Single-nozzle impactor for aerosol collection with subsequent spectroscopic and ultramicroscopic characterization

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INTRODUCTION

Respirable dosage forms are the most commonly used forms of medication for treatment of asthma and chronic obstructive pulmonary diseases, using delivery devices like pressurized metered dose inhalers (pMDI) [1] or dry powder inhalers [2]. Properties of drugs in these devices need to be tested during shelf life and simulated usage, because the properties of the dispersed particles are directly related to efficacy in patients [3]. Since inhalation devices produce millions of respirable sized particles upon every actuation, individual, representative characterization of the dispersed particles can be very difficult. Moreover, analysis of bulk properties, *e.g.*, composition, demands a larger amount of particles, which need to be gathered with a suitable sampling technique, ideally from a single actuation of a delivery device.

In this study, a new impactor was designed to concentrate dispersed particles for subsequent bulk properties analysis. The cascade impactor is a very widely used particle sizing instrument for pharmaceutical applications using the inertia of aerosol particles in curvilinear motion for collection or separation. Ideal impactors collect particles larger than a specific diameter, which is usually referred to as the cutoff diameter, $d_{a,50}$, and let all smaller particles pass through [4]. For a well-controlled cutoff diameter and maximal sharpness of collection efficiency curve, the nozzle diameter, d_j, nozzle length, T, and jet-to-plate separation distance, *i.e.*, the distance between nozzle exit and impaction plate, S, should follow the design criteria [5]

described in Equation (1)-(3), where *Re* is the Reynold's number of gas flow in the nozzle. The new impactor was designed to meet these basic standards:

$$500 \le Re \le 3000 \quad (1) \qquad S / d_j \ge 1 \quad (2) \qquad T / d_j \ge 1 \quad (3)$$

The motivation for designing such a new impactor is that most currently available impactors use multiple nozzles making them inefficient for concentrating aerosol into a single sample spot.

MATERIALS AND METHODS

A commercial meter dose inhaler, Seretide® 250 Evohaler® (GSK) containing 250 µg fluticasone propionate and 25µg salmeterol xinafoate, was used in this study to produce dispersed respirable aerosol particles. Reported size distributions of the two ingredients [6] were used to configure the impactor for collection. For comparison, a traditional freezing-evaporation method was used to extract the total powder contained in the pMDI canister. For this, the aluminum canister was immersed in liquid nitrogen to freeze the propellant and then opened by removing the valve using a mechanical cutter. The frozen and cut canister was then put into a dry box at room temperature to allow slow propellant evaporation. Residual dry powders were transferred into glass vials for subsequent analysis.

The macro-Raman instrument used for characterizing collected powders was a custom designed dispersive Raman system using an Argon ion laser operating at a wavelength of 514.5 nm as excitation source [7]. A scanning electron microscope (EVO MA10, Zeiss, Oberkochen, Germany) was used for imaging the morphology of collected particles on standard collection stubs. Double sided adhesive conductive carbon tape was applied on the stub when collecting powders for SEM imaging to avoid electron charging mainly because of the poor conductivity of the pharmaceutical particles.

RESULTS AND DISCUSSION

A cross-section of the new impactor in a configuration with multiple stages stacked and clamped by a sleeve clamp is displayed in Figure 1. A standard United States Pharmacopeia (USP) throat was directly connected to the inlet of the impactor and acted as the induction port. Doses from the pMDI were actuated into the induction port with the assistance of a suitable adaptor. A standard SEM sample stub embedded in the collection plate functioned as a removable impaction plate for easy sample transfer. Detailed specifications of the impactor stages are listed in Table 1. The impactor, when operated at a volume flow rate of 0.5 L/min covers theoretical cutoff diameters from 0.6 µm to 21.1 µm using up to 12 available stages.

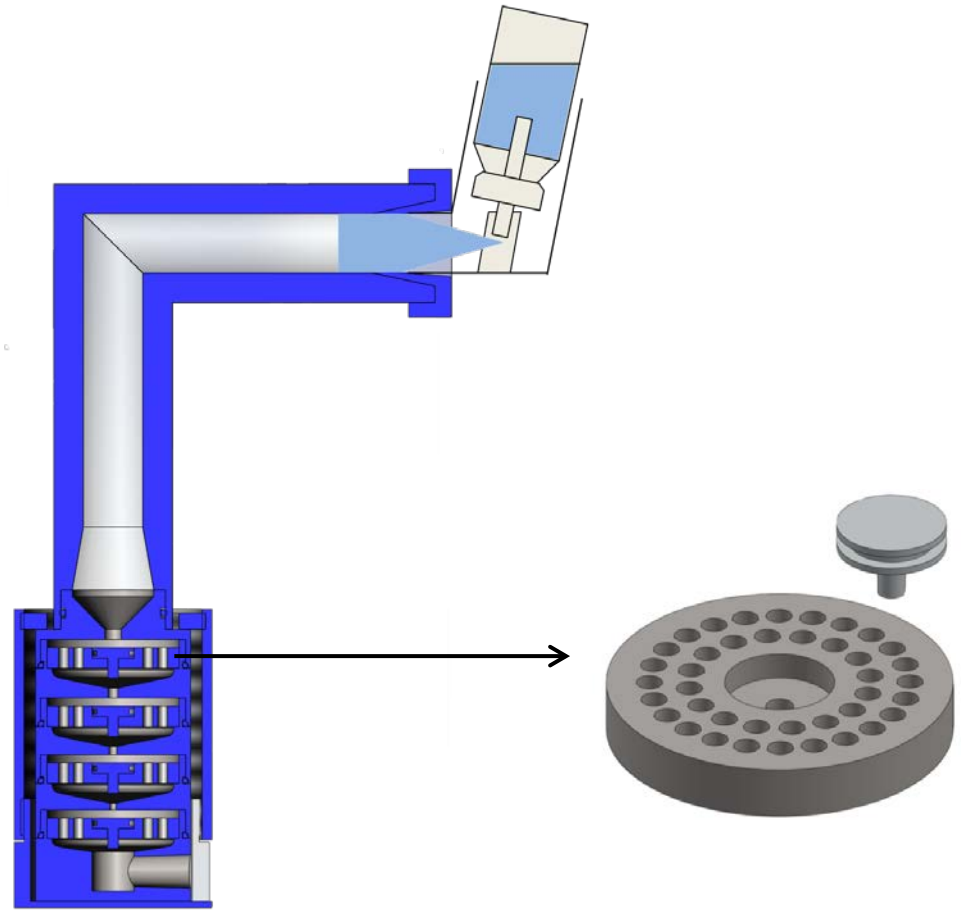

Figure 1. Cross-sectional view of the new single-nozzle impactor with attached induction port and pMDI. The inset to the right shows a collection plate with removable sample stub.

Table 1. Specifications of the designed impactor for a flow rate of 0.5 L/min

Stage	d_j (mm)	*T* (mm)	*Re*	S/d_j	T/d_j	$d_{a,50}$ (µm)
0	4.95	3.00	142	0.51	0.61	**21.1**
1	3.00	3.00	234	0.83	1.00	**9.92**
2	2.40	2.50	292	1.04	1.04	**7.08**

3	1.90	2.00	369	1.32	1.05	**4.96**
4	1.65	2.00	425	1.52	1.21	**4.00**
5	1.40	1.50	501	1.79	1.07	**3.12**
6	1.20	1.50	585	2.08	1.25	**2.45**
7	1.00	1.00	702	2.50	1.00	**1.84**
8	0.85	1.00	825	2.94	1.18	**1.43**
9	0.70	1.00	1002	3.57	1.43	**1.05**
10	0.60	1.00	1169	4.17	1.67	**0.82**
11	0.50	1.00	1403	5.00	2.00	**0.60**

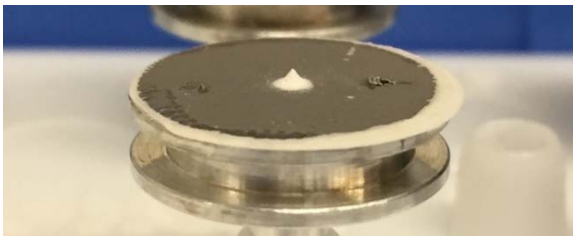

Figure 2. Collected powder from one actuated Seretide® 250 Evohaler® pMDI dose containing 250 µg fluticasone propionate and 25µg salmeterol xinafoate.

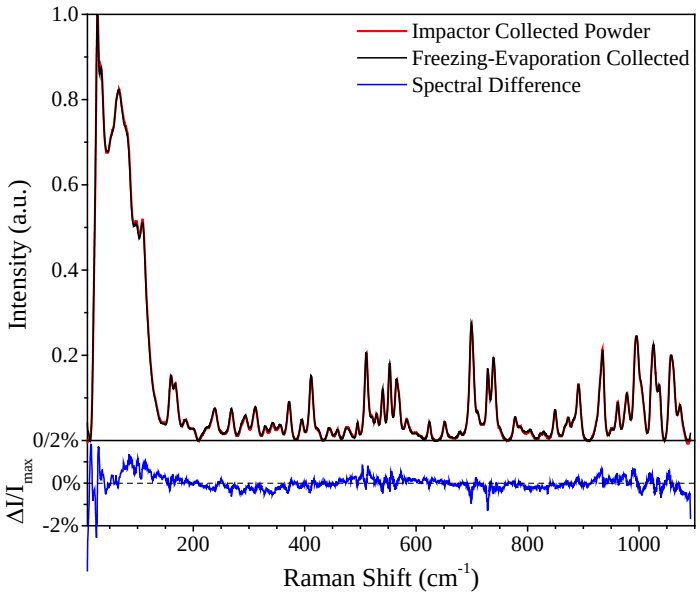

Figure 3. Raman spectra of pharmaceutical powder collected by different methods: Single actuation sampling using the newly designed impactor *versus* the standard freezing-evaporation extraction method. Spectral differences ($\Delta I/I_{Max}$) of the two spectra in percentage of the highest peak intensity are lower than 2% over the whole spectral range.

In an application example demonstrating sampling from a pMDI, only stage #9 with a theoretical cutoff diameter of 1.05 µm was used to collect particles emitted from a single pMDI actuation. As shown in Figure 2, the particles collect on the sampling stub as expected. Approximately 200 µg of powders were sampled. The powder was successfully measured with Raman spectroscopy. The spectrum, presented in Figure 3, was compared with that of a powder sample extracted by the freezing-

evaporation extraction method and they superimpose well with less than 2% spectral difference along the whole spectrum. This indicates representative sampling of the bulk material contained in the pMDI canister using only a single dose. The collected powder was also imaged using SEM with morphology of the particles displayed in Figure 4.

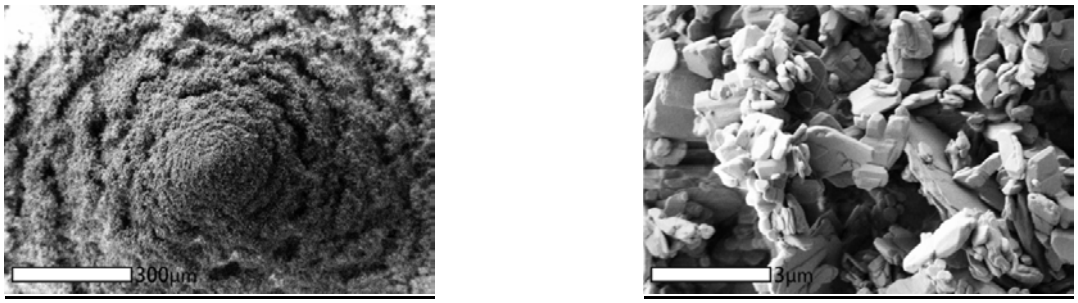

Figure 4. Morphology of collected particles on Stage #9 with cutoff diameter $d_{a,50}$=1.05 µm

CONCLUSIONS

The newly designed single-nozzle impactor is applicable to collect highly dispersed respirable particles, *e.g.*, aerosol produced by commercial metered dose inhalers, for subsequent spectroscopic and ultramicroscopic characterization. Its excellent aerosol concentration capability enables non-destructive, convenient and fast sample preparation of aerosol particles for characterization techniques requiring bulk powders. Taking a common time-dependent stability study on a pMDI product for example, this new sampling device can not only greatly reduce the high cost associated with destructive sampling methods, but also provides potentially better sample consistency between measurements in comparison to sampling from multiple canisters, which may have inter-canister sample variations.

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