

Evaluation of Different Setups to Combine Spraytec and Unidose™ to Assess the Particle Size Distribution of Dry Powder Inhalers

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INTRODUCTION

The therapeutic effect of a dry powder depends on numerous formulation physico-chemical and device factors which will play a key role in the fluidization of a static powder bed under patient air flow [1]. These factors affect the performance of dry powder inhalers (DPIs) by influencing the fluidization, deaggregation aerodynamic particle size distribution and dissolution/permeation rate of the API [2–5]. Recently, an apparatus (Unidose™, see Figure 1) has been developed to capture the whole impactor sized mass (ISM) dose onto a filter which can subsequently analysed in terms of microstructure, dissolution and morphology directed Raman microscopy (MDRS) [5, 6].

The objective of this study was to combine Spraytec with Unidose™ to evaluate the particle size distribution of the impactor sized mass dose by laser diffraction and automated imaging.

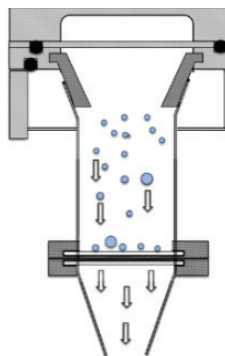


Figure 1. Schematic representation of the Unidose collection system housed at stage 2 of an NGI.

METHODS

The commercial devices, Advair® Diskus® (fluticasone propionate and salmeterol xinafoate inhalation powder) 250/50 (HP6N), Spiriva® Handihaler® (801797) and Ultibro® Breezhaler® (BFR65) were used in this study.

Several setups were tested during method development to combine the Unidose apparatus (Nanopharm Ltd, Newport, UK) with the Spraytec (Malvern Panalytical Ltd, Malvern, UK) to allow the simultaneous analysis of particle size distribution, aerosolization properties, MDRS and dissolution. A United States Pharmacopeia (USP) inlet port (with and without pre-separator) (Copley Scientific, Nottingham, UK) or a realistic anatomical throat model (OPC medium anatomical throat, Emmace, Lund, Sweden) were used with a modified Next Generation Impactor (NGI). The NGI had the nozzle jets removed to enable the uniform deposition of the whole ISM onto a single, high surface area filter membrane under laminar flow and low impaction velocity.

Experiments performed using Spraytec equipped with an inhalation cell accessory and Unidose enabled measurements to be carried out at 60 Lmin^{-1} for a duration equivalent to 4 L of volume running through the device. Test duration was set at 4000 ms on Spraytec with an acquisition frequency of 2500 Hz to ensure that the whole actuation event was captured and the complete aerosol plume had been transported through the measurement zone. Each experiment was performed with six repetitions and the particle size distribution data was evaluated.

Morphologi 4-ID (Malvern Panalytical, Worcestershire, UK) automated imaging analysis was performed on the commercial products ISM dose collected on the Cellulose Acetate filter using Unidose.

RESULTS AND DISCUSSION

Development setups used to combine the Unidose with the Spraytec are presented in Figure 2.

Setup	Description
Setup 1	Device > Mouthpiece > Inhalation Cell (Horizontal) > Unidose™
Setup 2	Device > Mouthpiece > USP Throat > Inhalation Cell (Vertical) > Unidose™
Setup 3	Device > Mouthpiece > USP Throat > Pre-separator > Inhalation Cell (Vertical) > Unidose™
Setup 4	Device > Mouthpiece > Anatomical Throat > Inhalation Cell (Vertical) > Unidose™
Setup 5	Device > Mouthpiece > Anatomical Throat > Pre-separator > Inhalation Cell (Vertical) > Unidose™
Setup 7	Device > Mouthpiece > Anatomical Throat > Modified NGI > Inhalation Cell (Vertical) > Unidose™

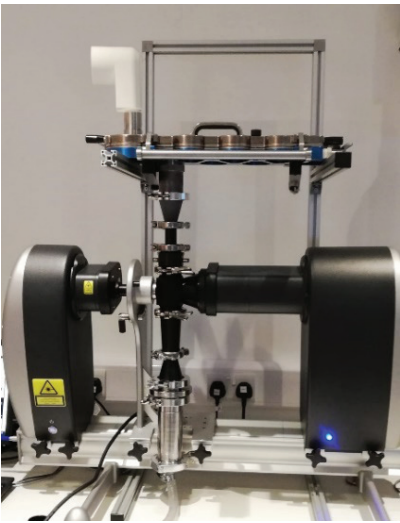
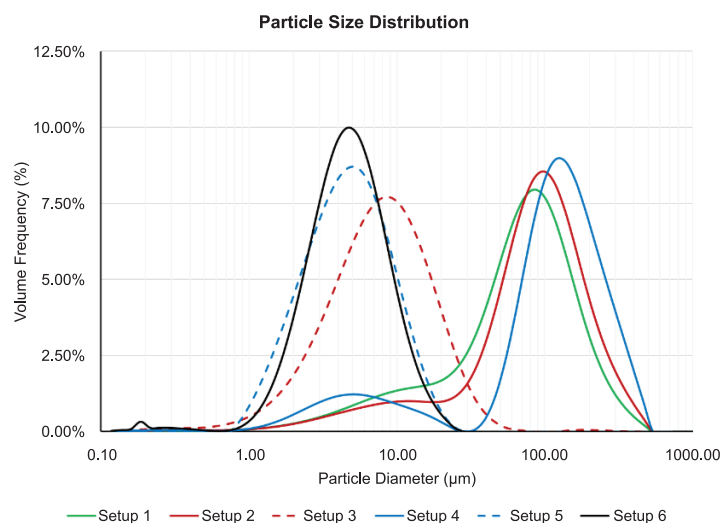


Figure 2. Description of all the different setups used on the left and schematics of setup 6 for the combination of Spraytec with the Unidose on the right.

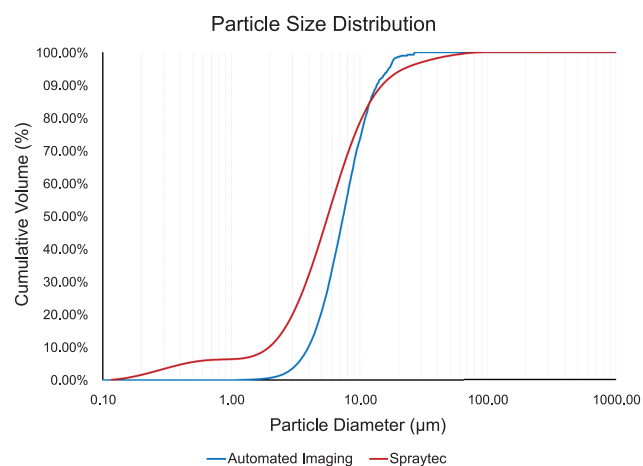
The particle size distribution data for the different setups are presented in Figure 3. As expected, using an anatomical throat (setup 4 and 5) instead of a USP throat (setup 2 and 3) reduces the number of large particles passing in front of the laser as these are retained on the throat. The addition of a pre-separator to the setup reduces dramatically the number of large particles going through the laser (setup 3 and 5). Setup 6 (Figure 2) allows the analysis of the particle size distribution of fine particles only, by analyzing the ISM dose.



Setup	Dv10 (µm)	Dv50 (µm)	Dv90 (µm)	% < 5 µm	% < 10 µm
1	10.18	66.02	165.28	4.59	9.90
2	13.02	80.98	196.11	4.44	8.53
3	2.32	7.20	18.54	32.89	66.36
4	6.19	109.7	253.36	8.33	13.18
5	1.73	4.31	9.95	58.40	90.14
6	1.93	4.32	9.33	59.59	91.94

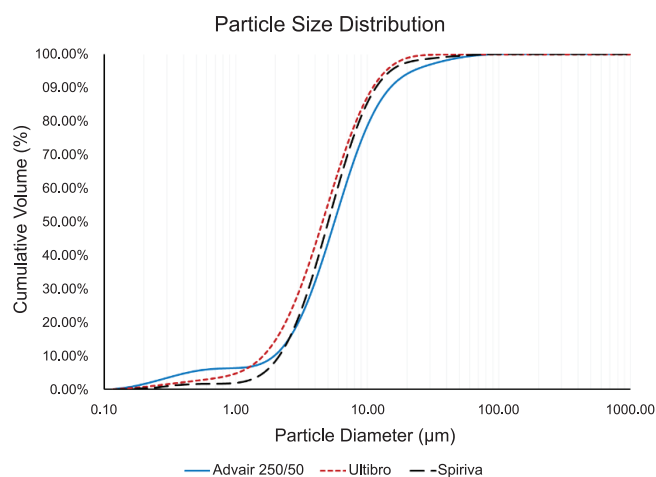
Figure 3. Volume Particle Size Distribution (PSD) for 6 different setups on Spraytec with Advair® 250/50.

The filters collected from setup 6 were analyzed on Morphologi 4-ID and the particle size comparison between both techniques is presented on Figure 4. Both techniques present differences in PSD due to the lower limit of detection of laser diffraction which shifts the Dv10 and Dv50.



Technique	Dv10 (µm)	Dv50 (µm)	Dv90 (µm)
Laser Diffraction	1.97 (0.13)	5.65 (0.36)	16.04 (4.14)
Automated Imaging	3.92 (0.52)	7.24 (0.56)	13.11 (1.23)

Figure 4. Volume PSD for setup 6 on Spraytec and Morphologi 4-ID with Advair® 250/50.



Technique	Dv10 (µm)	Dv50 (µm)	Dv90 (µm)	%V < 5µm	%V < 10µm
Advair	1.97 (0.13)	5.65 (0.36)	16.04 (4.14)	43.44 (3.41)	78.54 (5.19)
Ultibro	1.62 (0.04)	4.57 (0.18)	10.98 (0.63)	55.00 (2.28)	87.26 (1.70)
Spiriva	2.14 (0.22)	5.04 (0.16)	12.00 (1.70)	49.45 (2.13)	85.44 (2.88)

Figure 5. Volume particle size distribution by laser diffraction of Advair® Diskus® 250/50, Spiriva Handihaler®, Ultibro® Breezhaler® at 60 L/min.

Different commercial products were evaluated with this setup and the data are presented on Figure 5. These data suggest that Ultibro has the higher amount of fine particles below 5 μm . This can be associated to the presence of a force control agent such as magnesium stearate which might enhance the deagglomeration of the different components of the aerosolized formulation [7].

CONCLUSIONS

The Spraytec was successfully combined with the Unidose to evaluate the particle size distribution of the ISM dose by laser diffraction. The PSD by laser diffraction of the ISM dose of Advair was then compared with the automated imaging data. Although automated imaging was not able to capture finer particles, both techniques had an equivalent Dv_{90} . The particle size distribution of the ISM dose of different RLD products was successfully measured, with observed differences between them. Further studies should be performed to investigate these differences in PSD.

REFERENCES

1. TelkoMJ, Hickey AJ: Dry powder inhaler formulation. *Respir Care* 2005, 50(9): 1209–1227.
2. Staniforth JN: Performance-modifying influences in dry powder inhalation systems. *Aerosol Sci Technol* 1995, 22(4): 346–353.
3. Begat P, Morton DAV, Shur J, Kippax P, Staniforth JN, Price R: The role of force control agents in high-dose dry powder inhaler formulations. *J Pharm Sci* 2008, 98(8): 2770–2783.
4. Buttini F *et al.*: Effect of flow rate on *in vitro* aerodynamic performance of NEXThaler® in comparison with Diskus® and Turbohaler® dry powder inhalers. *J Aerosol Med Pulm Drug Deliv* 2016, 29(2): 167–178.
5. Price R, Goncalo F, Ganley WJ, Shur J: Demonstrating Q3 Structural equivalence of dry powder inhaler blends: new analytical concepts and techniques. *RDD 2018* 2018, 265–276.
- 6] Price R, Shur J: Apparatus and method for determination of the fine particle dose of a powder inhalation formulation. US20180275022A1, 2018.
7. Jetzer MW, Morrical BD, Schneider M, Edge S, Imanidis G: Probing the particulate microstructure of the aerodynamic particle size distribution of dry powder inhaler combination products. *Int J Pharm* 2018, 538(1–2): 30–39.

Notes