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Metered-dose inhalers. II. Particle size measurement variation

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Abstract

Three apparatuses, the Andersen Cascade Impactor (ACI), the Marple-Miller Impactor (MMI) and the Twin Impinger (TI) were compared in the measurement of particle size distribution (PSD) of four commercially available salbutamol metered-dose inhalers (MDIs). The ACI was fitted with two induction ports. One was that currently described in the United States Pharmacopeia (USP) and the second had a larger volume. Parameters calculated included Mass Median Aerodynamic Diameter (MMAD), Geometric Standard Deviation (GSD) and Fine Particle Dose (FPD). The results demonstrated that several of these parameters were device-dependent and that all of the apparatuses were able to detect differences between some of the MDIs. The larger induction port allowed more drug substance to enter the ACI which may be advantageous in some PSD work. © 1997 Elsevier Science B.V.

Keywords: Metered-dose inhalers; Particle size; Andersen cascade impactor; Marple-Miller impactor; Twin impinger

1. Introduction

There is a need for valid in vitro criteria to assess products for inhalation by regulatory agencies, manufacturers and standard setting organizations. Draft Canadian guidelines were developed (Health Protection Branch, 1992) to aid manufacturers in addressing regulatory issues with these products. The guidelines specified that subsequent entry products must have identical ingredients in the same proportions as the original product, similar delivered doses and similar particle size distributions (PSD). The evaluation of the similarity of PSD of products presents difficulties due to the number of apparatuses available and the differences in the measured parameters derived from the apparatuses.

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Several recent reports have described the use of combinations of PSD apparatuses for the evaluation and comparison of MDIs. Ventolin® was compared to two formulations of MDI salbutamol prepared in-house using three particle sizing apparatuses (Phillips et al., 1990). Subsequently, a collaborative study carried out by Group of Experts No. 12 of the European Pharmacopoeia Commission (Aiache et al., 1993) evaluated four inertial particle separation apparatuses using one salbutamol MDI formulation. Most recently, four apparatuses (Holzner and Müller, 1995) were used to compare several formulations of cromolyn sodium and beclomethasone dipropionate MDIs. The apparatuses used in these studies vary in their complexity, particle size resolution capability and efficiency. Generally, the results indicated the ability of some apparatuses to detect differences in some of the tested products.

The United States Pharmacopeia (USP) currently describes three apparatuses (US Pharmacopeia XXIII, 1995) but the USP Advisory Panel on Aerosols has proposed (USP Advisory Panel on Aerosols, 1994) that for official purposes, only one apparatus, the Andersen Cascade Impactor (ACI), be used for particle size determination. While this apparatus, because of its eight stage design, provides the greatest resolution in particle size distributions, its operation is more resource intensive than others. This former characteristic makes it superior for the full characterization of products, particularly during the development stage, but the relevance of its superior resolution to the routine testing of products is debatable (Newman and Kenyon, 1994). The Twin Impinger (TI) represents the opposite scale of particle size test apparatuses in that it provides only a measure of particles smaller and larger than 6.4 μm. Despite this limitation, this apparatus has been adopted by the BP for the determination of the deposition of emitted dose, in monographs applicable to salbutamol (British Pharmacopeia, 1993) and beclomethasone dipropionate (British Pharmacopeia, Addendum, 1994). The Marple-Miller Impactor (MMI) (Marple et al., 1995) represents a compromise between these two apparatuses in affording three stage resolution of particles between 0.625 and 5 μm.

The USP describes several parameters which can be used to characterize sprays from MDIs. The respirable dose is, 'the total mass of drug found on the stages of the impactor...that captured the drug in the respirable particle-size range appropriate for the particular drug.' However, there has been no proposal to specify the particle size ranges for the various drug substances presented in MDI dosage form. The USP also describes the calculation of model dependent measures such as Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD).

Previous studies on the particle size distribution of MDIs in our laboratory have focused on changes in PSD, using the ACI, of single versus multiple sprays (Graham et al., 1995) from salbutamol MDIs and the comparison of beclomethasone MDIs (LeBelle et al., 1996). The latter report was our first attempt at comparing products from various manufacturers.

The purpose of this study was to compare the two apparatuses, ACI and MMI, in the measurement of the PSD of four salbutamol MDI products currently on the Canadian market and to compare the amounts of drug substance delivered to a defined fine particle dose (FPD) determined with each of three different apparatuses, ACI, MMI and TI, by the different commercial products. In addition, two inlet throats which differed in volume and internal diameter were compared using the ACI.

2. Materials and methods

2.1. Test samples

Several canisters from three lots of each of four commercially available MDIs were obtained by inspectors from the Health Protection Branch directly from Canadian manufacturer sites. Samples were coded by a capital letter to represent the manufacturer and an arabic number to represent the lot. All canisters were labelled to deliver 100 μg (ex-valve) of salbutamol per dose and were formulated with oleic acid, dichlorodifluoromethane and trichlorofluoromethane (Com-

pendium of Pharmaceuticals and Specialties, 1995). The inhalers tested were not from consecutive manufacturing or production lots, except for manufacturer C, where two of the lots were manufactured on successive days (lots 2 and 3).

2.2. Impactors

A vacuum pump (GAST, General Electric Corporation, Model 0522-V4B-G180DX) was used to draw untreated ambient air through the impactors and the air-flow rate was measured before each spray with a Primary Standard Airflow Calibrator (Gilian Gilibrator).

2.2.1. Andersen cascade impactor (ACI)

The ACI Mark II was operated at 28.3 l/min. At this flow rate it has the following effective cut-off diameters (ECD) for the eight stages, starting at stage 1; 9.0, 5.8, 4.7, 3.3, 2.1, 1.1 and 0.6 and 0.4 μm.

Two induction ports were used with this test apparatus. The first was as specified in the USP (US Pharmacopeia XXIII, 1995). The design of the second which has a larger volume was recently described (Van Oort and Downey, 1996). Both were manufactured locally from aluminum. Each impaction plate and corresponding stage of the ACI was washed with methanol into a 25 ml volumetric flask. The washings from the induction port of the ACI and actuator and valve of the MDI were not collected.

2.2.2. Marple-Miller impactor (MMI)

The Marple-Miller model 160 cascade impactor (MSP Corporation, Minneapolis, MN) was assembled with an EPM-2000 (Whatman) glass fibre filter and the flow rate was adjusted to 60 l/min at the inlet. The surface of the cups were uncoated. The ECDs at this flow rate for stages 1–5 are 10.0, 5.0, 2.5, 1.2 and 0.6 μm, respectively. Each cup and the filter were washed with methanol into 25 ml volumetric flasks. The induction port and filter were washed into separate 50 ml volumetric flasks.

2.2.3. Twin impinger (TI)

A single-stage impinger was used (USP single-stage impactor apparatus 2 (US Pharmacopeia XXIII, 1995)). Prior to use, the upper and lower impingement chambers were filled with 7 and 30 ml of methanol, respectively and the flow rate was set to 60 l/min. Stage 1 (upper) and stage 2 (lower, representing the particles < 6.4 μm) were washed with methanol into 25 and 50 ml volumetric flasks.

2.3. Sample collection

2.3.1. Apparatus comparison

With the ACI and MMI, two canisters from the three lots from each of the four manufacturers were sampled over 12 days in a replicated 4×4 Latin Square design. The first 10 sprays from each new canister were wasted before sampling. Duplicate particle size distributions for each canister were determined using two consecutive primed sprays for each. With the TI, only two of the three lots were sampled using a similar study design. After each determination the canister and actuator were disassembled and washed with methanol and allowed to air dry. All canisters were stored valve down at all times during the work. The shaking and firing sequence for the collection of sprays has been well described elsewhere (Graham et al., 1995).

2.3.2. Induction port comparison

Two canisters from one randomly selected lot from each manufacturer were sampled as described above. The same two canisters were used in the two studies.

2.4. Analytical methodology

2.4.1. Analytical method

The analytical method used was one previously developed and validated in our laboratory (Beaulieu et al., 1990).

2.4.2. Chemicals

Methanol (BDH, 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 was obtained from Cipla (Bombay, India).

2.4.3. Chromatographic conditions

Two HPLC instruments were fitted with 3 μm hexyl bonded phase columns (Spherisorb, 100 × 4.6 mm). The mobile phase consisted of a mixture of 600 ml acetonitrile, 400 ml water and 1 ml concentrated (85%) phosphoric acid. The flow rate was 1 ml/min and the detection wavelength was 229 nm.

2.4.4. HPLC system for ACI work

The liquid chromatograph (Varian Star) consisted of a model 9010 ternary pump, a model 9095 autosampler equipped with a 100 μl loop (Valco Instruments), a model 9050 variable wavelength UV-VIS detector, and a 9020 Workstation with revision C software.

2.4.5. HPLC system for MMI and TI work

The HPLC system consisted of a Waters model 510 pump, a Perkin-Elmer ISS-100 autosampler equipped with a Rheodyne model 7125 injector and a 20 μl loop, a Varian model 2050 detector and a Varian model 4270 integrator.

2.4.6. Calculation of amount of drug

Calibration curves (ranging from 0.025 to 5 μg/ml for the ACI, 0.05–4.2 μg/ml for the MMI and 0.10–5.2 μg/ml for the TI) were generated daily and analyzed using a weighted least squares regression. The square of the correlation coefficient was calculated daily and always exceeded 0.9813 (ACI), 0.9975 (MMI) and 0.9807 (TI). The lowest concentrations were equivalent to: 0.6 μg/stage (ACI); 1.3 μg/stage (MMI) and 5.0 μg/stage (TI). The coefficients of variation at the lowest concentrations were 15%, 5%, 18% for the ACI, MMI and TI curves, respectively. The coefficients of variation of six injections of a 0.25 μg/ml solution, for the two HPLC systems, were less than 3%.

The amounts of drug found on impactor stages reported in the tables are expressed per single dose determined from the two doses that were collected.

2.5. Calculations and estimation of particle size distribution parameters

Raw data manipulation was performed using standard functions available in SAS® software. The amounts of drug were calculated using a weighted least squares regression.

2.5.1. Model-dependent parameters

To estimate the parameters of the log-normal distribution two procedures were used. The USP (US Pharmacopeia XXIII, 1995) and the LIFEREG™ (SAS Institute Inc., 1988) were used to estimate MMAD and GSD using the algorithms described previously (Graham et al., 1995).

2.5.2. Model-independent parameters

Model-independent parameters are simply various combinations of summing the amount on the plates and other parts of an apparatus to estimate amount of drug in the various regions. These parameters include:

$\text{Total}_{\text{app}}$—The total amount of drug deposited in the apparatus, not including the induction port for the ACI and MMI. This does not include the amount left on the actuator or the valve which, in this study, was not measured.

Fine particle dose (FPD)—The total mass of particles found on selected stages of a particular apparatus ranging in particle size between ≈ 1 and 5 μm. For the devices used in this study, we have defined FPD as the total of particles with the following particle size diameters: ACI (0.6–4.7 μm); TI ($< 6.4\mu$m); and MMI (0.6–5.0 μm).

2.6. Statistical methods

Analysis of variance (ANOVA) was used to eliminate inter-day differences and to estimate an inter-lot standard error for comparisons between apparatuses. Main effects included apparatus and manufacturer along with an interaction This interaction term measures whether the results found for a particular apparatus are consistent for all manufacturers.

Table 1
Total comparison for three apparatuses[a]

Parameter	Apparatus	A	B	C	D
FPD (μg)	ACI (0.6–4.7 μm)	21 (14)	21 (12)	30 (11)	19 (12)
	MMI (0.6–5.0 μm)	33 (11)	29 (6)	40 (6)	29 (8)
	TI (<6.4 μm)	50 (7)	44 (7)	57 (8)	46 (12)
$Total_{app}$ (μg)	ACI	26 (14)	24 (12)	34 (11)	21 (11)
	MMI	42 (10)	36 (5)	47 (7)	35 (7)
	TI	100 (4)	88 (2)	104 (6)	96 (6)

[a] Mean (CV), $n = 12$ for ACI and MMI, $n = 8$ for TI.

3. Results

3.1. Apparatus comparison

3.1.1. Total to apparatus and FPD

The $Total_{app}$ and FPD for each product examined are given in Table 1. We defined the FPD with the ACI to be particles of 0.6–4.7 μm which closely corresponds to the 0.6–5.0 μm FPD of the MMI. Both parameters determined with the MMI were significantly greater ($p < 0.001$) than the corresponding ACI values. The TI had significantly more drug ($p < 0.001$) in both the FPD and $Total_{app}$ than did the other two apparatuses. Fig. 1 is a histogram of these values. The height of each bar represents $Total_{app}$; the darker portion represents the FPD. The differences between apparatuses are clearly visible.

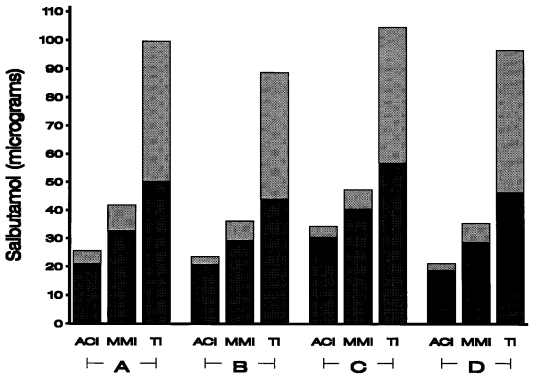

Fig. 1. Drug particle distributions of salbutamol sprays—different apparatuses. Major group: manufacturers; subgroup: apparatuses. Area 1 (solid): FPD; Area 2 (hatch): the deposited in the impactor/impinger that was not in the FPD.

3.1.2. Particle size distribution

The particle size distributions, averaged over all determinations for the four manufacturers, determined with the multi-stage impactors, ACI and MMI, are displayed in Fig. 2. The USP induction port was attached to the ACI. The vertical bars on the curves represent the range of values at each stage. Table 2 presents the inter-lot means and coefficients of variation of the MMAD and GSD values calculated from the ACI and MMI apparatuses. Both methods of MMAD calculation gave results that were significantly higher for the ACI than the MMI ($p < 0.001$). The GSD values, regardless of the calculation method, were significantly smaller for the ACI than the MMI ($p < 0.001$) for all products.

3.2. Manufacturer comparison

3.2.1. Andersen cascade impactor

Fig. 2 shows the particle size distribution profiles of the four products determined using the ACI (solid lines). Products B and D were very similar, with the greatest amount of drug on stage 5 and a significant amount on stage 4; steadily declining amounts were found on the other stages. In contrast, products A and C deposited the largest amount on stage 4 with significant amounts on both stages 3 and 5 which resulted in a broader peak shape.

Product C delivered a statistically greater ($p <$ 0.001) amount in the FPD (Table 1) when compared to the other three products. Product A delivered an amount of drug in the FPD comparable to products B and D. However, a larger proportion of the particles of product A were

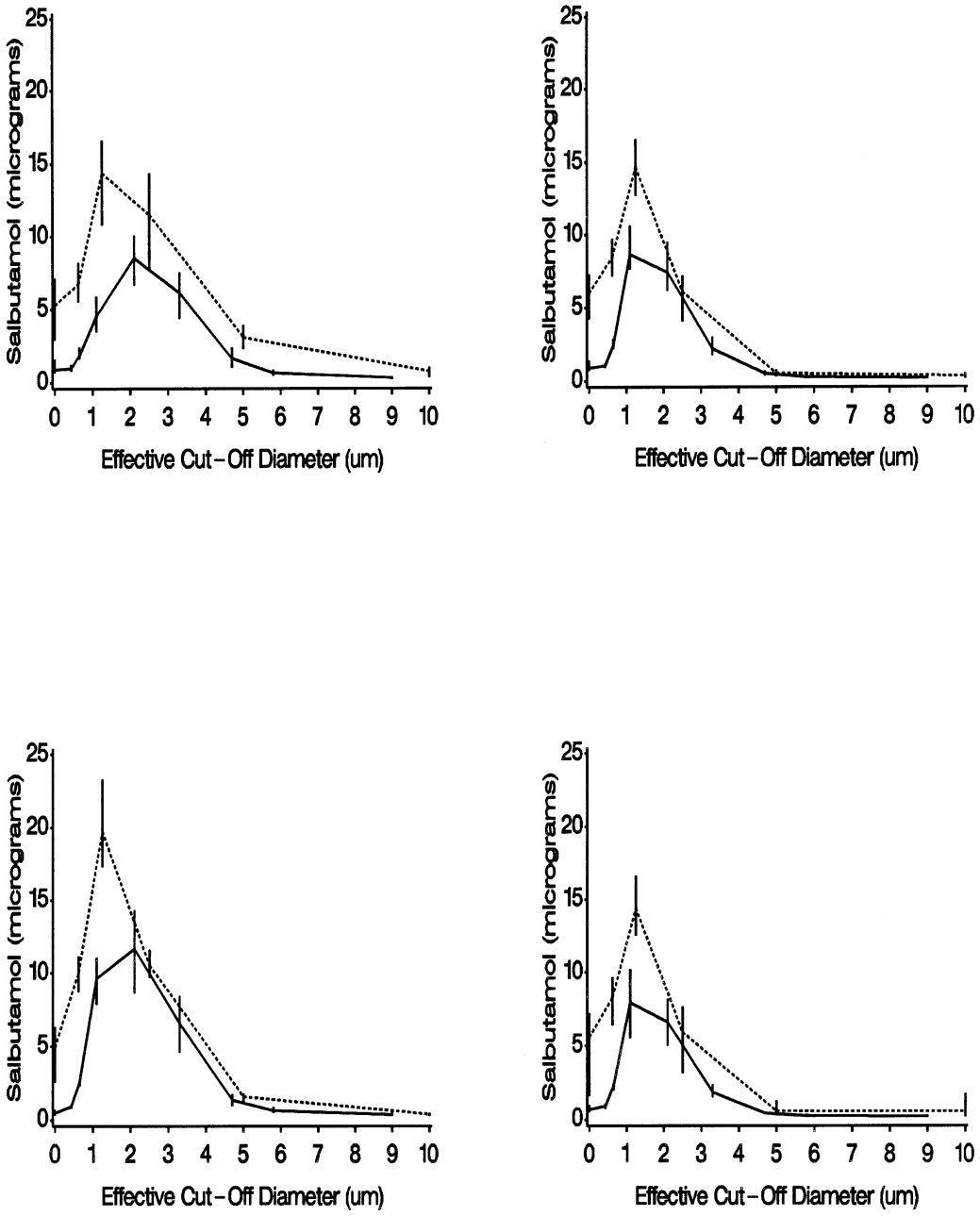

Fig. 2. Particle size distribution profiles of salbutamol sprays. y-Axis—micrograms deposited on the stages; x-axis—effective cut-off diameter (ECD) of each stage. The vertical lines on the curves indicate the range of observed values at each of the stages. Dashed line, MMI; solid ACI. Top left, Product A; top right, Product B; bottom left, Product C; bottom right, Product D.

Table 2
Parameter comparison for two apparatuses[a]

Parameter	Apparatus	A	B	C	D
$MMAD_{SAS}$ (μm)	ACI	2.3 (4)	1.8 (3)	2.2 (3)	1.8 (2)
	MMI	1.8 (8)	1.4 (6)	1.6 (3)	1.4 (11)
$MMAD_{USP}$ (μm)	ACI	2.1 (4)	1.6 (4)	2.0 (4)	1.6 (3)
	MMI	1.8 (9)	1.3 (6)	1.6 (4)	1.4 (12)
GSD_{SAS}	ACI	2.0 (4)	1.9 (2)	1.8 (2)	1.9 (3)
	MMI	2.3 (4)	2.1 (4)	2.0 (3)	2.1 (4)
GSD_{USP}	ACI	2.3 (3)	2.0 (2)	2.0 (2)	2.0 (3)
	MMI	2.4 (3)	2.0 (4)	2.0 (3)	2.1 (4)

[a] Mean, (CV), $n = 12$ for ACI and MMI.

impacted on stage 3 (ECD 3.3 μm) in comparison to products B and D. The FPD and MMAD values for individual lots using the ACI are shown in Tables 3 and 4. Product C also delivered a statistically greater total amount to the Andersen, $Total_{app}$, than the other three products.

The MMAD values in Table 2 reflected the differences in the size distributions. Products B and D, which had such similar particle distribution curves yielded MMAD values, calculated according to both the USP and SAS® procedures, which were not statistically significantly ($p > 0.1$) different from each other. And likewise products A and C had similar MMADs and both were significantly ($p < 0.001$) different from the MMADs for B and D.

3.2.2. Marple-Miller impactor

The particle size distribution profiles shown in Fig. 2 (broken lines) indicate that products B, C and D are most similar due to the preponderance of drug particles deposited on the third stage (1.2 μm). Product A demonstrated a higher proportion of particles on the stage with an ECD of 2.5 μm. This is reflected in the MMAD values.

The FPD values determined with the MMI (Table 1) showed a similar trend to those determined with the ACI. Product C delivered significantly more drug ($p < 0.001$) in the defined particle size range. Product A also delivered, to the FPD, a greater amount of drug than products B and D. The intra-lot comparison of the products using the MMI is shown in Tables 3 and 4. Product C also gave $Total_{app}$ values greater ($p < 0.001$) than the other three products and product A values exceeded ($p < 0.001$) those of both product B and D.

3.2.3. Twin impinger

The FPD defined for this device includes only particles that have diameters less than 6.4 μm. Product C again delivered more ($p < 0.001$) to the FPD than the other products. The FPD value for product A was also greater than product B but not significantly different than product D. The individual FPD data for each of the two lots tested are shown in Table 3. Only the $Total_{app}$ value of product B was significantly different ($p < 0.001$) than all other products.

3.3. Induction port comparison

3.3.1. Total to apparatus and FPD

The $Total_{app}$ and FPD values with the two different induction ports attached to the ACI are shown in Fig. 3 and summarized in Table 5. There were greater amounts of drug impacted in the ACI ($p < 0.001$) with the larger volume induction port; the FPD was also higher ($p < 0.001$).

3.3.2. Particle size distribution

The large volume induction port gave slightly greater MMAD values (Table 5) for both calculation methods although this was only significant for $MMAD_{SAS}$ ($p < 0.014$). There was no significant differences the GSD values. The particle size distribution profiles derived from this study are shown in Fig. 4.

Table 3
Lot comparison—FPD ($n = 4$, mean (CV))

MFG lot	A			B			C			D		
	1	2	3	1	2	3	1	2	3	1	2	3
ACI	22 (8)	24 (7)	18 (8)	20 (5)	21 (14)	22 (14)	33 (9)	30 (9)	28 (11)	20 (13)	19 (6)	17 (12)
MMI	36 (4)	30 (14)	32 (6)	28 (7)	30 (2)	29 (8)	40 (8)	39 (4)	42 (6)	31 (6)	28 (6)	27 (3)
TI	49 (10)	51 (3)	—	42 (6)	46 (6)	—	—	56 (9)	57 (9)	46 (15)	47 (10)	—

Table 4
Lot comparison—$MMAD_{SAS}$ ($n = 4$, mean (CV))

MFG lot	A			B			C			D		
	1	2	3	1		3	1	2	3	1	2	3
ACI	2.4 (1)	2.3 (3)	2.2 (5)	1.8 (2)	1.8 (2)	1.8 (4)	2.3 (2)	2.2 (3)	2.2 (2)	1.8 (1)	1.8 (2)	1.8 (3)
MMI	1.9 (4)	1.7 (3)	1.9 (10)	1.3 (4)	1.4 (10)	1.4 (5)	1.6	1.6 (4)	1.6 (2)	1.5 (13)	1.4 (7)	1.4 (12)

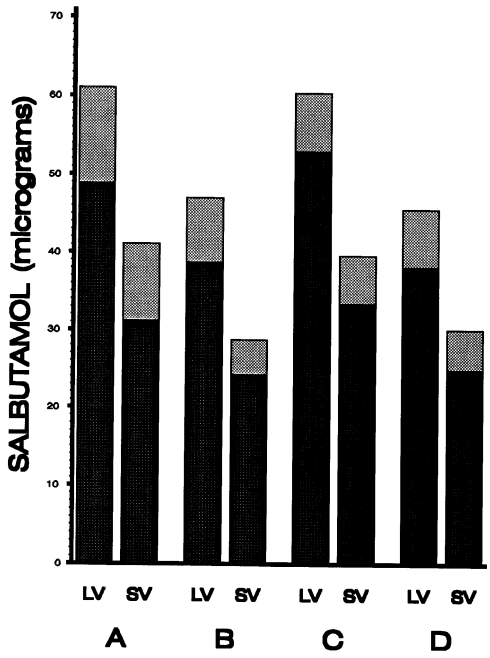

Fig. 3. Drug particle distributions of salbutamol sprays—different induction ports on the ACI. Major group: manufacturers; subgroup: induction ports, Large (LV) and Small (SV). Area 1 (solid): FPD; Area 2 (hatch): the amount deposited in the impactor that was not in the FPD.

4. Discussion

The results from these studies clearly show that both the total amount of drug delivered to the impactor and in the FPD is different for the three apparatuses studied. The relative amounts of these parameters were in the order ACI (USP port) < MMI < TI.

Both methods of calculation gave MMAD values that were higher for the ACI in comparison to the MMI. The MMAD determined with the MMI had greater variation because less points were used to calculate it. There are limitations in the USP method of calculating MMAD, particularly due to the summing of errors in the mass of drug detected on each stage. However, this method was used because of its current regulatory status. Alternative methods such as the LIFEREG procedure used here and that recently described by Van Oort and Downey (1996) are available. The MMI yielded significant amounts of drug (≈ 5 μg) on the filter indicating a sizable proportion of the drug particles had diameters less than 0.6 μm. This conflicted with the ACI results which indicated all products delivered minimal amounts ($\approx$ 1 μg) of drug particles in this particle size range. This may be due to more evaporation of propellant in the MMI, a result of its higher flow rate or to less complete capture of drug particles on the uncoated impaction surfaces of the MMI.

The particle distribution profiles shown in Fig. 2 indicate that both the ACI and MMI yielded very similar profiles for products B and D. Both

Table 5
Total and parameter comparison for two induction ports on the ACI[a]

Parameter	Induction port	A	B	C	D
PD (μg) (0.6–4.7 μm)	Large	49 (14)	39 (6)	53 (14)	38 (13)
	Small	31 (5)	24 (10)	33 (18)	25 (14)
$Total_{app}$ (μg)	Large	61 (14)	47 (6)	60 (14)	46 (12)
	Small	41 (7)	29 (7)	40 16)	30 (13)
$MMAD_{SAS}$ (μm)	Large	2.7 (4)	2.2 (8)	2.4 (6)	2.2 (4)
	Small	2.5 (4)	2.1 (8)	2.3 (2)	2.1 (6)
$MMAD_{USP}$ (μm)	Large	2.5 (5)	2.1 (11)	2.3 (7)	2.1 (8)
	Small	2.4 (5)	2.0 (11)	2.2 (4)	2.0 (8)
GSD_{SAS}	Large	2.0 (4)	2.0 (4)	1.8 (3)	2.0 (5)
	Small	2.1 (3)	2.0 (9)	1.9 (1)	2.0 (7)
GSD_{USP}	Large	2.4 (4)	2.3 (6)	2.0 (5)	2.2 (8)
	Small	2.6 (3)	2.1 (11)	2.1 (3)	2.2 (10)

[a] Mean (CV), $n = 4$ for A, C, D; $n = 3$ for B.

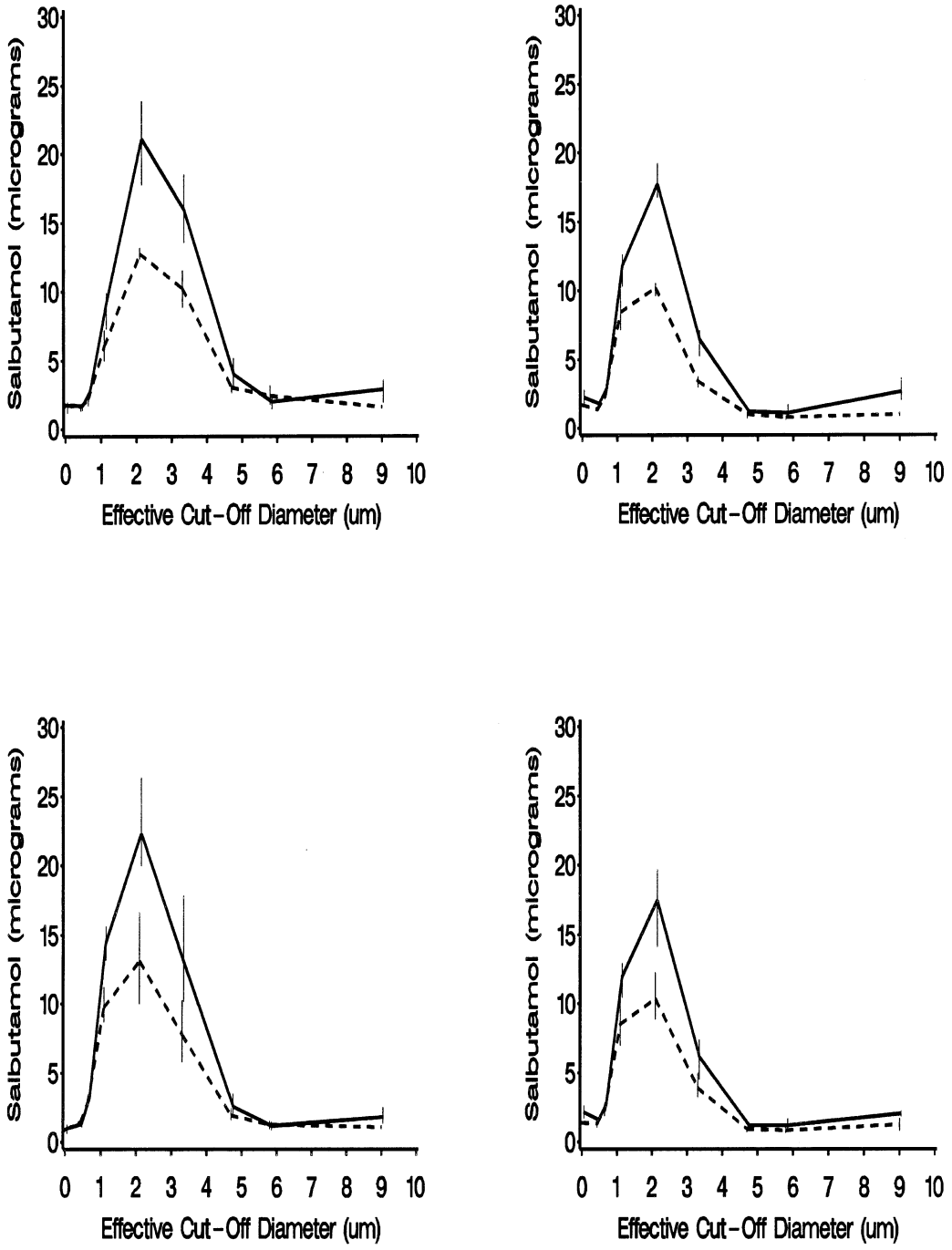

Fig. 4. Particle size distribution profiles of salbutamol sprays—different induction ports. *y*-Axis—micrograms deposited on the stages; *x*-axis—effective cut-off diameter (ECD) of each stage. The vertical lines on the curves indicate the range of observed values at each of the stages and are shifted slightly to permit visual identification of the range of values. Dashed line, small volume; solid line, large volume port. Top left, Product A; top right, Product B; bottom left, Product C; bottom right, Product D.

apparatuses were readily able to distinguish product A which contained a higher proportion of larger particles. In the case of product C, the discriminatory power of the ACI, due to its higher resolution, was evidenced. The MMI yielded a distribution profile qualitatively similar to products B and D although the amounts on several of the stages were greater with product C. However, the ACI indicated a higher proportion of particles impacted on the 2.1 μm stage in relation to the 1.1 μm stage thereby differentiating this product from B and D. These differences among the products were reflected in the MMAD values and confirmed the capability of this parameter to characterize MDIs.

The FPD values also discriminated among the products. All apparatuses gave values of FPD for product C which were greater than any other product. The FPD values with the MMI also indicated that product A was greater than both B and D whereas the TI values for products A and D were not significantly different and the ACI values for products A and B and A and D were not different.

The larger volume induction port allowed significantly greater amounts (about 50%) of drug from all products to pass to the ACI. This difference probably reflects the relative amounts of drug impacted in the induction ports although this amount was not determined. Previous unpublished data (Graham et al., 1995) indicated that with Canadian salbutamol MDI products about 60% of the labelled dose (60 μg) is impacted in the USP induction port. Less impaction in the larger volume induction port might be expected due to the decreased air stream velocity in the first chamber as a result of its larger diameter and to the larger volume of this chamber in comparison to that of the USP induction port (about 24 cm^3 versus 10 cm^3). The particle size distribution profiles (Fig. 4) indicate that much of the ballistically impacted particles in the USP induction port are of small diameter. The increase in FPD and only slight increase in $MMAD_{SAS}$ values ($p = 0.1$) with the larger induction port was consistent with the trends reported by Van Oort et al. (1994).

It may be noted, when comparing the results from Table 1 to those in Table 5 with the USP induction port for products A and D, a significant difference in the amount of drug in the FPD was detected. For example, product A was reported as having delivered 21 μg in the FPD in the series of experiments yielding the values in Table 1 and delivered 31 μg in the series of experiments yielding the values in Table 5. This is in part due to differences in the number of samples analyzed using the two induction ports. Table 1 represents the mean of three lots; individually the lots (two canisters) yielded FPD results of 22, 24 and 18 μg (Table 3). It was the second of these lots only that was used to generate the data in Table 5. In the case of product D, the lot used to obtain the 33 μg value in Table 5 yielded 20 μg in the series of collections in Table 1 (lot 1, Table 3). These results were significantly different ($p < 0.001$ for both products A and D) and could not be rationalized on the basis of day to day variation since analysis of variance indicated there was no significant difference in the results due to day to day variation. However, the data presented in Table 5, the induction port comparison, were generated (August) approximately 5 months after the results in Table 1 were obtained (February/March). It is possible, that in the case of the lots from products A and D which were found to be different, the canisters' delivery changed between the two experiments.

The particle size distribution profiles for products B and D with the USP induction port attached to the ACI during the two studies were also different (Figs. 2 and 4). The profiles from the induction port comparison work indicate that both of these products yielded greatest drug mass deposition on stage 4 whereas the profiles from the apparatus comparison gave profiles with greatest mass deposition on stage 5. This apparent shift in particle distribution was reflected in the MMADs.

5. Conclusions

Progress towards test procedures for the characterization and of MDI products depends on the adoption of standardized test devices. The results presented here clearly indi-

cated that the three devices used in this study and the ACI with either of two induction ports attached yielded different values for parameters such as FPD and MMAD which are considered important in the evaluation of MDIs. The differences in the three test apparatuses examined support the principle underlying the USP proposal (USP Advisory Panel on Aerosols, 1994) to specify a single test apparatus for the official determination of product quality of MDIs. The superior resolution of the ACI enabled the detection of PSD differences that were not seen with the MMI. However, the need for the more labour intensive ACI is questionable. Similar trends in product parameters were detected using the ACI, MMI or TI. The results support the retention of multi-stage impaction apparatuses other than the ACI for pharmaceutical development and indicate that an apparatus such as the TI could be used for quality control of the products tested if the variables that affect delivery are well characterized (Atkins, 1992; Webb, 1994).

The results from the comparison of the two induction ports indicated that the larger volume port permits more drug to enter the ACI. This may be analytically advantageous in single spray work and in studies with other drugs that are formulated to deliver lower doses or for which the analytical method is less sensitive. In view of the similarity of the particle size distribution profiles resulting from the USP and larger induction port, the latter should be considered for use in future evaluations of MDIs.

As we found with beclomethasone, the two methods of calculation, USP and SAS®, used for the determination of MMAD and GSD yield consistent but numerically different results. Other methods of calculation such as the routine suggested by Van Oort and Downey (1996) may again yield different results. These differences in calculation methods further highlight the need to standardize procedures to permit a more universal characterization of MDIs. Also as we found with beclomethasone, the results here indicated that the MMAD is both discriminatory and precise. However, the need for the continued use of this parameter needs to be assessed. The detailed calculations used in the USP method and the computer resources required for the use of SAS® in calculating the MMAD could be eliminated by the adoption of other parameters.

The FPD may be more closely related to the efficacy of the product in that it gives a direct measure of the mass of particles within specified size ranges. However, the use of an ad hoc parameter such as this may require the identification of a range appropriate for each particular drug. This would contrast with the approach adopted by the BP which, at least in the case of salbutamol and beclomethasone, specifies the same broad range of particles ($< 6.4\ \mu$m) as being indicative of the quality of different drug substances.

It would seem from the data presented here that, based on the product comparisons, it may be possible to develop a suitable range of particle sizes and specifications for salbutamol. All of the products tested here have been subjected to at least limited clinical trials that have demonstrated their efficacy. If the products tested are similar to those used in those trials, the differences detected between the products, using the in vitro methods applied in this study, may have limited clinical significance.

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