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The effect of device resistance and inhalation flow rate on the lung deposition of orally inhaled mannitol dry powder

Michael Y. Yang[a], Jordan Verschuer[b], Yuyu Shi[c], Yang Song[c], Andrew Katsifis[b], Stefan Eberl[b,c], Keith Wong[d], John D. Brannan[e], Weidong Cai[c], Warren H. Finlay[f], Hak-Kim Chan[a,*]

[a] Advanced Drug Delivery Group, Faculty of Pharmacy (A15), Science Road, University of Sydney, NSW 2006, Australia
[b] Department of PET and Nuclear Medicine, Level 7, Building 63, Royal Prince Alfred Hospital, NSW 2050, Australia
[c] School of Information Technologies, University of Sydney, NSW 2006, Australia
[d] Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, and Central Clinical School, University of Sydney, Camperdown, NSW 2050, Australia
[e] Department of Respiratory and Sleep Medicine, John Hunter Hospital, New Lambton, NSW 2305, Australia
[f] Department of Mechanical Engineering, University of Alberta, Edmonton, AB T6G2G8, Canada

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ABSTRACT

The present study investigates the effect of DPI resistance and inhalation flow rates on the lung deposition of orally inhaled mannitol dry powder. Mannitol powder radiolabeled with ^{99m}Tc-DTPA was inhaled from an Osmohaler™ by healthy human volunteers at 50–70 L/min peak inhalation flow rate (PIFR) using both a low and high resistance Osmohaler™, and 110–130 L/min PIFR using the low resistance Osmohaler™ (n = 9). At 50–70 L/min PIFR, the resistance of the Osmohaler™ did not significantly affect the total and peripheral lung deposition of inhaled mannitol [for low resistance Osmohaler™, 20% total lung deposition (TLD), 0.3 penetration index (PI); for high resistance Osmohaler™, 17% TLD, 0.23 PI]. Increasing the PIFR 50–70 L/min to 110–130 L/min (low resistance Osmohaler™) significantly reduced the total lung deposition (10% TLD) and the peripheral lung deposition (PI 0.21). The total lung deposition showed dependency on the *in vitro* FPF ($R^2 = 1.0$). On the other hand, the PI had a stronger association with the MMAD ($R^2 = 1.0$) than the FPF ($R^2 = 0.7$). In conclusion the resistance of Osmohaler™ did not significantly affect the total and regional lung deposition at 50–70 L/min PIFR. Instead, the total and regional lung depositions are dependent on the particle size of the aerosol and inhalation flow rate, the latter itself affecting the particle size distribution.

1. Introduction

The dry powder inhaler (DPI) is a cornerstone in the treatment of pulmonary diseases such as asthma and COPD. For inhaled dry powder drugs to be efficacious, it is necessary to achieve a sufficient dose in the desired regions of the lungs. This is dependent on not only the formulation but also on the flow rate. Since the flow rate, for a given inhalation effort or pressure drop across device, is inversely proportional to the resistance (expressed in $kPa^{1/2}$ min/L), the inhaler resistance becomes critical in controlling the airflow that de-agglomerates and transports the dry powder aerosol into the lungs.

DPIs are available in different resistances. Thus, for a given inhalation effort, the flow rate generated differs between devices. The effect of flow rate on lung deposition has been studied previously amongst low, medium and high resistance DPIs. For low resistance DPIs like the Spinhaler (0.016 $kPa^{1/2}$ min/L), the lung deposition is flow dependent where inhalation at 120 L/min gave higher total lung deposition (13.1%) than inhaling at 60 L/min (5.5%) (Newman et al., 1994). For high resistance DPIs like the Turbuhaler® (0.039 $kPa^{1/2}$ min/L), the peak inhalation flow rate (PIFR) is usually lower (Krüger et al., 2014). The total lung deposition when inhaled using maximum inspiratory effort from Turbuhaler® at 60 L/min (24–33%) was

Abbreviations: DPI, Dry powder inhaler; DTPA, Diethylenetriaminepentaacetic acid; FPF, Fine particle fraction; FEV_1, Forced expiratory volume in 1 s; MMI, Marple Miller Impactor; MSLI, Multi-Stage Liquid Impinger; MMAD, Mass median aerodynamic diameter; PIFR, Peak inhalation flow rate; PSD, Particle size distribution; PI, Penetration index; ROI, Region of interest; TLD, Total lung deposition; USP, United States pharmacopeia.

* Corresponding author.
E-mail address: kim.chan@sydney.edu.au (H.-K. Chan).

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shown to be significantly greater than the total lung deposition inhaled using moderate inhalation effort at PIFR of 30 L/min (14–22%) (Pitcairn et al., 2005; Borgstrom et al., 1994). Similar lung deposition dependency on the flow rate has also been reported for the Inhalator™ (0.062 $kPa^{1/2}$ min/L), where the lung deposition at 43 L/min and 63 L/min were 13% and 30%, respectively (Glover et al., 2006). On the other hand, the percentage of total lung deposition for some of the high resistance inhalers such as Pulvinal® (11 ± 2% at 27 L/min, 14 ± 3% at 46 L/min), Air™ (28 ± 6% at 37 L/min, 26 ± 6% at 72 L/min) and Taifun® (30 ± 6% at 21 L/min, 34 ± 6% at 36 L/min) showed little dependency on the inhalation flow rate (Pitcairn et al., 1994, 2000; Hirst et al., 2002).

These previous studies have looked at lung deposition using different resistances at different flow rates. Yet there has been no lung deposition study that investigated DPI resistance at the same inhalation flow rate. The resistance of a DPI is an important factor for aerosol drug delivery from the DPI because, apart from its role in influencing flow and powder dispersion, the resistance of a DPI can influence oropharyngeal airway structure during inhalation (Pritchard and McRobbie, 2004). The upper airway is known to be collapsible and this is largely governed by the anatomical properties and the internal pressure of the upper airway (Gold and Schwartz, 1996; Bilston and Gandevia, 2014; Kato et al., 2015). Because high resistance DPIs have a greater inspiratory pressure drop at a given flow, this contributes to a greater negative upper airway pressure that may narrow the oropharyngeal air space (Morrell et al., 1998; Ritter et al., 1999). Thus the structural changes associated with DPI resistance deserves attention because the oropharyngeal geometry is a primary factor in determining the flow streamlines responsible for aerosol deposition in the upper airway. Surprisingly we do not know the extent to which the structural changes associated with different resistance and oropharyngeal pressure can affect aerosol deposition at a comparable inhalation flow rate.

The Osmohaler™ is a dry powder inhaler device used to deliver mannitol through two versions of the device: low resistance (0.021 $kPa^{1/2}$ min/L) and high resistance (0.036 $kPa^{1/2}$ min/L). The low resistance Osmohaler™ is used for mannitol bronchial challenge tests (Aridol®) to identify bronchial hyperresponsiveness, a key clinical feature of asthma. The high resistance Osmohaler™ is used in oral inhalation of mannitol powder for treating cystic fibrosis by improving mucus clearance in the lungs (Brannan et al., 2005; Jaques et al., 2008). Both versions of the inhaler have the same design and dispersion mechanism but are different in air inlet dimensions, which control the resistance to the airflow.

The present study aims to investigate the effect of DPI resistance on the lung deposition of orally inhaled dry powder mannitol at comparable inhalation flow rates and to further understand how the lung deposition can be affected by different combination of resistance and inhalation flow rates. For this purpose, we used radiolabeled spray dried mannitol powder with low and high resistance Osmohaler™ over two different ranges of peak inhalation flow rate (50–70 L/min and 110–130 L/min). Mannitol powder was chosen for the deposition study because it is the drug powder used in the commercial product for the Osmohaler™ devices (Aridol® and Bronchitol®). Diethylenetriaminepentaacetic acid (DTPA) is a commonly used complexing agent for ^{99m}technetium (^{99m}Tc) to increase the molecular weight and reduce the pulmonary clearance rate of the radiolabel (Eberl et al., 2001).

2. Materials and methods

2.1. Materials

Mannitol powder was purchased from Mallinckrodt, NJ, USA. Technetium-99m in 0.9% saline for injection was eluted from a Gentech Sterile 99mTc generator (ANSTO Health, Australia). DTPA was purchased from Global Medical Solutions, Australia. A Sureguard (Bird Healthcare, Australia) filter was attached to the spray dryer air inlet to ensure uncontaminated air was used during spray drying.

2.2. Manufacture of radiolabeled mannitol

Mannitol powder for inhalation was radiolabeled using a method adopted from a previous study (Glover et al., 2008). Briefly, 0.128 g/mL mannitol containing ^{99m}Tc-DTPA was spray-dried (BÜCHI Mini spray dryer, B-191, *Switzerland)* at 4.6 mL/min feed rate, using 450 L/min atomization air flow rate, 110 °C inlet temperature, 69–85 °C outlet temperature, and 100% aspirator rate. ^{99m}Tc-DTPA was prepared by adding 5 GBq of ^{99m}Tc in 0.9% Saline to DTPA. The resulting mixture was added to the mannitol solution and filtered through a 0.22 μm sterile syringe filter (Sartorius Stedim, Germany).

Bioburden of the spray-dried mannitol powder (conducted by AMS Lab, Sydney) showed a total viable aerobic count and yeast count $<10^2$ cfu/g. Thin layer chromatography on the radiolabeled mannitol, using saline as the mobile phase, confirmed that ^{99m}Tc-DTPA purity remained >95%. The purity of the spray dried mannitol containing the 99mTc-DTPA was >99%.

2.3. Particle size measurement

The volumetric median diameter of the spray-dried mannitol powder was measured by Mastersizer 2000 (Malvern Instrument, UK) using dry dispersion at 4 bar dispersion pressure. To examine the effect of dispersion air flow rate on the aerodynamic particle size distribution of the mannitol powder delivered from the inhalers, unlabelled mannitol powder was dispersed from both the high and low resistance Osmohaler™ into the Alberta Idealized throat (AIT) connected to the Multi-Stage Liquid Impinger (MSLI) running at a flow rate corresponding to the average PIFR measured in the in vivo study for the respective Osmohaler™ resistance. For each impaction run (n = 3), two capsules containing 30 mg of unlabelled mannitol powder were dispersed.

2.4. Validation of radiolabeled mannitol

To confirm that the radiolabeling process did not change the particle size distribution of the mannitol powder, a HMPC capsule containing 30 mg of the spray-dried mannitol powder (with and without the radiolabel), was dispersed from a low resistance Osmohaler™. The *in vitro* dispersion of mannitol powder was conducted at 90 L/min for 2.7 s using a Model 160 Marple Miller impactor (MSP Corp., MN, USA) connected to an USP induction port.

During each impaction run, the collection cups were silicone greased (Slipicone®) to minimize particle bounce. A known amount of deionized water was used to rinse the capsule, device, throat, the 5 MMI collection cups, and the fibreglass filter for mannitol collection. The amount in the collected samples was quantified by HPLC. To ensure that the radioactivity distribution follows the particle size distribution measured from the chemical assay, the radioactivity was measured with a CRC dose calibrator (Capintec INC, NJ, USA).

2.5. Mannitol challenge test

Mannitol challenge test was conducted by administering 0 mg, 5 mg, 10 mg, 20 mg, 40 mg, 40 mg, and 40 mg using a low resistance Osmohaler™ to the subjects. This was followed by spirometry. Spirometry was performed using standard spirometric techniques