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Research Article

Optimized Inhalation Aerosols. I. The Effects of Spherical Baffle Size and Position upon the Output of Several Pressurized Nonaqueous Suspension Formulations

Peter R. Byron,[1,4,5] Richard N. Dalby,[2,4] and Anthony J. Hickey[3,4]

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Baffles contained in conventional actuators may be a convenient alternative to some of the extension devices used presently with metered-dose inhalers (MDIs). Actuators were modified to determine whether baffles could be used to decrease the output of large "nonrespirable" droplets. These actuators were tested using a series of nonaqueous suspension aerosols containing 0.1 to 2.0% micronized disodium fluorescein (DF) as the model drug, stabilized by sorbitan trioleate in a constant blend of fluorocarbons 11, 12, and 114. A 25-μl metering volume was used throughout. Aerosol output was characterized by cascade impaction. Baffle size and position had pronounced effects on actuator retention and aerosol output. Increasing baffle size resulted in increased retention in the actuator. The total output of the MDI in the "respirable" range (aerodynamic diameter, D_{ae}, <5.5 μm) was greater in the unbaffled actuator than in all baffled actuators. However, all baffles increased the respirable fraction (DF with D_{ae} <5.5 μm: total DF leaving the actuator), R, when compared to their unbaffled controls. For example, for a 0.1% DF, 0.14% surfactant formulation, R was increased from 0.40 (unbaffled) to 0.71 by incorporation of a 0.6-cm-diameter sphere 1.3 cm from the jet of the actuator. In these cases, aerosol segregation occurred due to droplet inertia in the high velocity gas flows. Increasing the respirable fraction at the expense of the total respirable output may obviate undesirable clinical effects.

KEY WORDS: aerosol; suspensions; particle size; formulation; inhalation; baffles; sprays; inertial capture.

INTRODUCTION

Metered-dose inhalers (MDIs) deposit small fractions of their discharged dose in the lung (1,2). Desirable aerodynamic diameters for targeting the alveolar regions, while avoiding significant oral deposition, require particle sizes of less than 5 μm (3,4). Most of the aerosol output consists of droplets which are either too large or traveling too fast to be respirable (2,3). To improve this situation it is necessary either to ensure the production of smaller droplets or to reduce the emission of nonrespirable droplets and particles or both (3).

Baffles have been used successfully to prevent the emission of nonrespirable aerosols from nebulizers (1,3,5). Oropharyngeal deposition is known to be much lower for nebulizers as compared to MDIs despite their empirical design (5). The lung penetration efficiency is apparently enhanced (6) because of the continued reaerosolization of liquid retained by baffles (3).

Unfortunately, little is known about the mechanism of droplet formation following actuation of MDIs. It is unusual for formulation, valve, and actuator combinations to be codesigned in order to provide optimal spray characteristics. The purpose of this paper is to describe the effects of baffle size and placement upon MDI output from different suspension formulations.

Factors defining particle and droplet sizes emitted for inhalation at the mouthpiece of an MDI relate to both the formulation and the sequence of events during actuation. Figure 1 shows a schematic of the container, valve, and actuators used in this study, which, with the exception of the baffles, are typical of presently marketed MDIs. The formulations are usually a suspension of micronized, hydrophilic drug, "sterically stabilized" by the presence of a hydrophobic surfactant, in a volatile fluorocarbon propellant blend (7–9). "Steric," as opposed to "electronic," stabilization is believed to be the major mechanism preventing caking in suspensions with a low dielectric continuous phase. The initial particle size of the solid drug in suspension and the tendency to aggregate upon generation have been noted as sig-

[1] Department of Pharmacy and Pharmaceutics, Virginia Commonwealth University, Box 581, MCV Station, Richmond, Virginia 23298-0581.

[2] Fisons plc., Pharmaceutical Division, Research and Development Laboratories, Bakewell Road, Loughborough, Leicestershire, U.K.

[3] College of Pharmacy (M/C 880), University of Illinois at Chicago, 833 South Wood Street, Chicago, Illinois 60612.

[4] Work performed at College of Pharmacy, University of Kentucky, Lexington, Kentucky 40536-0082.

[5] To whom correspondence should be addressed.

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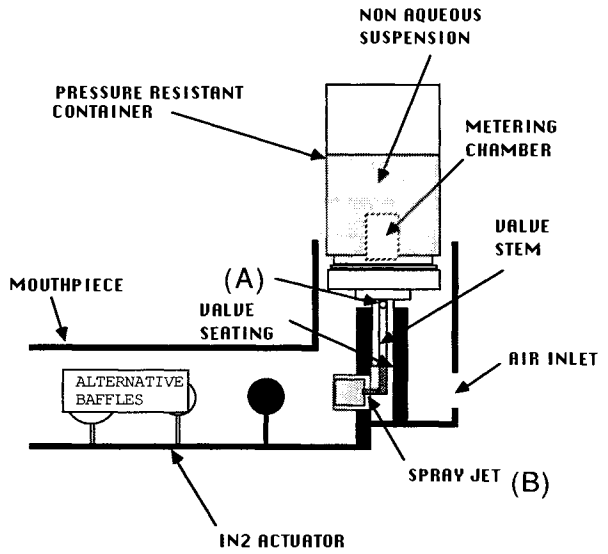

Fig. 1. Schematic diagram of modified MDI and Valois IN2 actuator showing position and representative sizes of brass spheres with respect to the 0.4-mm-diameter spray jet. Spheres were absent in the unmodified actuator. The orifice A had a diameter of 0.56 mm, while the internal diameter of the valve stem was 1.32 mm. The total volume of the metering chamber and valve stem arrangement (up to the spray jet) was 50 μl.

nificant formulation considerations in conventional inhalation aerosol formulations (9,10). Various suspension concentrations were employed in the present studies. In most cases the surfactant/drug ratio was held constant at a previously determined optimum (8).

The quantity of surfactant in many formulations is roughly equivalent to that of the drug. During actuation the metering chamber, valve stem, and seating within the actuator act as an expansion chamber. Thus, the first stage of the discharge process involves vapor incorporation within the suspension and may be conceived as the formation of an expanded foam. Foam characteristics depend upon the formulation, the volume of the metering chamber, and the relative sizes of the orifice (A) and spray jet (B) (Fig. 1). The primary (11) atomization of this foam and any subsequent droplet breakup [secondary atomization (12–14)] are the phenomena responsible for droplet formation. Atomization of a more expanded foam, produced by minimizing the ratio of the volume of the metering chamber to that of the valve stem, may yield sprays with different sizes. In these studies a single (metering chamber: valve stem) volume ratio was utilized to eliminate this factor as a variable in droplet formation.

The inclusion of obstacles within jet nebulizers (in the flight path of the aerosol) has been purported to enable mechanical breakup of fluid sheets and large droplets as well as preventing the emission of nonrespirable aerosol (3,5,15). While it is possible to break very large drops into smaller ones using impaction plates (11), it is unlikely that such a mechanism can be used to reduce the size of drops as small as 20 μm. Whether baffles allow the emission of respirable aerosol but prevent the exit of larger droplets and particles requires, first, that they do not impede atomization and, second, that they retain large droplets preferentially. In an MDI, the distance from the jet at which the spray is completely formed is difficult to determine. Equally, it is presently impossible to predict the efficiency of unstable aerosol capture by baffles placed in turbulent airstreams. Experiments were performed to determine practically the effects of baffle position upon the particle size distribution of aerosol output from MDIs.

MATERIALS AND METHODS

Preparation of Pressurized Aerosol Units

A series of suspension aerosols was prepared using micronized disodium fluorescein (DF; Fisher Scientific, St. Louis, Mo.) as the dispersed phase at concentrations of 0.1, 0.5, 1, and 2% (w/v). Sorbitan trioleate (Span 85, Fluka AG, Ronkonkoma, N.Y.) was employed as suspending agent, at a weight ratio 1.4:1, surfactant:DF, except in one case when a 0.1% suspension was prepared containing 1.4% Span 85. One fluorocarbon propellant blend was used throughout (Dymel 11, 12, and 114, 1:2:1 by weight, DuPont, Wilmington, Del.), with a calculated vapor pressure of 41.4 psi (gauge) and a density of 1.4 g/cm^3 (21°C). The solubility of DF in all cases was negligible.

Disodium fluorescein was milled prior to use (Trost Gem T research jet mill, Garlock, Inc., Plastomer Products, Newtown, Pa.) operated at 70 psig with dry air, and the resulting powder sized by optical microscopy (Reichert Zetopan large research microscope, Vienna, Austria). The same batch of DF was used for all formulations, having a count median and volume median diameter of 2.6 and 4.9 μm, respectively, assuming sphericity. All other reagents and materials were used as supplied. Micronized DF was manually levigated to a smooth, uniform paste with sorbitan trioleate (7). Aliquots of the resulting pastes were transferred to plastic-coated glass pressure-resistant bottles (Wheaton Glass, Mays Landing, N.J.) and fitted with 25-μl/actuation, inverted metered-dose valves (Valois DF 10, BLM Packaging, Inc., Greenwich, Conn.). Propellant was added through the valve. Valve crimping and propellant filling were performed using Pamasol small-scale aerosol pressure packaging equipment (Pfaffikon, Switzerland). Each assembled aerosol unit was tumble mixed using a Turbula mixer (Model T2C, Glenn Mills, Inc., Maywood, N.J.) operated at maximum speed for 1 hr. Investigations were performed on each aerosol unit within 2 days of manufacture to avoid the possibility of storage dependent changes in aerosol output.

Actuator Design

Valois IN2 actuators (BLM Packaging, Inc., Greenwich, Conn.), 2.8 cm^2 in cross-sectional area at the mouthpiece were modified by the insertion of a single brass sphere which was 0.3, 0.6, 0.9, or 1.2 cm in diameter centered 1.3, 2.4, or 4.2 cm from the spray jet (B; Fig. 1). Each sphere or "baffle" was positioned by a 1/16-in. (diam.) bolt and secured by a nut on the lower, outer surface of the actuator mouthpiece. The actuator housing and circular spray orifice (0.4 mm) designed for spraying suspensions were constant.

Determination of Output Particle Size Distributions

Each aerosol unit was shaken vigorously for 30 sec, fitted with a modified or unmodified actuator (Fig. 1), and attached to the inlet port of an evaporation chamber (7) located atop a calibrated cascade impactor (Delron Research Model DCI-6, Powell, Ohio) through which air was drawn at 12.45 liters/min. Following actuation, DF deposited in the actuator (all cases) and in the evaporation chamber and impactor (unmodified actuator and those containing 0.6-cm-diameter spheres) was determined spectrophotometrically. The apparatus and procedure have been described in detail previously (7). The size parameter which was measured by cascade impaction was the aerodynamic diameter (D_{ae}), which assumes sphericity and unit density. Three replicates of each experiment were performed.

RESULTS AND DISCUSSION

Ideally, no drug in particles or droplets with a D_{ae} much greater than 5 μm would be emitted from MDIs for oral inhalation (3,4). If this could be achieved, nearly all of the drug leaving these devices would be respirable (in practice, about 10% of each metered dose is capable of lung penetration). The 50% cutoff diameter of the second stage of the cascade impactor was 5.5 μm. This diameter was assumed to be the practical upper limit for respirable particles in these studies. Cascade impaction was considered the most appropriate dynamic sizing technique since sizes obtained by laser light-scattering methods may give erroneous results with rapidly evaporating fluorocarbon droplets.

Effects of Baffle Size and Position

A suspension containing 2.4% (w/v) nonvolatile material (1% DF and 1.4% Span 85) was employed for pilot experiments to determine the optimal baffle size and position. The nominal metered dose was 350 μg DF. Deposition in the unmodified actuator, expansion chamber, and cascade impactor (Fig. 2 in Ref. 7) was 32.4, 34.8, and 32.8 (18.9% of the dose had D_{ae} <5.5 μm, while 13.9% had D_{ae} between 5.5 and 11.2 μm), respectively. Thus, more than 48% of the dose (expansion chamber + DF in the size range 5.5–11.2 μm) was emitted from the unmodified actuator, as an aerosol with D_{ae} >5.5 μm. In practice, this "nonrespirable" material would almost certainly be deposited in the back of the throat and laryngeal regions (7). Table I shows the results from a series of experiments designed to determine the increases in actuator retention induced by the presence of any one of four spherical baffles of varying diameter, positioned differently with respect to the spray jet. Deposition was determined while drawing air through the actuators at 12.45 liters/min. While it may be theoretically possible to prevent the emission of virtually all nonrespirable drug, it is not helpful if this is achieved at the expense of the respirable dose (this would require multiple inhalations to achieve therapeutic levels). Based on the data for the unmodified actuator the 0.6-cm-diameter baffles appeared to retain more nonrespirable particles than other baffles while allowing the passage of more "respirable" particles. This assumes that (a) aerosol emissions >5.5 μm result in oropharyngeal deposition and (b) baffles themselves cannot reduce the size of passing droplets or particles. Smaller spheres produced inadequate retention of nonrespirable particles, while those with diameters of 0.9 and 1.2 cm obstructed aerosol emissions of both respirable and nonrespirable particles.

Table I. Percentage of Metered Dose Retained in Actuators Containing Spherical Baffles of Different Sizes[a]

Baffle size[b]	Baffle position[c]	% in actuator[d]
None	None	32.4 (1.3)
0.3	1.3	49.5 (6.7)
	2.4	45.2 (3.3)
	4.2	40.8 (1.3)
0.6	1.3	77.1 (0.9)
	2.4	71.7 (0.9)
	4.2	62.6 (4.1)
0.9	1.3	93.9 (12.7)
	2.4	89.0 (13.8)
	4.2	79.2 (3.3)
1.2	1.3	91.7 (4.9)
	2.4	90.7 (3.9)

[a] Data collected for 1% suspension of micronized disodium fluorescein stabilized by 1.4% sorbitan trioleate in fluorocarbon blend (11:12:114 = 1:2:1) by weight.
[b] Sphere diameter (cm).
[c] Distance between jet and center of sphere (cm).
[d] Percentage of dose emitted from 25-μl metering valve. Mean of three replicates; 0.5× range of experimental results in parentheses.

Spherical, 0.6-cm-diameter baffles, when placed directly in the trajectory of the aerosol (Fig. 1), produced changes in actuator retention and the emission of respirable DF (<5.5 μm) versus nonrespirable DF (Table II). In the case of spheres centered 1.3 or 2.4 cm from the spray jet, substantial increases in the fraction of respirable aerosol, R, occurred where

$$R = \frac{(\text{DF with } D_{ae} < 5.5\ \mu\text{m})}{(\text{total DF leaving actuator})} \quad (1)$$

Although the spherical baffle centered 4.2 cm from the jet caused additional DF retention in the actuator, the value of R remained virtually unchanged from that determined in its absence (baffle = none in Table II). Baffles placed closest to the jet (1.3 and 2.4 cm) retained primarily DF which fell in the nonrespirable (>5.5-μm-D_{ae}) range. Although the 0.6-cm-diameter spherical baffle at 4.2 cm also increased actuator deposition, it lacked the ability to cause preferential retention of the large aerosol material. When deposition in the modified actuators was subdivided into loss on the baffle itself and "wall and jet" losses, about 50% of the retained DF was located on the spherical baffle. This observation was independent of baffle position, although results showed more variation in the case of the baffle at 4.2 cm. A baffle centered 2.4 cm from the jet allowed the escape of more nonrespirable DF from the actuator, while the respirable dose was similar to that found with the baffles positioned 1.2 cm away. The observations in this paragraph were independent of the formulation tested (Table II) and have several interesting implications:

(a) baffles which separate droplets based upon their in-

Table II. The Effects of 0.6-cm-Diameter Spherical Baffles upon Aerosolized Drug Output from Modified Metered-Dose Inhalers Containing Different Formulations

DF[a]	Baffle[b]	Percentage of dose[c]				R^e
		Actuator	Exp. Ch.[d]	5.5–11.2 μm	<5.5 μm	
0.1%	None	29.4 (1.4)	31.3 (3.4)	11.6 (0.5)	27.9 (0.7)	0.40
	1.3 cm	73.0 (0.2)	4.6 (0.2)	3.4 (0.1)	19.1 (0.3)	0.71
	2.4 cm	65.6 (3.2)	11.6 (0.2)	4.1 (0.3)	18.7 (0.8)	0.54
	4.2 cm	61.0 (3.1)	19.4 (0.8)	4.0 (0.2)	15.6 (0.2)	0.39
0.5%	None	31.0 (1.4)	34.6 (1.3)	15.2 (0.3)	19.2 (0.2)	0.28
	1.3 cm	75.7 (0.1)	5.2 (0.4)	4.8 (0.2)	14.3 (0.3)	0.59
	2.4 cm	66.0 (0.6)	13.2 (0.6)	6.5 (0.1)	14.3 (0.3)	0.42
	4.2 cm	60.7 (1.0)	22.8 (0.7)	5.5 (0.5)	11.0 (0.1)	0.27
1%	None	32.4 (1.3)	34.8 (2.0)	13.9 (1.0)	18.9 (0.6)	0.28
	1.3 cm	77.1 (0.9)	4.2 (1.4)	5.4 (0.6)	13.3 (0.4)	0.58
	2.4 cm	71.7 (0.9)	11.7 (0.2)	5.2 (0.5)	11.4 (0.5)	0.40
	4.2 cm	62.6 (4.1)	19.9 (2.4)	5.7 (0.6)	11.8 (0.4)	0.32
2%	None	32.8 (1.4)	40.0 (0.6)	15.2 (1.0)	11.9 (0.5)	0.18
	1.3 cm	85.9 (0.5)	4.6 (0.2)	3.1 (0.4)	6.4 (0.2)	0.45
	2.4 cm	78.4 (1.8)	10.6 (0.8)	4.4 (0.7)	6.6 (0.4)	0.31
	4.2 cm	68.1 (2.1)	18.7 (1.0)	5.8 (0.5)	7.5 (0.6)	0.24
0.1%[f]	None	32.4 (0.5)	33.8 (1.7)	15.0 (0.8)	18.8 (0.3)	0.28

[a] Suspension formulation containing 1.4:1 Span 85:DF by weight; values are percentage (w/v) micronized disodium fluorescein.
[b] 0.6-cm-diameter baffle position; distance between jet and center of sphere.
[c] Values in parentheses are 0.5× the actual experimental range ($N = 3$).
[d] 380-cm^3 expansion chamber (atop cascade impactor).
[e] Equation (1).
[f] Containing 1.4% Span 85.

ertial properties can be employed successfully in MDIs;

(b) the atomization process is probably complete very close to the jet (distance between sphere surface and jet is <1 cm for closest baffle); and

(c) increases in the value of the respirable fraction, R, can be achieved by retaining the larger droplets in the actuator, and thus most of the drug which will ultimately be considered respirable is contained in smaller "satellite" droplets (3) at the outset.

Formulation-dependent results can be seen most clearly in the values for R in Table II. More dilute suspensions (lower DF and surfactant concentrations), enable larger respirable fractions to be emitted from baffled and unbaffled actuators. This is due to low surfactant concentration and minimal aggregation (10). With the exception of the 2% suspension, about 70% of the respirable dose (determined in the absence of baffles) remained as aerosol output from the actuators baffled at 1.3 cm (68.5, 74.5, 70.4, and 53.8% for 0.1, 0.5, 1, and 2% DF, respectively). Conversely, for this baffle position and all formulations, the emission of nonrespirable DF was less than one-fifth of its value when compared to an unbaffled actuator. It is important to recognize that when results are presented solely in terms of mass-median aerodynamic diameters, taking the whole MDI output into account, and allowing sufficient time to enable almost complete evaporation to occur [see the pioneering work of Polli *et al.* (9)], it is easy to mask some of these effects. The dynamic sizing technique and data treatment used in the present paper are more able to discriminate between formulations than those reported by Polli *et al.* (9).

Effects of Suspension Concentration

A range of DF concentrations was reviewed in order to assess the importance of multiple-particle inclusion in sprayed droplets and the effects upon D_{ae} (10). Table II shows the results of detailed studies which were performed to determine the effects of 0.6-cm baffles upon aerosol output, as a function of suspension concentration. In the unmodified actuator (baffle = none in Table II) increasing the suspension concentration decreased the proportion of the dose which was respirable (<5.5-μm D_{ae}). Nominal metered doses of these 0.1, 0.5, 1, and 2% suspensions were 35, 175, 350, and 700 μg, respectively. The trend of these results is consistent with previous observations (9) and with theory (10) where the number of particles in each spray droplet must increase as a function of the volumetric concentration provided that the initial droplet size distribution is known and that the whole metered dose is collected and sized as evaporated aerosol droplets.

Since the sizing technique employed in these investigations was dynamic (3), increasing the surfactant concentration (proportional to DF) may have reduced the droplet evaporation rate and consequently the resultant percentage of the dose <5.5 μm. In an attempt to estimate the magnitude of this effect, the aerosol output was characterized from a second 0.1% (w/v) DF suspension stabilized with 1.4% (w/v) Span 85 (footnote *f*, Table II). This output was compared to another 0.1% DF suspension in which the surfactant/DF ratio was 1.4 as in all other cases. Neglecting effects due to density differences and spray droplet size (10), the diameter of a primary particle should be increased by

multiplying by a factor of about 1.34 ($2.4^{1/3}$) throughout most of Table II but 2.5 ($15^{1/3}$) in the case of the 14:1 surfactant: drug ratio. These statements refer to propellent-free particles, not droplets. Unbaffled actuator retention was similar for all formulations investigated. The remainder of the deposition profile of the 0.1% DF, 1.4% surfactant formulation closely resembles that of the 1% suspension (which also contained 1.4% surfactant); results indicate a larger aerosol size distribution than that shown for the 0.1% suspension containing 0.14% surfactant. Comparing the first and last rows of data in Table II, the DF coating with surfactant following propellant evaporation from the 14:1 surfactant:DF ratio in the 0.1% DF suspension should mean that single particles from this formulation have larger aerodynamic sizes (about 2.5/1.34× the diameter) than those from the 1.4:1 surfactant:DF suspension. It is thus possible that multiple-particle inclusion in single droplets, droplet evaporation kinetics, or both influence these results. This comparison illustrates the difficulty in differentiating the effects of aggregation due to suspension concentration (10) and reduced droplet evaporation rates related to surfactant concentration (7). Nevertheless, increasing the suspended drug or the surfactant concentration produced larger, less respirable aerosols. The reduction in aerosol size, which was observed previously to be due to the inclusion of sorbitan trioleate in dexamethasone sprays (9), was almost certainly due to a reduction in interfacial tension, reducing the initial spray droplet sizes (11).

The vapor pressure, valve, actuator, and spray jet design has been held constant in these studies but the baffle size and positions reported here may not be appropriate for other pressurized systems. Increased vapor pressure, for example, will contribute directly to droplet inertia and impaction efficiency by increasing the speed of expulsion from the jet (18).

Delivery of all of the metered dose of a pharmaceutical inhalation aerosol in the form of respirable particles is currently unattainable (1). Investigations utilizing highly volatile, low-concentration, solution formulations result in 40% of the output aerosol falling in the respirable range (7), compared with 10% from conventional suspension formulations (19). Available spacer and reservoir devices represent some improvement on the MDI alone but they are cumbersome, difficult to use (20), and unsuccessful in removing the nonrespirable material from the aerosol. The studies presented here have shown that baffles may be used to remove nonrespirable drug from the aerosol output of MDIs without blockage problems or impeding the airflow. The respirable doses emitted from optimized baffled actuators in these studies were similar to those from their unbaffled controls. In contrast, the nonrespirable fraction was collected in the baffled actuators rather than emitted for oropharyngeal deposition. Hence despite some reduction in the fraction of the total dose available for pharmacologic action, there was a significant decrease in material which would be available for oropharyngeal deposition, which is associated with undesirable side effects [e.g., steroids–oral candidiasis (6)].

On a practical note, the drug substance retained by the baffle was easily removed by rinsing the actuators with water, something that is necessary even for unbaffled systems. Baffled actuators have the advantage over spacers that they remain small, portable, and unobtrusive. However, baffle size and position in the actuator should be optimized for each formulation—valve combination under development.

CONCLUSION

Pressurized aerosol units have been prepared and used to examine the effects of (a) baffle size and position on "respirable" and "nonrespirable" aerosol output and (b) suspension concentration in conjunction with baffle size and position on respirable and nonrespirable aerosol output. It was concluded that the ratio of the respirable:nonrespirable fractions of the total aerosol output could be maximized ($R = 0.71$, with a baffle size of 0.6 cm, positioned 1.3 cm from the jet, formulated with 0.1% DF and 0.14% surfactant), with only a small reduction in respirable dose in comparison with an unbaffled actuator.

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