The AER_X™ Aerosol Delivery System

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Purpose. We describe the AER_X™ aerosol delivery system, a new, bolus inhalation device that is actuated at preprogrammed values of inspiratory flow rate and inhaled volume. We report on its *in vitro* characterization using a particular set of conditions used in pharmacokinetic and scintigraphic studies.

Methods. Multiple doses of aerosol were delivered from single use collapsible plastic containers containing liquid formulation. The aerosol was generated by forcing the formulation under pressure through an array of 2.5 micron holes. Air was drawn through the device at 70 LPM, and the aerosol was collected onto a filter or Andersen cascade impactor. The emitted dose was quantified from the filter collection data, and the particle size distribution was obtained from the best fit log-normal distribution to the impactor data.

Results. 57.0 ± 5.9% of the dose of drug placed as an aqueous solution in the 45 μL collapsible container was delivered as an aerosol (n = 40). The best fit size distribution had an MMAD = (2.95 ± 0.06) μm and a geometric standard deviation σ_g = 1.24 ± 0.01 (n = 6).

Conclusions. The AER_X aerosol delivery system generates a nearly monodisperse aerosol with the properties required for efficient and repeatable drug delivery to the lung.

KEY WORDS: drug delivery; aerosols; inhalational therapy; morphine; analgesia.

INTRODUCTION

Aerosol delivery to the lung presents an opportunity for non-invasive medication administration. Regions of the lung can be targeted by control of the properties of the formulation (1), aerosol size distribution (2), and initial velocity (3). Repeatability can be enhanced by releasing the medication at an optimal inhalational rate and volume (4).

The AER_X system was developed in our laboratories to make possible the delivery of reproducible doses of liquid medication with characteristics appropriate for either topical lung therapy or systemic medication delivery. The device monitors the inhalation rate and gives flow rate feedback, presenting a flashing red light if flow rate is too fast or a green light if the flow rate is appropriate. If the flow is within a pre-programmed flow rate range, the AER_X system will deliver a single bolus of aerosolized medication at a predetermined inhaled volume during the inspiration.

Theoretical Background

The human respiratory system can be divided into three compartments, the upper airways (oropharynx and trachea), the bronchial airways, and the pulmonary region (5). In the pulmonary compartment, the large area of thin epithelium separating air from the circulatory system makes this region an attractive target for systemic medication delivery (6). Low velocity particles of diameter less than 4 μm will mostly avoid deposition in the oropharynx and bronchial airways when inhaled through the mouth (7), and particles of diameter greater than 1 μm will deposit via gravitational sedimentation during a breath hold of 10 seconds (8). Thus, a design goal for this system was the generation of 1–4 μm particles.

Aerosols in the μm range can be created by generating liquid jets which spontaneously break up into droplets. These jets can be formed by pressurizing a reservoir behind an array of small nozzle holes. The pressure must be sufficient to propel the liquid at the minimum jet streaming velocity, given by (9):

$$V_{min} = \sqrt{\frac{8\sigma}{\rho d_{Jet}}} \quad (1)$$

where σ is the surface tension, ρ is the density of the liquid, and d_{Jet} is the jet diameter. For 2.5 μm jets, a velocity of 1500 cm/s is required. The jets are unstable to axial perturbations of wavelength $>\pi d_{Jet}$ (10), with the optimum wavelength for instability of 4.508 d_{jet} (11). The implied range of generated particle diameters is 1.74–2.19 d_{jet}. The break up will occur in a time given by (12):

$$t = \left[1 + \frac{1}{4095}\left(\frac{\sqrt{\rho\sigma d_{Jet}}}{\mu}\right)^{3/2}\right] B \sqrt{\frac{\rho d_{Jet}^3}{\sigma}} \quad (2)$$

where μ is the viscosity of the liquid and B is a measure of the amplitude of initial axial perturbations, and has an empirically determined value of 10.56. This expression gives a time to breakup of 5 μs for a water jet of diameter 2.5 μm. This time, together with the minimum streaming velocity above, give a length of the jet before breakup of 75 μm.

Once the breakup of the jets into droplets is complete, further evolution of the size, velocity, temperature, and other properties of the aerosol distribution is possible. Elevated temperature and reduced relative humidity can cause the size of droplets to decrease (13). Upon inhalation, the 37° temperature and 99.5% relative humidity in the distal lung can cause the formulation making up the droplets to approach isotonic concentrations (1), although 2 μm aerosols of dry salt may theoretically penetrate into the alveolated region under certain conditions (14).

MATERIALS AND METHODS

Unit Dose Packages

In order to store and subsequently deliver unit doses of aqueous medication formulation, a 45 μl dosage form was developed (see Figure 1). This dosage form is a three layer laminate assembled using heat sealing techniques. A cylindrical container, 0.20 cm deep and 0.56 cm in diameter, was drawn into the bottom layer. Four round indexing holes were cut into the part to facilitate alignment with the other layers and to aid in accurate placement of the final assembled packet in the device. The container was filled with 45 μl of aqueous formulation (25 mg/mL morphine sulfate and 6 mg/mL NaCl) and

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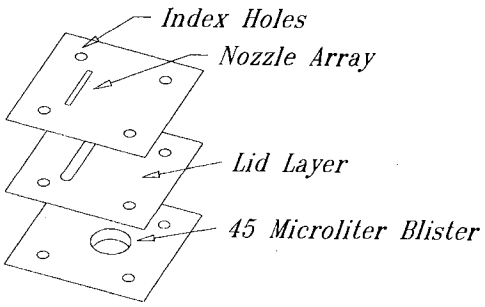

Fig. 1. Schematic of 45 μl packet.

heat sealed to a middle layer. This formulation was used in a pharmacokinetic study, to be discussed in an upcoming publication. In addition to alignment holes identical to those in the bottom layer, this middle layer has a die cut oval of dimensions 0.71 cm by 0.10 cm.

A polymer film nozzle layer was attached to this package such that the nozzle was positioned in the area above the die cut oval in the lid layer. For this work, an array of 150 laser drilled holes with exit diameters of 2.5 μm was used. The holes were arranged in a staggered rectangular grid, 5 rows of 30 holes per row. The hole to hole spacing along a row was 100 μm and the row to row spacing was 50 μm, giving a "nearest neighbor" hole to hole spacing of 71 μm.

When pressure was applied to the container, the heat seal separating the dose from the oval peeled open, allowing the formulation to flow to the nozzle. The formulation then flowed through the holes, forming jets that spontaneously broke up into an aerosol.

The Bench Top Prototype Instrument

To develop and test the delivery from the unit dose package described above, a fully instrumented bench top device was developed (Figure 2). This instrument was used for the *in vitro* characterization described here, in addition to *in vivo* studies (15).

A linear actuator applied pressure to the packet via a piston to generate an aerosol from the formulation (850B-05-HS, Newport Corporation). This actuator was capable of transmitting an axial force of 10^7 dynes (20 Lb.) to a piston which is 0.50 cm in diameter, 0.06 cm less than the outside diameter of the container. This difference corresponds to four times the thickness of the side walls of the container, allowing the side walls to roll up as the formulation is extruded. Between the actuator and the piston is a load cell (484B11, PCB Piezotronics, Inc.) to measure force, and a proximeter (7200, Bentley Nevada Corporation) to measure position. A Proportional-Integral-Differential (PID) servo control using the load cell output for feedback provided a constant force, yielding constant pressure. The voltage supplied to the actuator was controlled by an operational amplifier (LM12, National Semiconductor) with a gain of +3. The control signal is supplied by a digital to analog converter (see below) and the power was sourced by a +/−15 V power supply (HBB15-1.5-A, Power One). The entire extrusion was done at a constant force of 4.45×10^6 dynes.

To control the temperature of the air during the delivery, air was drawn past resistance wire. This wire had a specific resistance of 2.3 Ω/cm. 16 wires, 17 cm long were wired in

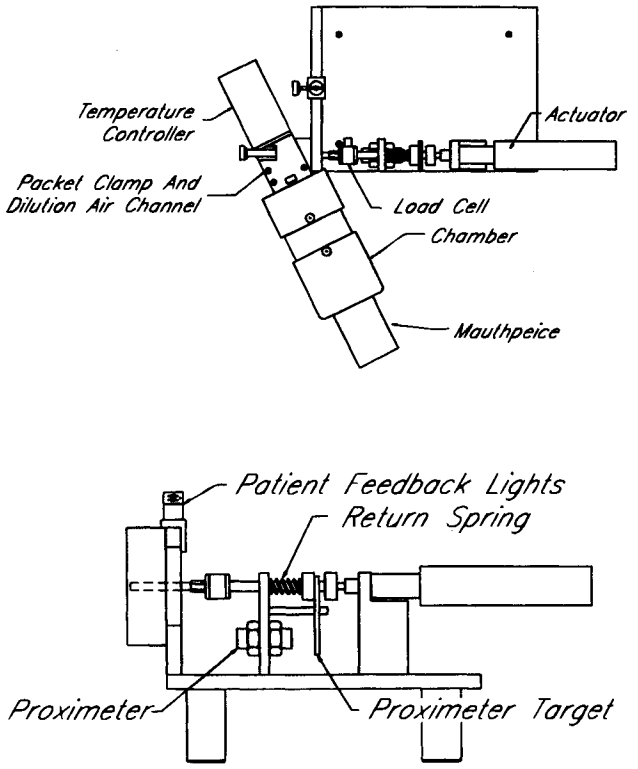

Fig. 2. Top view and side view of the AER$_X$ system. For clarity, the temperature controller packet clamp, and chamber have been omitted from the side view.

parallel to give a total resistance of 4.9 Ω. Current was driven through the wire using a 30 V power supply (TPS-4000, Topward Electric Instruments Company, LTD.) which was controlled by two LM12 amplifiers. Two "E" type thermocouples were used in the temperature control circuit. These thermocouples had a diameter of 0.13 mm, and a response time in moving air of less than 80 milliseconds. One was used for temperature feedback by the control system. A second thermocouple was placed in the chamber to monitor the temperature at this location. For this work, the aerosol was delivered from the AER$_X$ unit at 37°C.

The air was subsequently introduced into an air channel that was 0.71 cm wide, 0.32 cm high, and 0.76 cm long. The water jets were directed into this channel, where they broke up into droplets. The air dispersed the droplets, and carried them into the chamber. This chamber had a volume of 167 mL, which at 70 Lpm air flow rate implies a residence time of 143 ms. The aerosol was then drawn into a tapered section which fit tightly into a 90° glass twin impinger throat (Part number 007-04, Erweka Corporation). This glass throat was attached to a filter holder for a measure of the total emitted dose, or a cascade impactor for measurement of the emitted dose and particle size distribution.

The pressure depression in the chamber was monitored by using a pressure transducer (NPH-8B-.002.5GH, Lucas Nova Sensor). From this pressure drop a flow rate was calculated, and integrated to find a volume. If the flow rate and volume were determined to be correct, a TTL signal was sent to the control computer, and delivery commenced. This technique is identical to that used in the Smart Mist™ system[4]. For this

work, a correct flow rate was one in the range of 65–80 Lpm, and a correct volume was one in the range of 0.25–0.5 liters.

A computer using a 80486 DX2 processor running at 50 MHz monitored and displayed the flow information. The data acquisition and control for the pressure and temperature control was done with a 66 MHz 80486 DX2 processor and a combined 8 channel 12 bit 20 kHz A/D and 2 channel 12 bit D/A Board (CIO-DAS08/AO, Computer Boards, Inc.). The temperature, position, and force data were displayed graphically at the end of each delivery, and stored to disk for further analysis. Programming was done using Quickbasic (Version 4.5, Microsoft Corporation)

Aerosol Delivery and Sampling

To measure overall device efficiency, defined here as the emitted dose divided by the dose initially in the packet, aerosol from a single administration was collected onto a 47 mm glass fiber filter (61631, Gelman Sciences). The filter and glass twin impinger throat were then washed and assayed for morphine content by a reversed phase HPLC method (Thermo Separation Products, autosampler AS3000, pump P2000, detector UV2000) in conjunction with Beckman, Ultrasphere, ODS, C-18, analytical column, 4.6 mm × 150 mm, 5 μm particle size. Morphine sulfate pentahydrate, RS, was used as the reference standard. The mobile phase was 8% acetonitrile, 92% buffer (0.03 M $NaH_2PO_4 \cdot H_2O$, 2.0 mM $C_5H_{11}O_3SNa$, pH adjusted to 2.50 +/ − 0.02 with phosphoric acid), flow rate 1.0 mL/min, run time 10 min, injection volume 25 μL, UV detection at 225 nm. This measurement was repeated 40 times.

To measure the particle size distribution, the complete aerosol bolus was drawn through the glass throat into an Andersen cascade impactor (Mark II, Graseby-Andersen). The glass throat and impactor plates were washed and the amount of morphine sulfate on each stage was measured by HPLC. The size distributions were obtained from the fit of the data to the log normal distribution with minimum residual sum of squares (RSS). The fits were arrived at by non-linear regression, and the RSS near the best fit point were inspected to ensure that a minimum had been found. Six replicates were performed.

RESULTS

The pressure and piston position during one of the extrusions are presented in Figure 3. These data show that following an initial positioning maneuver, the PID control maintained a constant pressure in the container, resulting in a constant extrusion rate.

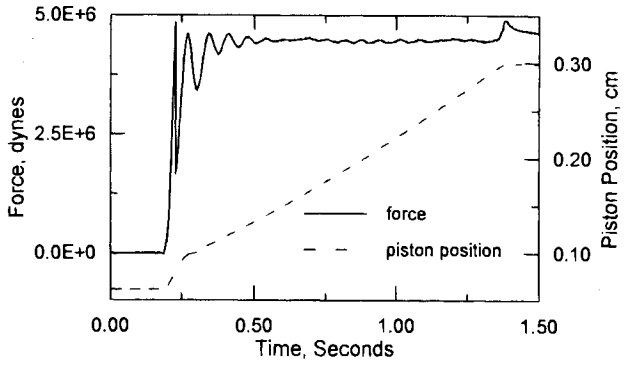

Fig. 3. Extrusion pressure and piston position during aerosol generation.

Table 1 shows the data from the measurement of efficiency using filter collection. The data show the high level of repeatability achievable with this type of delivery.

The results of six cascade impactor experiments are presented in Table 2. Each run gathered the emitted dose from 6 packets. The amount in the impactor is defined as the percentage of the morphine sulfate loaded into the packet that was recovered in the impactor.

DISCUSSION

The data in figure III show that during the aerosol generation, constant pressure was maintained in the container. The piston does not move for the initial 200 milliseconds. This is done to allow the temperature controller to equilibrate. The piston then moves forward until it contacts the container, at which time the pressure can be seen to rise. After the initial rise in pressure, a dip is seen as the heat seal peels open, allowing the formulation to flow into contact with the nozzle array. During aerosol generation, the pressure was $4.45 \times 10^6 \pm 1.38 \times 10^5$ dynes. The aerosol was delivered for ~1 second, as measured by the linear portion of the position profile. After the container was empty (shown in this graph by constant position) the pressure control was less precise, but this does not affect delivery. The fact that a constant pressure gives rise to a linear piston position profile gives confidence that no significant changes in the properties of the nozzle, such as hole size, were occurring during the delivery. While this type of data has proven invaluable to the development of the AERx dosage form, this sophisticated pressure control and monitoring will not be required in a commercial device.

The run of 40 filter recovery experiments was large enough to ensure an accurate determination of emitted dose variability. The standard deviation of the emitted dose, 5.9% of the loaded dose, was very low, and would allow for precise dosing. The data also exceed the requirements of the United States Pharmacopeia for pressurized meter dose inhalers (16) which state "the requirements for dose uniformity are met if the amount of the active ingredient in not more than 1 of the 10 dosage units . . . lies outside the range of 75.0% to 125.0% of label claim and no unit is outside the range of 65.0% to 135.0% of the label claim." In the 40 runs, the lowest dose collected on the filter was 82% of the average, and the highest was 125%, clearly exceeding the current USP standard.

The six cascade impactor runs showed a particle size consistent with our design objectives. The MMAD of the aerosol

Table 1. Emitted Dose Uniformity Data

n	Percent on filter	Standard deviation	Percent in glass throat	Standard deviation	Percent of dose emitted	Standard deviation
40	53.4%	7.0%	3.7%	2.7%	57.0%	5.9%

Note: All values are percent of dose loaded into the container.

Table 2. Cascade Impactor (CI) Data

Run number	Amount in throat, %	Amount in CI, %	MMAD, μm	σ_g
1	1.8	61.9	2.88	1.25
2	2.5	55.7	2.92	1.25
3	1.9	47.9	3.00	1.23
4	1.4	48.7	3.00	1.23
5	2.8	47.9	2.99	1.24
6	3.1	54.5	2.90	1.25
Mean ± SD	2.25 ± 0.65	52.77 ± 5.64	2.94 ± 0.05	1.24 ± 0.01

Note: All values are percent of dose loaded into the container.

measured in the cascade impactor was 2.95 ± 0.06 μm and σ_g was 1.24 ± 0.01. An average of 52.8% of the loaded dose was measured in the cascade impactor, consistent with our filter collection data.

These data show that AER$_X$ delivers narrowly distributed small particle aerosol, with high efficiency and repeatability. This *in vitro* performance is a prerequisite for efficient and reproducible drug delivery. However, the correct breathing maneauver and its synchronization with drug delivery are essential to transfer these characteristics to similar *in vivo* performance.

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