulation. The profiles shown in Figure 2 represent the DDV plotted as a function of the metering chamber volume. An excellent linear relationship ($r^2 = 1.000$) was found between the DDV and metering chamber volume for measurements obtained at the beginning and end of the cans. This suggested that the model drug was well dispersed in the HFA 134a propellant and that the valve components of the Valois DF10 RC valve did not adversely influence the DDV.

The aerodynamic particle size distribution for the three metering chamber volumes investigated was evaluated by cascade impaction. A material balance was done for each determination to check the validity of the run. The percent recovery,

Table 1. Summary of Dose Delivery Through the Valve (DDV) and Aerodynamic Particle Size Distribution Obtained by Cascade Impaction

Metering chamber volume	Beginning of can			End of can			Aerodynamic particle size distribution								
	DDV[a] (μg)	SD	RSD (%)	DDV[a] (μg)	SD	RSD (%)	MMAD[a] (μm)	SD	RSD (%)	GSD[a]	SD	RSD (%)	RF[a] (%)	SD	RSD (%)
50 μl	229.3	12.2	5.34	206.3	31.2	15.12	4.85	0.05	1.03	1 62	0.07	4.32	16	0.60	3.88
75 μl	305.9	9.3	3.06	292.3	8.9	3.05	4.77	0.15	3.14	1.60	0.08	5.00	14	1.78	12.69
100 μl	411.9	1.5	0.37	395.2	21.8	5.51	5.24	0.29	5.53	1.60	0.02	1.25	12	0.40	3.31

Note: MMAD is the mass median aerodynamic diameter, GSD is the geometric standard deviation and RF is the respirable fraction. (SD = standard deviation; RSD = relative standard deviation).
[a] Mean (n = 3).

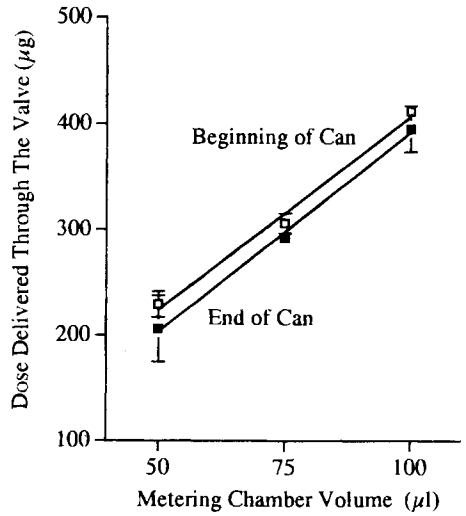

Fig. 2. Influence of metering chamber volume on the dose of model drug delivered from the valve determined at the beginning and end of the pMDI can.

defined as the total mass of drug collected from the valve stem to the final impactor stage divided by the total mass of drug theoretically delivered from the pMDI during the measurement (14), was excellent and ranged between 96 and 102%. The data revealed that about 70% of the total emitted dose of drug was deposited on the actuator and the induction port, and only about 30% entered the cascade impactor. This suggested that significant oropharyngeal deposition would occur with this formulation and actuator *in vivo*. Dalby and Byron (15) reported similar results for micronized disodium fluorescein dispersed in a CFC based propellant formulation.

The profiles shown in Figure 3 represent the cumulative percent by weight less than the stated size plotted as a function of the logarithm of the effective cut-off diameter. The results indicated that the aerodynamic particle size distributions were

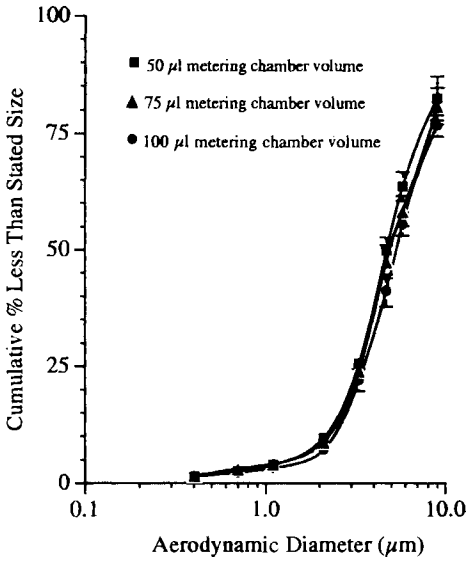

Fig. 3. Aerodynamic particle size distribution obtained by cascade impaction plotted for the 50, 75, and 100 μl metering chamber volumes.

similar for the three metering chamber volumes investigated. The aerodynamic particle size distributions were described by the MMAD, GSD, and percent RF as defined by the USP (14), and the results are shown in Table 1. The MMAD was 4.85, 4.77, and 5.24 μm for the 50, 75, and 100 μl metering chamber volumes, respectively. No statistical difference was found between the three metering chamber volumes investigated ($p > 0.05$). The GSD ranged between 1.60 and 1.62 for the three valves. GSD is an indication of polydispersity of the particle size distribution. It has been suggested that when the GSD is less than 1.22, the aerosol is considered monodisperse, otherwise the aerosol is polydisperse (20). The GSD calculated for the model drug prior to admixture with the formulation excipients was 4.38. This indicated that the particle size distribution was polydisperse. The GSD decreased after the drug was suspended in alcohol and HFA 134a indicating a shift to a less polydisperse distribution at the expense of the smaller particles in the distribution. RF is a useful parameter to compare data (19), and represents the particles small enough in diameter that can penetrate to the pulmonary-alveolar region (18,21). It was derived from the amount of drug delivered to the Andersen cascade impactor, and for this investigation represents the percent of drug delivered from the actuator having a particle size less than 5 μm in diameter. The RF was 16%, 14% and 12% for the 50, 75, and 100 μl metering chamber volumes, respectively. No significant differences were found between the values ($p > 0.05$).

Influence of Water

The water content of the components of the formulation was determined by Karl Fisher titration. The model drug had the highest moisture content (29,702 ppm) but was present in the lowest amount by weight in the formulation. It contributed about 88 ppm of water to the final pMDI formulation. The high content of water is consistent with the hygroscopic propensity of micronized powders. The higher variability may be attributed to uneven exposure of the powder to the environment during storage or unevenly distributed amorphous regions created during the micronization process that have a greater propensity to take up water (22). The water content of the anhydrous ethanol was 1.477 ppm. The water content of HFA 134a was 310 ppm, and contributed the largest amount of water to the formulation because it was present in the largest amount by weight. HFA 134a and anhydrous ethanol contributed about 306 and 15 ppm of water to the final pMDI formulation, respectively. The levels of water chosen for the experiments resulted in concentrations of water in the final product consistent with stability data modeled for various temperature and humidity conditions by Reynolds and McNamara (23).

The profiles shown in Figure 4 represent the water concentration measured in the emitted dose plotted as a function of the sequence of actuation from the can (beginning, middle, and end). The results indicated that no differences were found in the water concentration between beginning, middle, or end actuations for the control and the 6μl spiked sample. The concentration of water determined for the 9 and 12 μl spiked samples decreased slightly but significantly between the initial and middle actuations, and remained constant for the end actuation. The plots shown in Figure 5 illustrate the beginning, middle, and end DDVs measured on samples spiked with 6, 9, or 12 μl of water. The results indicated that the magnitudes of

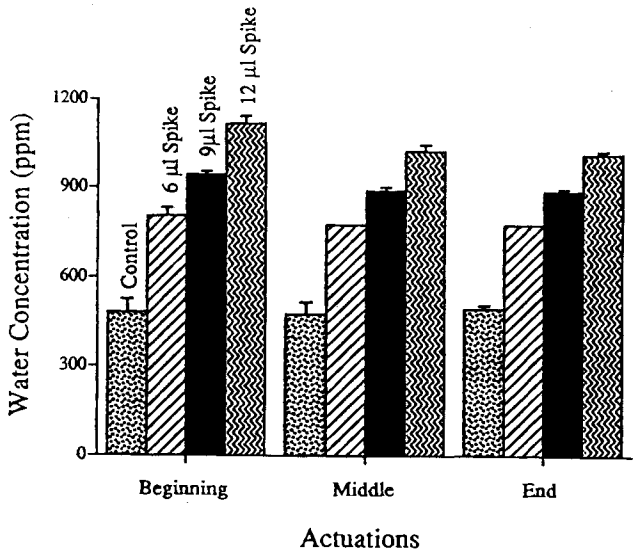

Fig. 4. Water content of the emitted dose for the control and spiked formulations determined at the beginning, middle, and end of the pMDI can.

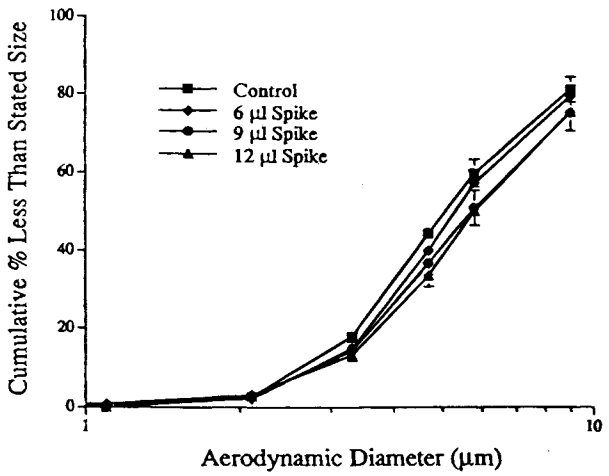

Fig. 6. Aerodynamic particle size distribution obtained by cascade impaction plotted for the control and the 6, 9, and 12 µl spiked water samples.

the DDV were similar for the beginning and middle actuations for the spiked samples, but decreased dramatically for actuations taken from the end of the can. The DDV of the control sample was high for actuations taken at the beginning of the can, then decreased and remained constant for the actuations taken at the middle and end of the can. Therefore the data indicated that the water present in the formulations was homogeneously dispersed in the formulation throughout the dosing sequence, whereas extemporaneously adding varying levels of water to the pMDI formulation decreased the amount of drug delivered from the valve for actuations measured at the end of the can.

The aerodynamic particle size distributions for the spiked water pMDI samples are shown graphically in Figure 6. The results indicated excellent recovery of the model drug that ranged between 96 and 102%. Figure 8 represents the MMAD, GSD, and percent RF plotted as a function of increasing water concentration in the pMDI formulation. The MMAD of the 6 µl spiked sample was not shown to be significantly different than the control, but the MMAD of the 9 and 12 µl spiked samples was significantly higher ($p < 0.05$). The magnitude of the GSD was not influenced by increasing the concentration of water in the formulation. The results shown in Figure 7 indicated that the change in percent RF was insignificant ($p > 0.05$) as the concentration of the water in the can was increased. The presence of increasing amounts of water in the pMDI formulation may cause aggregation of the drug particles resulting in a fewer number of particles in the respirable range (10), or delayed evaporation of the propellant resulting in larger aerosol droplets after actuation which are more readily deposited in the upper stages of the cascade impactor (12). Water is considered an impurity in pMDI systems, and the amounts will be variable depending on the level contained in the raw materials and ingress by diffusion through the metering valve during storage (24). The presence of minute amounts of water influence suspension stability by increasing interparticulate attraction and drug adhesion onto the walls of the can (25). The presence of water also influences the solubility of the suspended drug. The results found in this investigation may have been caused by

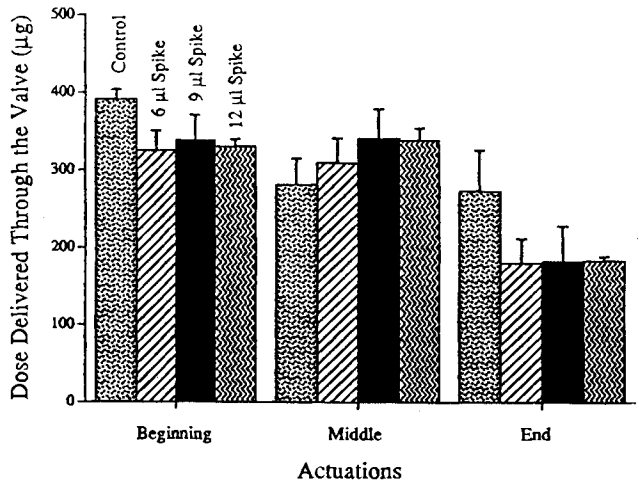

Fig. 5. Influence of water content in the pMDI formulation on the amount of drug delivered from the valve determined at the beginning, middle, and end of the canister.

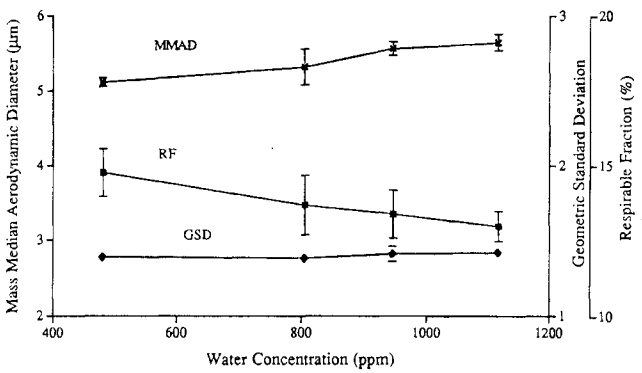

Fig. 7. Influence of water content on the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), and respirable fraction (RF) determined by cascade impaction.

water spiked into the formulations, but additional confirmatory experiments must be conducted. The presence of water in HFA 134a based pMDI products will have negative effects on the emitted dose as the level of water is increased. Therefore water should be controlled and minimized for pMDI formulations.

CONCLUSIONS

The results of this investigation showed that the DDV increased linearly as the metering chamber volume of the valve was increased. The DDV measurements determined for the initial actuations were slightly higher than the end DDV values. Valves with larger metering chamber volumes demonstrated slightly less variability in the DDV measurements for doses taken from the initial actuations of the can, whereas the 50 μl metering chamber valve displayed significantly greater variability in DDV than either the 75 or 100 μl metering chamber valves for doses taken from the end of the can. The aerodynamic particle size distributions were similar. The concentration of water determined for actuations taken from the beginning, middle, and end of the can remained constant, whereas the addition of varying amounts of water decreased the amount of drug delivered from the valve for actuations taken from the end of the can. The aerodynamic particle size distribution increased as the level of water in the formulation was increased.

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