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1. EXECUTIVE SUMMARY

The aerosol Particle Size Distribution (APSD) and Delivered Dose from a Ventolin Pressurised Metered Dose Inhaler (PMDI) with Bird's cardboard spacer was studied using the Next Generation Impactor (NGI).

The NGI study showed a deposition profile with most of the drug deposited on stages 3-5 and the Throat + Mouthpiece. The Mass Median Aerodynamic Diameter (MMAD) was 2.16 ± 0.02 μm and Fine Particle Fraction (FPF) was 79.03 ± 0.29 %, with a delivered Fine Particle Dose (FPD) (<5 μm) of 35.31 ± 0.72 μg.

2. TABLE OF CONTENTS

3. INTRODUCTION

The particle size distribution of aerosols emitted from a Ventolin PMDI with Bird's Spacer was evaluated using the NGI. The NGI was performed according to USP-NF <601> INHALATION AND NASAL DRUG PRODUCTS: AEROSOLS, SPRAYS, AND POWDERS—PERFORMANCE QUALITY TESTS and <1603> GOOD CASCADE IMPACTOR PRACTICES. The purpose of the experiments was to evaluate how the performance of the spacer impacted quality attributes of the aerosol from a commercially available inhaler (Ventolin).

4. MATERIALS

- Standard laboratory equipment.
- Next Generation Impactor (S/N NGI-0994) with USP Induction Port (S1-0821)
- Copley Flow controller TPK2000 (S/N 36119)
- Vacuum pump (Westech Scientific Instruments, UK)
- Mass Flow Meter 4040 (TSI Precision Measurement Instruments, Germany)
- Analytical balance (Shimadzu, System No: 2-01815)
- Custom-moulded silicone rubber adapter for Bird Healthcare's Spacer
- Salbutamol (Albuterol) Sulphate USP Standards (USP Lot No.: R110E0)
- Hydrochloric acid (P/N: 30721, 1L, Sigma-Aldrich)
- Ventolin Evohaler 100 micrograms salbutamol (as sulphate) per actuation (200 metered actuation, B/N: SS3W)

5. METHODS

5.1. *NGI setup and sampling*

The NGI testing was performed as per *ABI-BIRD-PRT-005 APSD Determination of pMDI with Spacer using NGI*. Briefly, the NGI and induction port were used for testing at room temperature with the temperature and humidity recorded. The NGI was connected to the spacer as shown in Figure 1. A flow meter was used to adjust the flow through the impactor to 30 L/min using the flow controller and connected pump.

The Ventolin PMDI was primed with 4 pumps into the fume hood with shaking by inversion of the device before each pump. The initial weight was then taken as W_0. The pMDI was shaken by inversion through 180° for 5 times and then quickly inserted into the Spacer inlet, the can was depressed for 3 seconds then released for the next 7 seconds, the pMDI was then removed and reweighed. This was repeated for a total of 5 shots. The weights were recorded after each pump as W_1 to W_5. After testing, the pump was turned off.

The impactor was disassembled and deposited aerosols from each collection cup were washed by adding the fixed volume of diluent (0.01M HCl) into each part as per protocol *ABI-BIRD-PRT-005.* Drug concentration in each formulation was determined by HPLC (ABI-BIRD-PRT-006) and converted to mass collected on each stage by correction for extraction volume.

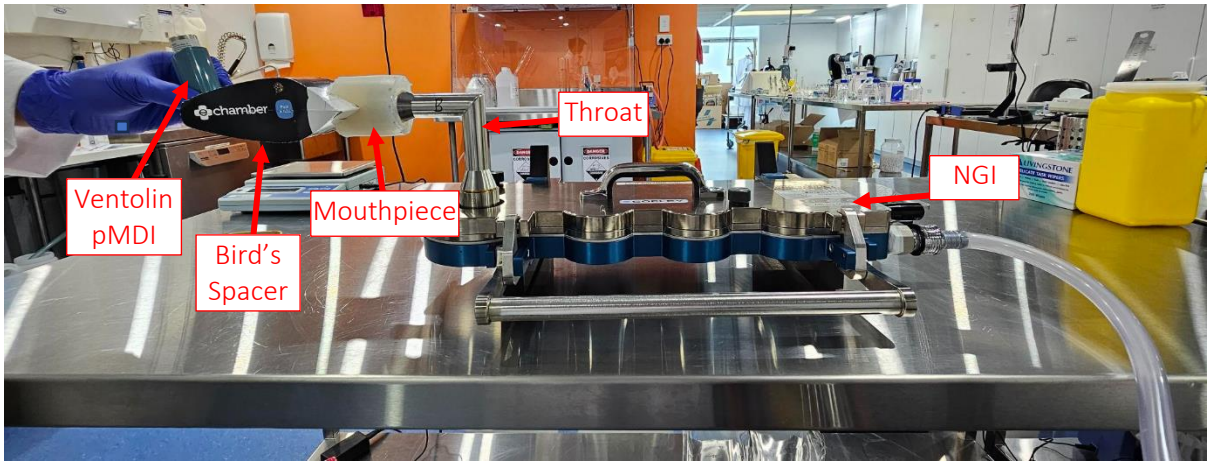

Figure 1. NGI setup of pMDI with Bird's Spacer.

5.2. Data analysis

The data are presented as mean ± standard deviation (STDev) of three independent experiments. The deposition profiles and aerosol particle size statistics (FPD, FPF, MMAD, GSD) of Ventolin are determined using Inhalytix software. The stage depositions data were presented as a distribution graph of delivered dose using GraphPad Prism 10.1.1.

6. RESULTS AND DISCUSSION

The percentage NGI stage deposition for each formulation are shown in Figure 2 below.

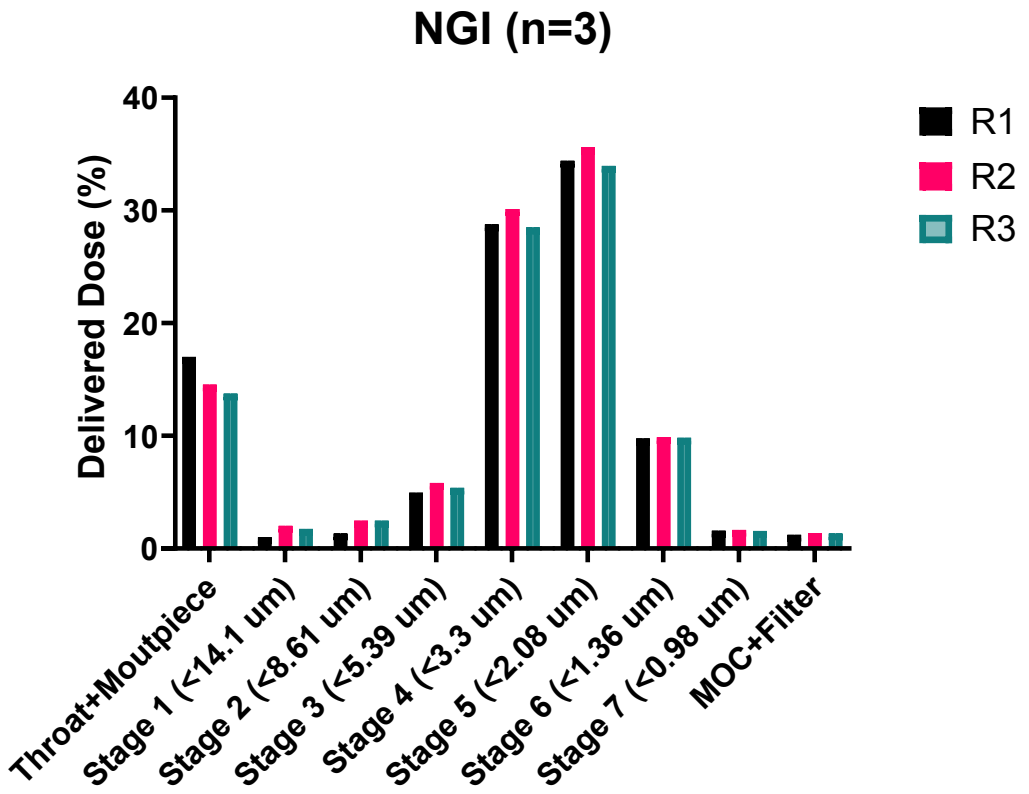

Figure 2: Stage deposition profiles.

The NGI study showed a deposition profile with most drug deposited on stages 3-5 and the throat + mouthpiece. The Inhalytix data summary is shown in Table 1.

Table 1: NGI product and particle size statistics of Salbutamol from Ventolin with Bird's Spacer using the NGI (n=3).

	R1	R2	R3	MEAN	STDev
Delivered dose (μg) (per shot)	44.39	45.91	43.75	44.68	0.91

FPD (µg ≤5 µm)	34.90	36.32	34.70	35.31	0.72
FPF (% ≤5 µm)	78.64	79.12	79.33	79.03	0.29
MMAD (µm)	2.14	2.18	2.17	2.16	0.02
GSD	1.55	1.57	1.57	1.57	0.01

On average, the pMDI with Bird's cardboard spacer delivered 44.68 ± 0.91 µg of Salbutamol in one shot. The Mass Median Aerodynamic Diameter (MMAD) was 2.16 ± 0.02 µm and Fine Particle Fraction (FPF) was 79.03 ± 0.29 %, with a delivered Fine Particle Dose (FPD) (<5 µm) of 35.31 ± 0.72 µg.

7. ABBREVIATIONS

USP	United states pharmacopeia
NGI	Next generation impactor
L/min	Litre per minute
STDev	Standard deviation
MMAD	Mass Median Aerodynamic Diameter
FPF	Fine Particle Fraction
FPD	Fine Particle Dose
GSD	Geometric standard deviation

8. REFERENCES

- USP Chapter 5 Droplet size USP FDA guidelines.
- USP-NF <601> INHALATION AND NASAL DRUG PRODUCTS: AEROSOLS, SPRAYS, AND POWDERS—PERFORMANCE QUALITY TESTS
- USP-NF <1603> GOOD CASCADE IMPACTOR PRACTICES.
- ABI-BIRD-PRT-005 - aPSD Determination of pMDI with Spacer using NGI
- ABI-BIRD-PRT-006 - HPLC-DAD METHOD FOR QUANTIFICATION OF SALBUTAMOL SULPHATE INHALATION SOLUTION

9. VERSION CONTROL

Version	Document Revision / Change	Updated By	Date
001	New Document	Tram Ngo	14 DEC 2023