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RESEARCH PAPER

Influence of Temperature on the Emitted Dose of an Oral Metered Dose Inhaler

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ABSTRACT

The performance of metered dose inhalers is critical for the efficient delivery of drugs to the intended site of deposition in the respiratory tract. The temperature at which metered dose inhaler products are used by patients may influence the physicochemical characteristics of the emitted dose. Product performance characteristics of a metered dose inhaler containing beclomethasone dipropionate and oleic acid in a blend of chlorofluorocarbon propellants, Freon-11 and Freon-12, were determined by cascade impaction analysis and dose delivery through the valve after the metering chamber was loaded and actuated at 4°C, 23°C, and 40°C. The dose delivered from the valve was not affected by the temperature at which the metering chamber was loaded and actuated. The mass median aerodynamic particle size of the emitted aerosol decreased and the percentage respirable fraction increased as the temperature was increased. The geometric standard deviation of the particle size distribution was not significantly affected by the temperature at which the metering chamber was loaded and actuated. The temperature at which a metered dose inhaler is used by a patient may influence the amount of drug that is potentially respirable; therefore, the dose expected to be delivered and the corresponding therapeutic effect may also be affected.

The efficiency of drug delivery to the respiratory tract from pressurized metered dose inhalers is determined by the physicochemical characteristics of the formulation (1), design of the actuator and spacer adapter (2,3), physiology of the respiratory tract, and the proficiency and technique of the patient using the inhaler device (4,5). For suspension-based metered dose inhaler formulations, the particle size of the suspended drug and the vapor pressure affect the aerodynamic particle size distribution and lung deposition of the emitted dose of aerosols (6,7). The

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performance of a metered dose inhaler system may be influenced by the temperature of the inhaler device since temperature influences vapor pressure and density of the formulation (8). Recently, June et al. (9) evaluated the effect of temperature within the range −20°C to 20°C on the performance of a marketed metered dose inhaler containing beclomethasone dipropionate. They found that, as the temperature was decreased, the total amount of drug delivered from the mouthpiece and the respirable fraction decreased. The changes in product performance were attributed to changes in the vapor pressure and density of the metered dose inhaler formulation (9). The objective of this study was to evaluate the performance of a metered dose inhaler product at temperatures that simulate various conditions used by patients. Product performance characteristics, such as the drug content in the dose emitted from the valve and the aerodynamic particle size distribution of the dose emitted from the actuator, were determined after equilibration of the pressurized metered dose inhaler device at either 4°C, 23°C, or 40°C.

EXPERIMENTAL

Materials

The model pressurized metered dose inhaler product was a suspension formulation containing beclomethasone dipropionate in a mixture of chlorofluorocarbon propellants (Freon-11 and Freon-12) and oleic acid (Vanceril, Schering Corporation, Kenilworth, USA).

Methods

Temperature Equilibration and Metering Chamber Loading

Three cans of the model pressurized metered dose inhaler were equilibrated for 1 hr at 4°C, 23°C, or 40°C in a calibrated environmental stability chamber. The aerosol cans were designated such that cans labeled 1, 2, and 3 were evaluated at 23°C; cans labeled 3, 4, and 5 were evaluated at 4°C; and cans labeled 7, 8, and 9 were evaluated at 40°C. After equilibration, each can was removed from the environmental stability chamber, shaken, and actuated three times into a waste collection vessel. After the third actuation, the metering chamber of the can was loaded with the sample for testing. Each test was conducted in triplicate. Cans were equilibrated at the temperature being investigated between each of three test actuations to maintain the correct temperature of the metering chamber.

Dose Delivery Through the Valve

Dose delivery through the valve was used to evaluate the total amount of drug emitted from the valve per actuation. A single actuation from each can was collected in a dosage unit sampling tube (26.6 × 37.7 × 103.2 mm; 50-ml volume, Jade Corporation, Huntingdon Valley, United States). Methanol (EM Science, United States) was added to the dosage unit, and the amount of drug emitted per actuation was determined by ultraviolet (UV) analysis (Hewlett Packard Diode Array 8425A spectrophotometer, Hewlett Packard, Germany) at 240 nm. A total of 200 actuations were available from each can. The dose delivered through the valve was determined throughout the life of each can and is defined in Table 1.

Cascade Impaction

An eight-stage cascade impactor (Andersen I ACFM Non-Viable 8-Stage Cascade Impactor with a USP Induction Port, Mark II, Graseby-Andersen, Smyrna, United States) was used to determine the aerodynamic particle size distribution of the emitted dose. For each cascade impaction determination, 31 actuations were collected. Glass-fiber filter paper (Graseby-Andersen, Smyrna, United States) was used as the collection substrate. Methanol was used to solubilize the drug from the glass filter substrate. The amount of drug collected at each stage was determined by UV analysis as described in this text.

Statistical Analysis

The data were compared using one-way analysis of variance (ANOVA) to evaluate each treatment effect. Re-

Table 1

Definition of Actuation Sequence Through the Life of a Can

Shot Range	Determination	Designation
1–35	20% of the can	A
36–70	40% of the can	B
71–110	60% of the can	C
111–140	80% of the can	D
141–175	100% of the can	E

sults were judged to be significant based on the 95% probability values ($p < 0.05$).

RESULTS AND DISCUSSION

Dose Delivery Through the Valve

The amount of drug emitted from the valve of a pressurized metered dose inhaler depends on the volume of the metering chamber and the concentration of drug in the liquid phase of the propellant (7). Temperature significantly influences the vapor pressure of the propellant such that, at elevated temperatures, less propellant is in the liquid state, which acts to concentrate the components of the metered dose inhaler formulation (10). The metered dose inhaler formulation tested utilized a blend of chlorofluorocarbon propellants, Freon-11 and Freon-12. Their boiling points range from 23.82°C for Freon-11 to −29.79°C for Freon-12 at 1 atm (11). Related to the boiling point is the vapor pressure, which is dependent on temperature, but is independent of the quantity of material in a closed system. The vapor pressures of Freon-11 and Freon-12 are −1.3 psig and 70.3 psig at 25°C, respectively (11). Blends of the two propellants result in vapor pressures that are within the range of the pure components and can be predicted by Raoult's law (12). The results presented in Fig. 1 show the dose delivery through the valve of a pressurized metered dose inhaler with metering chambers that were loaded at 4°C, 23°C, or 40°C. The differences among the average dose delivery through the valve of cans loaded at the test temperatures were not significant ($p > 0.05$). The average dose delivery through the valve at all temperatures and shot ranges was 57.40 μg ± 5.397 mg, with an average %RSD (percentage relative standard deviation) of 9.027%. The results indicated that the amount of drug emitted from the valve was not significantly influenced by the temperature at which the metering chamber was actuated and loaded. Also, the results displayed in Fig. 1 indicate that the dose of beclomethasone dipropionate delivered through the valve remained constant throughout the life of the can at each temperature tested.

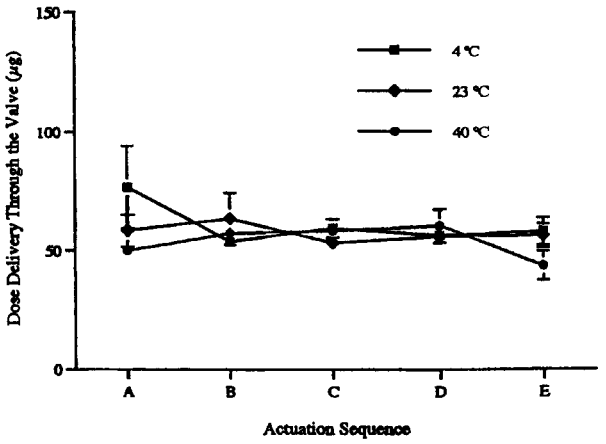

Figure 1. Dose delivery through the valve for cans loaded at 4°C, 23°C, and 40°C ($n = 3$).

Aerodynamic Particle Size Distribution

The amount of drug that is deposited in the respiratory airways is dependent on the aerodynamic particle size distribution of the emitted spray. Multistage cascade impaction was used to describe the deposition of the dose emitted from the actuator of a metered dose inhaler system. The dispensation of drug from the metering chamber and valve can be divided into three general collection areas: the actuator and spacer device, the USP Induction Port of the Andersen Cascade Impaction apparatus, and the eight stages of the Andersen Cascade Impaction apparatus. The amount of drug deposited on the inside of the actuator and spacer of the metered dose inhaler device represents the amount of drug lost and not available for delivery to the lung as a result of actuation. The amount of drug that is deposited inside the induction port represents the amount of drug that may be deposited in the oropharynx region of the patient. The amount of drug deposited on the eight stages of the cascade impaction apparatus corresponds to the fraction of the emitted aerosol with an aerodynamic diameter less than 10 μm and is related to the fraction of the aerosol cloud that may be respirable per actuation of the metered dose inhaler (13).

The results shown in Table 2 illustrate the amount of drug deposited in the actuator, induction port, and stages 0 through 7 of the cascade impactor and the percentage of the total amount emitted from the valve after 31 actuations. The data indicate that temperature did not influence the amount of emitted drug that was deposited onto the actuator, induction port, and eight stages of the multistage cascade impaction device. The fraction of the total amount of drug emitted from the metering chamber that was deposited in the actuator and induction port was consistently greater than 65%. Irrespective of the temperature at which the metering chamber was loaded and actuated, approximately 30% of the emitted dose was de-

Table 2

Distribution of Drug from the Valve of a Can at Different Metering Chamber Loading Temperatures, Mean and Standard Deviation (in Parentheses)

Loading Temperature	Total (μg)	Actuator (μg)		Induction Port (μg)		Cascade Impactor (μg)	
4°C	1925 (110.9)	194.2 (23.50)	10.09%	1225 (102.0)	63.66%	505.3 (86.80)	26.25%
23°C	1845 (164.3)	207.8 (31.40)	11.14%	1130 (121.4)	59.42%	559.7 (82.00)	29.44%
40°C	1874 (224.8)	185.9 (28.62)	9.92%	1131 (250.4)	60.36%	557.1 (82.52)	29.72%

posited in the eight stages of the cascade impaction apparatus for each determination.

However, it was found that the aerodynamic particle size distribution of the fraction of dose deposited on the eight stages of the cascade impactor was affected by the temperature at which the metering chamber was loaded and actuated. The aerodynamic particle size distribution of the emitted spray is related to the particle size of the suspended drug in the propellant and the vapor pressure of the formulation (6,7). Temperature influences the vapor pressure of the formulation and results in a change in volume of the liquid phase of the propellant. As the density of the propellant is influenced by temperature, a corresponding change in the concentration of drug in the liquid phase of the propellant results (10). Changes in the concentration of formulation components may affect the equilibrium solubilities, and therefore the particle size distribution of the suspended drug may be influenced (6). In addition, the effect of temperature on the vapor pressure and atomization of the aerosol droplets has been shown to influence the aerodynamic particle size distribution of the emitted spray. An increase in vapor pressure generally reduces the aerodynamic particle size distribution of the emitted dose (7,8). The mass median aerodynamic diameter of the emitted aerosol was determined at loading temperatures of 4°C, 23°C, and 40°C. The results shown in Fig. 2 illustrate that the mass median aerodynamic diameter decreased as the loading temperature was increased. This was due to an increase in vapor pressure of the propellant at the elevated temperature (7,8). The decrease was not significant ($p > 0.05$), but the trend was apparent.

The deposition fraction into various compartments of the human respiratory tract is dependent on the aerodynamic diameter of inhaled aerosols (14,15). Aerodynamic particle size helps to determine the fraction of inhaled particles that deposit in the lung region. Targeting of drug to specific sites in the lung for absorption or for a local effect may be compromised as the aerodynamic diameter of the aerosol is changed. A change in the fraction of the inhaled aerosol that is deposited at the intended site in the lung may alter the bioavailability of the dose and the corresponding therapeutic effect (16).

The geometric standard deviation of the aerodynamic particle size distribution is a measure of the polydispersity of the emitted aerosol cloud. The profiles in Fig. 3 show that the magnitude of the geometric standard deviation was not significantly influenced ($p > 0.05$) by the temperature at which the metering chamber was loaded and actuated. The average geometric standard deviations

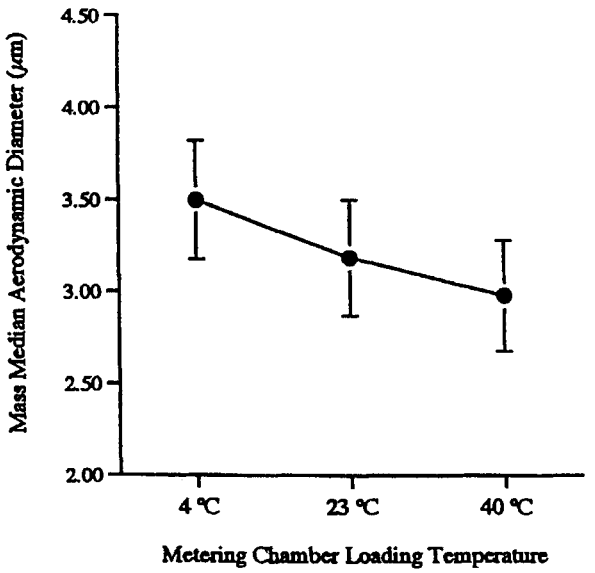

Figure 2. Mass median aerodynamic diameter of the aerosol emitted from cans loaded and actuated at 4°C, 23°C, and 40°C ($n = 3$).

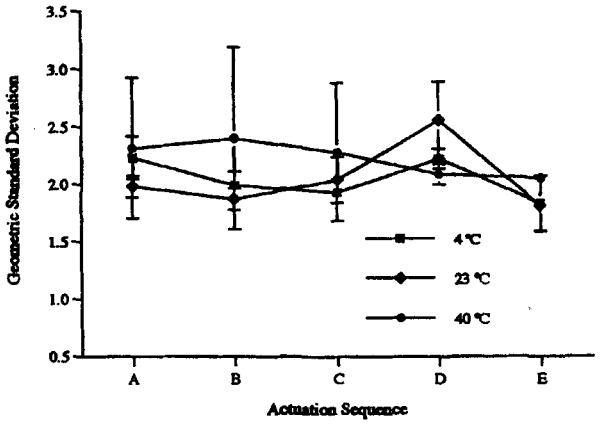

Figure 3. Geometric standard deviation of the aerosol emitted from cans loaded and actuated at 4°C, 23°C, and 40°C (n = 3).

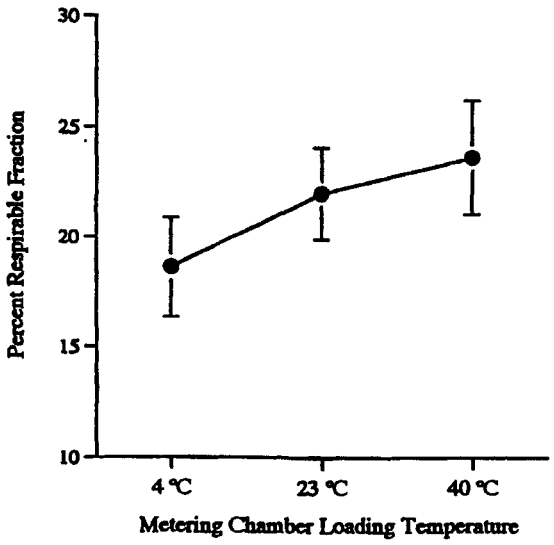

Figure 4. Percentage respirable fraction of the aerosol emitted from cans loaded and actuated at 4°C, 23°C, and 40°C (n = 3).

for distributions measured at 4°C, 23°C, and 40°C were 2.04, 2.08, and 2.20, respectively. Since the geometric standard deviations were greater than 1.22, the aerodynamic particle size distributions of the aerosols were considered to be polydispersed (17). Theoretical studies show that the polydispersity of the emitted aerosol influences the total and regional deposition fraction of drug in the lung (18–20). Diu and Yu (18) found that increasing polydispersity increases the deposition fraction for aerosols with mass median aerodynamic diameters between 0.04 and 2.0 μm and decreases the deposition fraction for aerosols with mass median aerodynamic diameters outside this range. The effect of increasing polydispersity is to decrease the dependency of the total and regional deposition fraction on the mass median aerodynamic particle size of the emitted dose. Increased aerosol monodispersity allows better prediction and control of deposition patterns (18–20). Increasing the temperature at which the metering chamber was loaded and actuated tended to increase the polydispersity of the emitted aerosol plume. However, significant statistical differences between the geometric standard deviations in the aerodynamic particle size of the dose loaded at 4°C, 23°C, and 40°C were not found ($p > 0.05$).

The percentage respirable fraction is the portion of the emitted spray having a mass median aerodynamic diameter less than 4.7 μm (13). Figure 4 shows the percentage respirable fraction of the emitted dose from metering chambers loaded and actuated at 4°C, 23°C, and 40°C. The percentage respirable fraction of the dose emitted from the metering chamber increased as the loading temperature was increased. The average percentage respirable fraction of the emitted dose was 18.3%, 22.2%, and 24.0% at 4°C, 23°C, and 40°C, respectively. Due to an increase in vapor pressure at 40°C, a small decrease in the amount of the emitted aerosol deposited onto the upper stages of the multistage cascade impaction apparatus occurred, resulting in an increase in the amount of drug deposited onto the lower stages. An increase in the vapor pressure of the metered dose inhaler system may be beneficial for targeting the dose to the lower airways. However, drug deposition is also dependent on the patient's breathing pattern (21,22). The multistage cascade impaction test for aerodynamic particle size distribution is conducted at an airflow rate of 28 L/min, which may not be attainable by patients using inhaler products (4,23,24). A combination of the aerodynamic particle size of the emitted aerosol cloud and patients' breathing patterns influences the targeting of drugs to specific lung regions (25).

In conclusion, due to the sensitivity of the propellant to temperature, the amount of drug emitted from the valve and the aerodynamic particle size distribution of the aerosol plume were influenced. At temperatures at which metered dose inhaler products would be used by patients, the dose delivery through the valve was not significantly affected. However, the particle size distribution of the emitted spray was influenced by the temperature at which the metering chamber was loaded. The mass median aerodynamic diameter decreased and the percent-

age respirable fraction increased as the loading and actuation temperature of the metering chamber was increased. The results of this study demonstrated that the temperature at which a metered dose inhaler is used by a patient may influence the amount of drug that is respirable, and therefore the theoretical dose delivered and the corresponding therapeutic effect may also be affected.

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