A Cascade Impactor Entry Port for MDI Sprays with Collection Characteristics Imitating a Physical Model of the Human Throat

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Purpose. This work was performed in order to compare and contrast results obtained from cascade impactor measurements on metered dose inhalers (MDIs) using a variety of inlet ports.

Methods. The collection characteristics of four cascade impactor ports (a physical model of the human throat, a simplified geometry intended to mimic the physical model, and two currently-used ports) were measured on a variety of MDI formulations.

Results. The portion of the MDI spray which collects on the entry port depends in a complicated fashion on the characteristics of the formulation; in these studies the fraction of the total dose which was collected on the port ranged between about 20% and 90% of the total emitted dose. The collection characteristics of the simplified geometry closely corresponded to the physical model. The length of the flow path between the port and the impactor was varied, and found not to have a strong effect on the measured size distribution passing the port.

Conclusions. Ranking of various MDI formulations according to performance criteria as measured with a cascade impactor should be expected to depend on the particular inlet port which is used.

KEY WORDS: MDI; aerosol; entry port; cascade impactor; size.

INTRODUCTION

Particles intended for delivery via inhalation commonly are generated by nebulizers, dry powder delivery devices, and pressurized metered dose inhalers (MDIs). Both nebulization and dry powder devices generate particles suspended in an air stream which is moving at a speed not greatly different from the inhalation rate, and the velocity of the particles essentially matches that of the air stream. MDIs are quite different. The aerosol particles generated by an MDI are released in a dynamic jet comprising drug particles, unevaporated propellant droplets (some of which contain clusters of drug particles), propellant gases, and air incorporated into the expanding gas jet. At the instant the particles leave the generating device, they have a high velocity, approximately 30 to 50 m/s (1). The subsequent evaporation of propellant droplets and deceleration of the gas jet depend on the geometry and thermal properties of the environment. Environmental factors of humidity and temperature have been postulated to be important in determining growth of the individual drug particles. The size characteristics of inhalable particles generated by MDIs are thus more complex than those produced by other common means.

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Characterization of any dosage form requires an attempt to measure those parameters which are relevant to the end use (patient) situation. The size and velocity of the particles in the MDI spray are acknowledged to be critical aerodynamic parameters which determine deposition site in patients. The size of the particles in an MDI spray changes rapidly after the dose is released, and the rate of change depends on the environment into which the particles are sprayed as well as the characteristics of the formulation and the spray-generating device. Therefore, in order to characterize the relevant properties of an MDI spray, it is appropriate to generate and direct the spray into an environment which approximates the pertinent characteristics of the end use situation. Among the environmental aspects which are likely to be important are those related to the dimensions of those portions of the airway exposed to the jet from an MDI spray. One of the challenges of inhalation product characterization, of course, is that of selecting specific values for laboratory variables to correspond to the myriad characteristics in the end use situation.

Cascade impactors are instruments designed to measure the aerodynamic size of particles suspended in a gas stream, and have been used widely to measure the size of sprays from MDIs. With all cascade impactors, the introduction of an MDI spray sample into the instrument presents a practical difficulty, since all of the (diverging) spray must be passed through the impactor, and the central axis of the impactor inlet is customarily (but not always obligatorily) positioned vertically, which is an unnatural orientation for the actuator outlet of an MDI. Therefore, an auxiliary flow channel is used to form an inlet port, and a variety of inlet ports have been described (2–9) for use with MDIs. Each of these inlet ports introduces ambiguity in data interpretation, because the inlet port inevitably collects some material from the spray. Some of the collection in the inlet port is a result of the high velocity of the propellant gases, and not necessarily because the solids are of an aerodynamic size which would cause them to be collected if it were not for the high propellant gas jet velocity which is superimposed on the flow of ambient atmosphere through the inlet.

There were three principal phases in the study reported here: First, the collection characteristics for MDI sprays of a physical model of a human throat were characterized. Second, a simple geometry was developed to mimic the collection characteristics of the physical model. Finally, the collection characteristics for a variety of formulations were compared for some commonly used entry ports.

MATERIALS AND METHODS

Rubber Throat

A rubber cast model was developed as an accurate physical model of the human anatomy (10). It was based on two anatomical teaching models (GS4 Larynx and Tongue, and #6650 Human Head Section, Anatomical Chart Co.) by sculpting a faithful representation from wax. These portions were placed together with a smooth junction to make the model of the throat. An impression mold was made from silicone rubber. The original wax representation was then removed. Melted paraffin was poured into the silicone impression mold, and allowed to solidify. The silicone mold parts were removed to

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yield a wax replicate of the original wax model. This wax replicate was then dipped briefly into uncured silicone rubber and the adhering viscous liquid film allowed to cure. The dipping process was repeated until a sufficient number of coatings (four or five) enabled the rubber to become self-supporting. The wax core was removed by soaking the assembly in hot water. An inlet was fashioned by cutting away a portion of the silicone rubber corresponding to the mouth, leaving a circular shape large enough to accommodate an MDI actuator. The finished throat is shown in Figure 1. Aerosols were released into this throat when the actuator was placed within the cut-away portion.

Model Throat

The final design of the inlet port will be designated for convenience in this paper as the "model throat." The dimensions of the model throat are shown in Figure 2. The throat was machined from aluminum. For some experiments, the slender vertical portion of the throat was extended with metal tubing of the same internal diameter as the outlet of the port.

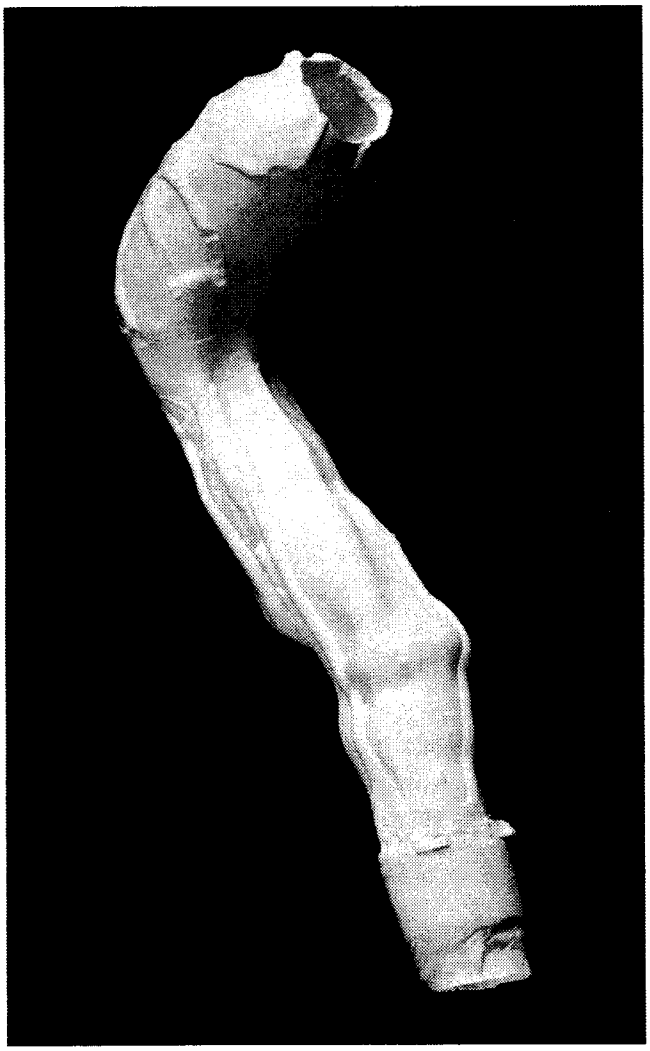

Fig. 1. Photograph of rubber throat model.

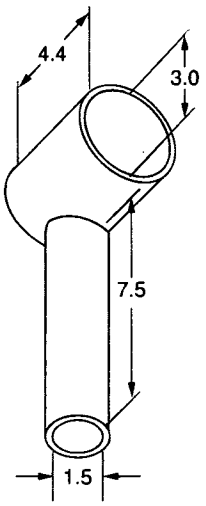

Fig. 2. Drawing of model throat. Dimensions are in centimeters.

The length of the horizontal portion of the model throat was reduced from a larger initial value to the length shown in Figure 2, which was obtained by successively reducing the length until drug penetration approximately matched that for the rubber throat using Formulation G (described below).

Glass Inlet Port

The glass inlet port (Ace Glass part # 5070-15) is made of Pyrex glass, approximately 2 cm diameter and 20 cm long, bent at approximately a 100 degree angle, with male 29/42 standard taper ground fittings at both ends. It was included as an example of a port which had been used for convenience in at least one laboratory for many years.

USP Inlet Port

This port is the one currently described in USP (11). It is made of aluminum, and the flow path consists of 1.9 cm cylinders intersecting at a 90 degree angle, with tapered sections at the entry and exit. Total flow path length is approximately 20 cm.

MDI Formulations

The behavior of a variety of formulations was investigated. The formulations included commercial products as well as experimental formulations, and were selected to cover a range of propellant volatilities, surfactant concentrations, drug sizes and drug concentrations, and actuators. All of these variables might be expected to affect particle size of the MDI spray. Details of the formulations are shown in Table I.

Formulation A was a solution; the others were suspensions. The description of the formulations is intended merely to illustrate the wide range of formulation characteristics which were examined.

Drug Capture

The outlet of each test inlet was adapted with an external rubber stopper to fit the inlet of a filter funnel (Gelman 4201) equipped with a 47 mm polyvinyl chloride filter (Gelman VM-

Table I. Test Formulations

Code	Surfactant Concentration	Drug Concentration	Propellant Blend	Pressure, psig
A	—	.5	P12/P114/EtOH	40
B	.25	1.8	P12	70
C	.25	.7	P12	70
D	.8	.5	P11/P12/P114	50
E	.5	.4	P134a/EtOH	75
F	.05	.5	P134a	80
G	.5	.5	P11/P12	60

1). (This filter was demonstrated to capture adequately all aerosolized drug.) The test MDI was fired into the test inlet after the prescribed ambient air flow was established through the filter funnel. The amount of drug which passed through the test inlet was determined by placing the filter in a measured volume of solvent, including solvent used to wash down the walls of the filter funnel. Various solvent systems were used, depending on the drug to be assayed, and assay was performed spectrophotometrically or by HPLC depending on the specific drug. The assay result yielded the mass of drug passing completely through the inlet port, here termed the "penetration." This indirect measure of throat holdup was used in preference to collecting material directly from the throat for two reasons: 1) it removed uncertainties in recovering drug by means of solvent contact with the complex internal surfaces of the silicone rubber throat model, and 2) it offered considerable operational expediency for all of the test inlets. This approach had the disadvantage, however, of increasing variability in the results: because the total mass of drug leaving the actuator was not determined on the same dose for which the penetration was determined, the variability in drug delivery from the actuator was superimposed upon the variability in penetration measurements.

Variable Air Flow Rate Control

A flow control system was assembled, comprising a flow control valve (Sierra 740-N2-2) mated with an analog/digital I/O board (Data Translation DT2805) attached to a personal computer, shown schematically in Figure 3.

The flow control valve included a flow rate sensor as well as a valve actuator. With the valve in the fully open position, the flow measurement portion of the circuit was used to measure

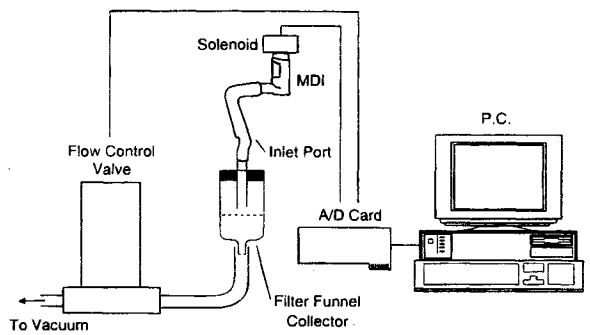

Fig. 3. Schematic diagram of flow control system for simulating breath flow pattern.

and record the flow rate as a human subject inhaled a slow breath through the flow meter.

With the human subject replaced by a vacuum source, the measured flow data were subsequently used as an input signal for the flow controller. Thus, the air flow through the controller represented a close approximation to the flow produced by a human subject.

The MDI was actuated by means of a pneumatic cylinder (NCQ1 B20, SMC Corp) triggered by a solenoid energized by a signal from the I/O board of the computer.

Steady Air Flow

For experiments at steady and constant air flow rates, the flow was adjusted to target values by a manually adjusted valve, with the flow monitored by a mass flow air meter (Sierra Top-Trak, 821-1). The MDI was actuated manually.

Penetration as a function of the distance between the actuator and the impaction surfaces in the rubber throat was measured with reference to the normal position of the actuator placed at the throat opening corresponding to the mouth. A point of closest approach was obtained by pushing the actuator into the rubber throat as far as possible without distorting the flexible side walls, and was found to be 1.3 cm from the normal position. A point of distant separation was arbitrarily defined at 2.0 cm by inserting a small cardboard tube of the same internal diameter as the actuator, between the actuator and the mouth of the rubber throat, so as to lengthen the flow path for the MDI jet. Three replicate determinations of penetration at 30 L/m were made at each of the three position conditions for formulations A, B, D, E, and G.

Size Distributions

Size distributions were measured using an Andersen Sampler Mark II cascade impactor. Flow rate was maintained at 28.3 L/m, and a variety of inlet ports were used. For any particular inlet port, the MDI was fired into the inlet of the port, with the port outlet attached to the inlet of the Andersen Sampler. Data in one series of measurements were gathered on a modified version of the model throat, in which extensions to the vertical portion of the throat were obtained by inserting a tube of the same internal diameter as that portion, between the throat outlet and the impactor inlet. The length of the vertical portion of the unmodified model throat was 5 cm. Two extensions were used, one of which produced a total vertical length of 14 cm, and the other, 28 cm.

Test Conditions for Rubber Throat

The specific dimensions and the general shape of the rubber throat were anticipated to have strong effects on the amount of MDI spray captured. To obtain estimates of the sensitivity of the collection characteristics to throat shape, the penetration of formulation G was measured while various manipulations were made on the flexible rubber cast. The nomenclature for those manipulation is as follows: *Standard* refers to flow through the unmodified, self-supported throat. *Mineral oil* indicates that the entire interior surface of the rubber cast was coated with heavy mineral oil immediately prior to testing, to simulate the effects of a mucous coating. *Closed cords* indicates that the portion of the throat with the simulated vocal cords was

pinched manually, to approximately one-half the rest position. *Open cords* indicates that the same portion was pinched so as to minimize the flow obstruction, by making the cross section approximately circular. *Up 30°, Up 15°,* and *Down 20°* indicates the approximate displacement in degrees of the axis of the mouth portion to the throat portion from the rest position. *Tongue up* and *Pucker* refer to distortions of the mouth portion of the cast, again achieved by manually distorting the rubber, so that the original height and width dimensions were reduced to approximately one-third of the rest values. The *40°C* and *40°C sat* refer to measurements made in an environmental storage chamber held at 40°C, in order to simulate air flow into a warm human body. In addition, the *40°C sat* measurement incorporated high humidity air, which was obtained by bubbling air through a large container of water heated to 40°C, then passing this air through a shroud surrounding the MDI actuator. This humidified air flow was maintained at greater than 30 L/m, so that essentially all air drawn through the sample collector was humidified.

RESULTS, DISCUSSION

Results are discussed for each of the areas of study. The distinctive collection characteristics of the rubber throat are described. The collection characteristics for each of the inlet ports is compared for a variety of test formulations. The size distributions as measured with the model throat with various extensions are reported. Finally, distinctive characteristics of the model throat are discussed.

Collection Characteristics of the Rubber Throat

The measured flow rate from a human subject is shown as the dashed line in Figure 4. The subject was instructed to breathe according to the instructions often provided with MDIs; i.e., following a full exhalation, a slow steady inhalation was performed, followed by a few seconds of breath holding prior to slow exhalation. The pattern selected was one of the subject's typical attempts to approximate the "ideal case" of a rapid initiation of a slow, nearly constant, flow rate, coupled with a rapid decrease to zero flow rate at the end of inhalation, followed in turn by breath holding. Only the inhalation and part of the breath-holding portion of the breathing cycle are shown. The solid line in Figure 4 shows the measured flow rate through the collection apparatus in a succeeding experiment, when the former flow rate was introduced as an input signal to the controller. This measured flow rate was the flow rate profile which existed in the collection apparatus when each of the subsequent penetration measurements were made. Also shown on this figure are individual penetration measurements on MDI sprays which were released at the indicated point in the flow cycle. The same air flow rate pattern was used for each of the individual penetration measurements shown. The total time required for the drug to be released from the MDI was estimated at approximately one-fourth of a second. The data demonstrate that penetration is significant even when the dose is released slightly before the air flow is established; i.e., when there is actually very low flow through the throat. There is no apparent dependence of penetration on the point in the inhalation cycle once the flow has been initiated.

Figure 5 shows the penetration measured with various constant and steady flow rates through the collection apparatus. Total dose was measured in separate experiments by releasing the MDI spray directly into the collection apparatus (i.e., without any inlet port), with the same drug measurement procedure. The penetration shows little, if any, dependence on flow rate in the range studied. This is comparable to Swift's (12) report involving a different physical model of a human throat and a different formulation. In that study, a clear dependence on flow

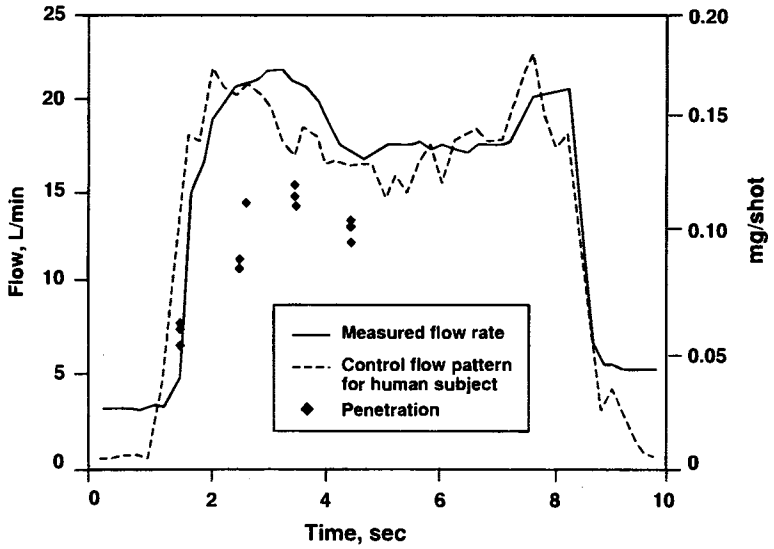

Fig. 4. Flow rate for a simulated breath, showing MDI drug penetration for formulation G through rubber throat for various release points within breathing cycle. Flow rate is on left axis, with solid line showing measured flow rate, dotted line showing the control signal which was a previously measured flow pattern in a human subject. Penetration is on right axis, with points plotted on abscissa at the instant in the flow cycle that MDI was actuated.

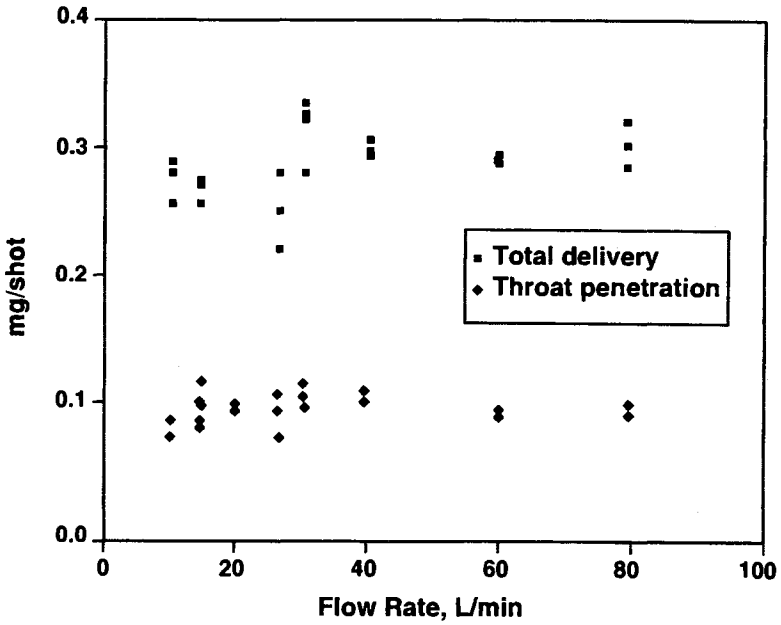

Fig. 5. Rubber throat penetration and total drug delivery for formulation G measured at various flow rates.

rate was apparent over the entire flow rate range of 1 to 50 L/m; however, the penetration changed little above a flow rate of approximately 25 L/m, while the penetration at 10 L/m was approximately half that at the highest flow rate. The present study focused on a different range of flow rates (10 to 80 L/m), and penetration differences at low flow rates which may be due to formulation or throat model were not explored.

The observation from Figure 4 that the penetration is not sensitive to the point of actuation in the inhalation cycle may be combined with the observation from Figure 5 that the penetration is not a strong function of flow rate above 10 or 15 L/m to support the inference that changes in the pattern of inhalation flow rate are unlikely to result in differences in penetration.

For the series of experiments in which the shape of the throat was changed by hand manipulation, eight measurements were made at the *Standard* experimental condition, with three measurements at each of the other conditions. The *Closed cords* condition resulted in a statistically significant ($P < .005$) decrease in penetration (by approximately 50%), while the *Up 15°* condition resulted in a significant increase in penetration (by approximately 30%). Other conditions resulted in, on average, less than 10% differences from *Standard,* and these differences were not statistically significant. Thus, provided the airway was not actually occluded by partial blocking due to closed vocal cords, the orientation was remarkably insensitive in affecting the penetration. When the portion corresponding to the vocal cords was nearly blocked, of course, there was a significant decrease in the amount which penetrated the throat. Temperature, humidity, or sticky surfaces likewise did not have strong effect on the amount of drug collected. This suggests that the precise shape of the model throat is not an important variable.

The measurements of penetration as a function of the relative positions of the actuator in the rubber throat did not yield simple relationships. Formulations A and C showed statistically significant ($p < .001$) decreased penetration (approximately −25% for both formulations) at the point of closest approach between actuator and inlet compared to the normal position. Likewise, these formulations showed an increased penetration (+25% and +15%, respectively) when the actuator separation was increased by the use of an extension tube. This is the pattern which would be expected from the effect of spray impacting on collecting surfaces due to its high initial, but rapidly decreasing, speed. Formulations B, D, and F showed the same general pattern, but the data showed larger variation and trends were small and not statistically significant.

The rubber throat model was a single specimen made according to the methods described. As such, of course, it is difficult to assess the degree to which it represents a "typical" human body geometry—oral deposition data for MDIs show wide inter-subject variability, and the relationship of deposition in vivo to the geometry of anatomic structures has not been reported.

Comparison of Collection Characteristics for Various Ports

The collection characteristics of the various inlet ports are shown in Figures 6 and 7. Figure 6 compares the penetration, expressed as percentage of drug released from the valve, of various formulations measured at 30 L/m, with the formulations arranged in the order of increasing penetration through the rubber throat. The amount of drug which penetrates the various inlet ports obviously varies among the formulations, by a factor of four or five between the most- and least- penetrating formulations. Each inlet port shows a slightly different pattern among the formulations, and quantitative comparisons are complicated.

Figure 7 shows measurements on the formulations with the flow rate at 60 L/m. (Formulation B was not studied in this series.) Again, the formulations show considerable and

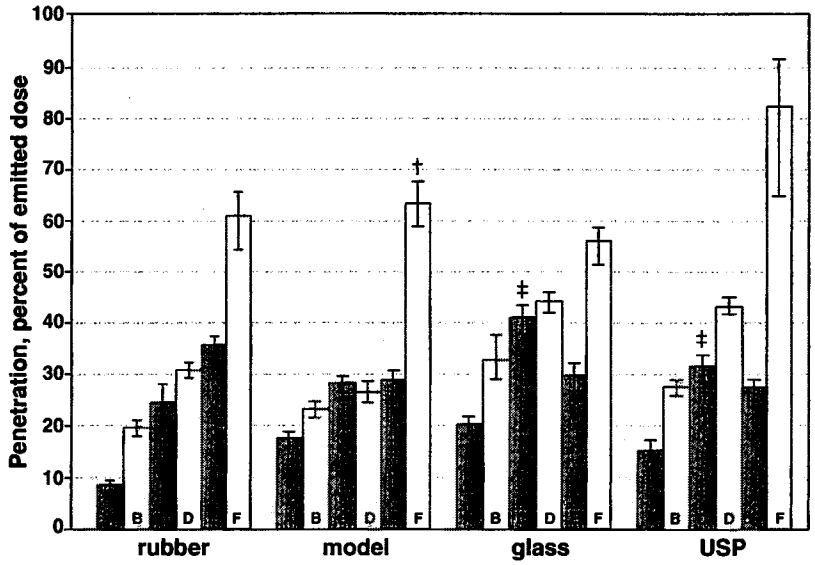

Fig. 6. Inlet port penetration for various formulations measured at 30 L/m. Formulation designations are shown at the base of each bar, bar height represents the average of three measurements except as noted, and maximum and minimum values are indicated by the symbol at the top of the bar. † N = 6, ‡ N = 4.

significant variation in penetration for all of the inlet ports, and ranking and quantitative comparisons are complicated.

A statistical analysis of the data was conducted. The analysis of variance model contained three main effects (inlet port, formulation, flow rate), all three two-way interactions, and the three-way interaction. The following factors were statistically significant ($p < .001$): port, formulation, port*formulation, flow rate*formulation, and port*formulation*flow rate. According to the analysis, data obtained with the model throat were not significantly different from those with the rubber throat; data from the USP inlet were not significantly different from the glass inlet; while the two groups were significantly different from each other.

Size Distribution Measurements with Model Throat

Size distribution measurements were made on formulation G, using the model throat as the entry port for the cascade impactor at 30 L/m, with various extensions to the vertical portion of the port. These different extension tube lengths had the effect of changing the time that was available for the aerosol to equilibrate with the ambient air before it was sized in the cascade impactor. The size distributions for formulation G, which had formulation characteristics in the midrange of the test formulations, showed a very small trend towards smaller size with increasing vertical tube lengths (MMAD of 2.97, 2.90, 2.88, 2.86, 2.82, 2.76 for measurements made with vertical tube length at 7, 7, 14, 14, 28, 28 cm, respectively). Thus, once the spray passed the collecting surface of the inlet port, the size distribution was at most only very weakly affected by the time which was available for the spray to equilibrate with the surrounding air. Likewise, the mass of drug collected on the inlet port did not depend on the length of the vertical tube portion, so the total mass reaching the impactor was not affected.

The measured size distributions were, however, slightly different for each of the inlet ports: for formulation G, mass median aerodynamic diameters of 2.6, 2.8, 3.0, and 3.1 μm were measured using the rubber, model (without extension tubes), USP, and glass ports, respectively. In contrast, in Figure 6 and 7, the total amount of spray which penetrates the inlet port shows considerable variation among the ports. This indicates that the portion of the dose which is collected in the inlet port depends on the equilibration time/distance of the spray before it reaches the place in the inlet port where it is collected. Furthermore, the rank order of MMAD's for formulation G is the same as the rank order of penetration at 30 L/m shown in Figure 6. Presumably this is also related to equilibration time/distance phenomena: inlets allowing shorter time prior to capture would be expected, ipso facto, to selectively collect larger droplets and aggregates.

Distinctive Characteristics of the Model Inlet Port

A primary feature of the model throat port is that its capture performance has been compared with, and demonstrated to be comparable qualitatively to, a replica of the biological system. The replica itself does not lend itself to use as an inlet port because of its fragility and the difficulty of recovering drug deposited on its internal surfaces.

A secondary feature is that it has a simple geometry which lends itself to reproducible measurements. The horizontal portion of the inlet port, being a straight-walled cylinder terminated by a flat surface perpendicular to the axis, is geometrically precisely defined, and this orientation would be expected to diminish any effects of misalignment of MDI spray with the inlet port. The diameter of the inlet (the "mouth") is large enough to accommodate all actuators in current use.

CONCLUSIONS

Collection characteristics for MDI sprays by a representational model of the human throat have been measured. Most

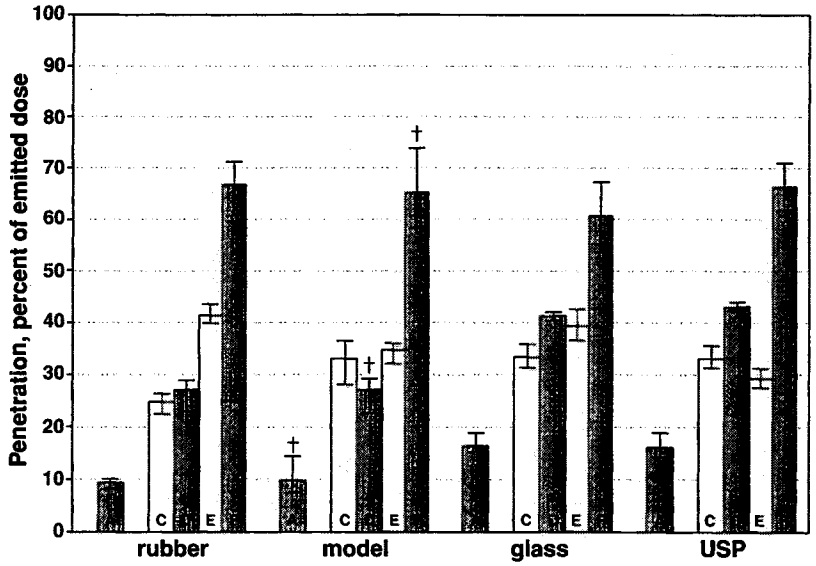

Fig. 7. Inlet port penetration for various formulations measured at 60 L/m. Same display conventions as Figure 6.

variations in air flow rate and shape of this model did not strongly affect the collection characteristics. For some of the formulations tested, but not all of them, the depth that the actuator was placed into this throat did markedly affect penetration.

A model throat with simple geometry and shape has been described. The collection characteristics of the representational model are more closely matched by this model throat than by some other inlet ports. Although differences in the mass penetration among the various inlets are not large for any particular formulation, the inlets show some differences in rank order of formulations with varying properties.

The differences in collection characteristics among the inlets tested are not likely to be of significance in quality assurance or stability evaluation applications, although they may become important during product development studies aimed at optimizing the in vivo performance of new formulations or attempting to match the biological efficacy of existing formulations, since economic considerations usually necessitate the selection of a small number of formulations and delivery systems to be clinically tested.

The fraction of the total dose that penetrates any of the tested inlet ports is related to MDI formulation composition in a complicated way. The size distribution of material passing the inlet port exhibits a weak dependence on the mass of material collected on the inlet, with smaller sizes associated with inlets which collect greater amounts of spray. The size distribution does not show significant dependence on the amount of time allowed for equilibration with the air flow, within wide limits, once the spray has passed the inlet. It may be inferred that differences in size distribution for a specific formulation measured with varying inlets are due primarily to the collection characteristics of the ports, rather than to differences in air flow path lengths.

ACKNOWLEDGMENTS

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