Use of gamma scintigraphy to understand inhaled device/formulation variables on delivery efficiency and deposition profile for systemic therapies

Peter Scholes PhD and Karen Jones PhD

Pharmaceutical Profiles, Mere Way, Ruddington Fields, Ruddington, Nottingham, NG11 6JS, UK

Introduction

Systemic delivery of both small molecules and macromolecules via inhaled therapies is an area of significant ongoing research[1]. The pulmonary route offers the physiological benefits of a highly vascularised, large surface area for absorption which can promote high bioavailability and a rapid onset of action. For biomolecules such as peptides, proteins and nucleic acid derivatives, inhaled drug delivery can also provide a viable alterative to intravenous administration. Critical to success will be the development and validation of drug delivery technologies capable of reproducibly administering medicaments in a respirable form to specific regions of the pulmonary system.

The ideal characteristics of an inhaler for systemic drug delivery are summarised in Table 1:

Table 1. Device Characteristics for Inhaled Systemic Delivery

- **Portable and easy to use**
- **Cost-effective**
- **Breath actuated**
- **Active (powered) delivery**
- **Flow-rate independence**
- **Maintain stability & activity of drug molecule**
- **Delivery capability for wide range of dose sizes**
- **Efficient & reproducible deep lung delivery**
- **Provide evidence of successful dosing**

The use of gamma scintigraphy to visualise and quantify lung deposition has proven to be a valuable tool in assessing some of these key attributes, and hence determine commercial product or technology viability[2].

In this case study, we report on the scintigraphic evaluation of the novel breath-actuated Otsuka Dry Powder Inhalation (ODPI) System for the delivery of peptides and proteins to the lung[3]. The device directs jets of air at a low density freeze-dried drug cake to generate fine particles which are entrained before they leave the mouthpiece (Fig. 1). Breath-actuation however relies on the subject's inspiratory effort which can vary significantly both between and within subjects, potentially leading to variability in dose delivery[4]. The purpose of this study was therefore to determine the *in vivo* drug delivery characteristics of the ODPI system by gamma scintigraphy, when different inspiratory efforts were used.

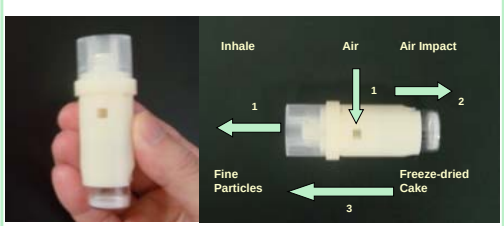
Methods

Formulation
The formulation consisted of a freeze-dried cake containing a peptide molecule and other excipients.

Flow rate selection
Using an in-house inhalation profile recorder (IPR) system the resistance of the ODPI system was determined to be 0.074kPa$^{0.5}$.min/L (hence requiring a flow rate of 27L/min to produce a fixed 4.0kPa pressure drop). Initial investigations demonstrated that when a hard and fast inhalation was targeted, healthy volunteers (n=10) could consistently generate peak inhaled flow rates (PIFs) through the device of between 30L/min and 40L/min. Flow rates of 20 and 40L/min were therefore selected to bracket the likely range of inspiratory effort produced by healthy volunteers using this ODPI system.

***In vitro* testing**
The aerodynamic particle size distribution and emitted dose (ED) of the formulation were evaluated at flow rates of 20, 30 and 40L/min using Multi-Stage Liquid Impinger. Fine particle fraction (FPF, <5µm) and ED data were calculated as a percentage of the metered dose.

***In vivo* testing**
Radiolabelling studies were performed which confirmed the suitability of the TechneCoat™ radiolabelling method[5] in accordance with appropriate standards[6]. A clinical study was then completed in 7 healthy volunteers in which the whole lung deposition of the formulation was determined by gamma scintigraphy after inhalation at targeted PIFs of 20 and 40L/min. The actual flow profiles and PIF values for each inhalation were recorded.



Inhalation through the mouthpiece causes air to enter an inlet (1) and be directed at the freeze-dried cake (2) from which fine particles are dislodged and entrained (3) for inhalation

Results

The FPF<5µm (% of the metered dose) as determined by *in vitro* testing was shown to be dependent on the flow rate through the inhaler (Figure 2). There was however, no apparent reduction in lung deposition *in vivo* at the lowest flow rate tested, and lung deposition was shown to be independent of PIFs (Figure 3). Furthermore, the *in vivo* dose delivery of the ODPI system was characterized by high lung deposition (mean: 60.4% of the metered dose).

Figure 2. *In vitro* Dose Delivery Characteristics

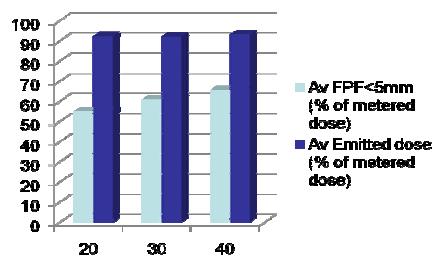
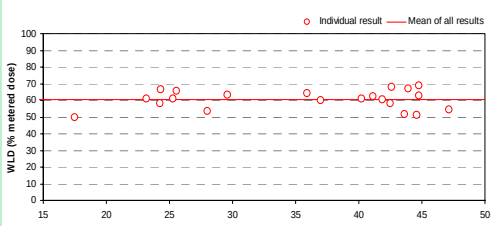


Figure 3. Effect of PIF on Lung Deposition relative to the Metered Dose

WLD: Whole Lung Deposition
PIF: Peak Inspiratory Flow Rate



Conclusions

Gamma scintigraphy has enabled the *in vivo* performance assessment of a novel inhalation device. The data generated also illustrated the limitations of *in vitro* testing as a predictor of performance in man. The ODPI System consistently delivered drug to the lungs with high efficiency and *in vivo* lung deposition was independent of inspiratory effort over a clinically relevant range of PIFs. This confirms suitability of the device for the reproducible deep lung delivery of therapeutics intended for the treatment of systemic indications.

References

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Correspondence

Peter Scholes Ph.D
Tel: +44 (0) 115 974 9000
Email: enquiry@pharmprofiles.com
www.pharmprofiles.com