

Shuguang Hou¹, Robert N. Anderson¹, Kimberly Kriesel¹, Alessandro Bodria² and Diego Copelli²
¹3M Drug Delivery Systems Division, St Paul, MN 55144, USA and ²Chiesi Farmaceutici SpA, Parma 43100, Italy

Introduction

Both the Andersen cascade impactor (ACI) and next generation impactor (NGI) have been incorporated into the US Pharmacopoeia as an apparatus to measure the aerodynamic size of pharmaceutical inhalation aerosols (1). The objectives of this study were to compare the particle size distribution profiles of a solution MDI obtained between ACI and NGI, and to assess the impact of actuator orifice diameter on ACI and NGI results.

Methods

The solution HFA MDI tested in this study contained budesonide as one of the active drug substances, ethanol as a cosolvent, a mineral acid as a stabilizer and HFA-134a as a propellant. The particle size distribution of the MDI was evaluated using ACI at a flow rate of 28.3 L/min and NGI at a flow rate of 60 L/min. The ACI plates and NGI cups were uncoated. Ten actuations were collected for each measurement. Actuators (Bespak) with two different orifice diameters, 0.16 mm and 0.28 mm, were used. Budesonide deposition on ACI or NGI components was measured by validated HPLC methods with UV detection.

Data Analysis

The mass deposit of budesonide on ACI or NGI components was calculated as per actuation and is summarized in Table 1. Total recovery (ex-valve dose) is the sum of budesonide deposits in the actuator, induction port and impactor. Deposit in the impactor is the sum of budesonide mass collected from all the stages and the filter. Fine particle dose (FPD) is the sum of budesonide mass collected below stage 2 for both ACI and NGI. The size cutoff point of stage 3 is 4.7 μm for ACI at the flow rate of 28.3 L/min and 4.46 μm for NGI at the flow rate of 60 L/min. Fine particle fraction (FPF) is the percentage of FPD compared to the ex-actuator dose (sum of budesonide mass deposited in induction port and impactor).

Results

ACI and NGI gave the identical budesonide recovery of 84 μg (target = 80 μg), and the drug recovery was independent of the actuator orifice diameter. At both actuator orifice diameters, ACI showed less budesonide residual in the actuator and, thus a greater ex-actuator dose, than NGI. When the 0.16 mm actuators were used, the budesonide deposit in the impactor and the FPD were the same between ACI and NGI; however, ACI showed a slightly higher induction port deposit and lower FPF than NGI, due to the lower flow rate used in ACI. When the 0.28 mm actuators were used, the budesonide deposit in

the induction port increased dramatically in both ACI and NGI. ACI showed a much higher induction port deposit and, thus, lower FPD and FPF than NGI. It has been reported that the induction port deposition results from the turbulence induced from the mismatch between the high plume velocity and low air flow rate (2-3). As the actuator orifice diameter increased, the MDI plume velocity increased, which led to higher turbulence, thus higher drug deposition in the induction port. Because of the lower flow rate used by ACI, the higher turbulence in the induction port resulted in larger induction port deposition and lower FPD and FPF in ACI, as shown in Table 1.

Table 1 Summary of Particle Size Distribution of Budesonide

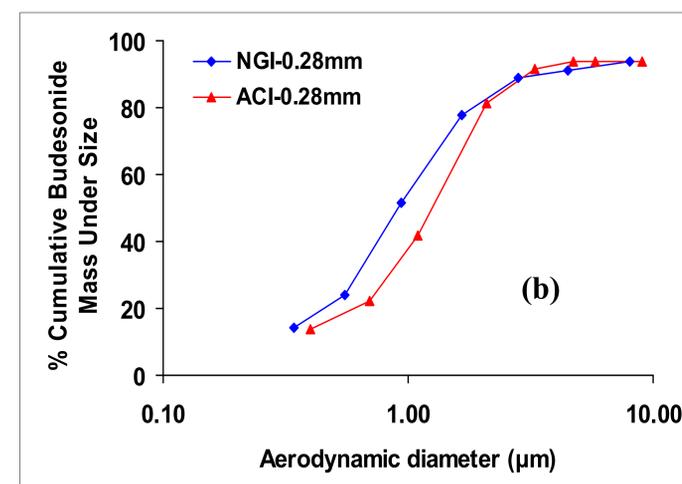
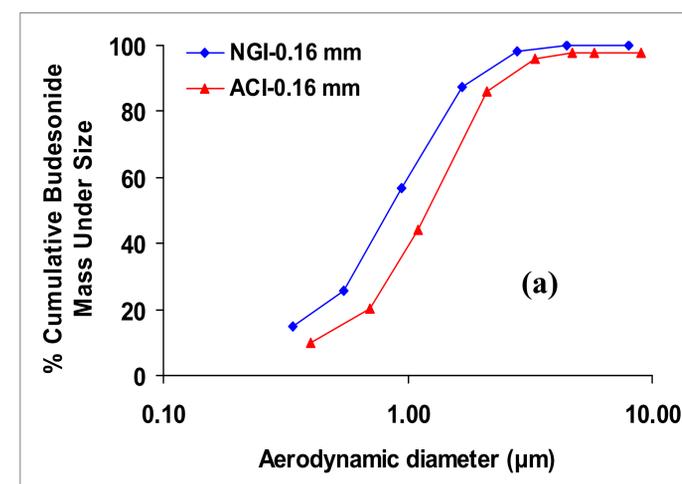
Budesonide Deposit per Actuation	0.16 mm Actuator		0.28 mm Actuator	
	ACI	NGI	ACI	NGI
Total Recovery (μg)	84 (2)	84 (1)	84 (5)	84 (1)
Actuator (μg)	7 (2)	14 (2)	8 (1)	14 (1)
Induction Port (μg)	18 (1)	12 (1)	48 (1)	30 (2)
Impactor (μg)	59 (2)	58 (3)	28 (4)	40 (2)
FPD (μg)	58 (2)	58 (3)	26 (4)	37 (2)
FPF (%)	75.1 (1.2)	83.2 (1.1)	34.0 (2.9)	52.5 (2.8)
MMAD (μm)	1.2 (0.0)	0.9 (0.0)	1.3 (0.1)	0.9 (0.0)

Results presented as mean (standard deviation)
 n = 5 for ACI and n = 3 for NGI

The MMAD of budesonide obtained by NGI was smaller than that by ACI, as shown in Table 1. Figure 1 compares the aerodynamic particle size distribution (PSD) profiles obtained between NGI and ACI. The drug deposition fractions for smaller size particles increased when being tested by NGI. This could be explained by the combination effect of the higher air flow rate, as discussed above, and the larger internal volume in NGI. The larger internal volume of the NGI (1000 mL versus 450 mL for ACI) allows for greater evaporation of the aerosol plume in the impactor, resulting in a larger FPD and FPF, and a smaller MMAD (4). This effect was observed when actuators with the large orifice diameter (0.28 mm) and, thus higher plume velocity, were used for the experiment. Enhanced particle bounce in NGI is another possible explanation for the smaller MMAD obtained from NGI (4-5). A separate study was conducted with the NGI using coated cups. Similar PSD profiles were obtained compared to those obtained from NGI with uncoated cups (data not shown in this poster). It was reported that particle bounce could be reduced following multiple actuations, as the collected aerosol modifies the surface properties of NGI cups (5). In this study, the use of 10 actuations per measurement probably minimized the particle bounce. In addition, the

non-volatile mineral acid in the formulation could make the aerosol particles tacky and, thus, more prone to adhere to the uncoated cup surfaces in NGI, which could also lead to the reduction of particle bounce (4).

Figure 1 Aerodynamic Particle Size Distribution Profiles Determined by NGI and ACI using (a) 0.16 mm and (b) 0.28 mm Orifice Diameter Actuators



Conclusions

The NGI and ACI gave the same drug depositions in the impactor when the MDI was tested using the 0.16 mm actuators. When the 0.28 mm actuators were used, the ACI showed higher induction port deposition and lower FPD and FPF than the NGI. With both orifice diameter actuators, NGI produced a smaller MMAD than ACI.

References

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