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RESEARCH PAPER

Influence of Propellant Composition on Drug Delivery from a Pressurized Metered-Dose Inhaler

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ABSTRACT

Hydrofluoroalkanes (HFAs) are used to replace chlorofluorocarbons (CFCs) as non-ozone-depleting propellants for pressurized metered-dose inhalers (pMDIs). HFA 134a and HFA 227 are used in combination to precisely manipulate the density and vapor pressure of pMDI formulations. The influence of propellant composition on the dose delivery characteristics of a suspension-based pMDI formulation was investigated. The results showed that as the density of the propellant blends approached the density of the suspended drug particles, the formulation became more physically stable and exhibited the most consistent dose delivery and greatest respirable fraction. The mass median aerodynamic diameter of the aerosolized particles contained in the emitted dose also was decreased by using propellant blends with higher vapor pressures. The performance of a suspension-based pMDI formulation was optimized by varying the propellant composition using HFA 134a and HFA 227.

INTRODUCTION

Pressurized metered-dose inhalers (pMDIs) have been employed extensively for treating bronchial and pulmonary diseases. A pMDI formulation contains an active ingredient and one or more propellants. Also, it may contain formulation adjuvants, such as surfactants and cosolvents. The propellant system is liquefied under pressure and kept in a pressure-resistant aerosol canister. The choice of composition of the propellant system is important because it serves as a dissolution or dispersion medium for the drug and excipients, and provides an energy source for the formation of the aerosol cloud as the dose is emitted from the metering device (1). In a suspension-based pMDI formulation, the density and viscosity of the propellant influence the physical stability of the

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*To whom correspondence should be addressed. Fax: (512) 471-7474. e-mail: williro@mail.utexas.edu suspension. The density of the continuous phase of a pMDI formulation can be varied by utilizing different compositions of the individual propellants in order to match the density of the suspended drug so that the physical stability of the pMDI suspension is maximized (2).

As a pMDI is actuated, an aliquot of the formulation flows through the metering valve and into the atmosphere as a solid and liquid mixture. The volatile propellant evaporates immediately as the formulation enters normal atmospheric conditions and undergoes a rapid volume expansion. A propelling force is evolved to drive the residual droplets out of the device. The resulting high-speed flow also generates a shear force which helps to further reduce the droplet size of the emitted dose. Therefore, the vapor pressure and the rate of evaporation of the propellant are critical to the dose delivery of pMDI formulations (3). The vapor pressure is usually manipulated by varying the molar ratio between propellants with high and low vapor pressures in pMDI formulations. It is also influenced by the other ingredients in the formulation, such as the drug, cosolvents, and surfactants.

The propellants used in the currently marketed pMDI products primarily consist of chlorofluorocarbons (CFCs), such as CFC 12, CFC 114, and CFC 11. However, CFC propellants have been reported to cause ozone depletion in the atmosphere (4). The discontinued production and restricted use of CFC propellants has caused the pharmaceutical industry to reformulate pMDIs with non-ozone-depleting propellants (5). Hydrofluorocarbons (HFAs) are currently the primary candidates for the replacement of CFC propellants in pMDI formulations (5). The differences between HFA and CFC in vapor pressure, boiling point, and density have posed many challenges for the reformulation efforts.

The objectives of this study were to investigate the influence of propellant composition using HFA 134a and HFA 227 on the vapor pressure of pMDI formulations as a function of temperature, and to investigate the influence of the propellant composition on the dose delivery characteristics of a prototype suspension-based pMDI formulation.

MATERIALS AND METHODS

Materials

Micronized triamcinolone acetonide (TAA, Upjohn Fine Chemicals, Kalamazoo, MI) was used as received. Anhydrous alcohol was purchased from McCormick Distilling Co., Inc. (Weston, MI). Methanol was purchased from EM Science (Gibbstown, NJ). All chemicals were used as received. The propellants, 1,1,1,2-tetrafluoroethane (HFA 134a; Dymel® 134a, DuPont Chemicals, Wilmington, DE) and 1,1,1,2,3,3,3-heptafluoropropane (HFA 227; Hoechst, Frankfurt, Germany) were used as received. The aluminum aerosol cans were kindly supplied by Cebal SA (Bellegarde, France). Metering valves (type DF 10/75 RC) and continuous spray valves (Afiane M continuous valve) were purchased from Valois of America, Inc. (Greenwich, CT).

Measurement of the True Density of the Micronized TAA

The true density of TAA was determined using a helium pycnometer (Micromeritics® AccuPyc 1330, Norcross, GA). The measurement was conducted in triplicate.

Preparation of the pMDI Product

A suspension was prepared by admixing TAA and anhydrous alcohol to obtain a TAA concentration of 2.99% w/w. The suspension was sonicated (Sonicator Cell Disrupter, model W-220F, Heat Systems Ultrasonics, Inc., Farmingdale, NY) in an ice bath for 5 min, and maintained at 0°C until used. A 130-mg aliquot of the TAA/alcohol suspension was dispensed into each aerosol aluminum can. A valve was immediately crimped onto each can and the canister was filled with the desired weight of HFA 134a and HFA 227 through the valve using a propellant compressor pump (Pamasol model P2005, Pamasol Willi Mäder AG, Pfäffikon, Switzerland) and a small-scale crimping and pressure filling machine (Pamasol model P2008). The total weight of the propellant system was 10 g for each aerosol formulation investigated. The weight ratios of HFA 134a:HFA 227 investigated were 100:0, 75:25, 50:50, 25:75, and 0:100, and the corresponding molar ratios of HFA 134a:HFA 227 were 1:0, 0.84:0.16, 0.63:0.37, 0.37:0.63, and 0:1. The crimp height was determined with a Socoge gauge (Socoge Int., Rueil-Malmaison, France). Metering valves were used for the dose delivery through-the-valve (DDV) and cascade impaction experiments.

The aerosol canisters were stored inverted at 24°C/60% relative humidity (RH) for a minimum of 3 days to allow for valve equilibration prior to testing. The DDV and the aerodynamic particle size distribution were determined for each formulation initially and after storage for 3 months at 24°C/60% RH.

Aerosol canisters were also prepared with continuous spray valves for vapor pressure determination. HFA 134a and HFA 227 were blended at the same ratios as those used for the TAA pMDI formulations. For these formulations, air was depleted from each empty aerosol can prior to crimping by dispensing an aliquot of the propellant mixture containing the corresponding propellant composition into the can such that it displaced the air from the can.

Vapor Pressure Determination

The vapor pressure was measured using a pressure test gauge (Pamasol Willi Mäder AG) at temperatures of 6, 16, 24, and 45°C. The aerosol canisters were equilibrated at the test temperatures for 3 hr before the vapor pressure was determined. Each determination was conducted in replicates of five.

DDV

DDV was determined using a dosage unit sampling tube (26.6 × 37.7 × 103.2 mm; 50 ml volume) purchased from Jade Corp. (Huntingdon Valley, PA) as previously reported (6). The aerosol canister was shaken prior to actuation. The canister was primed to waste. 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 TAA. The sampling tube was sonicated for 20 min for complete solubilization of the drug. The drug was assayed by UV spectroscopy (model 8425A diode array spectrophotometer, Hewlett Packard, Germany) at 240 nm. The DDV was determined for the beginning (actuations 1–35) and end (actuations 65–100) of the aerosol canister that had been stored for 3 days following preparation, and was determined for the beginning of the aerosol canister that had been stored for 3 months at 24°C/60% RH.

Aerodynamic Particle Size Distribution

Cascade impaction was used to determine the aerodynamic particle size distribution of the emitted dose (Andersen 1 ACFM Non-Viable 8-Stage Cascade Impactor [Mark II] with a USP Induction Port, Graseby-Andersen, Smyrna, GA) as previously reported (6). The airflow was maintained at 28.3 l/min during the sampling process. Glass fiber filter paper (Graseby-Andersen) was used as the collection substrate. For each determination, the aerosol canister was shaken for 5 sec, actuated three times to waste, and actuated 20 times into the cascade impactor using a mouthpiece adapter (Jade Corp.) to connect the actuator to the USP induction port (7). The USP induction port was constructed of aluminum, and the flow path consisted of two cylinders measuring 1.9 cm in diameter and intersecting at a 90° angle. The total flow path was approximately 20 cm. The aerosol canister was shaken for 5 sec after each actuation. TAA was solubilized from the glass filter substrate by methanol. Analysis of TAA content was performed as described previously for the DDV measurement. Each measurement was conducted in triplicate.

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

Vapor Pressure of the Propellant Blends

The results presented in Fig. 1 represent the vapor pressure of the propellant blends as a function of the propellant composition at 6, 16, 24, and 45°C. The gas phase that existed in the aerosol canister was composed

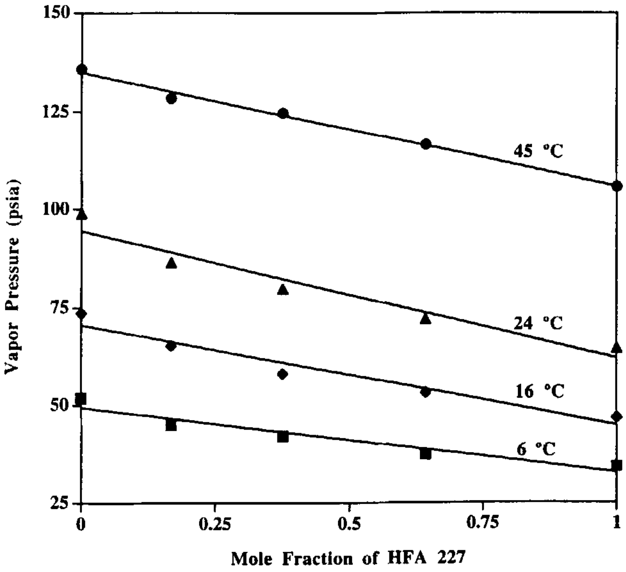

Figure 1. The influence of propellant composition on the total vapor pressure of the propellant blends equilibrated at 6, 16, 24, and 45°C.

of HFA 134a and HFA 227 vapor because air was depleted from the empty can prior to assembly of the aerosol canister. Therefore, the headspace pressure measured by the pressure test gauge approximated the vapor pressure of the formulation contained in the aerosol canister. As shown in Fig. 1, the vapor pressure of the propellant blends varied from 99 to 64 absolute pounds per square inch (psia) at 24°C, with a higher molar ratio of HFA 227 resulting in a lower vapor pressure. This is because HFA 227 has a lower vapor pressure than HFA 134a at any given temperature. The vapor pressure increased significantly as the temperature was increased to 45°C. Also shown in Fig. 1, a linear relationship was found between the vapor pressure and the mole fraction of HFA 227. According to Raoult's law (6), the mixture of HFA 134a and HFA 227 behaved as ideal solutions at the temperatures investigated.

Density of the Propellant Blends

The density of the propellant blends at 20°C was calculated using the following equation, assuming the blends were ideal mixtures:

$$D_{\mathrm{mix}} = v_{\mathrm{HFA134a}} D_{\mathrm{HFA134a}} + v_{\mathrm{HFA227}} D_{\mathrm{HFA227}} \tag{1}$$

where D_{mix} is the density of the mixture, v_{HFA134a} and v_{HFA227} are the volume fractions of HFA 134a and HFA 227, respectively, and were calculated from the mole fraction of each propellant. $D_{\mathrm{HFA\ 134a}}$ and $D_{\mathrm{HFA\ 227}}$ are the densities of the propellants, and they are 1.21 and 1.42 g/ml at 20°C (5), respectively. The calculated densities are shown in Table 1.

DDV

The results presented in Fig. 2 show the influence of the propellant composition on the DDV at the initial time point for the beginning and end actuations of the canister. The amount of drug emitted from the valve decreased as the molar ratio of HFA 134a to HFA 227 was decreased. The beginning DDV was slightly greater in magnitude than the end DDV, but the difference was not statistically significant ($p > 0.05$). The results obtained were similar to a previously reported study, in which the beginning DDV of a pMDI formulation containing TAA, ethanol, and HFA 134a was also slightly greater than the end DDV, but the difference was statistically insignificant (7). These results indicated that the dose of TAA emitted from the valve for the formulations was consistent through the life of the can.

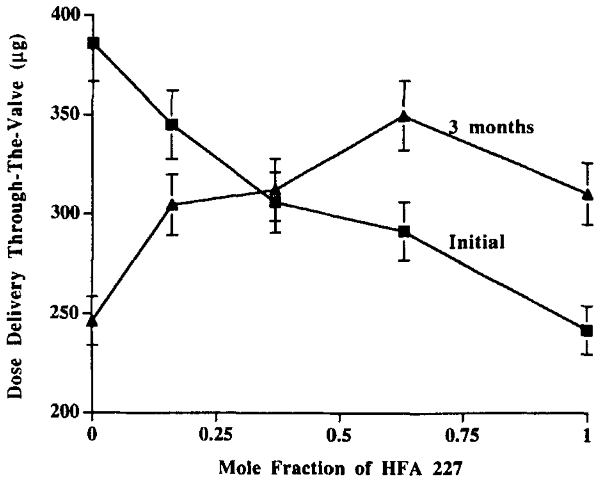

Figure 2. The influence of propellant composition on the DDV of the TAA-based pMDI formulation determined initially for the beginning and end actuations of the canister.

The density of TAA determined by helium pycnometry was 1.32 g/cm^3 (0.03% relative standard deviation [RSD]). The density of the dispersion media in the pMDI formulations (Table 1) was 1.21 when HFA 134a was the only propellant, increased to 1.31 when the propellant blend contained HFA 134a and HFA 227 at a molar ratio of 0.63:0.37, and further increased to 1.42

Table 1

Calculated Densities of the Propellant Blends of HFA 134a and HFA 227 According to Eq. (1)

Mole Fraction of HFA 134a	Volume Fraction of HFA 134a	Mole Fraction of HFA 227	Volume Fraction of HFA 134a	Density (g/ml)
1	1	0	1	1.21
0.84	0.78	0.16	0.22	1.26
0.63	0.54	0.37	0.46	1.31
0.37	0.28	0.63	0.72	1.36
0	0	1	1	1.42

when HFA 227 was the only component in the propellant system. Therefore, the density of the dispersion media was less than the drug particles initially when the mole fraction of HFA 227 was low, approached the density of the drug particles as the mole fraction of HFA 227 reached 0.37, and was greater than the drug particles when the mole fraction of HFA 227 was further increased. The DDV decreased from 386 µg initially when the mole fraction of HFA 227 was 0 to 242 µg when the mole fraction of HFA 227 was 1. A low drug content emitted from the valve occurred with propellant blends that were more dense than the drug particles. Creaming occurs in the formulation when the density of the dispersion medium is greater than the density of the suspended drug particles. Low drug output in the emitted dose has been reported for pMDI formulations in which creaming occurred (8). This was attributed to the pMDI being stored in the inverted position with the valve stem down, enabling the egress of drug particles out of the metering chamber by creaming, and leaving a propellant-rich suspension in the metering chamber (8).

The variability in the DDV measurements for the beginning actuations, as indicated by the RSD, was the least (3.62%) for the formulation containing HFA 134a and HFA 227 at a molar ratio of 0.63:0.37, and greatest (11.53%) for the formulation containing pure HFA 227 as the propellant. These results indicated that the formulation containing HFA 134a and HFA 227 at a molar ratio of 0.63:0.37 most closely matched the density of TAA, and had the least variable dose delivery. On the other hand, the formulation containing pure HFA 227 resulted in the most variable dose delivery because of the large difference between the densities of the HFA 227 and TAA. Therefore, the DDV variability was influenced by the density of the dispersion media. Ideally, when the density of the dispersion media matches the density of the suspended drug, a uniformly distributed dispersion is obtained. Large differences in the densities are likely to cause nonhomogeneous drug distribution in the formulation, and lead to inconsistent drug dosing (1).

The DDV determined for the formulations following 3 months storage at 24°C/60% RH is shown in Fig. 3. The DDV was similar prior to and after storage for the formulation containing HFA 227 at a mole fraction of 0.37, which provided a propellant blend that matched the density of TAA drug particles. When the mole fraction of HFA 227 was lower than 0.37 and the propellant blends were less dense than the drug particles, the DDV decreased after storage; and when the mole fraction of HFA 227 was greater than 0.37 and the propellant blends were more dense than the drug particles, the DDV increased after storage. In either case, the differences in DDV prior to and after storage increased as the differences between the density of the propellant blends and the drug particles were increased. Therefore, the dose delivery of the formulation containing HFA 227 at a mole fraction of 0.37 remained consistent after storage for 3 months at 24°C/60% RH, and the formulations containing pure HFA 134a or HFA 227 as the propellant resulted in the least consistent drug output after storage for the micronized TAA as demonstrated by the DDV measurements.

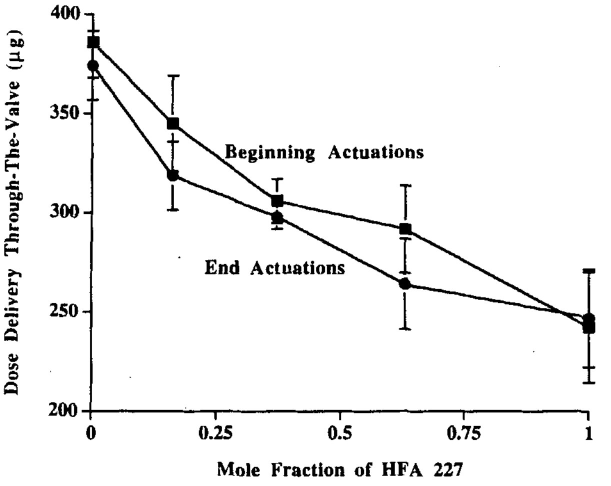

Figure 3. The influence of propellant composition on the DDV of the TAA-based pMDI formulation determined at the beginning of the canister prior to and after 3 months storage at 24°C/60% RH.

Aerodynamic Particle Size Distribution

The aerodynamic particle size distribution was determined by cascade impaction. It is described by the mass median aerodynamic particle size diameter (MMAD) of an aerosol cloud emitted from the actuator, geometric standard deviation (GSD), and percent respirable fraction (RF) as defined by USP 23 (9). The MMAD determined for the formulations prior to and after storage for 3 months at 24°C/60% RH is shown in Fig. 4. A similar trend was observed for the two conditions investigated. The MMAD remained unchanged as the mole fraction of HFA 227 was increased from 0 to 0.16 ($p > 0.05$), decreased slightly but significantly as the mole fraction of HFA 227 was increased to 0.37 ($p < 0.05$), and then increased significantly as the mole fraction of HFA 227 was increased further ($p < 0.05$). The results of MMAD analysis suggest that the aerodynamic particle sizes of

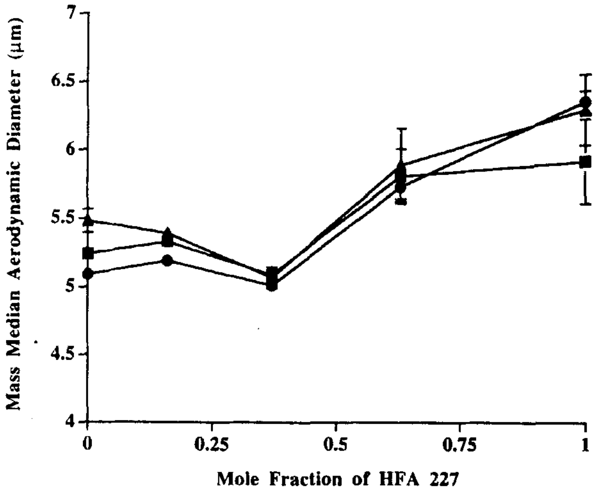

Figure 4. MMAD of the TAA-based pMDI formulation containing HFA 134a and HFA 227 at different compositions determined initially for the beginning (■) and end (●) actuations of the canister, and after 3 months storage at 24°C/60% RH (▲) for the beginning actuations of the canister.

the aerosols were lowest for formulation containing HFA 227 at a mole fraction of 0, 0.16, and 0.37. The lowest magnitude of the MMAD occurred for the formulation containing HFA 134a and HFA 227 at a molar ratio of 0.63:0.37. As the mole fraction of HFA 227 increased from 0.37 to 1, the aerodynamic particle size distributions of the aerosol formulations were increased significantly. This trend was directly related to the changes in vapor pressure as the propellant composition was changed. As shown in Fig. 1, the vapor pressure of the propellant blends decreased as the mole fraction of HFA 227 was increased. Harnor et al. found that as the vapor pressure of the propellants was increased, the propellant evaporated more rapidly, and therefore, the aerosol droplet traveling velocity was increased (10). This generates an increase in the shear force and reduces the droplet size (11). Consequently, the aerodynamic particle size distribution of the emitted aerosol was decreased by the incorporation of a more volatile propellant into the formulation, which increased the vapor pressure. This is in agreement with the results reported by Porush et al., in which the MMAD of isoprenaline particles was decreased from 3.7–4.0 µm to 1.9–2.5 µm when the headspace pressure of the pMDI was increased from 59.7 to 94.5 psia (12).

The aerodynamic particle size distribution of the formulation was monitored throughout the life of the canister (e.g., beginning and end actuations of the canister), and the results are shown in Fig. 4. The MMAD was consistent for each formulation through the life of the canister except for the formulation containing pure HFA 227 as the propellant, which showed a slight increase in MMAD for actuations at the end of the canister. These results indicated that the average aerodynamic particle size of the emitted aerosol cloud was similar throughout the life of the canister. It was found that the MMAD increased after the aerosol canisters were stored for 3 months at 24°C/60% RH for formulations containing pure HFA 134a or HFA 227 as the propellant, and remained unchanged for the other formulations investigated. The results suggested that the formulations containing pure HFA 134a or HFA 227 showed a more significant change in the dose delivery characteristics, substantiating the results of the DDV determination prior to and after storage for 3 months at 24°C/60% RH.

The GSD obtained for each of the formulations investigated is shown in Fig. 5. GSD indicates the degree of polydispersity of an aerodynamic particle size distribution. It was suggested that when the GSD is greater than 1.22, the aerodynamic particle size distribution is polydisperse; otherwise, it is monodisperse (13). It was found that the propellant composition did not significantly influence the GSD of the aerosol formulations investigated. All GSD values obtained were greater than 1.22, indicating polydisperse aerodynamic particle size distributions for the formulations investigated. The GSD determined initially for the beginning actuations of the canister was less than the GSD for the end actuations of

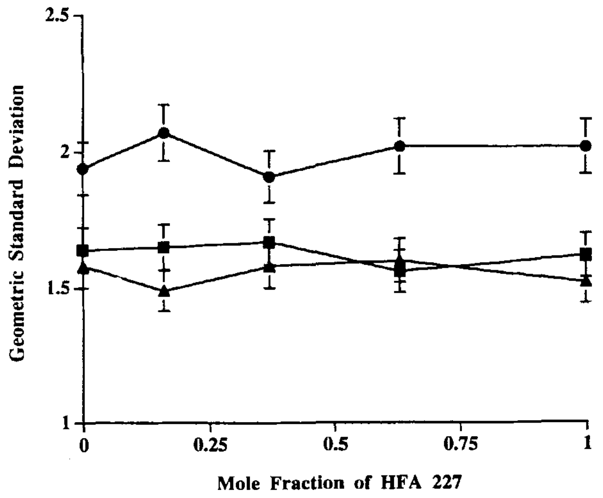

Figure 5. GSD determined as a function of propellant composition for the TAA-based pMDI formulation for the beginning (■) and end (●) actuations of the canister prior to and after 3 months storage at 24°C/60% RH (▲) for the beginning actuations of the canister.

the canister. This suggested that the aerosol particle size distribution became more polydisperse as more actuations were delivered from the pMDI canister. The GSD values remained unchanged after the aerosol formulations were stored for 3 months except for the formulation containing P134 to HFA 227 at a molar ratio of 0.84:0.16, in which case the GSD decreased slightly. Therefore, although the MMAD increased after storage for 3 months at 24°C/60% RH, the polydispersity of the aerosol formulation was not influenced significantly.

The percent RF calculated from each aerodynamic particle size distribution is shown in Fig. 6. The percent RF represents the fraction of particles small enough to penetrate to the lower airways (14). It is based on the aerodynamic particle size distribution data obtained with the Andersen 8-stage cascade impactor, and, in this study, was defined as the percent by mass of drug having a particle size less than 4.7 μm. The percent RF values determined initially increased slightly when the mole fraction of HFA 227 was increased from 0 to 0.37, and decreased significantly when the mole fraction of HFA 227 was increased to 1. This occurred because the decrease in vapor pressure associated with the increasing mole fraction of HFA 227 resulted in a lower propellant evaporation rate and larger aerosol particles (10,11). The formulation containing HFA 134a and HFA 227 at a molar ratio of 0.63:0.37 had the largest magnitude of percent RF, which was consistent with the smallest magnitude of MMAD for this formulation. The percent RF decreased significantly for the formulations in which the mole fraction of HFA 227 was 0 and 0.16 following storage for 3 months at 24°C/60% RH. It decreased slightly for the formulation in which the mole fraction of HFA 227 was 0.37, and was not changed significantly for the other two formulations, in which the mole fraction of HFA 227 was 0.63 and 1.

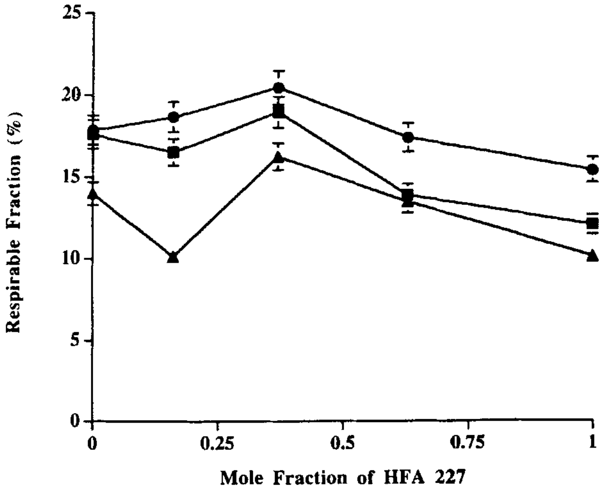

Figure 6. The influence of propellant composition on the percent RF of the TAA pMDI formulation determined initially for the beginning (■) and end (●) acutations of the canister, and after 3 months storage at 24°C/60% RH (▲) for the beginning actuations of the canister.

In conclusion, this study demonstrated that the propellant composition had a significant effect on the dose delivery characteristics of a pMDI formulation. Both the density and vapor pressure were manipulated by selecting the appropriate composition for a propellant system. In order to obtain a physically stable suspension-based aerosol formulation with optimum drug delivery characteristics, the density of the propellant system should match the density of the suspended drug particles, and the vapor pressure of the propellant system should be adequate to shear the particles in the aerosol clouds as the dose is actuated from the device. The propellant blend containing HFA 134a and HFA 227 at a molar ratio of 0.63:0.37 provided the optimum propellant system for delivering micronized TAA as a suspension-based pMDI. Compared to the other propellant blends containing HFA 134a and HFA 227, the aerosol formulation that employed the ratio of 0.63:0.37 had the least variable drug output, the lowest MMAD, and the highest RF. It was also shown that the dose delivery characteristics of this formulation remained constant after the formulation was stored for 3 months at 24°C/60% RH.

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