INHALATION PROFILE MODELING FOR FLUTICASONE PROPIONATE DRY POWDER INHALERS IN HEALTHY VOLUNTEERS DURING A FOUR WAY CROSSOVER BIOEQUIVALENCE STUDY

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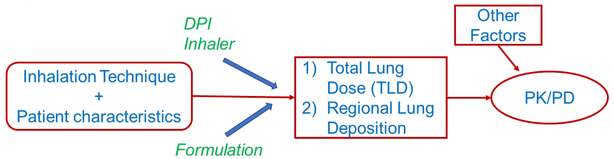
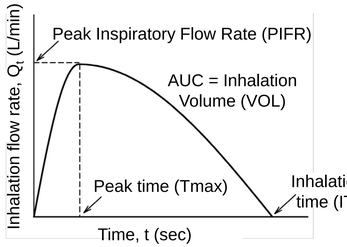
INTRODUCTION

Dry powder inhaler (DPI) drug products are breath actuated, i.e., they depend on patient's inspiratory flow rate for de-agglomeration of drug particles. Hence, **inhalation technique and subject characteristics** are important factors that can influence the lung dose, regional lung deposition and eventually the PK/PD of the drug.



A schematic representation of an idealized inhalation profile and sinusoidal model (Delvadia et al, 2016) is shown below:



Sinusoidal Model for Inhalation Flow Rate (Q_t):

$When\ 0 \le t < Tmax$

$$Q_t = PIFR \times \sin\left(\frac{\pi t}{2 \times Tmax}\right)$$

$When\ Tmax \le t < IT$

$$Q_t = PIFR \times \cos\left(\frac{\pi(t - Tmax)}{2\,(IT - Tmax)}\right)$$

OBJECTIVES

- To determine if inhalation technique and subject characteristics influence the inhalation profiles for the studied fluticasone propionate formulations.
- To characterize and describe the variability of inhalation profiles obtained for fluticasone propionate (FP) via the Aerolizer device in healthy volunteers using linear mixed effects modelling.
- To validate the linear mixed effects models via simulation-based analyses.

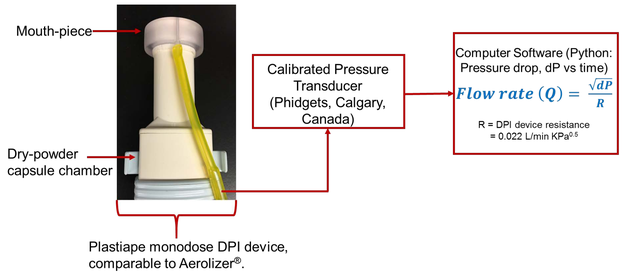
METHODS

Inhalation profiles (IP)

Correct inhalation technique training was provided to subjects during screening and at each visit. They received verbal instructions during each inhalation:

a) Exhale completely before inhalation.
b) Make a tight seal around the mouthpiece of the inhaler.
c) Take a deep breath and hold breath for 10 seconds after the end of the inhalation.

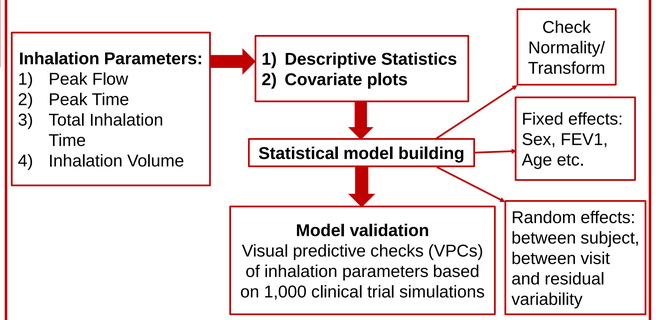
METHODS



- 24 healthy volunteers (13 Female; 11 Male) of age 18 – 48 years and forced expiratory volume in one second (FEV1) within the range of 2.45 L to 4.36 L
- Four visits per healthy volunteer
- Five 100 mcg FP capsules per visit; Inhaled at least twice per FP capsule
- 10-14 high-resolution inhalation profiles per visit per subject (total= 988)

Data Analysis

All statistical analyses were performed using the software R (v 3.3.2).



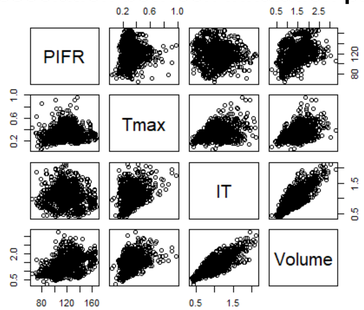
RESULTS

Descriptive Statistics

Inhalation Parameter	Mean	Min	Max	% RSD
PIFR (L/min)	120.10	65.17	166.70	16.24
Peak Time (Tmax, sec)	0.33	0.047	0.968	36.30
Inhalation Time (IT, sec)	1.073	0.39	2.114	30.19
Inhalation Volume (VOL, L)	1.46	0.262	3.265	33.16

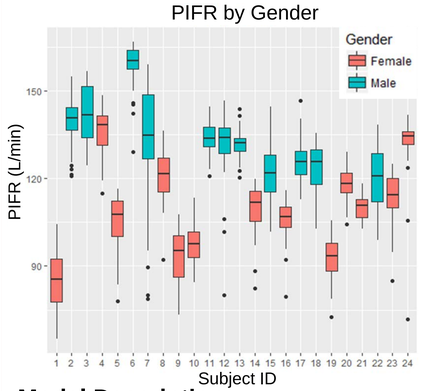
RESULTS

Association between inhalation parameters



- Inhalation volume was correlated with inhalation time (r=0.81), peak time (r=0.47) and PIFR (r=0.38).
- Peak time was correlated to inhalation time (r=0.38).

Covariate Plot



- Significantly higher PIFR for males (23.47 units higher, p-value < 0.001) compared to females.
- Sex accounts for 46% of variability in PIFR.

Model Description

Model 1: $PIFR_{ijk} = \beta_0 + \beta_1(Sex_i) + u_i + v_{ij} + e_{ijk}$

PIFR = Peak Inspiratory Flow Rate; Sex_i = 1 for males; 0 for females;
i = Subject; j = Visit; k = Replicate;
β_0 = 109.36 (101.62, 116.81); β_1 = 23.47 (13.35, 34.09);

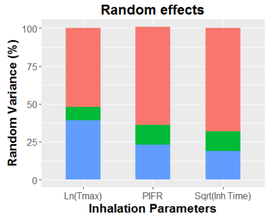
Model 2: $\log(Tmax_{ijk}) = \beta_0 + u_i + v_{ij} + e_{ijk}$

Tmax = Peak Time; i = Subject; j = Visit; k = Replicate;
β_0 = -1.17 (-1.28, -1.06);

RESULTS

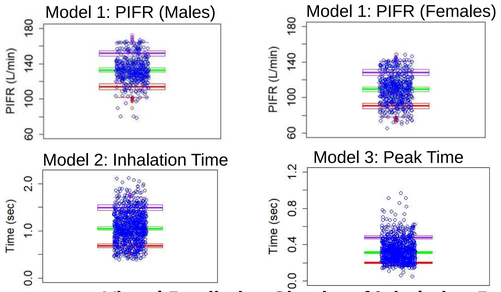
Model 3: $\sqrt{Inh\ Time_{ijk}} = \beta_0 + u_i + v_{ij} + e_{ijk}$

Inh Time = Total Inhalation Time; i = Subject; j = Visit; k = Replicate;
β_0 = 1.02 (0.96, 1.07);



- Between-subject and between-visit variability for PIFR, Peak Time and Inhalation Time were highly significant from parametric bootstrap of likelihood ratio statistic (p-value < 0.0001).

Model Validation



Visual Predictive Checks of Inhalation Parameters

- The model predicted inhalation parameters (PIFR, Peak Time, Inhalation Time and Inhalation Volume) agree well with the corresponding observed values.

CONCLUSIONS

- Sex was the most influential subject characteristic affecting the PIFR.
- Sex explained approximately half of the observed variance, whereas other subject properties had no or only a smaller impact on the inhalation profiles.
- Standardization and in-depth training of the inhalation procedure allowed us to achieve consistent inhalation profiles by all subjects. The between visit and residual variabilities for PIFR and inhalation time were small (~1/3 of total variance).
- The linear mixed effects modeling explained the variability of inhalation profiles well, as confirmed by visual predictive checks.
- These modeled inhalation profiles will be used as input for predictions of the deposited lung dose and regional lung deposition via the Preludium software.

ACKNOWLEDGEMENTS

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