Tuning Aerosol Performance Using the Multibreath Orbital® Dry Powder Inhaler Device: Controlling Delivery Parameters and Aerosol Performance via Modification of Puck Orifice Geometry

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ABSTRACT: The current study presents a new approach to tackle high-dose lung delivery using a prototype multibreath Orbital® dry powder inhaler (DPI). One of the key device components is the "puck" (aerosol sample chamber) with precision-engineered outlet orifice(s) that control the dosing rate. The influence of puck orifice geometry and number of orifices on the performance of mannitol aerosols were studied. Pucks with different orifice configurations were filled with 400 mg of spray-dried mannitol and tested in the Orbital® DPI prototype. The emitted dose and overall aerodynamic performance across a number of "breaths" were studied using a multistage liquid impinger. The aerosol performances of the individual actuations were investigated using in-line laser diffraction. The emptying rate of all pucks was linear between 20% and 80% cumulative drug released ($R^2 > 0.98$), and the amount of formulation released per breath could be controlled such that the device was empty after 2 to 11 breath maneuvers. The puck-emptying rate linearly related to the orifice hole length ($R^2 > 0.95$). Mass median aerodynamic diameters of the emitted aerosol ranged from 4.03 to 4.62 μm and fine particle fraction (≤6.4 μm) were 50%–66%. Laser diffraction suggested that the aerosol performance and emptying rates were not dependent on breath number, showing consistent size distribution profiles. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

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INTRODUCTION

Dry powder inhalers (DPIs), nebulizers, and pressurized metered dose inhalers have been developed for over 30 years for the treatment of various pulmonary diseases.[1,2] The principle of these inhalation devices has focused on delivery of inhalable medications for the treatment of asthma and chronic obstructive disease that usually require a small quantity of active pharmaceutical ingredient (API) per delivered dose.[3–5]

Various low-dose DPI inhaler devices have been successfully developed and marketed over the years and a number of commercial products contain doses ranging from tens of micrograms (e.g., formoterol ~6–12 μg; tiotropium ~18 μg; salbutamol ~100 μg; beclomethasone ~250 μg) up to a few milligrams (e.g., nedocromil and sodium cromoglycate ~2–5 mg). Suitable to deliver medicaments within the microgram range, such as corticosteroids[6] and β_2 agonists,[7] these devices lack the ability to deliver APIs requiring higher milligram quantities (i.e., 10–1000 mg), such as antibiotics[8] and mucociliary clearance reagents, such as mannitol.[9] Currently, TOBI Podhaler® is the only commercially available antibiotic (tobramycin) DPI with a high-delivery dose (~112 mg) and Bronchitol®, the only high-dose mucociliary clearance therapy containing mannitol as the active ingredient (~400 mg). However, the delivered dose for both these products is achieved by individually dispersing multiple capsules (4 × 28 mg in the case of tobramycin and 10 × 40 mg in the case of mannitol) through a multiple "load-prime-inhale" routine. This type of aerosol delivery strategy is time-consuming and can potentially result in poor therapy adherence.[10]

Mannitol, used as an inhaled dry-powder osmotic reagent, has been proven to be effective in the treatment of diseases where hyper-mucus production is prevalent, such as cystic fibrosis and bronchiectasis.[11,12] For example, patients with bronchiectasis showed marked improvement in mucus clearance in the central and intermediate lung regions (>20%) 75 min postinhaled mannitol intervention.[9] The solid content in sputum of CF patients was significantly reduced by approximately 2%[13] and forced expiratory volume increased by approximately 100 mL[14] with 2-week inhaled mannitol therapy. Although this unique therapy provides a means of enhancing clearance, as with other high-dose therapies, the delivery vehicle is based on a DPI that was originally designed for lower dose therapeutics, thus requiring a patient to load, actuate, and inhale from multiple capsules.

Recently, Pharmaxis developed a disposable, multibreath DPI device able to deliver large doses of active ingredients (~500 mg) through a number of inhalation maneuvers.[15,16] The Orbital® device (Fig. 1) consists of four major components—(1) a mouthpiece, (2) dispersion grid, (3) dispersion chamber with multiple tangential airstream inlets, and (4) a "puck" or aerosol sample compartment. During inhalation, the puck rotates within the dispersion chamber and releases the

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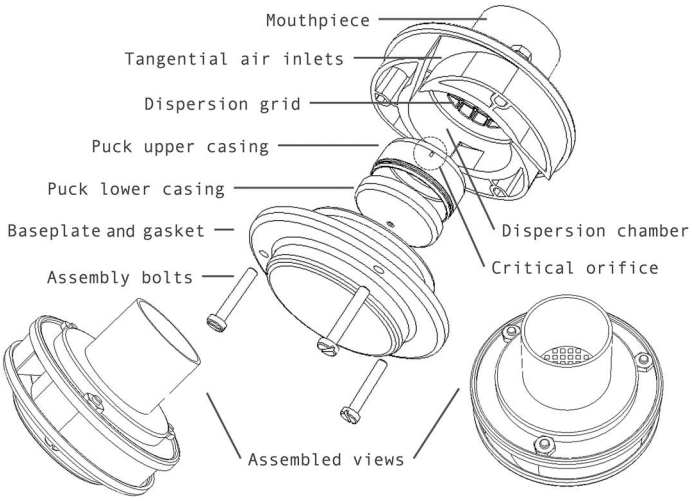

Figure 1. Schematic of the prototype Orbital® device.

formulation through precision-engineered orifice(s). Previous studies[15,16] have demonstrated that the device can successfully deliver high payloads of cohesive ciprofloxacin/mannitol and azithromycin/mannitol spray-dried formulations (~200 mg) via approximately 10 inhalation maneuvers (equivalent to the number of capsules that would be required in conventional DPIs), while obtaining respiratory fractions greater than 60%.

In these previous studies, the authors focused on engineering and characterization of novel spray-dried powders for infection and bronchiectasis. They demonstrated the Orbital® to be versatile for the delivery of a number of molecules when using standard prototype device configuration. However, features of the device such as resistance, dispersion grid, and puck dimensions may be modified to "tune" both the delivery profile and aerosol performance.

Here, we investigate the emptying properties and aerosolization performance of the Orbital® device as a function of puck hole number and geometry using mannitol as the model API, similar to that used in Bronchitol® for mucus clearance.

MATERIALS AND METHODS

Materials

Spray-dried mannitol (Batch ID: EXP 280) was supplied by Pharmaxis Ltd. (Sydney, Australia) and used as received. Prototype Orbital® DPI devices, including pucks with different orifice configurations (Table 1), were supplied by Pharmaxis Ltd. Water was purified using reverse osmosis (Merck Millipore, Bayswater, VIC, Australia). All other solvents were HPLC grade and purchased from Chemsupply (Port Adelaide, Australia).

Table 1. Puck Orifice Configurations

	Puck ID	Orifice Shape	Orifice Number	Orifice Geometry (mm)
1	P-002	Rectangular	1	0.5 × 0.77 (width × length)
2	P-003	Rectangular	1	0.5 × 0.9 (width × length)
3	P-013a	Spherical	1	0.6 (diameter)
4	P-028	Spherical	1	0.9 (diameter)
5	P-024	Spherical	2[a]	0.4 (diameter)
6	P-021	Spherical	2[a]	0.55 (diameter)

[a] Orifices at opposite sides of puck.

Scanning Electron Microscopy

The morphology of mannitol was visualized using a JEOL-6000 bench-top scanning electron microscope (SEM; JEOL, Tokyo, Japan). Prior to imaging, mannitol samples were deposited onto carbon tape mounted on an aluminum stub and coated with gold using a sputter coater (DII-29010SCTR; JEOL) at a coating thickness of approximately 15 nm. Imaging was conducted at an accelerating voltage of 5 keV.

Particle Sizing

The volume median size ($D_{0.5}$) of the spray-dried mannitol was measured by laser diffraction using a Mastersizer 3000 (Malvern Instruments, Malvern, UK) equipped with hydrodispersion unit. Samples were prepared by suspending approximately 40 mg of spray-dried mannitol in 5 mL of cyclohexane, which was then added dropwise to the hydrodispersion unit, operating at a stirring speed of 2000 rpm, until 5%–15% obscuration was achieved. Samples were measured with a density setting of 1.51 g/cm^3 and refractive index of 1.33. Each sample was analyzed in triplicate.

Multibreath-Delivered Dose Study

The puck and puck orifice is a key parameter that influences the emptying and aerosolization performance of the Orbital. By modifying the puck hole geometry, number of holes, and hole size, it becomes possible to modify the rate at which the powder is dispersed and thus the number of breaths required to achieve a target dose.

In the current study, different types of pucks (Table 1) were loaded with 400 ± 0.8 mg ($n = 3$) spray-dried mannitol and assembled in the Orbital inhaler device, to simulate standard treatment.[12] Because of the high payload delivered, a multistage liquid impinger (MSLI; Westech, Bedfordshire, UK) equipped with a United States Pharmacopeia (USP) induction port was used to collect the emitted aerosol to avoid filter clogging. The airflow rate through the assembly was calibrated at 60 ± 2 L/min using a flowmeter (TSI 4040; TSI Instruments Ltd., Shoreview, Minnesota).

The assembled Orbital device was inserted into a silicon mouthpiece adaptor, mounted onto the USP induction port, and powder dispersed at 60 L/min over a 4-s period to simulate one breath.[17] The weights of the assembled inhaler were recorded before/after each actuation/breath and shot weight of each actuation deemed as the weight difference (mg) of the two consecutive dispersions. The process was repeated with intermediate airflow calibration (60 L/min) for each shot until the difference between two actuations were less than 0.2 mg. The experiment was conducted in triplicate for each puck type.

Aerosol Particle Size Distribution Measured by Cascade Impaction

In addition to delivered dose, puck geometry may also have an impact on the aerosol performance of the emitted aerosol cloud. Therefore, the aerosolization efficiency of the Orbital inhaler device with the different pucks was investigated using a MSLI.

In brief, pucks (Table 1) were filled with 400 ± 0.5 mg of spray-dried mannitol ($n = 3$) and assembled in the Orbital device. The formulation was dispersed into the MSLI at 60 ± 2 L/min for 4 s per actuation ($n = 3$) until the puck was