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Manufacturing Process Implications on Aerosolized Submicron to Nano-sized Particles from Respiratory Drug Delivery Devices

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MANUFACTURING PROCESS IMPLICATIONS ON AEROSOLIZED SUBMICRON TO NANO-SIZED PARTICLES FROM RESPIRATORY DRUG DELIVERY DEVICES

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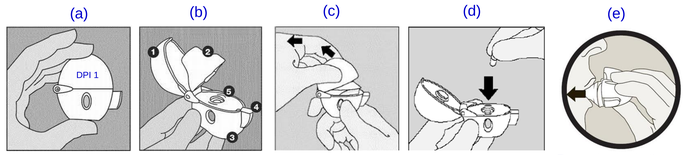
INTRODUCTION

The dry powder inhalers (DPIs) are a popular type of respiratory drug delivery devices (RDDDs), which generates inhalable aerosolized particulate form of medications for the treatment of asthma and chronic obstructive pulmonary diseases.

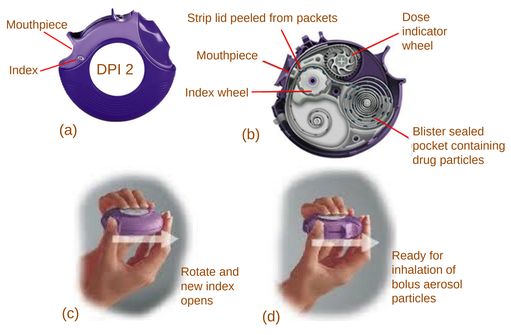
The manufacturing technologies related to the DPI drug dose preparation, releasing techniques, and mouthpiece geometries have been constantly improved in order to fulfill the requirements of the biomedical device industry. The device features have consequential relationships with the emitted drug/carrier powder aerosol properties [1].

The successful delivery of drugs into the deep lung depends on various aerodynamic and electromechanical properties of generated particles [2,3]. Precise quantification of these properties are not only convincing but also serve as a guide for better manufacturing techniques to satisfy growing RDDD industry.

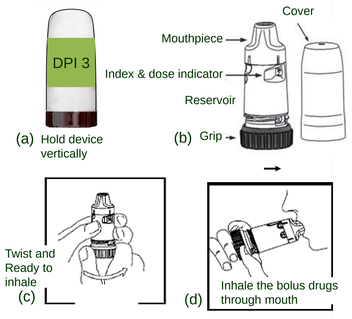
MATERIALS & METHODS



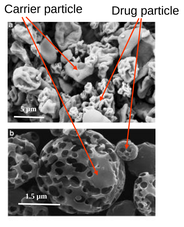
Mouthpiece Design Geometry and Working Principle of DPI-1 [4].



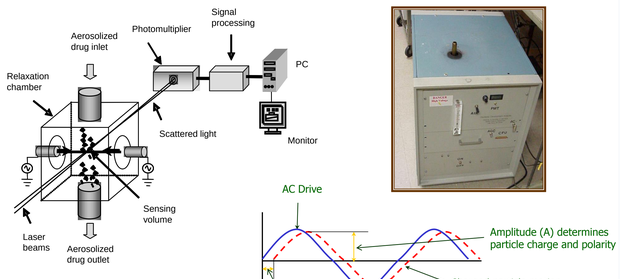
Mouthpiece Design Geometry and Working Principle of DPI-2 [5].



Mouthpiece Design Geometry and Working Principle of DPI-3 [6].



Drug particles attracted to carrier particles, in which particle size and charge play major roles

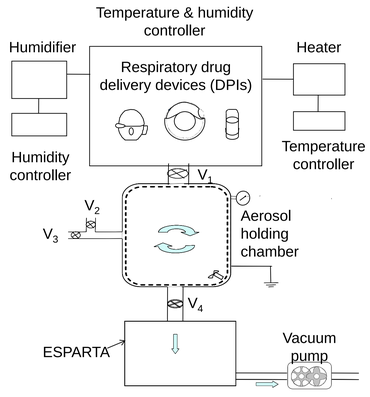


ESPARTA principle of operation: Laser Doppler Velocimetry [7].

ABSTRACT:

This experimental investigation presents the mouthpiece design geometry, manufacturing and powder mixture homogeneity effects of three respiratory drug delivery devices to the aerodynamic and electromechanical properties of generated inhalable nano and submicron particles. These devices are commonly known as dry powder inhalers (DPIs). Effects of the mechanistic behaviors of the DPI design geometry, and integration between device performance and powder formulations are warranted to be investigated. An electronic single particle aerodynamic relaxation time analyzer, which functions on the Laser Doppler Velocimetry principle, was employed to measure submicron particles' charge and size in real time. Analyzed results revealed that the generated aerosol particles from all three DPIs were found to not only have different size distributions but also varied in their charge distributions. The net charge to mass ratio of DPI 1, 2, and 3 particles were 3.80 µC/g, 1.37 µC/g, and 1.45 µC/g, respectively. Count and mass distributions of the particles were reproducible ($p<0.05$) for all DPIs. Variations in electrical, mechanical and aerodynamic properties of the DPI aerosols can be explained by the combined effects of triboelectrification charging between carrier and active drug powders, delivery device geometries, polymeric material surfaces of delivery devices, and drug/carrier homogeneities.

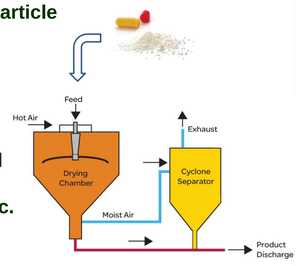
EXPERIMENTAL SETUP



RESULTS & DISCUSSION

Spray drying - Technology behind composite particle preparation;

- **Ideal for generating engineered particles with improved electromechanical and aerodynamic performance**
- **Mild flash drying can be adopted for careful control of particle properties e.g., particle size, bulk density, degree of crystallinity, etc.**

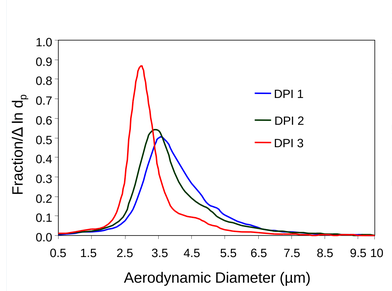


RESULTS & DISCUSSION

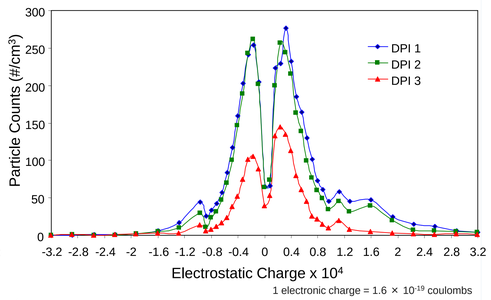
Summary of the three dry powder inhaler (DPI) aerosols aerodynamic size (micrometer) and electrostatic charge (micro-coulomb per gram) properties (mean ± SD).

DPI	Charged Particle (%)	+ve Counts vs. -ve Counts	Net Charge/ mass ratio (µC/g)	+ve Charge/mass vs. -ve Charge/mass (µC/g)	CMAD (µm) (Charged and uncharged)	MMAD (µm) (Charged and uncharged)
DPI 1	62 ± 4	1783 ± 20 1899 ± 24	+ 3.80 ± 06	+ 5.30 ± 14 - 6.61 ± 16	3.61 ± 0.07	4.99 ± 0.03
DPI 2	67 ± 5	1626 ± 29 2313 ± 31	+ 1.37 ± 03	+ 4.77 ± 13 - 6.30 ± 17	3.61 ± 0.19	5.29 ± 0.15
DPI 3	28 ± 2	475 ± 9 618 ± 12	+ 1.45 ± 04	+ 5.41 ± 11 - 6.63 ± 12	2.86 ± 0.02	3.65 ± 0.10

CMAD: Count median aerodynamic diameter, MMAD: Mass median aerodynamic diameter



Particle size distributions of three different DPI generated drug aerosols.



Particle charge distributions of three different DPI generated drug aerosols.

CONCLUSIONS

- ❖ **Variations in electrical, mechanical and aerodynamic properties of DPIs are combined effects of: a) Tribo-electrification charging between carrier and active drug powders; b) Delivery device mouthpiece geometries, polymeric material of device surfaces, and drug/carrier homogeneities.**
- ❖ **This work demonstrated a new method of real-time and simultaneous measurement of the aerodynamic size and electrostatic charge quantifications;**
- ✓ **All DPIs generated net electro-positively charged particles,**
- ✓ **All devices are capable to produce particles with desired electro-mechanical properties,**
- ✓ **Findings have practical values and biomedical device manufacturing implications,**
- ✓ **Developers of DPIs may consider electrodynamic effects while designing future improved products.**

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