Particle Size Distribution of Single and Multiple Sprays of Salbutamol Metered-Dose Inhalers (MDIs)

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INTRODUCTION

Historically, particle sizing of aerosols by impaction has been based on multiple actuations (1–6). Following the characterization of the "first-spray effect" (7) and the increase in sensitivity of analytical methodology, efforts have been made to characterize single sprays for both content uniformity (8,9) and particle size distribution (10) since single or two consecutive sprays are recommended by the manufacturer on the patient instruction insert and on the package. As a result, work was undertaken to characterize the particle size distribution of single sprays from three commercially available salbutamol metered dose inhalers (MDIs) against the particle size distributions obtained by multiple actuations. Particle size distributions were characterised by two distribution parameters, the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) using an eight stage Andersen cascade impactor, Mark II. The results of the experiments showed that the measured distribution from one manufacturer to another is not identical and that there is a shift in the measured distribution curve as the number of sprays into the impactor increased.

MATERIALS AND METHODS

Sample Collection

Sprays from the salbutamol inhaler products were collected in an Andersen 1 actual cubic foot per min (ACFM) non-viable ambient particle sizing sampler at a flow rate of 28.3 l/min. The induction port was as specified in the USP (1). The canister was primed by expelling three sprays to waste (shake 5 sec, let contents settle for 1 sec, depress valve for 1 sec, wait 30 sec between sprays, rinse actuator, dry). Place canister valve down when not in use. After setting the flow rate for the assembled apparatus, the canister was shaken for 5 sec, inserted into the mouthpiece coupler and the valve depressed for one sec. The vacuum generated air flow was stopped 5 sec after the initiation of the spray. The canister remained valve down at all times. Multiple actuations were made at 30 sec intervals, with the canister remaining valve down at all time and the air flow being started 10 sec before the spray. The actuator, induction port, mouthpiece coupler, Andersen top, and stages (with the accumulated depositions) were washed into appropriate volumetric flasks and made up to volume with methanol. The mass of salbutamol on each stage was divided by the number of sprays used in the collection to give an average value.

Sample Analysis

Salbutamol samples were analyzed by a liquid chromatographic method developed in this laboratory (11). A five point calibration curve (ranging from .025 to 5 μg/ml) was generated daily and analyzed using a weighted least squares regression. The pooled precision and accuracy coefficient of variation at .025 μg/ml was 9.5%. This lower limit of quantitation allowed measurement to approximately 0.4 μg per stage for single sprays. Since multiple spray amounts were divided by the number of sprays, lower amounts per stage are reported. The coefficient of variation of six injections of a 0.5 μg/ml solution was less than 3%.

Equipment

The liquid chromatograph (Varian Star) consisted of a model 9010 ternary pump, a model 9095 autosampler equipped with a 100-μl loop (Valco Instruments Co. Inc), a model 9050 variable wavelength UV-VIS detector, and a 9020 Workstation with revision C software. A vacuum pump (GAST, General Electric Corporation, Model 0522-V4B-G180DX) was used to draw the air flow through the impactor, air flow was measured with a Primary Standard Airflow Calibrator (Gilian Gilibrator).

Reagents

Methanol (BDH Inc, Toronto, ON) was HPLC grade and *o*-phosphoric acid (85%) (Fisher Scientific, Fairlawn, NJ) was spectrophotometric grade. Deionized water was prepared using a Sybron/Barnstead system. Salbutamol, 1,3-Benzene-dimethanol, α^1\{[(1,1-dimethyl)amino]methyl\}-4-hydroxy-; was obtained from Cipla Ltd. (Bombay, India).

Test Samples

The salbutamol metered-dose inhalers were obtained, directly from manufacturer sites, by inspectors from the Field Operations Directorate, Health Protection Branch. Samples were coded by a capital letter to represent the manufacturer and a number to represent the lot.

Experimental Design

Single primed sprays from the three manufacturers were sampled at the following spray numbers: 11, 15, 19, 23, 27, 31, 35, 39, 43, 47. For the comparison of single versus multiple sprays, each canister, after priming, was sampled (1, 2, 5, or 10 sprays) according to a 4 × 4 latin square.

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Calculation of MMAD and GSD

To estimate the parameters of the log-normal distribution two procedures were used. The USP (1) estimates the parameters using a method based on the cumulative normal distribution function after taking the logarithms of the ECDs. Since the weights of drug are cumulated, errors associated with each observation is also added, thus a weighted least squares algorithm was used with weights equal to the number of stages used in the summation. These estimates are subscripted WLS. LIFEREG (SAS® (12)) estimates the parameters based on the normal probability function after taking the logarithm of the ECDs. The actual weight of drug is used not the cumulative amount so weighting is not required, however, the observations are interval censored (*i.e.*, they are the mass of all particles sized between the ECD of the plate upon which it resides and the ECD of the plate above it) and the maximum likelihood routine of LIFEREG was appropriate with weight equal to the amount on the stage. Estimates of MMAD and GSD based on this method are subscripted CML.

RESULTS AND DISCUSSION

Single Spray

Figure 1 plots the mean mass and range (verticle line segments) of masses per stage for ten single sprays against effective cut off diameter of the stage (a particle distribution profile) for the three manufacturers. The range is indicative of the variation in the amount of drug observed on a given stage within a manufacturer. It can also be seen that the three manufacturers, visually, would seem to have different mean profiles, but the real question is whether these differences can be quantitated. The product codes are the same as those presented by Cyr *et al.* (7).

Table I presents the data illustrated in Figure 1 in three different ways. The first section of the table is the mean amount per stage and their CVs. The variation on the stages nearer the two tails is generally much larger than the variation on the stages where the distribution peaks. For all three products, the greatest amount of drug was deposited on stages 4 and 5 (corresponding effective cut-off diameter (ECD) 2.1 and 1.1 μm, respectively), accounting for over half the amount deposited in the impactor. To compare manufacturers by stage is a difficult process thus in order to summarize the data further, section two, collective stages is presented. Here certain stages have been summed in order to see how much drug is delivered in certain sized particles. The stages encompassing the particle sizes 9 to 0 μm represent the total amount entering the impactor while the stages containing particles in the range 5.8 to 1.1 μm could be defined as the fine respirable fraction (FRF) for salbutamol. Manufacturer B had the least amount of total drug both in the impactor and in the FRF range. There is a slight improvement in precision as measured by the CV for manufacturer comparisons using these summed stages when compared to the individual stages. Manufacturer C tends to have more variation than A and B.

The final section of Table I gives distribution estimates of location, MMAD, and of dispersion, GSD, of the particle distribution profiles. There is a marked decrease in the CV of these estimates making it easier to compare man-

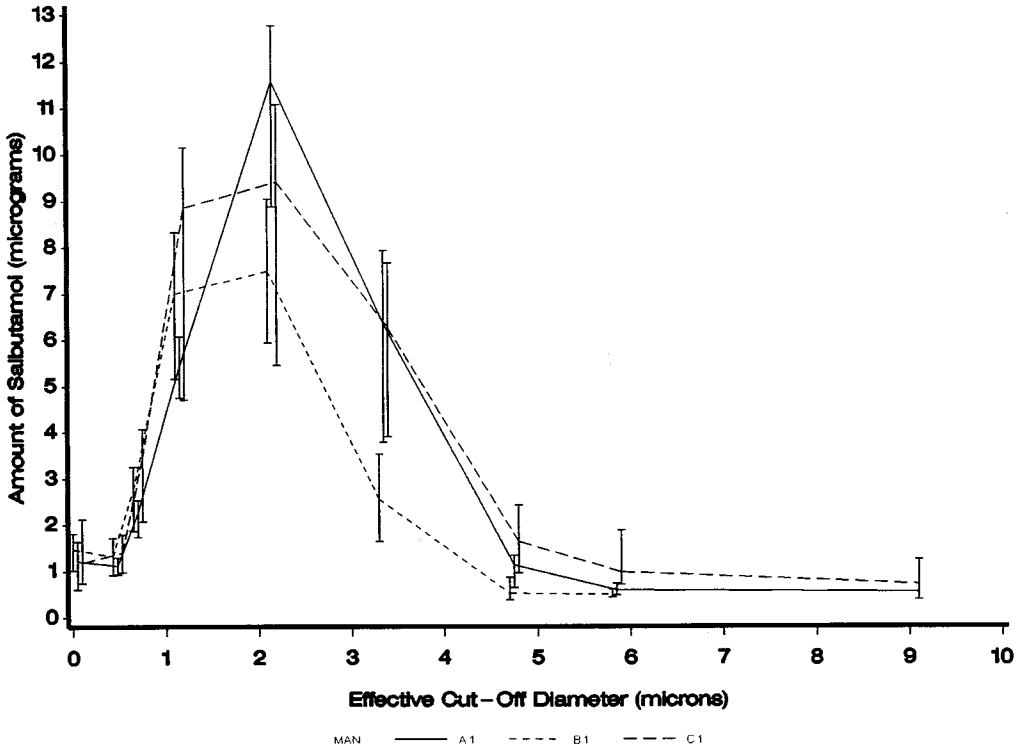

Fig. 1. Particle distribution profiles of the mean of ten single sprays from all manufacturers (the range of amounts on each stage is indicated by the vertical bars). To separate manufacturers values have been shifted slightly on the x-axis.

Table I. Mean (CV) deposition on stage (μg), single sprays

Manufacturer, Lot No. Sprays	A1 1[a]	B1 1[a]	C1 1[a]
Stage 0 (9.0 μm)[b]	BLQ[c]	BLQ	.7 (56)
1 (5.8 μm)	.6 (14)	.5 (20)	1.0 (37)
2 (4.7 μm)	1.1 (18)	.5 (31)	1.6 (25)
3 (3.3 μm)	6.4 (17)	2.6 (23)	6.3 (19)
4 (2.1 μm)	12 (10)	7.5 (14)	9.4 (19)
5 (1.1 μm)	5.4 (8)	7.0 (13)	8.9 (20)
6 (0.65 μm)	2.3 (13)	2.8 (13)	3.4 (17)
7 (0.43 μm)	1.1 (11)	1.3 (15)	1.4 (17)
F (0 μm)	1.2 (25)	1.5 (18)	1.2 (34)
Collective stages[d] (ECD)			
9.0–0	30 (11)	23 (13)	34 (17)
5.8–0	29 (12)	23 (13)	33 (17)
5.8–1.1	25 (11)	18 (13)	27 (18)
3.3–1.1	23 (11)	17 (13)	25 (19)
Distribution estimates			
$MMAD_{CML}$	2.2 (4)	1.7 (5)	2.1 (4)
GSD_{CML}	2.0 (3)	2.0 (3)	2.0 (8)

[a] Mean of 10 determinations.
[b] Effective Cut-off Diameter of the stage.
[c] Below the limit of quantitation.
[d] Values have been rounded to 2 significant figures.

ufacturers. Manufacturer B has a lower MMAD then A and C which show little difference. There is no difference in GSDs, however, the distribution for manufacturer A had a more sharply peaked curve than those for manufacturers B and C.

Single v. Multiple Sprays

Table II contains a comparison of single (one) versus multiple (2, 5, and 10) sprays for two manufacturers (A1 and B2). Each manufacturer was examined independently to identify differences between the number of sprays then, the amount deposited in specific size ranges was compared between manufacturers. For each sample, the amount collected per stage, the $MMAD_{CML}$, GSD_{CML} and amounts in discrete size intervals are given. The resulting particle size distribution for manufacturer B2 is shown in Figure 2. Also given in Table II are estimates of $MMAD_{CML}$ and GSD_{CML} from our routine using the SAS® LIFEREG program versus those based on the USP < 601 > method. There is little practical difference between the estimates of MMAD or GSD or their variation derived from the two methods.

The plots and summary characteristics show that the distribution changes from single to multiple actuations as was reported by Miller and Schultz (13) using the Marple-Miller Cascade Impactor and also noted by Nasr (9). There is a shift in the amount measured as larger particles and a concomitant decrease in the dispersion of the particles (measured by the GSD) as the number of sprays collected increased. This effect was observed with both manufacturers A and B. There is an increase of about 5.5% between successive multiple sprays $MMAD_{CML}$s. Likewise, there is a similar percentage decrease in GSDs between successive multiple sprays. The observed change in particle size distribution, indicates that in successive sprays more particles are being retained on stages with ECDs of 3.3 to 1.1 (see Table II). Although the primary route of deposition in the Andersen is by impaction it is possible that with successive sprays the particles already present on the impaction plate create a surface that will promote the deposition of particles by the process of interception (14,15). In this process, generally considered one of the less important mechanisms of

Table II. Mean (CV) deposition on stage[a] (μg), single and multiple sprays

	A1				B2			
Manuf., Lot No. Sprays	1	2	5	10	1	2	5	10
Stage 0 (9.0 μm)[b]	BLQ[c]	.3 (19)	.3 (19)	.3 (11)	BLQ	BLQ	.3 (11)	.2 (22)
1 (5.8 μm)	.6 (17)	.5 (14)	.4 (11)	.4 (10)	.5 (10)	.3 (10)	.3 (15)	.2 (8)
2 (4.7 μm)	1.0 (14)	1.0 (10)	.9 (10)	.9 (8)	.6 (11)	.5 (17)	.4 (22)	.4 (6)
3 (3.3 μm)	5.2 (13)	5.5 (11)	5.5 (3)	5.9 (4)	1.9 (13)	1.5 (6)	1.5 (14)	1.6 (17)
4 (2.1 μm)	11 (11)	11 (9)	12 (6)	13 (6)	6.4 (17)	6.0 (7)	6.9 (9)	7.3 (13)
5 (1.1 μm)	5.2 (9)	5.7 (12)	5.9 (6)	5.6 (3)	7.5 (14)	8.0 (12)	9.7 (8)	9.8 (10)
6 (0.65 μm)	2.2 (9)	1.8 (8)	1.2 (6)	.9 (2)	3.0 (8)	2.3 (11)	1.8 (5)	1.3 (9)
7 (0.43 μm)	1.1 (14)	.8 (7)	.4 (4)	.3 (6)	1.4 (6)	1.0 (8)	.6 (7)	.4 (7)
F (0 μm)	1.0 (17)	.6 (9)	.5 (11)	.3 (9)	1.4 (56)	.7 (30)	.7 (15)	.4 (7)
Collective stages[d] (ECD)								
9.0–0	27 (10)	27 (8)	28 (4)	27 (4)	23 (13)	20 (9)	22 (6)	22 (11)
5.8–0	27 (10)	27 (9)	27 (4)	27 (4)	22 (14)	20 (8)	22 (6)	21 (11)
5.8–1.1	23 (11)	24 (9)	24 (4)	25 (4)	17 (14)	16 (10)	19 (7)	19 (11)
3.3–1.1	21 (10)	23 (10)	24 (5)	24 (4)	16 (15)	15 (10)	18 (8)	19 (11)
Distribution estimates								
$MMAD_{CML}$	2.2 (2)	2.3 (2)	2.4 (1)	2.5 (1)	1.6 (6)	1.7 (3)	1.8 (2)	1.9 (1)
GSD_{CML}	2.0 (2)	1.8 (2)	1.7 (1)	1.6 (1)	2.1 (4)	1.9 (3)	1.8 (3)	1.7 (1)
$MMAD_{WLS}$	2.0 (3)	2.2 (4)	2.3 (2)	2.5 (1)	1.6 (6)	1.7 (4)	1.8 (2)	1.9 (1)
GSD_{WLS}	2.2 (1)	2.1 (2)	2.1 (1)	2.0 (2)	2.2 (6)	2.0 (4)	2.0 (3)	1.9 (1)

[a] Mean of 4 determinations.
[b] Effective Cut-off diameter of the stage.
[c] Below the limit of quantitation.
[d] Values have been rounded to 2 significant figures.

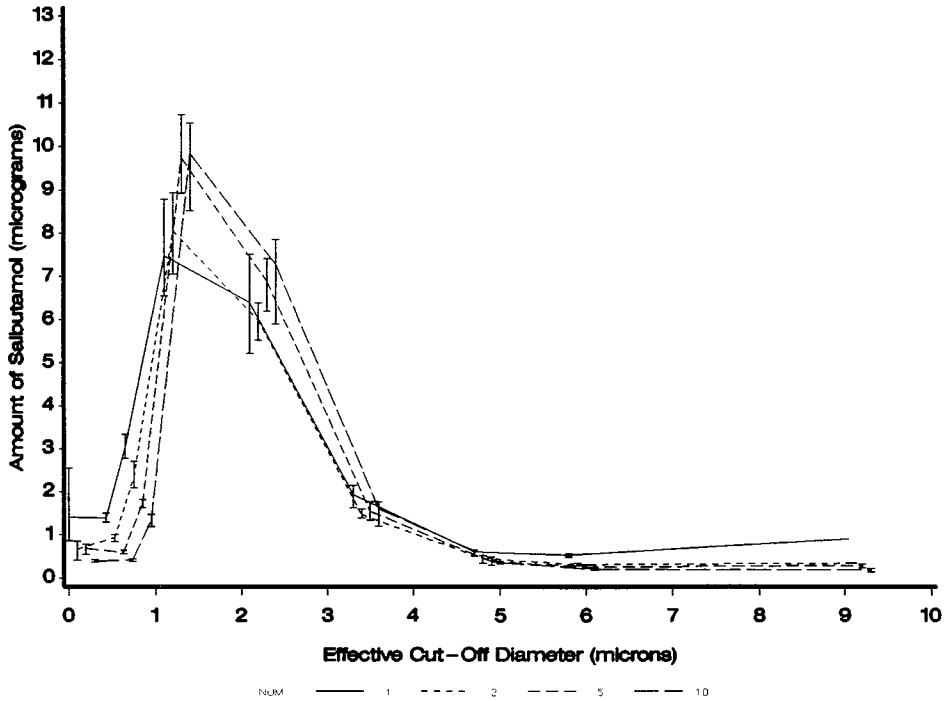

Fig. 2. Particle distribution profiles of single and multiple sprays of manufacturer B2. Values are normalized to one spray (the range of amounts on each stage is indicated by the vertical bars). To separate manufacturers values have been shifted slightly on the x-axis.

deposition, the particle, although it does not deviate from its gas streamline, contacts the airway surface. With successive sprays, the deposited particles on the impaction plate present an increasingly rugged surface heightening the chances of deposition by interception from the airstream. Thus some particles which would normally pass through to successive stages in the impactor are captured by the already deposited particles, from previous sprays, residing on the impaction plate. Such an interception process would cause a progressive increase in the MMAD (larger amounts being observed on earlier stages) and, a decrease in the GSD (the distribution of smaller particles being less discriminative). The inference is that there is no real change in the particle size as delivered to the impactor, however, the increasing role of interception in the deposition process creates an apparent change in the particle size distribution. In addition to this proposition would be the supposition that with the earlier sprays the amount of bounce and re-entrainment in the airstream is greater. Such a mechanism would lead to a similar observation, namely, as the number of sprays increase the number of particles that are re-entrained becomes less (due to interaction) and the increased retention on the larger particle stages results in a shift of the MMADs to larger values. Since both mechanisms would result in increasing retention of the particles on earlier impaction plates it is not possible to distinguish between them based on the data presented.

It is possible that the observed change in particle size distribution results not from the use of an Andersen Impactor but rather reflects a real change in the successive (30 to 60 sec between) sprays from the MDI. This is thought to be unlikely, the single sprays in Table I, although spaced by 20 min, do not show any trend towards a change in particle size distribution.

In conclusion, this work shows that particle size distributions, as determined using an Andersen Mark II impactor, are not identical between single and multiple actuations of salbutamol MDIs. The $MMAD_{CML}$ increases with the number of sprays, an increase of 18% is observed in going from 1 to 10 sprays. Caution is recommended when comparing particle size distributions which have been derived from collections of different sprays, especially more than two. The variation between manufacturers and within manufacturers is presently being examined with a view to investigate other parameters to define the particle size distribution.

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