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The development of a single-use, capsule-free multi-breath tobramycin dry powder inhaler for the treatment of cystic fibrosis

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ABSTRACT

The aerosol performance and delivery characteristics of tobramycin for the treatment of respiratory infection were evaluated using the Orbital™, a multi-breath, high dose, dry powder inhaler (DPI). Micronised tobramycin was prepared and tested in the Orbital and in the commercially available TOBI Podhaler (Novartis AG). Furthermore, the TOBI Podhaler formulation containing tobramycin as Pulmospheres was tested in both the commercial Podhaler device (T-326) and Orbital for comparison. By varying the puck geometry of the Orbital, it was possible to deliver equivalent doses of micronised tobramycin (114.09 ± 5.86 mg) to that of the Podhaler Pulmosphere product (116.01 ± 2.59 mg) over 4 sequential simulated breaths (60 L min^{-1} for 4 s) without the need for multiple capsules. In general, the aerosol performance of the micronised tobramycin from the Orbital was higher than the T-326 Podhaler device, with fine particle fraction (FPF) of 44.99% ± 1.09% and 37.03% ± 0.86%, respectively. When testing the Pulmosphere powder in the two devices, the T-326 had marginally better performance with a FPF of 68.77% ± 2.10% compared to 61.30% ± 3.45%. This is to be expected since the TOBI Podhaler and Pulmosphere are an optimised powder and device combination. The Orbital was shown to be capable of delivering high efficiency, high dose antibiotic therapy for inhalation without the need for the use of multiple capsules as used in current devices. This approach may pave the way for a number of antibiotic therapies and medicaments where high dose respiratory deposition is required.

1. Introduction

The use of inhaled antibiotics for diseases such as cystic fibrosis (CF), chronic obstructive pulmonary disease and bronchiectasis has been a core research area within the respiratory field (Brodt et al., 2014; Chmiel et al., 2014; Ryan et al., 2011; Traini and Young, 2009), still there are few therapeutic options available. The U.S. Food and Drug Administration (FDA) approved inhaled tobramycin in 1997 (Novartis TOBI®- Tobramycin) (Rose and Neale, 2010) and aztreonam lysine (AZLI, Cayston; Gilead Sciences, Foster City, CA) in 2010, as nebuliser-based therapies for treatment of respiratory infection; however, not specifically for chronic use (McCoy et al., 2008; Retsch-Bogart et al., 2008). Inhaled colistin (Colomycin; Forest Labs, New York, NY) is also used extensively in Europe and the UK as Colobreathe (125 mg single capsule Turbospin DPI), for treatment of chronic *Pseudomonas aeruginosa* infection, but is not FDA approved to-date (Schuster et al., 2013). Furthermore, a number of other antibiotics are in late-stage development (Quon et al., 2014) and will hopefully appear on the market in the near future.

Interestingly, only one antibiotic and one device have been marketed in the US that contains inhalable antibiotic dry powder: the TOBI Podhaler (T326 Inhaler-Novartis) (Geller et al., 2011; Maltz and Paboojian, 2011). The delivery of dry powders is considerably more convenient than nebulisation since the devices are portable, have shorter administration times and do not require cold chain storage (Geller, 2005).

However, conventional DPI devices were historically designed to deliver individual micrograms to individual milligrams active drug per dose; orders of magnitude less than the quantity of antibiotics required for respiratory therapy. Thus, innovative devices and particle engineering technology are required to deliver

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high doses of medication in a convenient package. In the TOBI Podhaler, Pulmosphere® technology (Inhale Therapeutic Systems; San Carlos, CA), (Duddu et al., 2002a; Geller et al., 2011; Newhouse et al., 2003; Weers et al., 2013) is used to enhance aerosolisation of such a high payload (112 mg) and is incorporated into an optimised device capable of delivering 4 sequential, 28 mg drug loaded capsules (Duddu et al., 2002b; Weers, 2000). This results in a formulation that is delivered over a number of minutes. However, there are some drawbacks to such a formulation. Firstly, the particles have to be engineered from the 'bottom-up' using advanced spray drying methodology, coupled with the use of excipients. Secondly, during patient use, multiple capsule loading, actuation, inhalation manoeuvres followed by reloading is required several times.

Moving forward, if we are to rapidly develop additional antibiotic therapies for a wide range of infections, while simultaneously improving ease of use (and the number of operational steps), we need to develop a new inhaler platform. Furthermore, if this platform is capable of incorporating the active pharmaceutical ingredient produced by both conventional 'top-down' micronisation processes as well as 'bottom-up' engineered particles (such as the TOBI Pulmosphere technology), this would offer a major advantage to respiratory scientists working within the field.

The Orbital DPI device (Fig. 1) is a novel inhaler that has been shown to be able to deliver high payload of active ingredients (up to 500 mg), without the use of carriers (Young et al., 2014a; Young et al., 2014b; Young et al., 2015; Zhu et al. 2015). High payloads are required for a number of therapies including Bronchitol (400 mg, Pharmaxis Pty., Ltd.) and in the use of high dose antibiotics as studied here. Briefly, the Orbital has been designed as a single use disposable inhaler (reducing re-infection risk) that delivers high doses of powder to respiratory tract over a number of inhalation manoeuvres (Young et al., 2014a,b). However, the device only requires one actuation step followed by multiple inhalation manoeuvres, significantly reducing usage time and potential patient error, enhancing compliance.

The Orbital device has 4 main components, (1) the mouthpiece, (2) dispersion grid, (3) aerosolisation chamber with tangential air inlets and (4) sample compartment or 'puck'. The puck allows for the delivery of a high dose without the need to 'fill-prime-inhale-dispose-re-fill' typical of current dry powder devices. Previously, work has been presented using this device with spray-dried material, describing its versatility in delivery high doses of engineered inhalation particles (Young et al., 2014a,b).

The aim of this investigation was to assess the capability of the Orbital device in delivering conventionally milled tobramycin via multiple breath manoeuvres, while only actuating the device once.

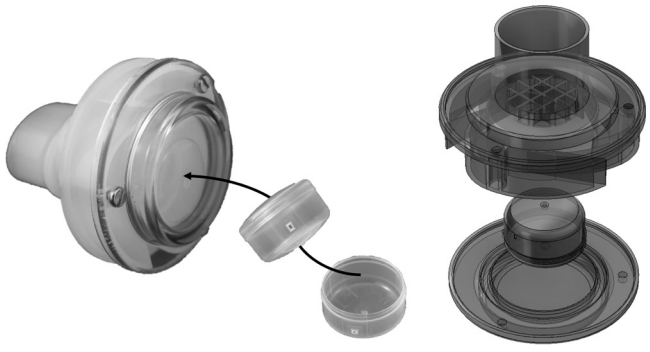

Fig. 1. Schematic and photograph of Orbital device and puck assembly.

We compared the aerosol performance and dosing of a non-optimised powder in the commercial multi-capsule device Podhaler and the gold standard TOBI-Tip Pulmosphere powder in both the Podhaler and Orbital.

2. Materials and methods

2.1. Materials

Tobramycin base was supplied by Lisapharma (Erba, CO, Italy). Tris (dydroxymethyl) aminomethane (TRIS) was purchased from Bio-Rad Laboratories (Hercules, CA, USA). Dimethylsulfoxide (DMSO), 1-Fluoro-2,4-dinitrobenzene, sulfuric acid (≥95%), ethanol (100%) and acetonitrile were of analytical/HPLC grade and used as provided by Sigma-Aldrich (Sydney, Australia). High purity water was purified by reverse osmosis (MilliQ, Millipore, France).

2.2. Micronisation and physico-chemical characterisation of tobramycin powder

To obtain a powder suitable for inhalation, the tobramycin was micronised using a Labomill jet milling system (Food Pharma System, Italy). A matrix of milling parameters was investigated and the following optimal settings were chosen: injection pressure 2.8 bar and grind pressure 3 bar. The resulting micronised powder size distribution was determined by laser diffraction (Mastersizer 3000, Malvern, Worcestershire, UK) at a refractive index of 1.65. A dry dispersion unit (Aero S) was used at a dispersion pressure of 4 bar, flow rate of 40 L min^{-1}, vibration feed rate of 100% and feed height of 0.7 mm.

The size and morphology of the micronised tobramycin particles was further investigated using a Scanning Electron Microscope (SEM) (JMC 6000 JEOL, Japan) operating at 15 keV. Samples were mounted on adhesive black carbon tabs (pre-mounted on aluminium stubs) and coated with gold, using a sputter coater (Smart coater DII-29030SCTR, JEOL, Japan) to a thickness of approximately 40 nm, prior to analysis. The micronised and raw tobramycin was studied in terms of thermal response using differential scanning calorimetry (DSC) (Model DSC-1 Mettler-Toledo, Schwerzenbach, Switzerland) at a heating rate of 10° C min^{-1} over a temperature ramp from 25 to 300° C. 3–5 mg samples were weighed into 40 μL aluminium DSC sample pans, which were crimp-sealed and pierced with a 1 mm pinhole to insure constant pressure, prior to analysis.

2.3. Emitted dose and aerosol performance of tobramycin

In order to evaluate the performance of the Orbital device in delivering multiple doses of tobramycin, both the emitted dose and aerosol performance were measured using conventional *in vitro* methods as outlined in the British Pharmacopoeia. A prototype Orbital device was used throughout this study with a resistance (ex. Puck) of 0.039 $kPa^{1/2}$/L min^{-1}.

2.3.1. Choice of orbital puck geometry

As previously discussed, the Orbital device is a single-use, disposable device containing a sample compartment "puck". The puck rotates within the aerosolisation chamber, during inhalation, releasing the formulation through a precision-engineered sample orifice that acts as a rate-limit step for powder release (Young et al., 2014a,b). Thus, prior to aerosol studies, optimum puck geometry must be chosen that controls powder release to chosen specifications.

Based on a dose of 112 mg, a targeted inhalation dose per breath of ca. 30 mg was chosen since it has been shown to be well