Video Characterization of Flume Patterns of Inhalation Aerosols

S. MISZUK *x, B. M. GUPTA ‡, F. C. CHEN *, C. CLAWANS ‡, and J. Z. KNAPP *

Received October 4, 1979, from **R&D Engineering Department and ‡Pharmaceutical Research and Development, Schering-Plough Corporation, Bloomfield, NJ 07003.* Accepted for publication January 30, 1980.

Abstract □ An *in vitro* technique was developed to characterize the intermittent flume patterns associated with the short bursts of metered-dose aerosols. Two orthogonal video images are utilized to describe the complex shape and direction of the flume pattern. This technique facilitates the evaluation of components manufactured by different suppliers.

Keyphrases □ Aerosols, inhalation—characterization of flume pattern, video technique compared with chemical analysis, delivery systems analyzed □ Delivery systems—inhalation aerosols, flume pattern characterized by video technique □ Distribution—of drug in lung alveoli, analysis of delivery systems, inhalation aerosols, flume patterns characterized by video technique

Various test procedures have been developed to evaluate aerosol products (1). The test methods for delivery rate, pressure measurement, unit spray sampling, container sampling, and propellents analysis are included in NF XIV (2). Particle-size analysis and spray patterns are among several tests that should be performed on inhalation aerosols to ensure their therapeutic effectiveness.

BACKGROUND

Extensive research (3) has been conducted on the relationship of the particle size of an active drug to its distribution and retention in the lungs. The conflict of theories and experimental results has been attributed to such variables as the species of animal used, nonuniform breathing rates, methods of measuring the particle-size distribution, methods of administering the agents used, and the effects of lung moisture content on the size of the inhaled particles (4–6). However, it generally is agreed that the depth of penetration increases with decreasing particle size while the whole lung retention increases with increasing particle size (7, 8). The optimum particle-size range for inhalation of medicinals into the lungs currently is accepted as 0.5–5 μm (9, 10).

While the importance of particle size in inhalation therapy has been well documented, other parameters affecting deposition and retention of inhaled matter have received less attention. Hayton (11) pointed out that, in many instances, a fairly high percentage of the formulation dispensed is retained in the oral adapter, the mouth, and the back of the throat instead of obtaining the desired deep penetration into the bronchi. Various methods have been useful for determining the aerosol dose delivered through an oral adapter to the desired portions of the lungs. Karig *et al.* (12) developed a compartmentalized lung chamber for the evaluation of oral inhalation aerosols. An *in vitro* method was established for evaluating the penetration of solid particles in the lungs using several aerosol generators. Sciarra and Cutie (13) developed a simulated respiratory system for the *in vitro* evaluation of two differently designed oral inhalation delivery systems and demonstrated that the deposition properties of the dose may be a function of the oral inhalation adapter.

The interest in therapeutic and diagnostic uses of inhalation aerosols can be directed at particles within the aerodynamic size range of 1–10 μm in diameter. When the alveolated regions of the lungs are the desired site of therapeutic action, the size is limited to 1–5 μm in diameter. The deposition of particles in the 1–10-μm aerodynamic diameter range is governed by inertial impaction and gravitational settling (14).

With the foregoing discussion, it can be concluded that the particle size and particle distribution within the aerosol cloud are the major factors affecting the site and mass of drug deposition in the airways. Other factors influencing aerosol penetration and deposition in the airways include the synchronization of the aerosol administration with inhalation and the aerosol mist characteristics. The spray pattern at different distances from the mouthpiece of the inhalation adapter can influence the penetration and deposition of particles in the desired portions of the lung. The nature of the flume pattern from an inhalation aerosol will be indicative of spray patterns at different distances.

The purpose of this study was to develop an *in vitro* technique to characterize the flume patterns to demonstrate physical equivalence of valve and actuator performance. With the same inhalation product, the technique also was used to screen actuators by studying their flume patterns. Manufacturers of inhalation aerosols must have alternative suppliers of package components, and this technique can be used as one criterion to demonstrate the equivalent performance of these alternative package components.

EXPERIMENTAL

Materials—The inhalation aerosol contained a suspension of a micronized corticosteroid in a fluorochlorocarbon propellent. The contents were packaged in a 16-ml aluminum can. Sixty-three-microliter valves and inhalation adapters from two suppliers (A and B) were used.

Video Systems—A high-resolution video camera[1] coupled with a macro lens[2] was used to capture the flume patterns of emitted sprays. These patterns were recorded on a 2.54-cm video tape recorder[3] (Fig. 1). This 2.5-cm broadcast quality video tape system provided a higher resolution of the flume patterns that the 1.3-cm video tape system in usual hobby use.

During playback, these flume patterns were displayed on a television monitor[4] from which the desired individual frames of flume pattern were photographed using a view camera[5]. Since video tape resolution is degraded by 50% whenever an individual frame is viewed, an accessory digital image enhancer[6] was employed to improve image contrast by gray-scale adjustment. The benefit of this adjustment was most visible along the fringe area of the aerosol flume. Image enhancement was applied only to the flume display on the video monitor. All of the original video data on the tape remained unchanged.

Imaging Requirements—Since the flume pattern is three dimensional, a single two-dimensional image cannot completely characterize

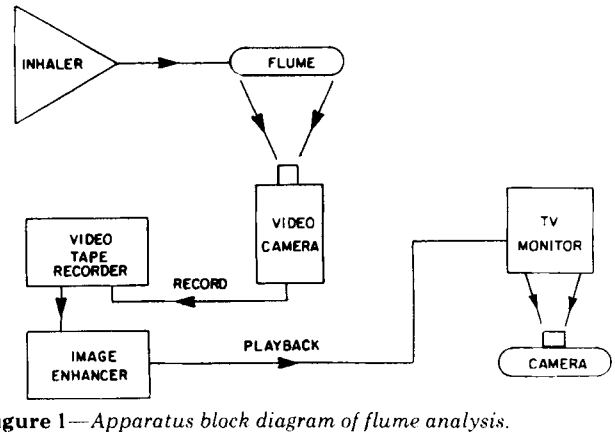

Figure 1—*Apparatus block diagram of flume analysis.*

[1] Model AVC 3200, Sony Corp., Tokyo, Japan.
[2] Cosmicar 25MM, Fl. 4 television lens, Cosmicar Corp., Tokyo, Japan.
[3] Model AV 3650, Sony Corp., Tokyo, Japan.
[4] Model TW19VL, Shiba Electric Corp., Tokyo, Japan.
[5] Model CC404, Calumet Corp., Elk Grove, Ill.
[6] Model 832, Dynasciences Corp., Chatsworth, Calif.

0022-3549/80/0600-0713$01.00/0

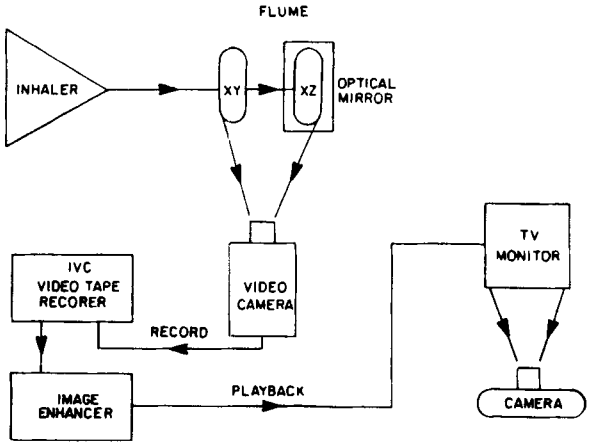

Figure 2—*Apparatus block diagram of flume analysis for orthogonal views.*

its complex shape and direction unless the pattern is symmetrical. When the flume pattern is asymmetric, a combination of two simultaneous orthogonal views is required to describe the character and direction of the flume pattern adequately.

In metered-dose aerosols, the total duration of the burst can be as short as 50 msec, so image delays between the two orthogonal views should be minimized. To achieve minimum delay, the same scan line was utilized for the corresponding image positions. This objective was accomplished by rotating the camera 90° from its usual viewing position. This action reduced the delay from milliseconds to microseconds for equivalent image portions, which was a prerequisite for accurate three-dimensional analysis.

For adequate visualization of the micrometer-sized aerosol droplets, a high-intensity light source was adjusted to deliver the scattered light from the flume droplets forward to the viewing lens (Fig. 2). For optimum contrast in orthogonal views, two flexible fiber optic bundles were used to ensure uniformity of the scattered light intensity in both views. A high quality optical front surface mirror, having a flatness of 0.5 λ, was positioned at a 45° angle to provide simultaneous images in the two orthogonal views of the video camera.

System Operation—Video and optical systems were assembled and arranged as shown in Figs. 2, 3, and 4 for orthogonal, side, and top views, respectively. A black screen was placed parallel to the flume as a background to achieve proper contrast.

The product to be tested, *i.e.*, an inhaler in its respective actuator, was placed in a fixed position (Fig. 4). An operator placed the recording system into the recording mode and subsequently actuated the product to emit a spray. After a single trial spray was emitted, flume patterns of the subsequent two sprays from that product were recorded by the video system. These series of sprays were identified on the video tape by an alphanumeric light-emitting diode configuration, which was recorded simultaneously during each spray burst. In the playback mode, the

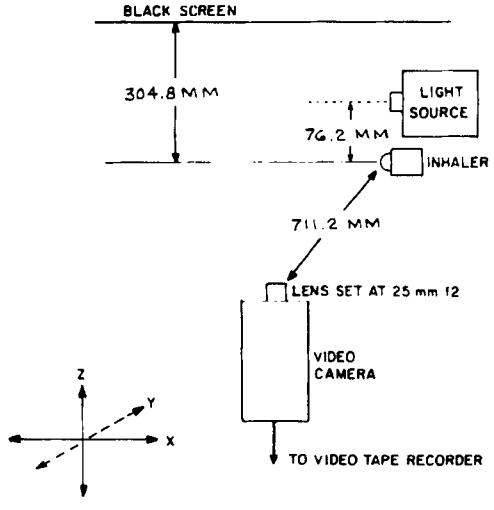

Figure 3—*Apparatus block diagram of flume analysis for side view.*

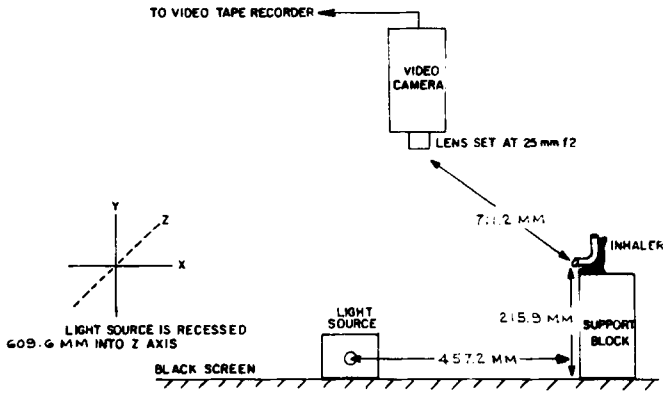

Figure 4—*Apparatus block diagram of flume analysis for top view.*

light-emitting diodes clearly identified the particular spray pattern being tested.

System Output—The output is a video image of the aerosol flume pattern that can be viewed on a video field basis (each field is spaced 16.7 msec apart). The total life of the flume pattern is available from the time it passes from the actuator until it is dissipated in the atmosphere. When flume patterns were observed on a frame-to-frame basis, flume size increased progressively up to the fourth frame (66.7 msec after flume commencement) and thereafter started dissipating. Therefore, the flume pattern in the fourth frame was selected to be photographed for comparison.

RESULTS AND DISCUSSION

Videotapes of flume patterns of the corticosteroid oral inhalers A and B were played and examined. Flume patterns were observed individually on a frame-to-frame basis; flume size increased progressively up to the fourth frame and thereafter started dissipating. For package components A and B, no significant difference was noticed in flume patterns of Sprays 1 and 2. Photographs of these flume patterns in the fourth frame for the top and side view are shown in Figs. 5 and 6, respectively. The similar shape and size of flume patterns for package components A and B indicate equivalent physical performance. This result suggests that the spray emitted from package components A and B will have a similar projectile and force to enter the throat and lung, suggesting equivalent dispensing of the drug by two different actuators to different parts of the respiratory system.

Application of this video system for screening actuators was extended to a nasal inhaler. Figures 7–9 are flume patterns of the orthogonal view of a nasal inhaler obtained using three actuators from the same lot. Each photograph also was taken during the fourth frame of a video field to establish a common basis for analysis.

A typical example for a good flume pattern is shown in Fig. 7. The aerosol spray patterns are symmetrical; if a line were drawn through the center of each flume, each half would be equal and that line would intersect the center of the actuator nozzle. This result indicates that the center of the aerosol spray pattern is at the center of the actuator. Moreover, the exit angles of the spray pattern in both views are parallel to the axis of the actuator nozzle in their respective views.

Marginal actuators yield poor flume patterns with one or more discrepancies with the described criteria for a good flume pattern as illustrated in Fig. 8. The flume patterns in both views exhibit a large displacement from the center of the actuator nozzle. This condition generally yields a poor or marginal delivery of product since a portion of the product is trapped on the inner wall of the nozzle and remains as a residue. In fact, with some actuators, the second burst showed streaking lines in the flume patterns. These lines were the corticosteroid, which was left as a residue in the nozzle and was evacuated with the second burst of propellent. Erratic delivery can be attributed to this actuator, *e.g.*, the first burst is low on product, and the second burst is much higher.

Figure 9 shows the flume pattern from an actuator with a defective nozzle; there is a slight burr around the exit jet of the nozzle. The right portion of the figure (the side view of the actuator) exhibits a very poor flume pattern with heavy streaking lines about the nozzle. These lines indicate a misdirection of the spray inside the nozzle piece. The other orthogonal view lacks these lines, which strongly suggests that two views are necessary for a proper flume definition.

Since the three actuators had a common canister of propellent and were evaluated at a similar video field, one actuator can be accepted as good,

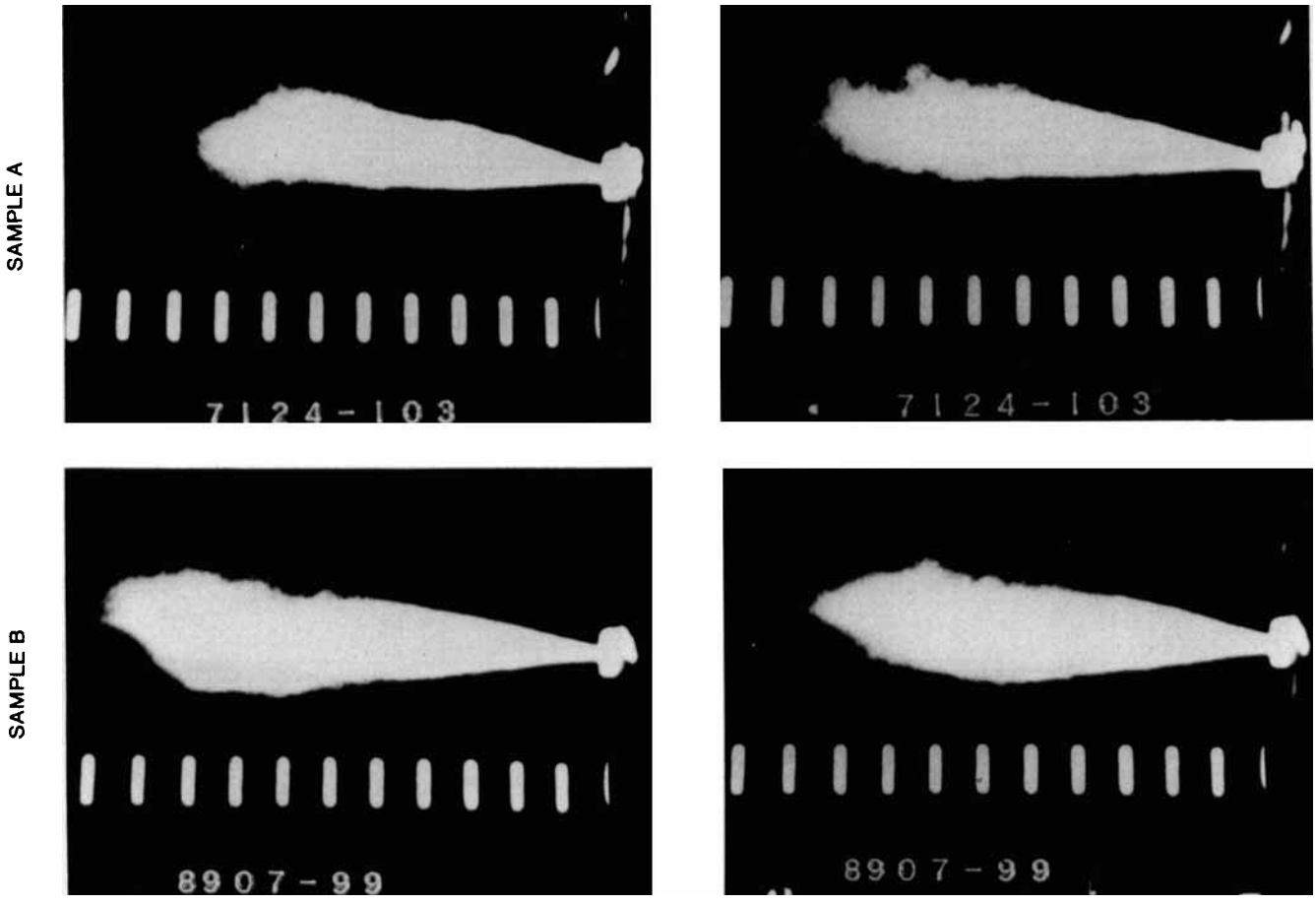

Figure 5—*Series of typical flume patterns that are shown in the top view.*

one as marginal, and one as bad. This video technique can be used to screen potentially bad actuators. To establish a comparison between the video technique and chemical analysis, 20 actuators were studied by both techniques. In the video technique, based on the described criteria, the quality of actuators was rated good (G), fair (F), and poor (P) (Table I).

The total amount of drug delivered from an actuator and the amount retained on the actuator were determined for 20 actuators by liquid chromatography. The ratio of B to A was calculated for each actuator, where A is the total amount of drug delivered through the actuator and B is the total amount of drug retained on the actuator. The smaller the ratio, the better is the rating. Actuators were rated from one to 20 based on the ratio. A rating of one was given to the actuator with the lowest ratio. Table I lists the ratings obtained by chemical analysis and the video technique. On the basis of these chemical analysis data, five actuators were rated as good, 10 as fair, and five as poor. These results compared very well with the results obtained by the video technique (Table II).

To increase the average amount of drug delivered through an actuator, the following two steps are necessary. First, the use of defective actuators should be eliminated by improving the incoming inspection of these units. Second, the design of the actuators should be modified to improve drug delivery.

The five actuators rated as good by the chemical test had an average delivery of 82%. However, the average yield of the five actuators rated as poor by the chemical test was 69%. To locate the defective parts of the actuators, the following experiments were performed.

The plastic inserts were replaced with machined-steel inserts, and the flume patterns were studied before and after the replacements. The replaced plastic inserts were inspected visually. These steel inserts gave an improved flume pattern after replacing plastic inserts with burrs inside

Table I—Comparison of Results Obtained by Chemical Analysis and the Video Technique

Actuator	B/A[a]	Analysis Ratings	
		Chemical	Video
I	0.185	2	G
II	0.636	20	P
III	0.515	18	P
IV	0.173	1	—[b]
V	0.224	6	F
VI	0.557	19	P
VII	0.345	13	P
VIII	0.229	8	F
IX	0.272	9	F
X	0.487	17	—[b]
XI	0.332	12	P
XII	0.199	4	G
XIII	0.214	5	G
XIV	0.307	11	P
XV	0.225	7	—[b]
XVI	0.467	16	P
XVII	0.304	10	G
XVIII	0.465	15	P
XIX	0.455	14	F
XX	0.197	3	G

[a] A is the amount of drug delivered through the actuator, and B is the amount of drug retained on the actuator. [b] Not available for video test.

Table II—Number of Actuators within Ratings According to Chemical Analysis and Video Technique

Rating Chemical Number	Number of Actuators within Rating Range	Video Ratings and Number of Actuators within Range		
		G[a]	F[a]	P[a]
1–5	5[b]	4	0	0
6–15	10[b]	1	4	4
16–20	5[b]	0	0	4

[a] G = good, F = fair, and P = poor. [b] One actuator not available for video test.

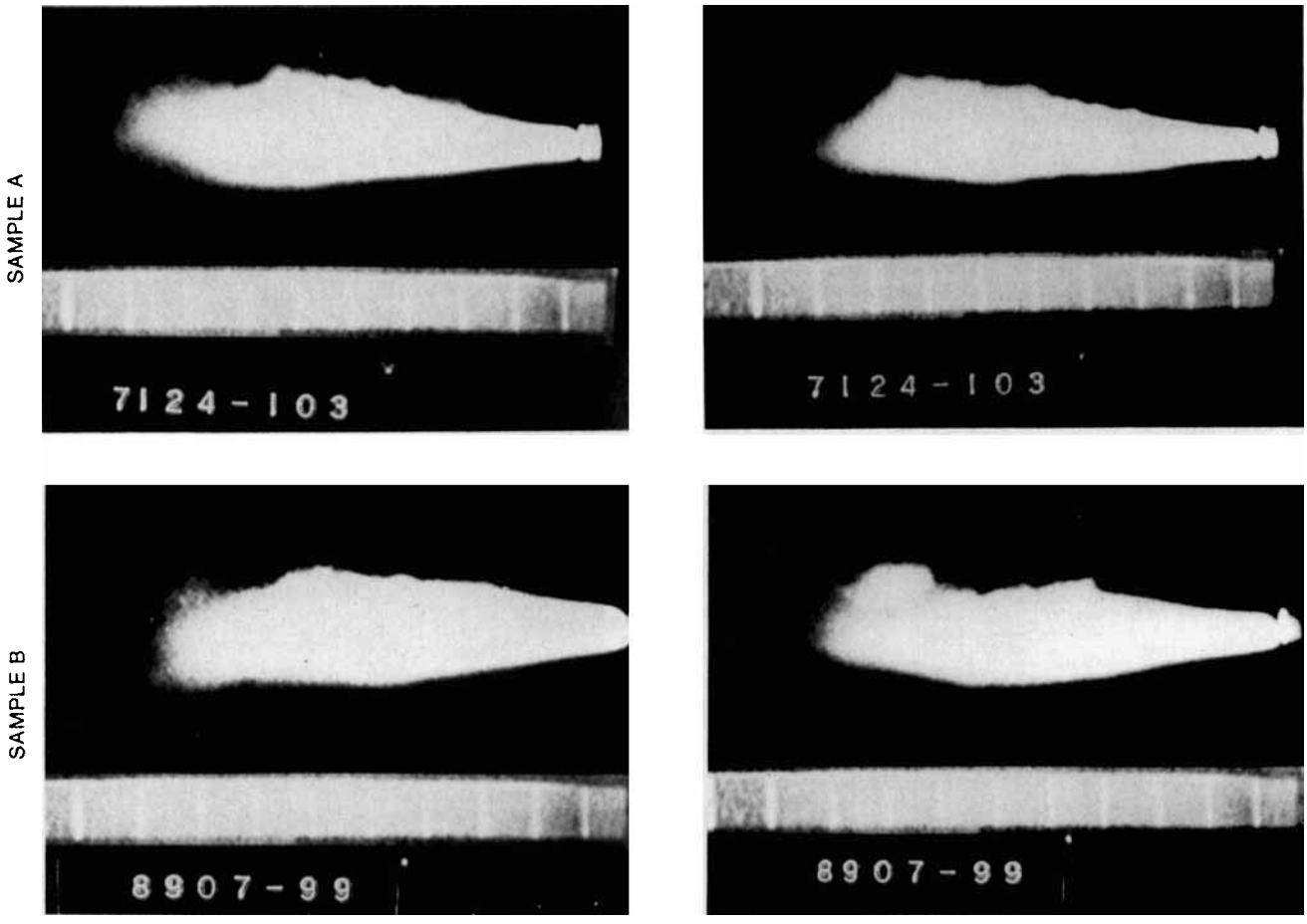

Figure 6—*Flume patterns in the side view of the same samples used in Fig. 5.*

the orifice or with irregular orifice shape. Otherwise, the flume patterns remained unchanged. This result shows that the aerosol ejected through the orifice with a nonzero exit angle with respect to the axis of the delivery tube was caused by skewed seating of the plastic insert. If the plastic inserts are inspected carefully before mounting in the actuators to eliminate those units showing burrs or other nonuniformity in either the rear or the insert tip, the yield of acceptable actuators can be improved.

The flume pattern of the vaporized liquid propellent shows that its spread was wider along the y axis than along the z axis because the propellent was accelerated first in the x–y plane and then along the x axis

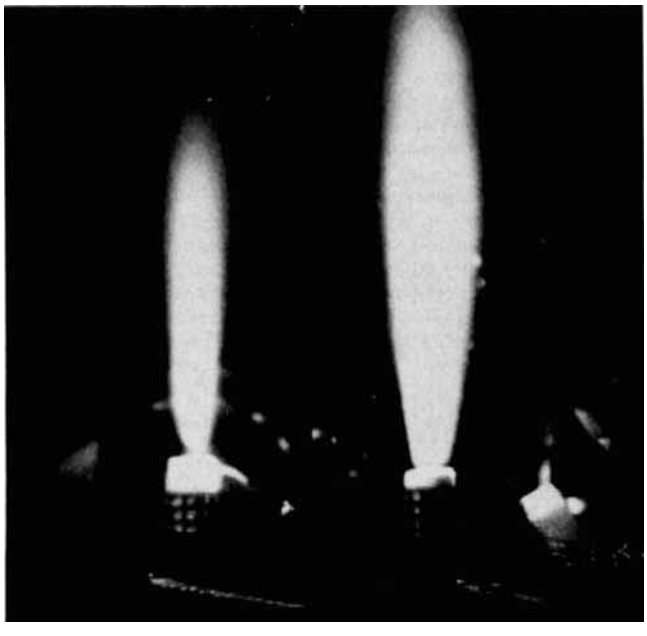

Figure 7—*Typical example of a good flume pattern in the orthogonal view.*

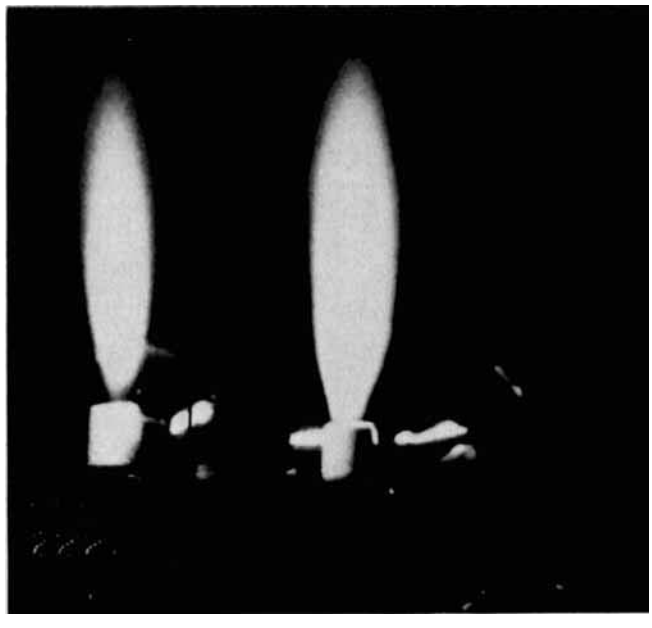

Figure 8—*Typical example of a marginal flume pattern in the orthogonal view.*

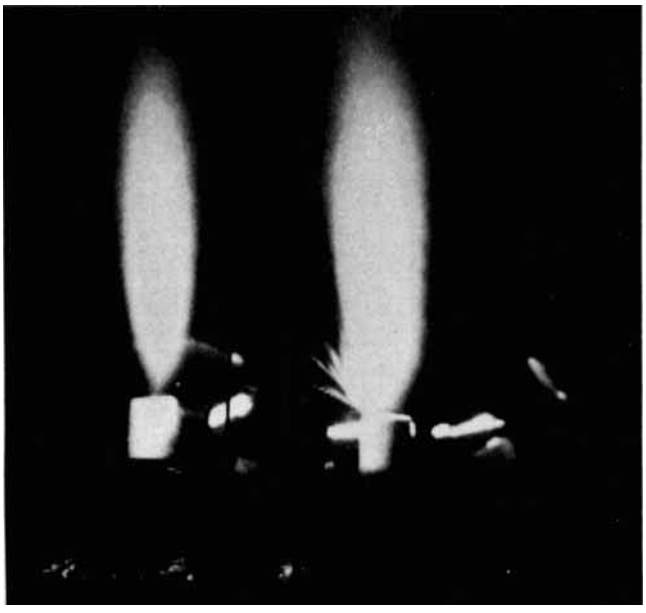

Figure 9—*Flume pattern from an actuator with a defect on its nozzle.*

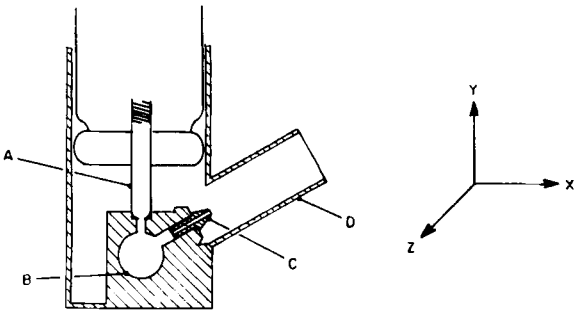

Figure 10—*Cross-sectional view of an actuator and product delivery system.*

(Fig. 10). Since the flume pattern was not cylindrically symmetrical, changing the cross section of the delivery tube from a circular to an elliptical shape with the major axis along the y axis can reduce the amount of drug trapped on the inner surface wall. The video technique also was used to study the flume patterns of an aerosol spray by varying the length of the discharging tip; as expected, the longer the tip, the narrower was the spread of the flume pattern. If the amount of drug retained inside the plastic insert is small compared with that retained on the inner wall of the delivery tube, the path length of the plastic insert could be increased.

After the propellent has been discharged and before it reaches Chamber B, the direction of acceleration has a negative component along the x axis. Thus, if one increases the angle between the axis of the plunger and the axis of the delivery tube, one can increase the drug delivery yield through the actuators.

REFERENCES

(1) "Aerosol Guide," Chemical Specialties Manufacturers Association, Washington, D.C., 1971.

(2) "The National Formulary," 14th ed., Mack Publishing Co., Easton, Pa., 1975, p. 849.

(3) L. Silverman, C. Billings, and H. W. First, "Particle Size Analysis in Industrial Hygiene," Academic, New York, N.Y., 1971.

(4) J. J. Sciarra and V. Lynch, *Aerosol Age*, **5**, 34 (1960).

(5) L. Dautrebande and W. Walkenhorst, *Arch. Int. Pharmacodyn. Ther.*, **162**, 194 (1966).

(6) J. L. Kanig, *J. Pharm. Sci.*, **52**, 513 (1963).

(7) L. Dautrebande, "Microaerosols," Academic, New York, N.Y., 1964.

(8) J. L. Kanig, *J. Pharm. Sci.*, **52**, 522 (1963).

(9) J. J. Sciarra, "International Encyclopedia of Pressurized Packaging Aerosols," Pergamon, New York, N.Y., 1966.

(10) A. B. Dobkin, "Ventilators and Inhalation Therapy," 2nd ed., Little, Brown, Boston, Mass., 1972.

(11) W. L. Hayton, *J. Am. Pharm. Assoc.*, **NS 16**, 201 (1976).

(12) A. W. Karig, G. E. Peck, and G. J. Sperandio, *J. Pharm. Sci.*, **62**, 811 (1973).

(13) J. J. Sciarra and A. Cutie, *ibid.*, **67**, 1428 (1978).

(14) P. E. Morrow, *Am. Rev. Resp. Dis.*, **110**, 88 (1974).

ACKNOWLEDGMENTS

The authors acknowledge Mr. Raymond Scharmach of the Food and Drug Administration for suggesting that flume patterns could serve as one way to show functional similarity between inhalation aerosol delivery systems.